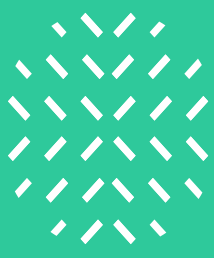
Dotmatics nQuery

User Manual



nQuery Advisor® Clinical Trial Design Platform

v. 9.4.1.0 User Manual

Statsols

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Contents

1 nQuery Basics

This chapter provides a quick guide for how to access nQuery Advisor (referred to as nQuery from hereon), an overview of nQuery's various user interface elements, a breakdown of nQuery's core features and a tutorial on how to conduct a basic sample size determination or power analysis. nQuery's more advanced features are described in more detail in subsequent chapters.

Note that nQuery installation is not covered in this tutorial. Installation guides will have been provided to you with the application and are also available online in your nQuery account or in the Knowledge Base at `www.statsols.com`.

1.1 System Requirements

The minimum system requirements for nQuery 9.4.1.0 are:

- Processor: Intel/AMD (x64-based)
- RAM: 2GB
- Memory: 1 GB
- OS: Microsoft Windows 11, Windows 10 (v1607 or higher)
- Other: Microsoft .NET 8

1.2 Help and Support

The easiest way to get statistical or technical support is to contact Statsols using your nQuery Community User account (see subsection 1.4.1) or to use the Help Centre button found in the bottom right of the nQuery application Home tab (see subsection 1.4.5). The nQuery support centre can also be found at the following URL:

- info.statsols.com/help-center

The official nQuery website is www.statsols.com. You can find additional detail on nQuery, contact information and access to resources such as worked examples and webinar recordings at our website.

1.3 Starting nQuery

There are multiple ways to open the nQuery application.

Firstly, nQuery can be opened by double-clicking on the **nQuery** desktop icon, if selected during installation.

Secondly, enter **nQuery** into the Windows search field - the search feature is either directly embedded in taskbar or within the **Start** menu depending on Windows OS version. Select the **nQuery** application (app) when it appears in the search results.

Thirdly, you can find nQuery within the list of applications in the **Start** menu. Select the **Start** menu in the lower-left. Scroll down to the **N** section in the alphabetised list of apps and select the **nQuery** folder. Click on the **nQuery** under that folder. Select **All Apps** if the full list of apps is not shown by default.

Alternatively, open the **nQuery.Application.exe** file from the nQuery installation folder. By default nQuery will be installed in C:\Program Files (x86)\Statistical Solutions Ltd\nQuery

1.4 nQuery Start-up and Layout

Once the user has launched nQuery, the application will appear as illustrated in Figure 1.1. The five major elements in the application on start-up are the Home tab (1), the toolbar (2), the menu bar (3), the tab menu (4) and the information bar (5). These are summarised in the following section.

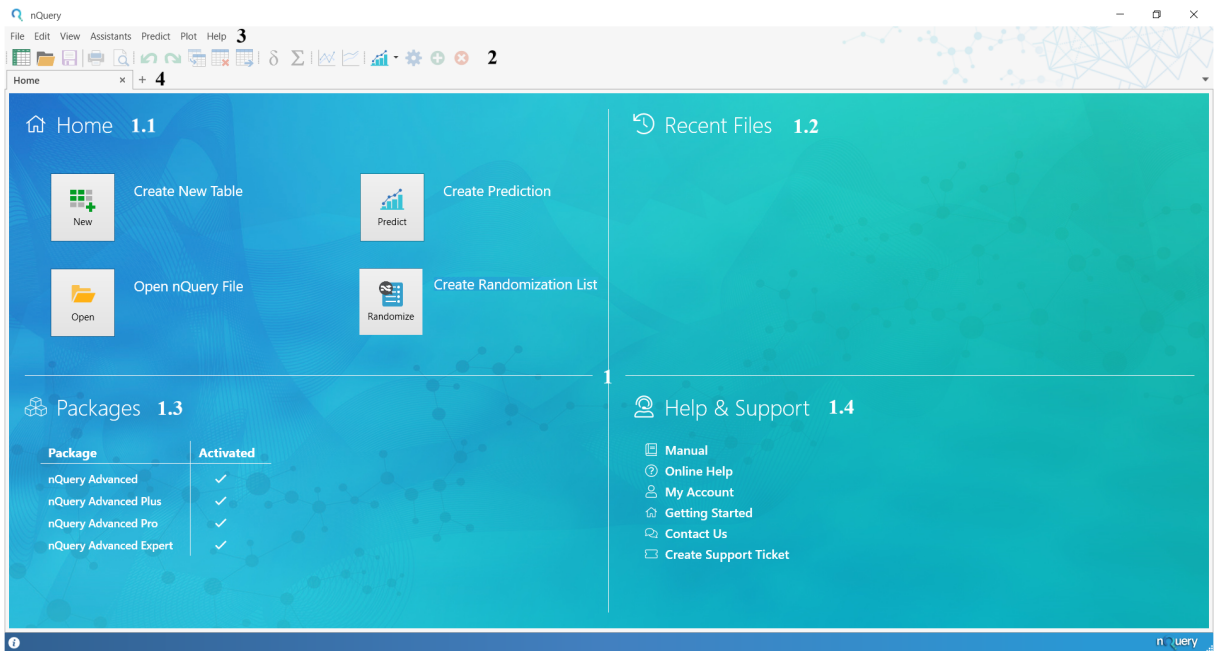


Figure 1.1: nQuery on Start-up

1.4.1 Home Tab (1)

When you open nQuery, the software will open the "Home" tab. This window contains options to open new tables or pre-existing nQuery files, open recent nQuery files, see which nQuery modules are currently active and support options if you need further help in using the software. The four quadrants (1.1 to 1.4 from top-left to bottom-right) in the Home tab are described in more detail below.

1.4.1.1 Home (1.1)

The Home quadrant (top-left) contains up to four buttons: **Create a New Table**, **Open an Existing Table**, **Create Randomization List**, **Create Prediction**

Selecting the **Create a New Table** button will open the **Select Table** window where you can open a new design table for sample size or power calculations. This window is described in section 1.5

Selecting the **Open nQuery File** button will open the **Open** window where you can open any pre-existing nQuery save file (.nqt, .nqp, .nqd, .nqrl, .nqgs) - the Open window will be a Windows Explorer dialog.

Selecting the **Create Randomization** button will open a new **Randomization List** tab. The Randomization List feature is described in detail in chapter 6.

Selecting the **Create Prediction** button will open the **New Prediction** window where you can upload interim data files for milestone prediction. nQuery Predict is described in detail in chapter 11. *This option will only be shown if an nQuery Advanced Expert license is active. Active packages are displayed in the Packages section (1.3 below). To purchase additional packages, see* `www.statsols.com`.

1.4.1.2 Recent Files (1.2)

The Recent File quadrant (top-right) will contain a list of all save files recently opened in nQuery. To open a file, select the required file from this list and this save file will open automatically. An example is provided in Figure 1.2.

Figure 1.2: Recent Files Example

1.4.1.3 Packages (1.3)

The Packages quadrant (bottom-left) will contain a list of the nQuery packages which are currently active under your current nQuery license. Packages which are active will have a tick to the right of the package name. *For details on nQuery packages and activating them, see section 5.2. To purchase additional packages, see* `www.statsols.com`.

The current packages in nQuery Advanced (largest areas covered in brackets) are:

- nQuery Advanced (Fixed Term Trial Sample Size)
- nQuery Advanced Plus (Bayesian Sample Size)
- nQuery Advanced Pro (Adaptive Design)
- nQuery Advanced Expert (Milestone Prediction)

1.4.1.4 Help & Support (1.4)

The Help & Support quadrant (bottom-right) contains a range of help, support and troubleshooting options for nQuery. These options are as follows:

1. Manual: This will open the User Manual *(this document)*
2. Online Help: This will open the nQuery Knowledge Base website. This website provides a comprehensive set of instructions for installation, using the software and common troubleshooting issues with solutions.
3. My Account: This will open the nQuery Account Administrator Portal. Your nQuery account website will contain access to the relevant installers, activation keys and installer guides.
4. Getting Started: This will open the "How to Use nQuery" website. This website contains videos and instructions on all the basic elements of using nQuery for clinical trial design.
5. Contact Us: This will open the "nQuery FAQ" website. This website will contain answers to frequently asked questions (FAQs) about nQuery and provides an "Ask a Question" facility where you can send a custom query to us online by filling out the relevant form.
6. Create a Support Ticket: This will bring you the "Contact nQuery" website. This page provides access to the multiple support channels available for different types of query.

1.4.2 Toolbar (2)

The toolbar provides easy access to the most commonly used functions in nQuery. The toolbar options can be split into five main categories: file options, print options, table options, side-table options, plotting options and nQuery Predict options. The toolbar is shown in detail in Figure 1.3.

Note that the nQuery Predict options (15 - 18) will be described further in chapter 11 but will not be displayed unless an nQuery Advanced Expert license is active. Active packages are shown in the Packages section of the Home tab.

Figure 1.3: Toolbar

There are fourteen options in the menu bar. These are as follows:

1. New Table (New): Open the Select Table screen
2. Open Existing Table (Open): Open nQuery table save files
3. Save Table (Save): Save the currently open nQuery table
4. Print: Print the currently open nQuery table
5. Print Preview: Open Print Preview of currently open nQuery table
6. Undo Action (Undo): Undo last action within currently open nQuery table
7. Redo Action (Redo): Redo last undone action with currently open nQuery table
8. Copy Table: Copy all contents of currently open nQuery table
9. Clear Table: Clear all entries from currently open nQuery table
10. Fill Right: Fill all entries to the right with the same selected cell value
11. Compute Effect Size: Open the Effect Size side-table (if available)
12. Compute Covariance Matrix: Open the Covariance Matrix side-table (if available)
13. Plot Power vs Sample Size: Plot Power vs Sample plot for selected column(s)
14. Plot User Selected Rows: Open custom plot dialog for selected column(s)
15. Create New Prediction Workspace (New Prediction): Open new nQuery Predict workspace. When selected a drop down with two options will be displayed:
    a) Prediction with Subject-level Data: Open "New Prediction - Import Datasets" dialog for uploading interim data
    b) Prediction with Fixed Parameters: Open new nQuery Predict Workspace.
16. Specify the Simulation Parameters (Configure): Return to the Setup stage in the current nQuery Predict workspace
17. Add a New Dataset to the Workspace (Add Dataset): Open Import Datasets dialog to add new dataset to current nQuery Predict workspace
18. Remove the Selected Dataset from the Workspace (Remove Dataset): Remove the selected Dataset in Data section from current nQuery Predict workspace.

These options will be explored in further detail later in this manual.

1.4.3 Menu Bar

There are six options on the menu bar: **File**, **Edit**, **View**, **Assistants**, **Plot** and **Help**. These are shown in Figure 1.4.

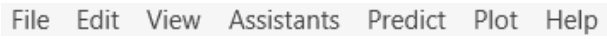


Figure 1.4: Menu Bar

The **File** menu enables the user to open new tables, existing files and provides access to additional software options. This menu contains options to open the *New* design table menu, *Open* an existing nQuery save file or save (*Save, Save as*) the currently open design table. The most common save file format in nQuery for design tables is the .nqt format. Complex nQuery features use their own file formats - nQuery Predict (.nqp), Randomization Lists (.nqrl), Group Sequential Simulation (.nqgs) and Data Entry (.nqd). The **File** menu also includes options for printing (*Print, Print Preview*), a dropdown for *Recent Files,* the nQuery *Options* menu and an option to *Close* nQuery.

The **Edit** menu enables the user to conduct common actions or changes within the current nQuery design table. This menu contains options to *Undo* and *Redo* actions within the current table, options to *Copy Table* or *Clear Table* for the entirety of the current design table and an option to fill all right-ward columns with the same value(s) from the currently selected column(s) using the *Fill Right* option.

The **View** menu enables the user to open and close specific nQuery user interface (UI) elements. The *Home* option will open or close the initial "Home" tab (subsubsection 1.4.1.1) in nQuery. The other options enable the user to open or close the table UI elements of the *Output* statement, the *Specify Multiple Factors* tool, the *Help* panel and the *Notes* tool. These table elements are described in section 1.8. Note all options other than *Home* are initially unavailable (greyed out) until the user opens a design table. A currently open element will have a tick on right-hand side of that option in the View menu.

The **Assistants** menu gives access to several useful tools that can help with a user's calculation. These include access to the *Calculate Effect Size* and *Specify Covariance Matrix* side-tables (if available in the currently open design table tab), access to utilities for deriving the *Standard Deviation*, access to cumulative *Distribution Functions* for multiple statistical distributions, a *Data Entry* tool, a *Survival Parameter Converter* tool, a *Bayesian Posterior Error* calculator (note this requires nQuery Advanced Plus or higher license), the *Report* feature, the *Randomization Lists* feature, the *Group Sequential Design Simulator* (note this requires nQuery Advanced Pro or higher license) and a shortcut to the native *Windows Calculator* (if available). These options are discussed in further detail in subsequent chapters.

The **Predict** menu gives access to options to create a new nQuery Predict workspace and to add or remove datasets in the currently open nQuery Predict workspace. *New Prediction* will open a menu with two options: *Prediction with Subject-level Data* and *Prediction with Fixed Parameters. Prediction with Subject-level Data* opens the "New Prediction - Import Datasets" dialog for uploading interim data. *Prediction with Fixed Parameters* opens a new blank nQuery Predict Workspace. *Add Dataset* opens the Import Datasets dialog to upload additional datasets to the current nQuery Predict workspace. *Remove Dataset* removes a dataset selected from the Data field in the current nQuery Predict workspace. *Note that the Predict menu will not be displayed unless an nQuery Advanced Expert license is active. For details on nQuery packages and activating them, see section 5.2. To purchase additional packages, see* `www.statsols.com`.

The **Plot** menu enables a user to generate plots in the current nQuery design table. Once a table has been opened and a column(s) has been filled appropriately, the user can use

this menu to create *Power vs. Sample Size* and *Plot User Selected Rows* plots. The table-specific *Survival vs Time* (for piecewise survival tables such as STT3) and *Multiple Boundary* (for Group Sequential (Lan-DeMets Only) tables such as MTT12) are also available in this menu.

The **Help** menu gives access to the *nQuery Manual* (this document), utilities for license management (*Activate/Renew License, Enable Modules* (i.e. higher license tiers)), an option *Check for Updates* to the latest nQuery version, the *Installation Qualification* (IQ) and *Operational Qualification* (OQ) tools and the *About* page containing the nQuery version information and license agreement

For functions which have keyboard shortcuts, these are provided on the right-hand side of that file menu option.

Below is a complete list of menu options:

File: New, Open, Save, Save As, Print, Print Preview, Recent (horizontal menu), Options, Close

Edit: Undo, Redo, Fill Right, Copy Table, Clear Table

View: Home, Specify Multiple Factors, Output, Help, Notes

Assistants: Compute Effect Size, Compute Covariance Matrix, Standard Deviation, Data Entry, Distribution Functions, Survival Parameter Converter, Posterior Error Rate Calculator (*nQuery Advanced Plus or higher*), Report, Randomization Lists, Group Sequential Design Simulator (*nQuery Advanced Pro or higher*), Windows Calculator

Predict: *nQuery Advanced Expert Only* - New Prediction (Prediction with Subject-level Data, Prediction with Fixed Parameters), Add Dataset, Remove Dataset

Plot: Power vs. Sample Size, User-Selected Rows, Survival vs Time plot (STT3/STT3u tables only), Multiple Boundary (Group Sequential Design (Lan-DeMets Only) tables only)

Help: nQuery Manual, Activate/Renew License, Enable Modules, Check for Updates, Installation Qualification, Operational Qualification, About

1.4.4 Tab Menu

The tab menu provides an easy way to navigate between different currently open tables within nQuery and quickly create fresh copies of open tables. It is shown in Figure 1.5 (note that we have opened some additional tables in nQuery for illustration purposes)

Figure 1.5: Tab Menu

There are three main elements to the tab menu: the tabs, the fresh table shortcut and the table navigation drop-down.

1. Tabs: Individual tabs for each table opened in the session and the "Home" tab. The tab also has an "x" button on its right-hand side to close an individual tab. The current open tab will be highlighted compared to the other tabs.

2. Fresh Tab: If the Home tab is selected or no tabs are available, will open the "Select Test" menu. If a nQuery table is selected, it will open a clean version of that table in a new tab. If a nQuery Predict workspace is opened, it will open a copy of the current workspace state in a new tab.
3. Tab Navigation Menu: If selected, will open a drop-down menu of all tabs currently open in nQuery. When a tab is selected, this table is displayed in nQuery.

1.4.5 Information Bar

The information bar provides information on the currently opened table and the currently selected cell in that table. It is shown in Figure 1.6 (note a specific cell was selected for illustration purposes)

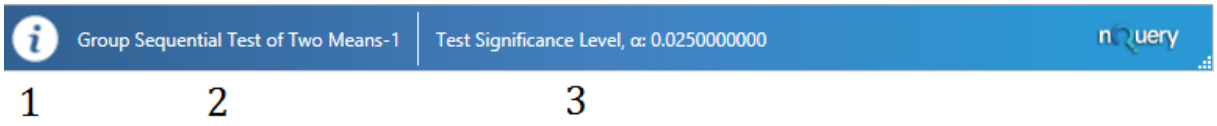


Figure 1.6: Information Bar

There are three main elements to the information bar: the *Help Centre*, the *Table Name* and current *Cell Information*

1. Help Centre: Selecting the information "i" symbol will open the online help centre in the default browser. It provides links to guides, troubleshooting and to create a support ticket
2. Table Name: Provides the name of the currently open table
3. Cell Information: Provides the name and the value (up to 10 decimal places) in the currently selected table cell

1.5 Opening a Design Table

The next aspect of the interface that will be reviewed is the opening of a new design table. A *design table* is the tool which is used to conduct clinical trial design calculations such as for sample size and power. There are three ways in which the user can open a new design table in nQuery:

1. Selecting New from the File menu
2. Selecting the New option from the menu bar 
3. Selecting the "+" symbol in the tab menu when the Home tab is open or no tabs are open in nQuery.

When these options are selected, the *Select Table* window will open. This is shown in Figure 1.7.

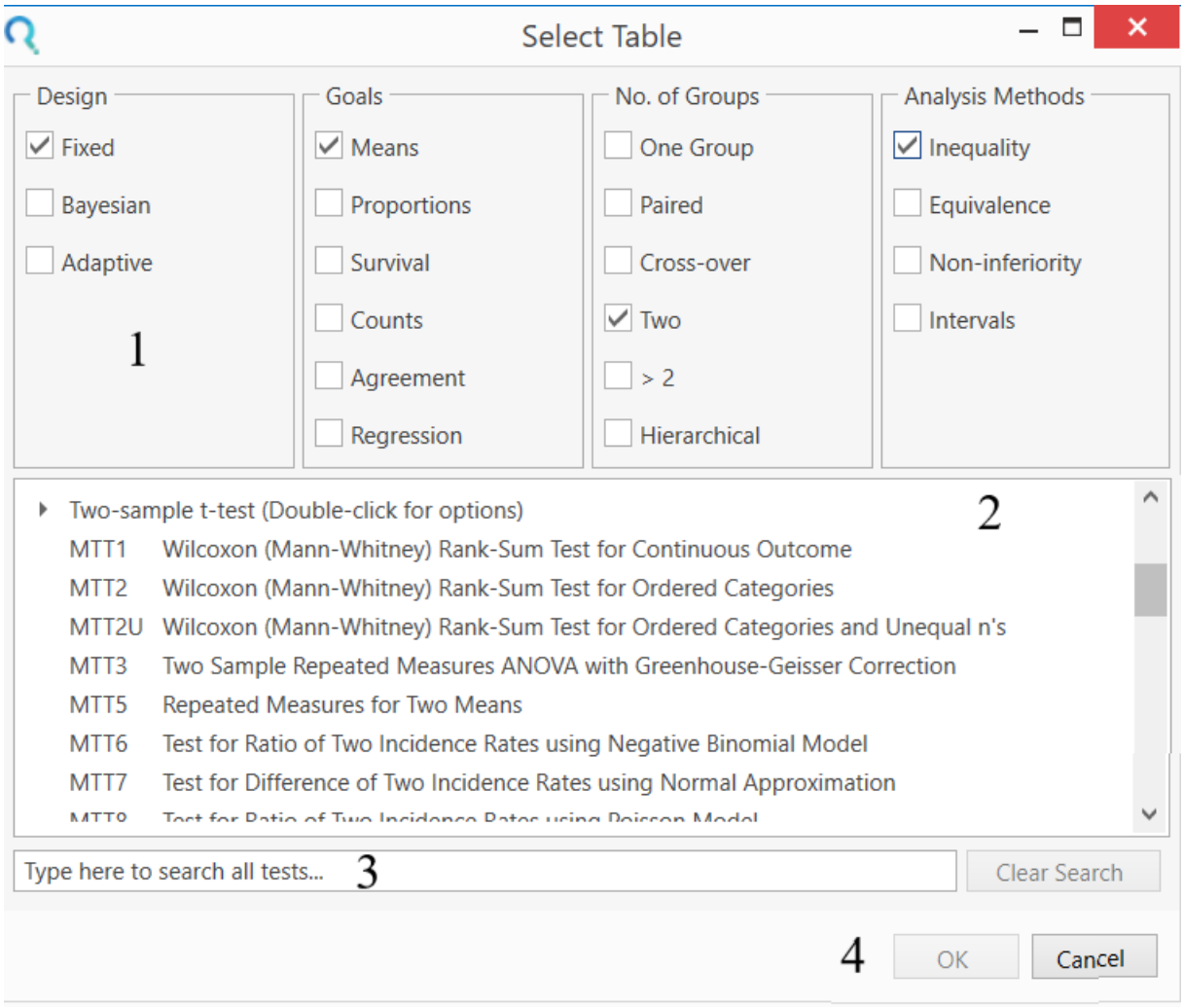


Figure 1.7: Select Table Window

The Select Table window consists of four main elements: the table selection menus (1), the table selection window (2), the table search bar (3) and the OK/Cancel buttons (4).

In nQuery, there are two main ways to find a specific design table: the table selection menus or the table search bar.

Table Selection Menus: The table selection menu consists of four radio button columns. These are for the *Design*, the *Goal*, the *No. of Groups* and the *Analysis Methods*. A brief description of these follows:

1. Design: Specify whether the study analysis will use a Fixed, Bayesian or Adaptive design.
2. Goal: Specify the type of data which will be analysed in the study. Choose between Means, Proportions, Survival, Counts, Agreement or Regression.
3. No. of Groups: Specify the number of groups which will be compared in the study. Choose between One Group, Paired, Cross-over, Two, >2 (Greater than Two) or Hierarchical
4. Analysis Type: Specify the type of analysis and hypothesis type which will be used in the study. Choose between Inequality, Equivalence, Non-inferiority, Intervals

By default no values are selected from the Table Selection Menus and the Table Selection Window (2, see below) will display a list of every table ordered alphabetically by Table Code to left of each design table name e.g. AOC0. As options are selected from the Table Selection Menus, the list is filtered to include only those tables which fulfil that radio button condition. Note tables can be shown for multiple options within a given radio button column. The tables filtered for with each radio button are as follows:

In the **Design** menu, *Fixed* will select all tables which assume a fixed term analysis i.e. analysis only occurs once all subject follow-up data is available. *Bayesian* will select all tables which either use Bayesian inference to improve power calculations or find the sample size for a specific Bayesian analysis, test or interval. *Adaptive* will select all tables which use an adaptive design i.e. where decisions or changes are made to the trial while it is on-going based on interim data.

In the **Goal** menu, *Means* will select all tables related to continuous data (e.g. t-tests, ANOVA) - this option also includes non-parametric (e.g. Wilcoxon Mann-Whitney U), incidence rate/counts (e.g. Poisson) or variances (e.g. F-test) analysis options. *Proportions* will select tables related to binary (e.g. Fisher's Exact Test), categorical (e.g. Chi-Squared Tests) and ordinal data (e.g. Proportional Odds Model) analysis. *Survival* will select tables related to time-to-event/survival (e.g. Log-Rank Test, Cox Regression) analysis. *Counts* will select tables related to counts or incidence rates (e.g. Poisson, Negative Binomial) analysis. *Agreement* will select tables related to agreement (e.g. Kappa), correlation (e.g. Pearson Correlation) or diagnostic screening (e.g. sensitivity, ROC) data analysis or testing. *Regression* will select tables related to regression analysis for continuous (Linear), binary (Logistic), survival (Cox) and incidence rate (Poisson) data.

In the **No. of Groups** menu, *One Group* will select all tables where a single group will be analyzed, most often against a reference parameter value. *Paired* will select all tables which are appropriate for a paired analysis (e.g. paired t-test, McNemar test). *Cross-over* will select all tables which use a cross-over design (e.g. 2x2 design). *Two* will select all tables where two independent (parallel) groups are compared. *>2 (Greater than Two)* will select all tables where more than two independent treatment groups are compared (e.g. ANOVA). *Hierarchical* will select all tables which analyze hierarchical data structures such as repeated measures, cluster randomized data or multi-center trials using methods such as mixed models.

In the **Analysis Methods** menu, *Inequality* will select tables where the power for an inequality (also commonly referred to as superiority) hypothesis test is of interest. *Equivalence* will select tables where the power of an equivalence hypothesis test is of interest e.g. bioequivalence analyses. *Non-inferiority* will select tables where the power of an non-inferiority hypothesis test is of interest - note this option will also include Superiority by a Margin (also known as Supersuperiority) tables, many non-inferiority tables can also be used for Superiority by a Margin analysis. *Intervals* will select tables where a specific width of confidence or other statistical interval (Bayesian Credible, Prediction, Tolerance) is targeted.

Table Selection Window: For a given set of table selection menu options or a specific table search query, the table selection window will display all of the tables which are consistent with the menu options or search query. For example, in Figure 1.7 the options selected from the Table Selection Menu are Fixed > Means > Two Groups > Inequality which corresponds to tables which use a fixed term analysis for the power of a test for a two sample superiority hypothesis. Relevant options for this combination of menu options

include common tests such as Two Sample t-tests, Wilcoxon/Mann-Whitney Rank-Sum (U) tests and Two Group Repeated Measure ANOVA tests.

To open a table, select the desired table from this Window and select OK in the bottom-right of the window.

If the number of available tables for a given selection criteria is high, you can use the scroll bar on the right-hand side to find tables further down the list for the given query.

Note that some types of statistical test have a large number of variants. These variants are then contained within a sub-menu to reduce the number of options shown by default for easier searchability. These sub-menus are indicated by a "▶" symbol and the test prompt "(Double-click for options)". To open the sub-menu select the ▶ symbol or double-click the table name and the options will appear automatically below the sub-menu title. For example, in Figure 1.7 the option of "Two-Sample t-test" is a sub-menu option. If we select the ▶ drop-down menu then the options will appear below the "Two-Sample t-test" option. This is shown in Figure 1.8.

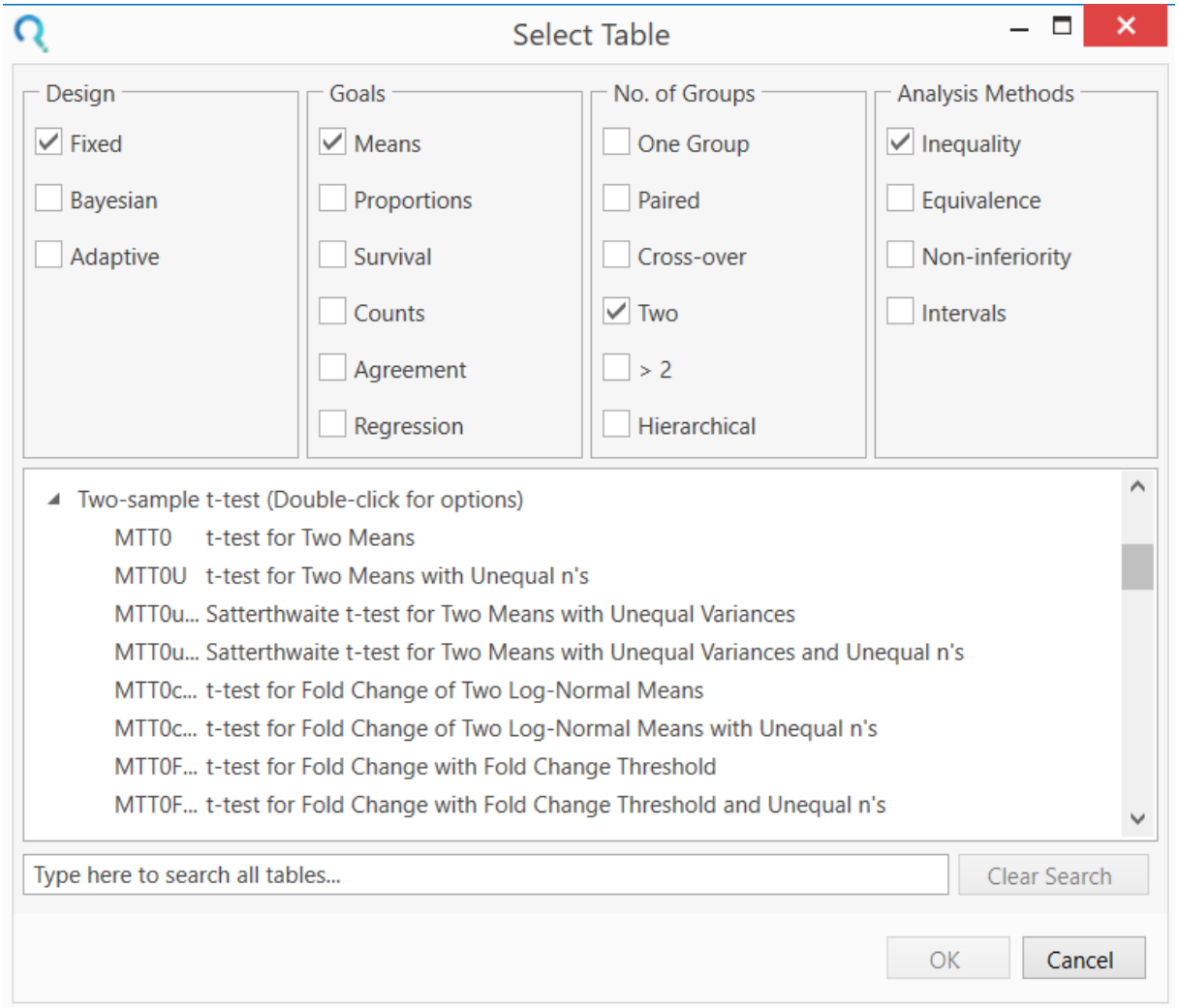


Figure 1.8: Select Table Drop-down

Table Search Bar: The table search bar allows the user to search for tables using a given text search query. For example if a t-test analysis was being considered, entering

"t-test" into this search bar field would show all of the potential t-test tables in nQuery. The tables which match the query will be shown in the Table Selection Window. To open the table, select the table in Table Selection Window and select "OK". An example of this is shown in Figure 1.9.

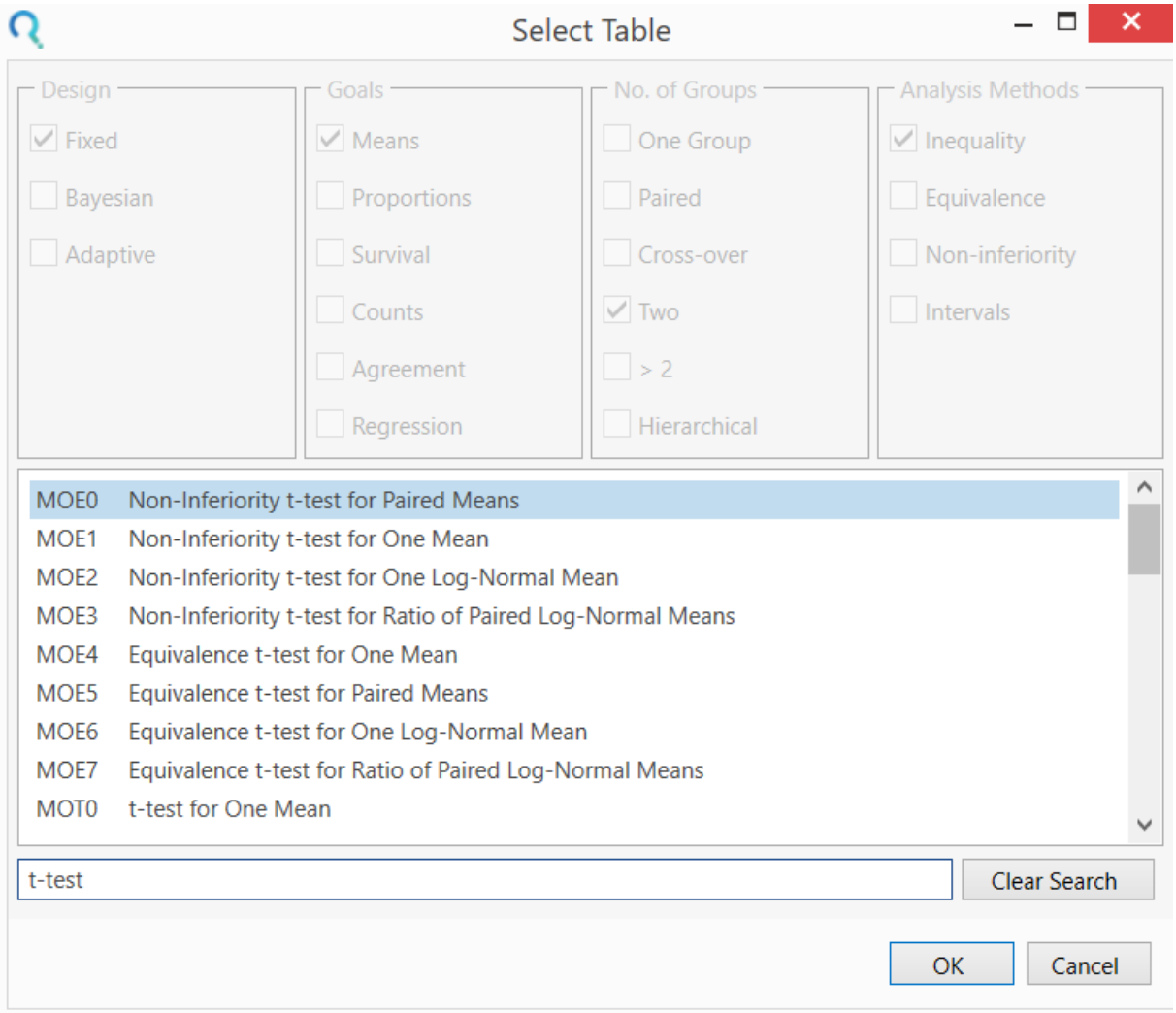


Figure 1.9: Table Search Query Example

Note that while a search query is active the Table Select Menu will be disabled (greyed out). To re-activate the Table Select Menu, click the "Clear Search" button.

OK/Cancel Buttons: These buttons complete the table selection process. When the desired table from the Table Selection Window is selected, click "OK" and that table will be opened in nQuery. To close the Select Test Design and Goal window without opening a table, select the "Cancel" button. Note that selecting the close window option in the top-right is equivalent to selecting "Cancel".

1.6 Design Table Layout

nQuery design tables have a large number of shared design elements. This section will outline the default layout of an nQuery design table and a brief description of these

elements and their usage. Many of these elements will be covered in more detail in future chapters. The default layout of the One Way Analysis of Variance (ANOVA) table is shown in Figure 1.10.

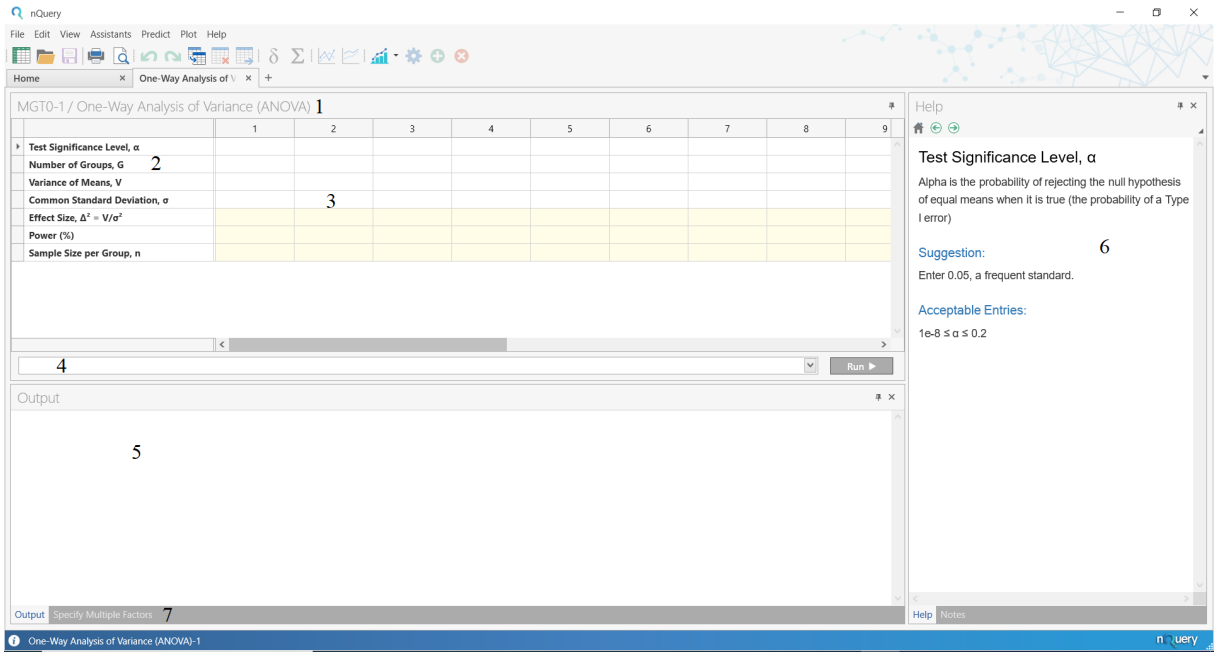


Figure 1.10: One Way Analysis of Variance Design Table

When a design table is opened, there are seven major elements of interest:

1. **Table Title:** This is the full name of the *design table* for the currently open table
2. **Design Parameter Row-Names:** The names of the *design parameters* required for the calculations in this *design table*.
3. **Main Design Table:** The table where the values of the *design parameters* will be entered for a specific calculation.
4. **Solver Drop-down Menu:** The menu containing the names of the available *solvers* in this design table and the "Run" button to manually activate *solvers*.
5. **Output Window:** The window containing the *output statement* summary for a *solver* calculation.
6. **Help Window:** The window containing the *help card* for each *design parameter* row.
7. **Window Selection Tabs:** Tabs to navigate between a window's options. In the *Output* window, we can select the *Specify Multiple Factors* Tool and in the *Help* window, the *Notes* tool.

The usage of each of these elements will be explored in the next section using a tutorial example from nQuery.

1.7 Using nQuery Design Tables

1.7.1 Introduction

In this section, a basic example of using an nQuery design table is provided. A *design table* is the tool which is used to conduct clinical trial design calculations such as for sample size and power. The additional tools and options to assist in conducting a sample size or power calculation in a design table are also illustrated.

For this example, the One-Way ANOVA table used in section 1.5 and section 1.6 will continue to be used. This table is shown in Figure 1.11.

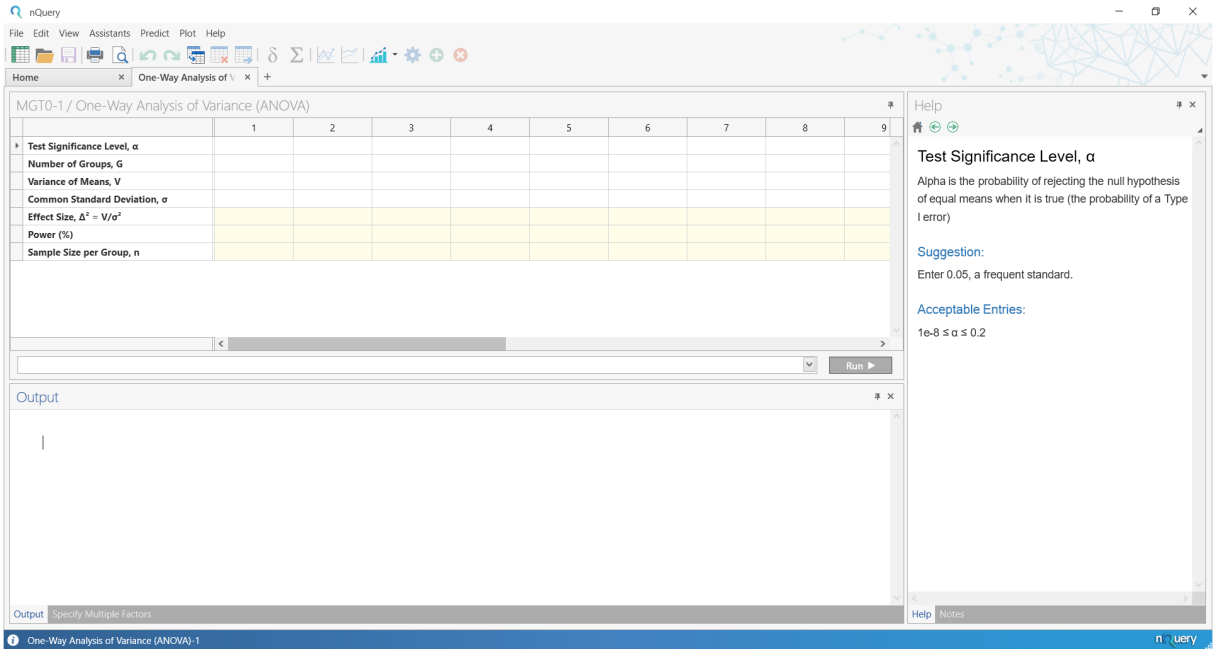


Figure 1.11: Clean One-Way ANOVA Table Example

In the main design table, each row corresponds to a **design parameter** which is set by the user and each column corresponds to an individual design specification. nQuery allows users to easily calculate the parameters of interest using multiple design specifications using its intuitive spreadsheet format.

Main table inputs will be either *Numeric Inputs* (within the allowable range, see subsection 1.7.2 and subsection 2.2.1) or *Dropdown Menus*.

Numeric inputs will either be floating point double values (e.g. Variance of Means, V), percentages (e.g. Power) or integers (e.g. Sample Size). Integer rows will automatically prevent decimal values being inputted.

Dropdown Menus will consist of a list of options for that row. For example, a list of possible tests for the current design scenario or a list of potential variance calculation options. The list of options is viewable by selecting the downwards arrow button on the left of the selected cell - this will open a drop down menu of all available options for that row. The user can then select the required drop down option for that specific column. In cases where the dropdown options are all numeric (e.g. 1 or 2 Sided?), the user can use the drop down menu or enter the numeric input directly.

For each row in the left-most column, the definition of that row parameter is given. In this example, the first row corresponds to the **Test Significance Level, α** of the proposed study design. For example, this could be set to 0.05, an common standard for test significance. Additional detail for each row is provided in the Help window on the right when that row is selected. See subsection 1.7.2 for details.

To conduct a **solver** calculation, the full set of mandatory input **design parameters** must be filled in a column except for the desired solver value of interest. A solver is the algorithm used to calculate a design parameter(s) of interest e.g. power, sample size, given all required algorithm inputs have been provided.

Input-only Rows are rows which are only inputs into one or more of the design table solvers. These rows will be white in nQuery. In most tables, all these rows are required for solver activation. However, in some tables one or more of these rows will be optional. For example in MGT0, the **Variance of Means, V** and **Common Standard Deviation, σ** are optional rows as the user can activate the power and sample size solvers directly using the **Effect Size** row without these two parameters - these rows exist to calculate the effect size more easily via an auto-calculation - see subsection 1.7.4.

Solver Rows are rows where nQuery can calculate the result for this row given all other mandatory inputs have been provided. These rows will be yellow in nQuery. In MGT0, these are the **Power, Sample Size per Group** and **Effect Size** design parameter rows. Note that in most cases, the other solver rows must be filled to activate a given solver e.g. the sample size solver requires inputs for the power and effect size.

Read-only Rows are rows which cannot be edited by the user. These rows will be grey in nQuery. These are usually additional outputs from the solver or an auto-calculation which are useful to the user.

In this table MGT0, the design parameters are the **Test Significance Level, α** (input), the **Number of Groups, G** (input), the **Variance of Means, V** (input - optional), the **Common Standard Deviation, σ** (input - optional), the (standarized) **Effect Size, Δ^2** (solver), the **Power (%)** (solver) and the **Sample Size per Group, n** (solver).

1.7.2 Table Help

To find additional information or guidance on a specific **design parameter**, use the **help cards** provided for that parameter. The **help card** is summary of currently selected rows including it's definition, allowable range and additional useful information and context. If a specific table row is selected, the **Help** window on the right-hand side (by default) will dynamically update to the relevant help card for that selected design parameter.

These help cards have four main potential sections: Main Text, Suggestion, Acceptable Entries, Aid

Main Text section provides a definition of the parameter for the design.

Suggestion section provides advice on common values for the selected design parameter or advice on how to derive a value from other potentially known parameters.

Acceptable Entries section provides the range of values which are allowed to be entered into a given row.

Aid section provides information on table assistants which can be used to derive this cell value from other known information (e.g. an Assistants file menu option such as **Compute Effect Size** side-table in MGT0 - see subsection 1.7.4)

Note that an Aid and/or Suggestion section may not be included in all help cards.

In Figure 1.11, the help card for the test significance level is shown on the right-hand side. This shows the definition of the significance level as the Type I error, the suggested value of 0.05 and the acceptable entries of 1E-8 to 0.20.

In Figure 1.12, the help card for the Variance of Means row is shown. In this help card, there is an example of an Aid section which refers to the usage of an Effect Size side-table to derive the value for this parameter.

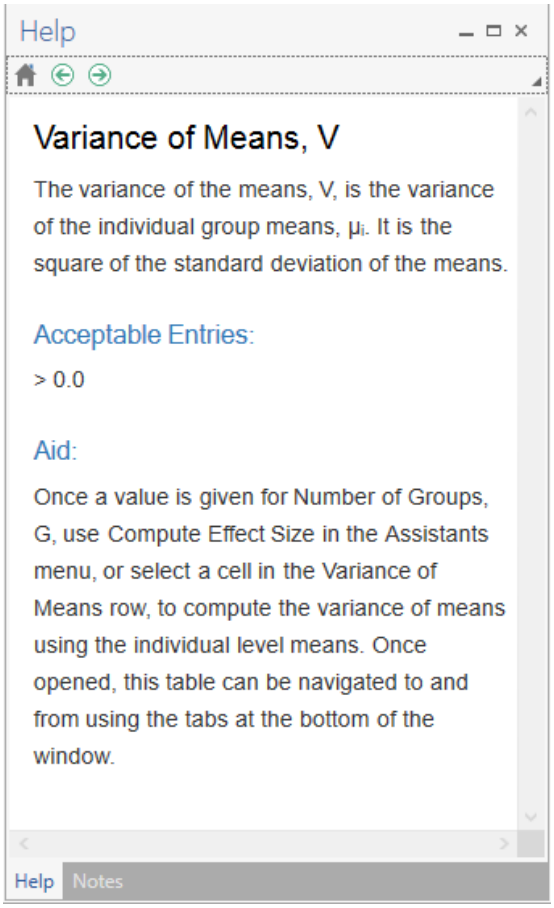


Figure 1.12: Variance of Means Help Card Example

If you want an overall summary for the table, select the **Home** icon at the top of the Help window. This will provide a brief summary on how to use the table and provide the **References** (academic articles, books, software) used for the design table solvers. The Home Card for this table is shown in Figure 1.13.

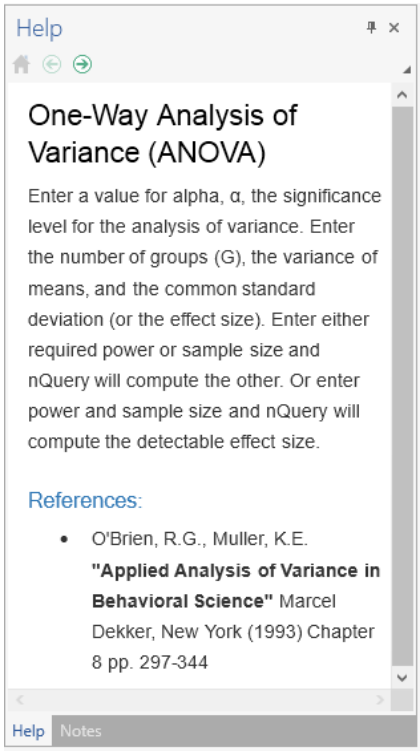


Figure 1.13: Home Card Example

1.7.3 Activating a Table Solver

To conduct a calculation of interest, we require the usage of a table **solver**. A solver is the algorithm used to calculate a design parameter(s) of interest e.g. power, sample size, given all required algorithm inputs have been provided.

Solver Rows are rows where nQuery can calculate the result for this row given all other mandatory inputs have been provided. These rows will be yellow in nQuery. In MGT0, these are the **Power, Sample Size per Group** and **Effect Size** design parameter rows. Note that in most cases, the other solver rows must be filled to activate a given solver e.g. the sample size solver requires inputs for the power and effect size.

The easiest and most common way to activate a specific solver is to fill in all of the other mandatory design parameters in a table column except for the parameter of interest. This will automatically select and calculate the remaining solver design parameter of interest. Manual methods for selecting and activating solvers are discussed in section 2.1.

After the values for the design parameters which will be used in this study design is decided, enter these into the relevant column. Each column in a design table corresponds to an independent solver activation i.e. activity in column 1 has no effect on activity in column 2.

In this example, assume a sample size calculation is requested and that values given in Table 1.1 were used for the mandatory design parameters. This design corresponds to a study which will use a one-way analysis of variance to test the null hypothesis that 3 independent group means are equal at the 0.05 significance level with 80% power, assuming a “medium” effect size of 0.5 [Cohen, 1988].

Table 1.1: Example Parameter Values

Parameter	Value
Test Significance Level	0.05
Number of Groups	3
Effect Size	0.5
Power	80

Remember that the *Variance of Means* and *Common Standard Deviation* are optional parameters and are thus not required for a solver to activate. These rows are provided for user convenience to derive the (standardized) effect size.

When these values are entered into column one of the design table, the *Sample Size per Group* row is automatically populated by the sample size solver algorithm due to it being a solver row and all other mandatory parameters being specified. This is illustrated in Figure 1.14

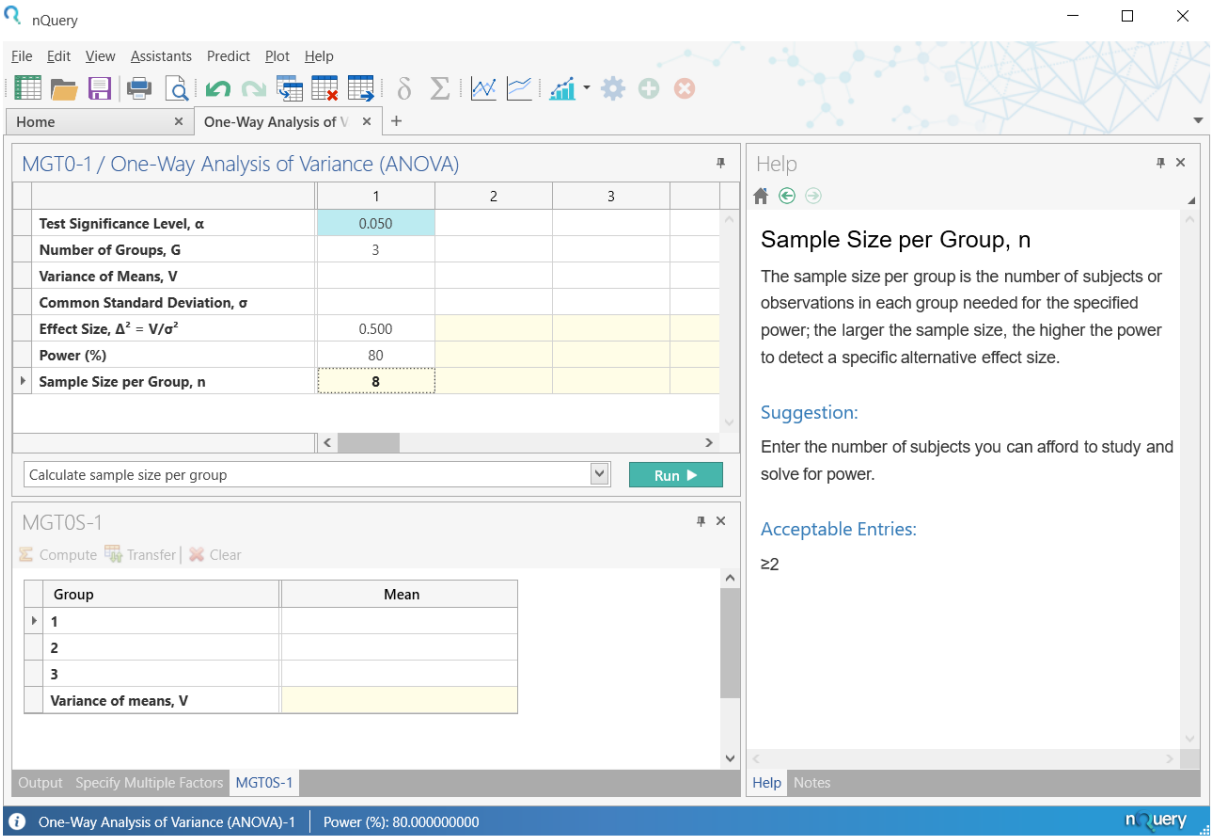


Figure 1.14: Example Solver Answer

In this example, the sample size per group required is 8. This corresponds to a total sample size of 24 (8 x 3).

When a solver is activated the solver output (in this case the sample size per group in column 1) will be the only cell still highlighted in yellow (*Power* and *Effect Size* are now input-only white) and that the text of the solver answer will be highlighted in bold. Note some tables will automatically update the power (or other parameters) to its exact value

after a non-power solver is used - in these cases the solver will highlight the row of interest **and** the power row which contains the exact power.

Any other solver can be activated initially in the same fashion - by inputting sample size but not power to calculate the power for example. However, in this example the "Calculate sample size per group" solver is now activated in column 1 and any subsequent change to this column will only re-calculate the sample size unless this column is subsequently fully cleared using the "Clear Table" option or "Clear" from the right-click context menu while that column is highlighted. For more detail on how to manually select and change solvers, see section 2.1.

This very basic example illustrates the ability of nQuery to easily and quickly find the appropriate sample size for your study.

1.7.4 Effect Size Side-table and Auto-Calculations

Let's expand upon this example by using the optional elements and effect size side table to derive the sample size for a study design where the user can take advantage of the additional information they have available to find better estimates for the required design parameter of the **Effect Size**.

For this example, assume that the common (within-group) standard deviation is assumed to be equal to 1.1. Assume that the expected group means are also known and are equal to the values in Table 1.2.

Table 1.2: Tutorial Group Means Example

Group #	Mean Value
1	1.1
2	2.3
3	3.0

To use these group mean values to derive the Variance in Means, use the **Compute Effect Size** side-table.

Side-tables are additional tables which allow the user to calculate design table (we will also refer to as "main table") inputs from commonly available existing information. Note that some design tables may have multiple side-tables and that some solvers may use side-table inputs directly - see section 3.1 for details.

To open this particular side-table, the *Number of Groups, G* row must be specified in that column. Once the number of groups is specified in a column, the *Compute Effect Size* options will become active in the Assistants menu and menu bar to open the side-table for the selected column(s).

However, the easiest way to open the side-table in a column is to select the derived row in that column (i.e. *Variance of Means, V* here in MGT0) and the side-table will automatically open below the main design table (i.e. in the same window as "Output").

Once the side-table is open, enter the group means into the relevant rows.

This will activate the *Calculate* button in the top-left of the side-table window. Select "Calculate" and this will show the calculated value of ~0.616 in the Variance of Means row in the side-table.

This activates the *Transfer* button. Selecting "Transfer" will transfer the value for the Variance of Means to the relevant row for the current side-table's column of the main table. This is shown in column two in Figure 1.15.

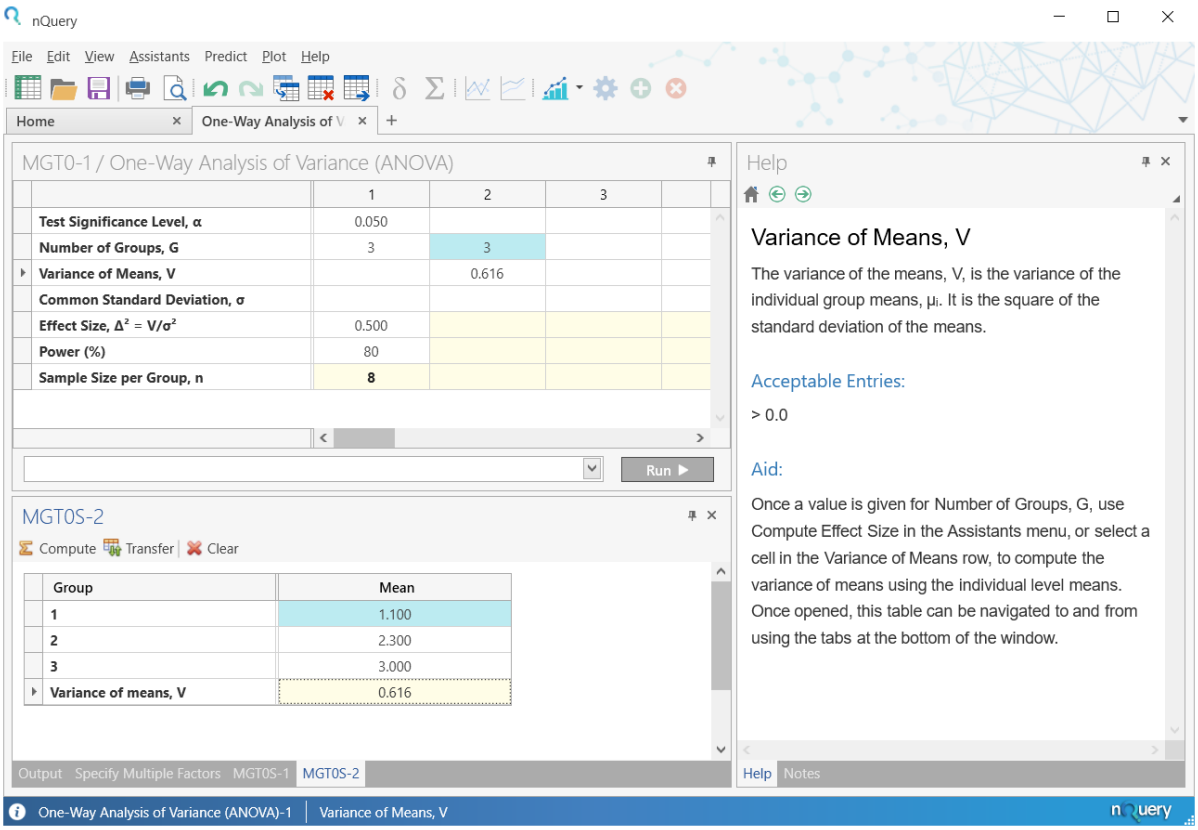


Figure 1.15: Side Table Example

Note that some side-tables tables will only have a *Transfer* button - in these side-tables the required outputs will be calculated automatically for the user in the side-table once it the side-table is filled appropriately. In other tables there will be neither a *Calculate* or *Transfer* button - in these cases the side-table will automatically calculate and transfer the required outputs to the main table when the side-table is filled appropriately.

Now enter the *Common Standard Deviation* value of 1.1 into the relevant main table row. In this table, the effect size can be derived from the variance in means and the common standard deviation and thus when these are both specified the effect size will automatically update to derived value for the values set for those two parameters. In this example, this equals approximately 0.509. This is shown in Figure 1.16.

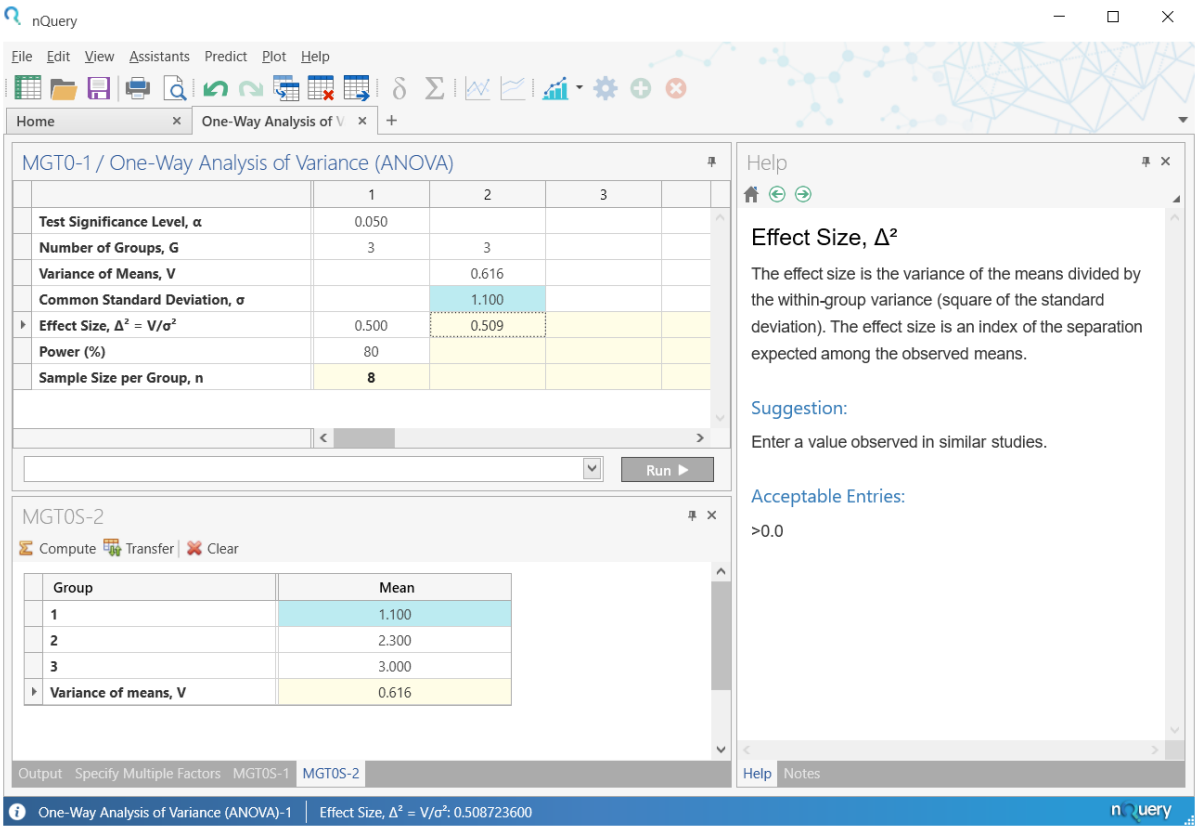


Figure 1.16: Effect Size Auto-Calculation Example

Note that entering two out of three of these parameters (Variance of Means, Common Standard Deviation, Effect Size) will always return the third value. Changing any one of these design parameters after all three are specified will cause one of the other parameters to change to ensure consistency (e.g. updating the Variance of Means or Common Standard Deviation would cause the Effect Size row to update).

To complete the example, enter the same significance level (0.05) and power (80) as per the previous example. This will give the same sample size per group of 8.

1.7.5 Saving and Opening nQuery Files

nQuery design tables can be saved in the nQuery specific file format named .nqt. This file format allows users to save their work and then share it with other nQuery users or use this file again in future sessions. The save file will retain the main design table and any side-tables, output statements, plots and notes generated at the time of saving.

To save an nQuery file, the user can use the **Save** or **Save as** options from the File menu or by using the Save option  icon in the tool bar.

If the design table has not been saved before or the user selects the Save as option then the Save menu will appear - see Figure 1.17. Select the desired folder and edit the default save name in the File Name field if desired. Select Save to save the file.

If the currently open design table has been saved before then selecting the Save option will automatically overwrite that file with the current updated state of the design table.

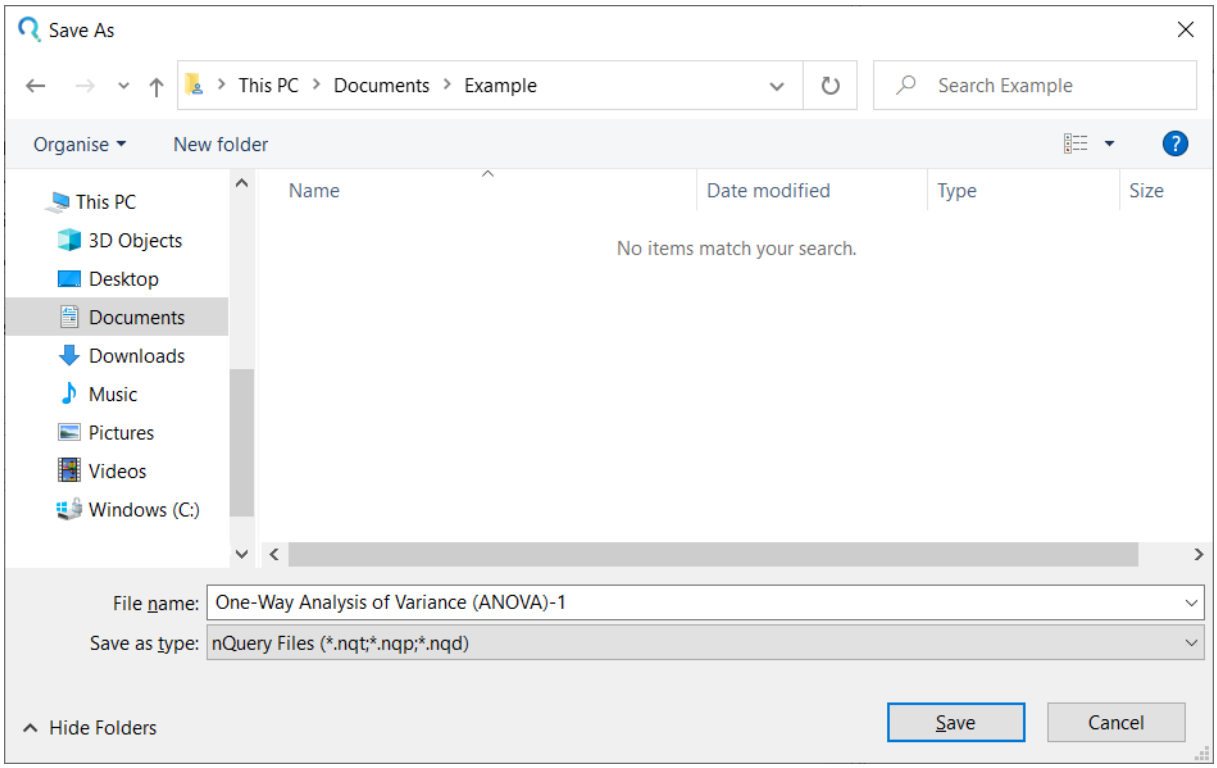


Figure 1.17: Save Window

To open an nQuery file, the user can select the **Open** option from the File menu or by using the Open option  icon in the tool bar.

This will open the Open menu. Select the folder which contains the previously saved .nqt file and select the file. Select Open to open the file in nQuery. You can also open an nQuery (.nqt) file by double-clicking the file directly e.g. in Windows Explorer. This will either open the save file in the last used open nQuery instance or open an instance of nQuery and open the file in this new nQuery instance.

1.8 Design Table Tools

nQuery features a number of additional tools to help users understand and summarise their calculations. The tools which will be covered in this section are the **Output** statement, the **Notes** tool, the **Specify Multiple Factors** tool and the **Plots** options.

1.8.1 Output Statement

The **Output** statement provides a verbal summary of the results given in a column after a solver has been activated. This statement can be used as a template for the sample size justification given in a study protocol, academic paper or similar document.

The output statement is shown by default in the window below the main design table in nQuery. In this example, due to the usage of the effect size side-table, that window

currently shows the effect size side table for column two of the main table instead of the output statement.

To return to the Output statement in this bottom panel, select the "Output" tab on the left of the tab bar at the bottom of the lower window. The output statement for the column two calculation will be shown below the main table as per Figure 1.18.

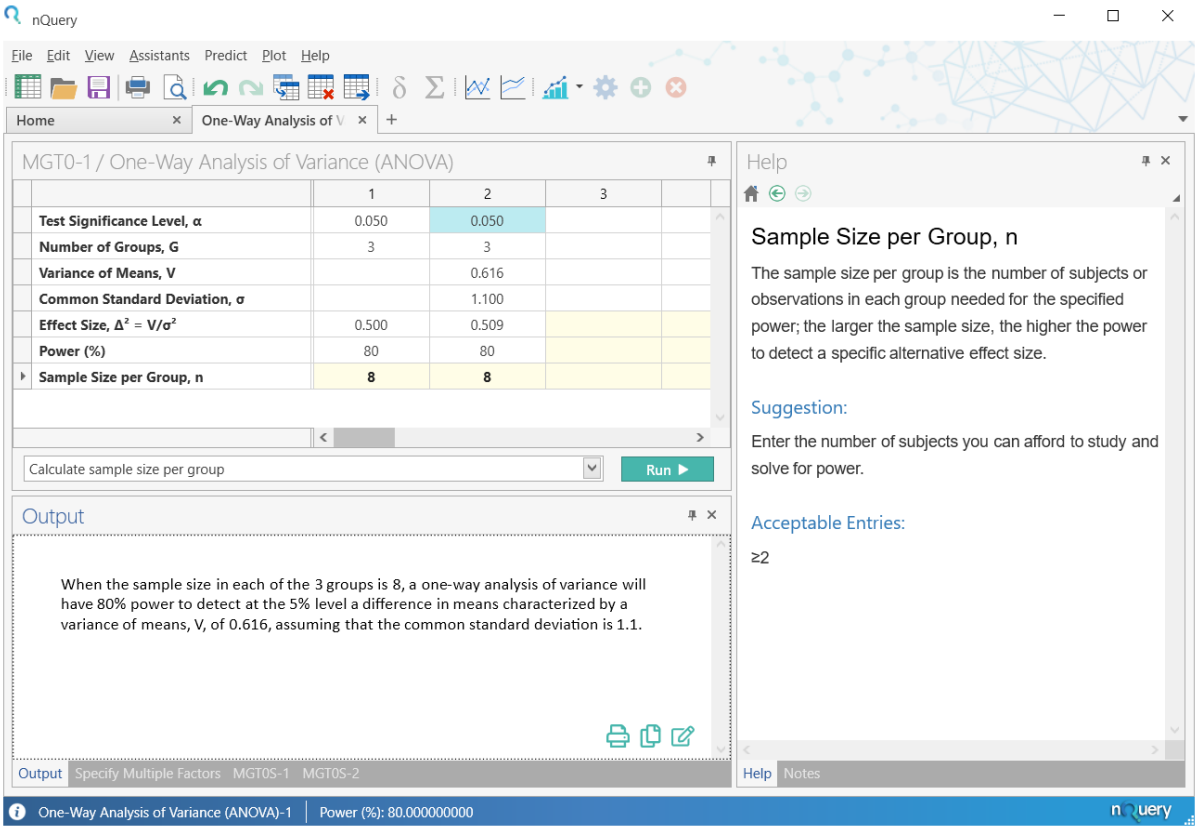


Figure 1.18: Output Statement Tutorial Example

The output statement contains multiple convenience functions to extract or edit this statement within nQuery from either the shortcut icons in the bottom-right of the Output panel or from the right-click context menu.

To **Print** the output statement select the Print button (1st icon - printer) in the bottom-right of the output statement window or use the Print or Print Preview options from the right-click context menu. Note the Print icon button will open the Print Preview window not the Print window directly.

To **Copy** the output statement to the clipboard, use the Copy All button (2nd icon - 2 stacked pages) in the bottom-right of the output statement window or from the right-click context menu to copy the entire output statement. Alternatively, use the Copy option in the right-click context menu to copy the currently selected text (e.g. via click and drag). Note that the Copy context menu option will default to Copy All if no text is selected.

To **Edit** the output statement, select the Edit button (3rd icon - pencil on paper) in the bottom-right of the output statement window or from the the right-click context menu. When finished editing, select the Stop Editing button (3rd icon - tick box) to return the output statement to read-only status.

To **Transfer** the output statement, select Add to Notes from the right-click context menu. The Notes tool allows a given output statement to be saved to prevent it being overwritten if a solver calculation is re-run in the same column. The notes tool also provides additional editing tools (see subsection 1.8.2) that may be of interest.

Note that where a table has optional design parameter rows, the output statement will change depending on whether the optional elements have been fully specified in the selected column. For example, the output statement in the column 1 example the output statement does not contain references to the unspecified optional elements (Variance of means, Common Standard Deviation) and instead only mentions the mandatory Effect Size design parameter - see Figure 1.19

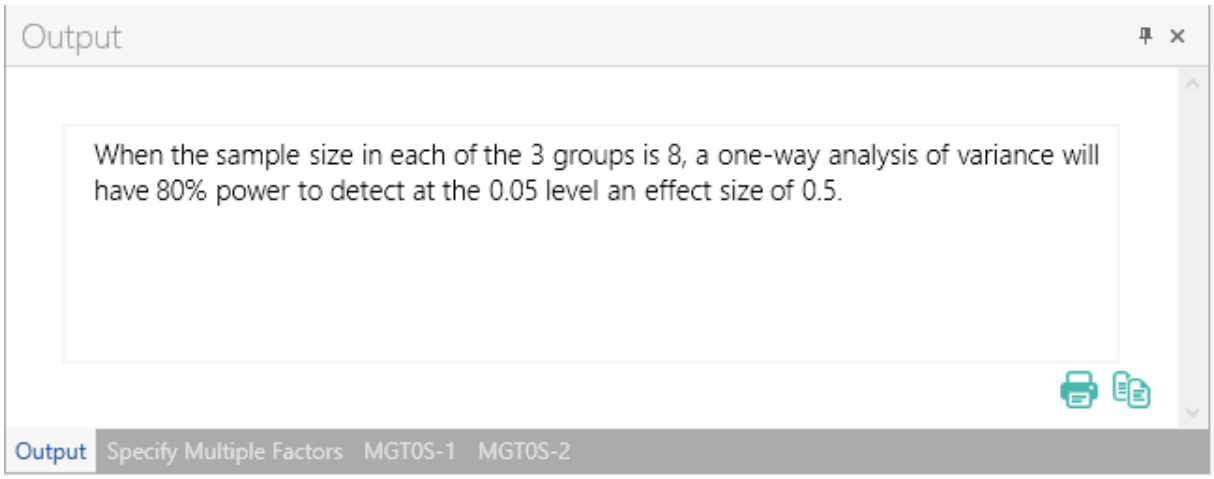


Figure 1.19: No Optional Elements Output Example

1.8.2 Notes Tool

The **Notes** tool is a word processor facility integrated into nQuery which allows users to write and save notes about their calculations directly into their nQuery save file.

By default, it is found in the window to the right of the main table. To open the Notes tool, select the "Notes" option from the bottom of the Help window in the tab bar. This Notes Tool window can be seen on the right-hand side of Figure 1.20.

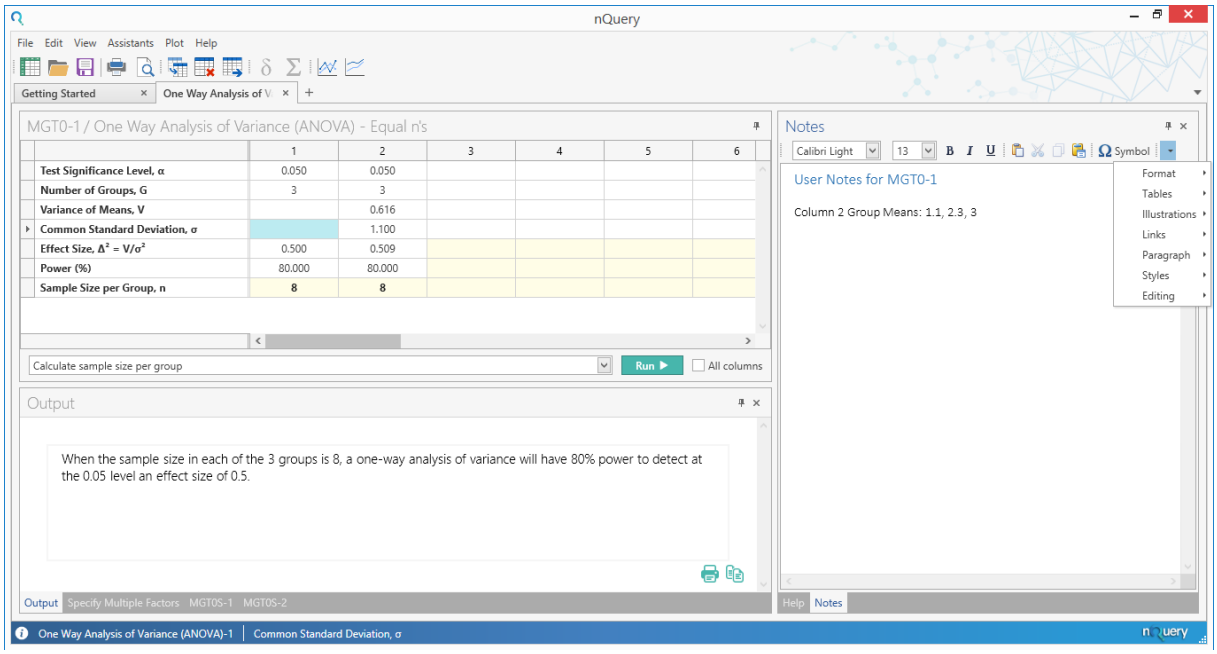


Figure 1.20: Notes Tool Example

At the top of the Notes tool, the toolbar will contain a drop-down for the font and text size and buttons for the style (bold, italics, underline), copy, cut, paste, paste special, print and a Symbols menu. The arrow on the right-hand side of the toolbar gives access to a large variety of advanced tools for formatting, tables, images and other options. Right-clicking within the editor will open a context menu containing the Edit tools (copy, cut, paste), indent options, font and paragraph menus, bookmark and hyperlink options.

subsection 1.8.1 shows that Output Statements can be transferred to the Notes tool using the "Add to Notes" option from the right-click context menu within the Output tab. This will be automatically placed below any material already in the Notes tab at that point in time.

1.8.3 Specify Multiple Factors Tool

The **Specify Multiple Factors** tool provides a method to quickly enter multiple values for design parameters and to generate all combinations if more than one design parameter is varied simultaneously.

The Specify Multiple Factors tool is found by default in the window below the main table. To open the Specify Multiple Factors tool, select the "Specify Multiple Factors" option from the bottom of the Output/Side-table window in the tab bar. This Specify Multiple Factors Tool window can be seen on the bottom of Figure 1.21.

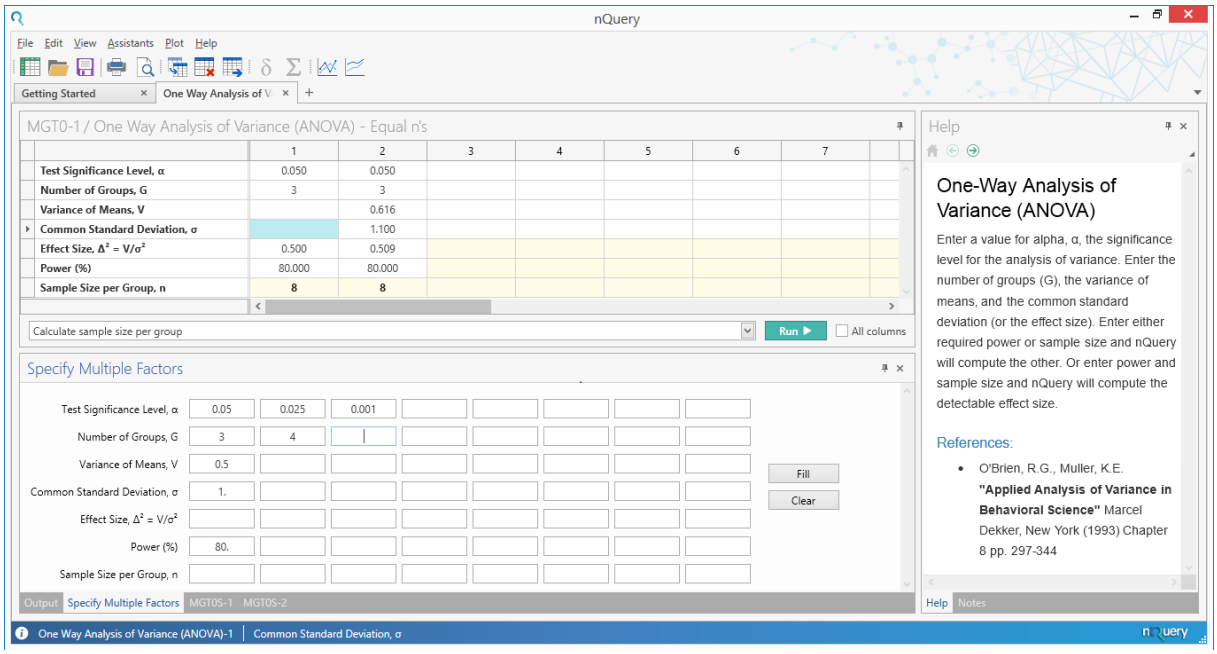


Figure 1.21: Specify Multiple Factors Tool Example

The Specify Multiple Factors tool allows a maximum of eight values per design parameter.

In this example, the **Test Significance Level** will be evaluated at 0.05, 0.025 and 0.001 and the number of groups will be evaluated at 3 and 4. The **Variance in Means, Common Standard Deviation** and **Power** will be fixed at 0.5, 1 and 80 respectively.

This will calculate the empty **Sample Size per Group** row automatically via the sample size solver algorithm for all 6 scenarios (3 x 2 x 1 x 1 x 1) specified by these inputs. Note that the **Effect Size** row is also left empty since it will be calculated from the Variance of Means and Common Standard Deviation transferred into the main table via an auto-calculation (i.e. formula given in the Effect Size rowname).

To clear the inputs from the Specify Multiple Factors tool and reset the tool, select the **Clear** button on the right of the window.

To transfer these inputs into the main table by selecting the **Fill** button on the right-hand side of the window. The results for this set of inputs is shown in Figure 1.22.

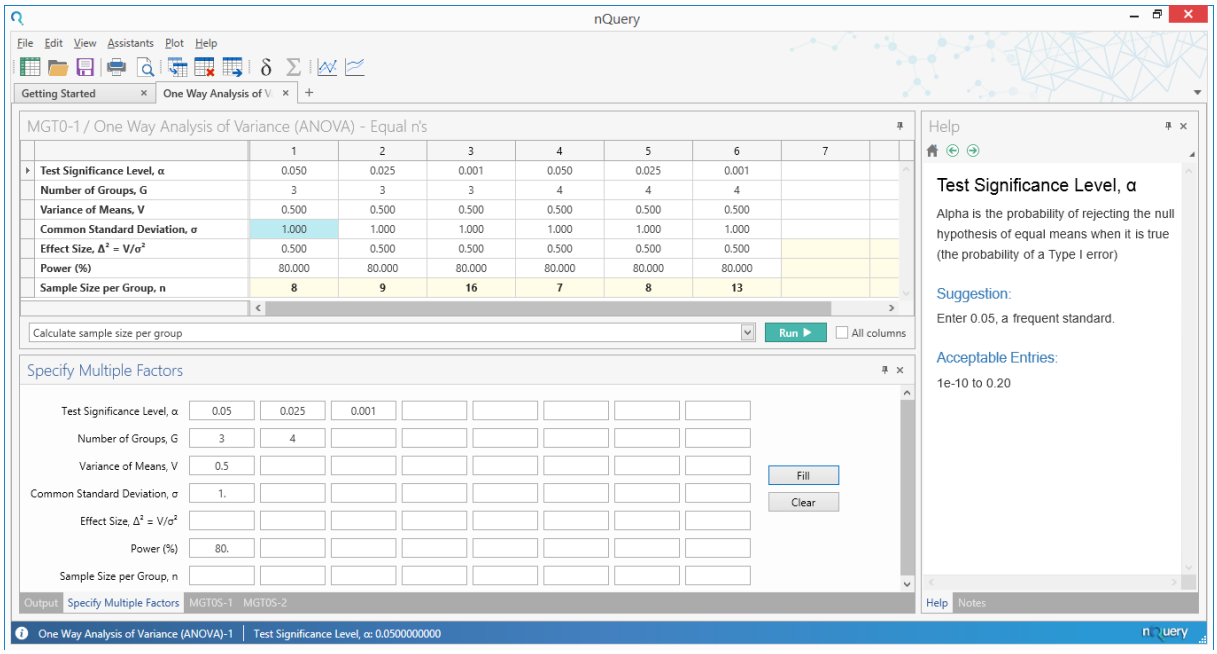


Figure 1.22: Specify Multiple Factors Output Example

If the number of column combinations exceeds the number of columns open in the table, the table will automatically create additional columns up to the maximum number of columns. If the number of column combinations exceeds the allowed maximum number of columns then a warning will be given and only the first number of combinations equal to the maximum number of columns will be shown. The maximum number of columns is configurable in Options menu - see section 2.3.

For rows which contain a dropdown menu (e.g. 1 or 2 Sided Test?), a drop down menu will exist for all cells for that row in the Specify Multiple Factors tool. By default, all cells will have the same drop down option selected but the user can manually select other drop down options as per the main table. If there are duplicate cells in that row of the Specify Multiple Factors tool, the duplicates will be ignored.

1.8.4 Plot Power vs Sample Size

The **Power vs Sample Size** plot provides a quick visual overview of the relationship between power and sample size over a reasonable range of power while fixing the other elements in calculation.

The Power vs. Sample Size plot can be activated in two ways: using the Plot menu drop-down option *Plot Power vs Sample Size* or using the tool bar *Plot Power vs Sample Size* button  . Note that both of these options will be inactive for a selected column until that column contains inputs for at least all of the mandatory design parameters except for the power and sample size. After selecting the desired Power vs Sample Size plot option, the plot will appear in a separate windown in the nQuery application foreground.

If you want to compare visually across multiple (appropriately filled) columns, select cells in all of the desired columns and select the plot options as above. A plot will be generated where all columns's results will be displayed simultaneously. The Ctrl+Left

Click (to select multiple individual cells) or Shift+Left Click (to select a range of cells) shortcuts may assist in selecting multiple columns in nQuery.

An example of an individual and multiple column versions of the Power vs Sample Size plot are shown in Figure 1.23. In this example, the plots are for the six columns generated from the Specify Multiple Factors example above, with the individual plot being from column 1.

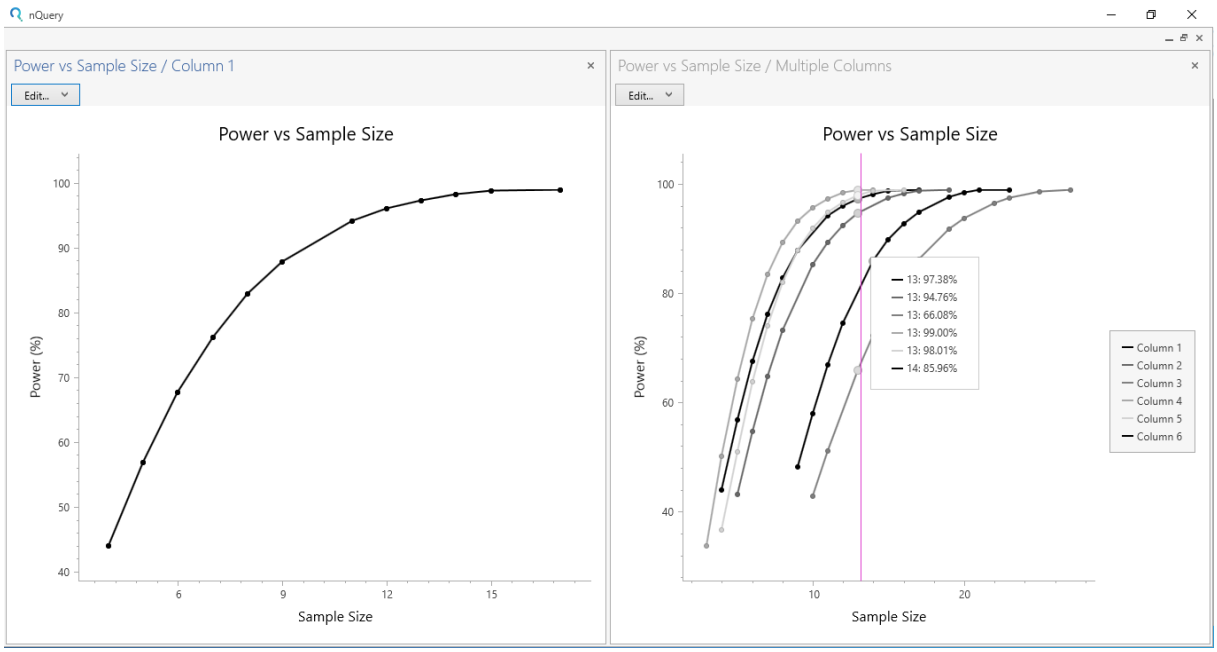


Figure 1.23: Power vs Sample Size Example

Highlighting a point in the plot will display the exact values for the X-axis and Y-axis value selected for each column - this can be seen in the multiple columns example on the right.

Right-clicking on the plot will open a context menu which provides options to Print, open a Print Preview, Save the plot as an image file and options to edit the plot (seesection 1.9). These options are also available from the **Edit...** menu in the top-left of the plot window.

1.8.5 Plot User Selected Rows

The **Plot User Selected Rows** plot provides a customisable tool to visually assess the relationship between any of the continuous/integer design parameters and any of the available solvers given all unselected design parameters are fixed.

The Plot User Selected Rows menu can be activated in two ways: using the Plot menu drop-down option *Plot User Selected Rows* or using the tool bar *Plot User Selected Row* button  . Both of these options will be inactive until a column is filled sufficiently for at least one valid custom plot to be available.

After a column is filled appropriately, select the Plot menu or menu bar option and this will open the **Select X-axis, Y-axis** window. This menu is shown in Figure 1.24.

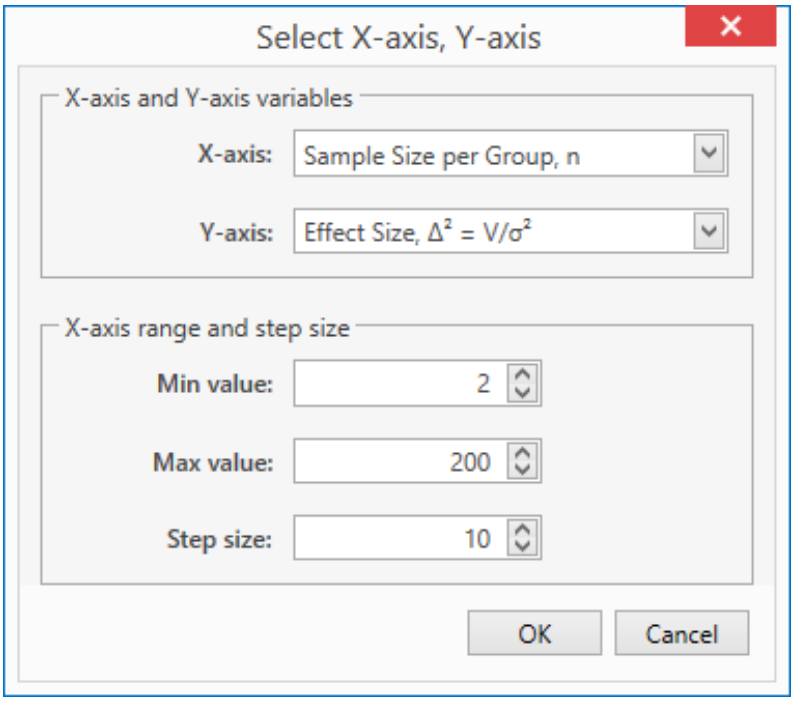


Figure 1.24: "Select X-axis, Y-axis" Plot User Selected Rows Menu Example

The **X-axis** drop-down will contain the full list of design parameters which are of either a continuous or integer type which would have an effect on the solver algorithm output.

The **Y-axis** drop-down will contain the list of the all the solvers available in the table. This table allows us to create a combination of any of these two lists to create a custom plot to assess the relationship between the select X and Y axis options.

When an X-axis option is selected, the user can specify the range over which that design parameter will be varied in the plot by specifying a minimum value and maximum value for this range by using the **Min value** and **Max value** options. The **Step Size** input is then used to specify the size/increment that will the X-axis parameter will increase by to reach the maximum from the minimum value. Default values will be given for the Max value, Min value and Step size for each X-axis option in a given table.

The number of steps can be found by dividing the range by the step size (round down if answer is a non-integer) i.e. (Max value - Min value)/(Step Size)

For example with the Sample Size per Group as the **X-axis** selection and a **Min value** of 2, a **Max value** of 200 and a **Step Size** of 10 the plotted values for the selected **Y-axis** solver (Effect Size or Power) along the X-axis will be 2, 12, 22 ... 172, 182, 192. Note where Step Size leads to an "overhang" the first value above Max Value will be ignored e.g. 202 would not be plotted in this example.

Note the OK button will be disabled if any of the inputs are inconsistent (e.g. **Max Value < Min Value)**, the **Min Value** or **Max Value** are inconsistent with X-axis option's **Acceptable Entries** or if the Step Size would lead to too few (<5) or too many (>1000) points on the plot.

However, it is still possible for a solver to generate an error for one or more of the specified X-axis values - in this case these points will be automatically be removed from the plot.

Where all points generate an error the plot will be empty except for an explanatory error at the top of the plot window.

If you want to compare visually across multiple (appropriately filled) columns, select cells in all of the desired columns and select the plot options as above. A plot will be generated where all columns's results will be displayed simultaneously. The Ctrl+Left Click (to select multiple individual cells) or Shift+Left Click (to select a range of cells) shortcuts may assist in selecting multiple columns in nQuery.

An example of an individual and multiple column versions of the Plot User Selected Rows plot are shown in Figure 1.25.

In this example, the plots are for the six columns generated from the Specify Multiple Factors MGT0 example above. The individual column plot is for column 1 where the X-axis option was the Test Significance Level, using the default 0.01 to 0.2 by 0.0095 X-axis range, and Y-axis option was the Effect Size. The multiple columns plot is for the six column where the X-axis option was the Sample Size per Group, with a custom range of 5 to 30 by 1 X-axis range, and Y-axis option was Effect Size.

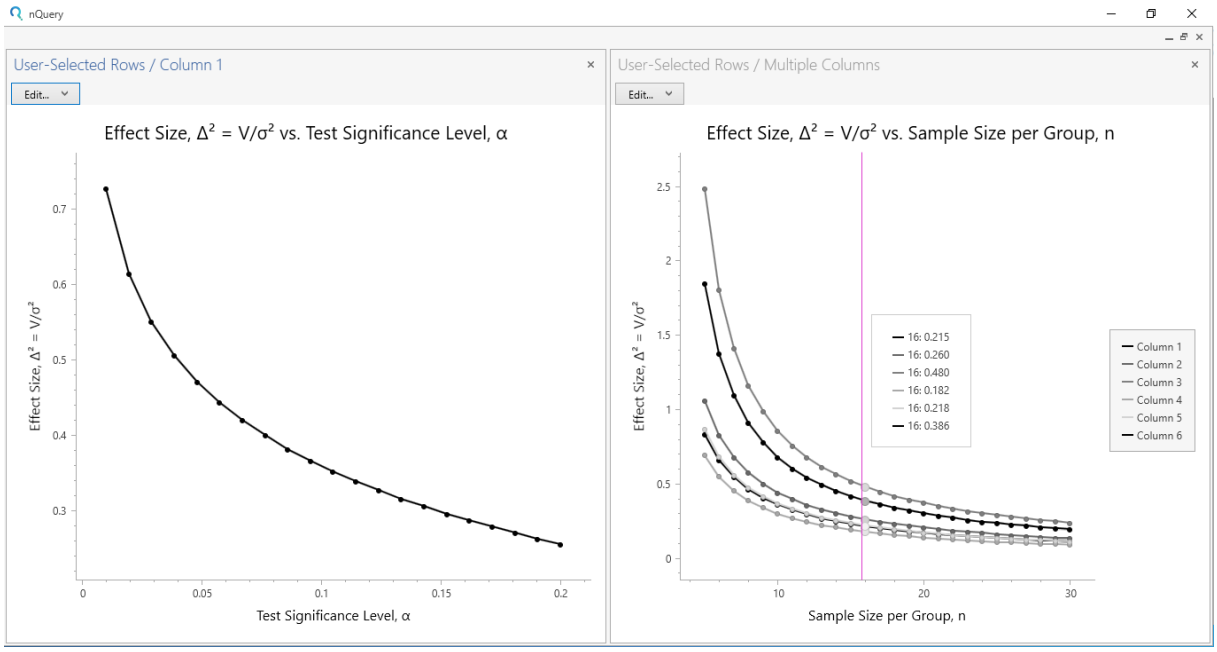


Figure 1.25: Plot User Selected Rows Example

Highlighting a point in the plot will display the exact values for the X-axis and Y-axis value selected for each column - this can be seen in the multiple columns example on the right.

Right-clicking on the plot will open a context menu which provides options to Print, open a Print Preview, Save the plot as an image file and options to edit the plot (seesection 1.9). These options are also available from the **Edit...** menu in the top-left of the plot window.

1.9 Editing Plots

nQuery provides options to edit the default Power vs N and User Selected rows plots. To edit these plots, select the **"Edit..."** button from the top-left corner of the plot or use the dropdown context menus available when right-clicking on the plot.

In the edit menu, there will be options for Print, Print Preview and Save As which allow the printing and saving of the current plot. There are the following options for editing a plot

1. Titles (Edit Table and Axis Titles)
2. Series (Edit Series names and colors)
3. Gridlines (Add and Edit Gridlines)
4. Legend (Add and Edit Legend)

1.9.1 Titles Options

The **Titles** menu contains options for the three main table titles: the **Chart Title** (above plot), the **X-axis Title** (below plot), the **Y-axis Title** (left of plot). Each of these titles has the same three options for editing:

1. **Hide/Show Title:** Hide or show selected title in plot
2. **Rename:** Rename title in separate **Rename Title** dialog window.
3. **Font:** Edit Font, Size, Style (Bold, Italics) and Text Color ("More Colors" for custom colors) in separate **Update Title Font** dialog window

1.9.2 Series Options

The **Series** menu contains options for updating the x-axis range and editing the color and name of each series (i.e. selected column) in the plot. If a single series is in the current plot, the following three options will be available:

1. **Update X-axis range:** Edit range of x-axis displayed in plot in separate **Update X-axis Range** dialog window - contains same Min Value, Max Value and Step Size options as per Plot User Selected rows
2. **Marker Style:** Edit range of x-axis displayed in plot in separate **Update X-axis Range** dialog window - contains same Min Value, Max Value and Step Size options as per Plot User Selected rows
3. **Marker Size:** Edit range of x-axis displayed in plot in separate **Update X-axis Range** dialog window - contains same Min Value, Max Value and Step Size options as per Plot User Selected rows
4. **Rename:** Rename series in separate **Rename Series** dialog window. This will update the series name shown in the plot Legend (if displayed). By default the series name will be set to Column 1, Column 2 etc. The user can manually change the column title in both the design table and the displayed series name here by double-clicking the column title number at the top of that column and editing the column title manually.

5. **Color:** Change the color used for series (column) in **Select Series Color** dialog window. Select an existing color or generate a custom color by selecting the **More colors** option. By default, nQuery uses a grayscale color scheme.

If more than two series (columns) are selected in the current plot, this menu will have the same **Update X-axis range** option but then separate dropdown options with the names of all the input series in the current plot. If you select a specific series dropdown, the **Rename** and **Color** options will be available for that specific series which will work as above.

1.9.3 Gridlines Options

The **Gridlines** menu contains options to add and remove gridlines for the X and Y axes. This menu contains the following options:

1. **Hide/Show X-axis gridlines**: Hide or show X-axis gridlines depending if shown at present
2. **Hide/Show Y-axis gridlines**: Hide or show Y-axis gridlines depending if shown at present

These main gridlines will be in-line with the tick marks for the relevant axis with four equally spaced minor gridlines between each main gridline.

1.9.4 Legend Options

The **Legend** menu contains options to add and remove the legend and to edit the horizontal and vertical position of the legend. This menu contains the following options:

1. **Hide/Show Legend:** Hide or show legend depending if shown at present
2. **Horizontal Position:** Selecting this will open a sub-menu for legend locations. This menu gives five options to place the legend: *Left inside, Left outside, Center, Right inside, Right outside.* Select the desired option to change the position
3. **Vertical Position:** Selecting this will open a sub-menu for legend locations. This menu gives five options to place the legend: *Top inside, Top outside, Center, Bottom inside, Bottom outside*. Select the desired option to change the position

Inside/Outside refer to whether the legend should be included in the plot area itself (inside) or placed outside the plot area (outside). Note that changing the line colors and legend series names is done using the Series options described above. Series names can also be edited using the column name feature by double-clicking the column title in the main table before creating a plot.

2 Advanced nQuery Table Features

2.1 Manual Solver Activation

In nQuery, the easiest way to generate a result is to use the auto-activation of a solver. An example of auto-activation is given in subsection 1.7.3. In short, a solver will automatically activate if all the mandatory elements in a design table are filled except for a solver row - solver rows are yellow in the design table.

However, in certain cases, a user may wish to fix a column to use a specific solver regardless of user inputs or change the solver being used in an already completed column. Both of these are covered in the following section and will make use of the **Solver Drop-down Menu and Run button** referenced in Figure 1.10.

2.1.1 Manually Fixing a Column Solver

To fix the solver which will be used in a given column, open a design table and select the column or columns which will have their solver fixed.

To do this, select a cell or cells in the column(s) of interest or select the full column(s) by selecting the column title(s). This can be achieved by clicking and dragging for multiple cells or by holding down Ctrl (individual cells/columns) or Shift (range of cells/columns) while selecting cells or columns.

After the cell(s) or column(s) are selected, the solver can be fixed by selecting a specific option from the Solver Drop-down menu. These options are illustrated for the One Sample Chi-Square Test in Figure 2.1.

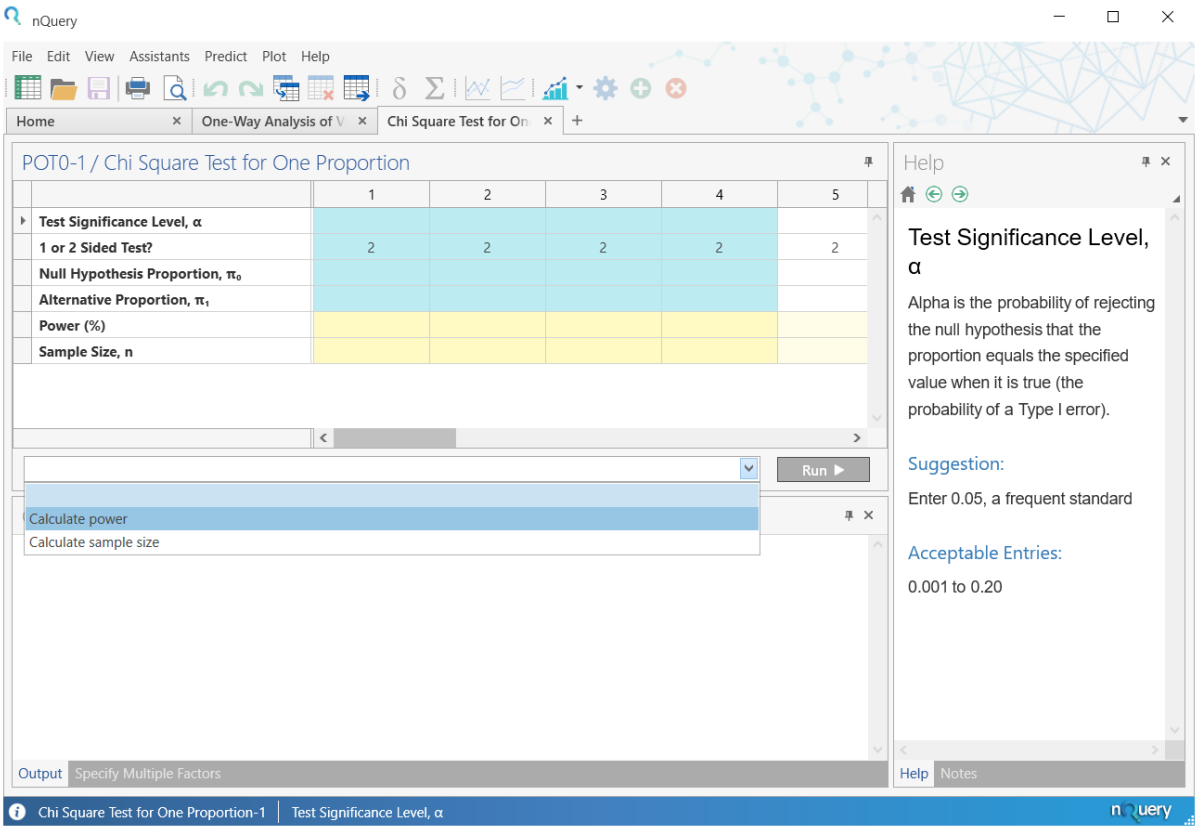


Figure 2.1: Solver Drop-down Menu Example

The One Sample Chi-Square test has two solvers available: **Calculate power** and **Calculate sample size**.

In this example, the power solver will be fixed for the first three columns of the table by selecting the "Calculate power" option from the solver drop-down while the first three columns are highlighted as in Figure 2.1.

As the solver is fixed for these three columns, entering the design parameters in a column which would activate the power solver will calculate the appropriate power for those design parameters. However, entering parameter values which would activate the sample size solver does not generate any solver output. This is illustrated in Figure 2.2.

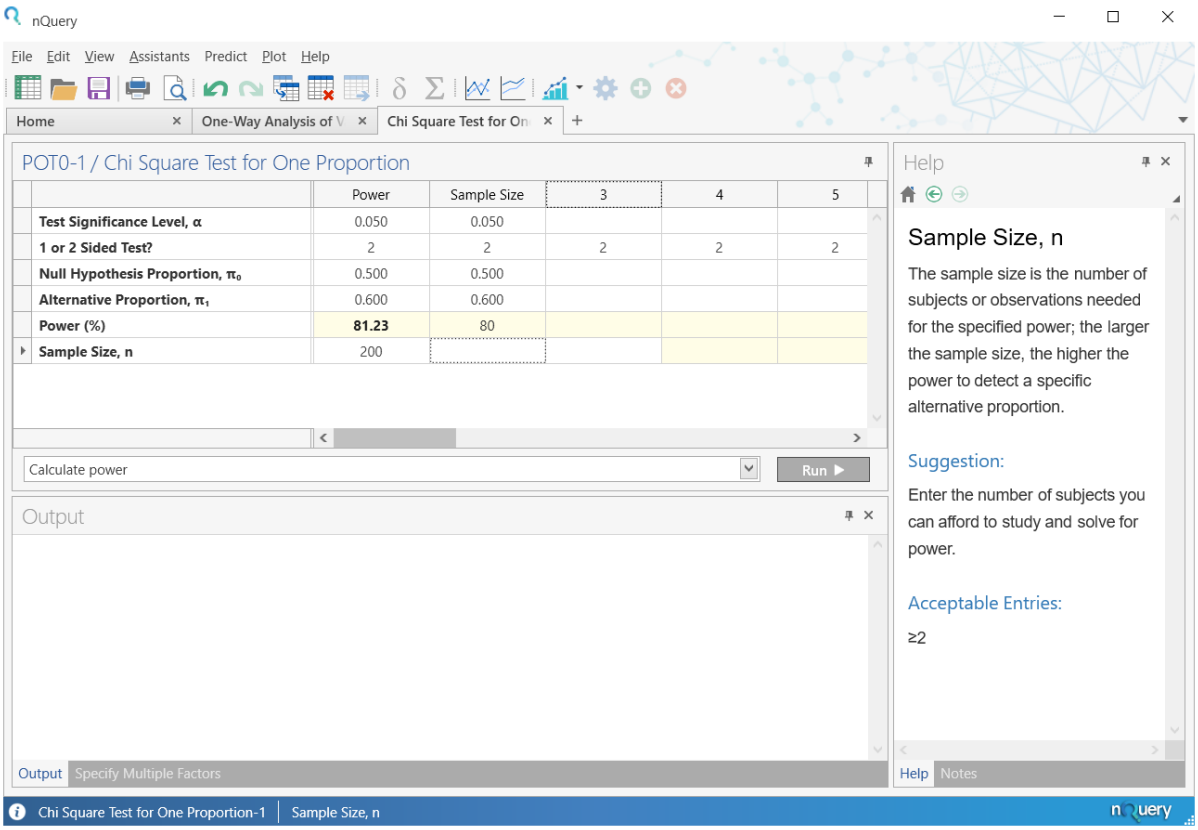


Figure 2.2: Solver Manual Activation Example

In this example, the first column has successfully generated the power but in the second column the values generate no result even though this column would generate the sample size if it was in its default initial state i.e. where solver dropdown was empty.

In every table the first option in the solver drop-down is a "blank" option. If this option is selected, the selected column(s) will reset to auto-selecting a solver as per subsection 1.7.3.

2.1.2 Changing a Filled Column's Solver

After a solver is activated and generates a solver output result (either automatically or manually) in a column, the user may be interested in changing the solver being used in that column. There are two main methods to achieve this: Reset the column or Select an alternative solver

2.1.2.1 Reset Column

To reset a column, there are three main methods: **Clear Table, Clear Column, Blank Solver** Option

1. **Clear Table:** Selecting Clear Table from the Edit menu or the menu bar will reset all columns to their default state where any solver can be automatically or manually activated.

2. **Clear Column:** Highlighting a column(s) by selecting the column title or all the cells in a column and then selecting "Clear" from the right-click context menu will return the column to its default state
3. **Blank Solver Option:** Selecting a column and selecting the first "blank" option from the Solver Drop-down menu will reset the column to its default state

Unlike the Clear options, the Blank Solver option can be used on a partially filled or a fully filled column. If a column if fully filled and the blank option is selected, a new calculation can be activated by changing a value in the affected column(s) or by selecting the "Run" button to the right of the solver drop-down menu. The first calculation in the solver drop down list will be selected by default if the column is completely full and either the Run button is used or a subsequent edit it made to activate the solver.

2.1.2.2 Select Alternative Solver

To select an alternative solver select the column(s) or interest, open the Solver Drop-down menu and select the solver which is desired. After an alternative solver is selected, it will be activated if a cell is changed in the affected column(s) or by using the **Run button** to the right of the solver drop-down menu. Selecting the sample size solver and using the Run button is illustrated in Figure 2.3.

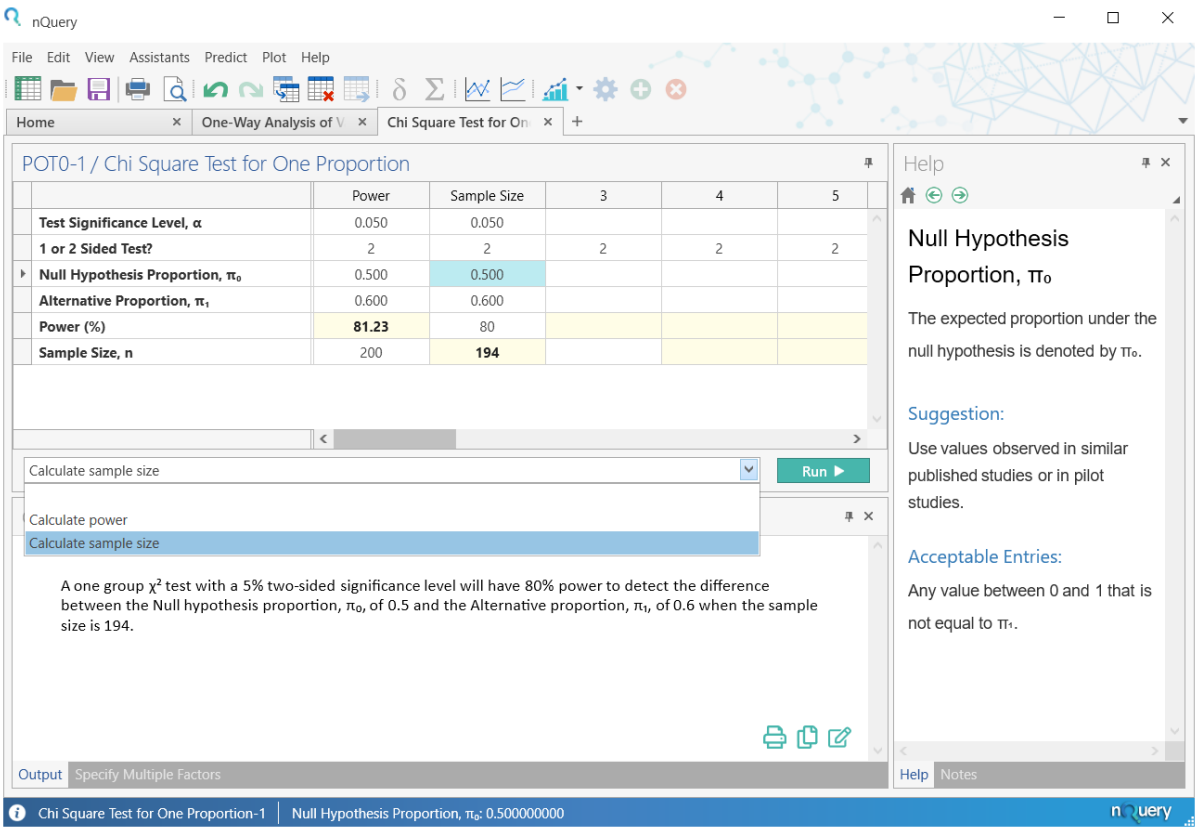


Figure 2.3: Manual Solver Change Example

2.2 Errors and Warnings

nQuery provides a number of errors and warnings to prevent incorrect values being entered or when a solver cannot find a legitimate answer. There are three primary types of errors and warnings in nQuery: Out of Range errors, Solver errors, Solver Warnings.

2.2.1 Out of Range Errors

Out of range errors occur when a value is entered into a design table or side-table cell which is outside the acceptable entries for that cell. The acceptable entries for a given cell can be found in the Help card for that cell (see subsection 1.7.2).

This error will typically occur due to incorrect direct user input but note that out of range errors can occur due to table auto-calculations.

For example, the auto-calculation for the **Effect Size** row in **MOT0 - One Sample t-test** can be outside the **acceptable entries of 0.1 to 40** when derived from the optional element values of the **Null Hypothesis Mean, Alternative Hypothesis Mean** and **Standard Deviation**.

Note these errors will also be generated in side-tables. A common scenario in side-tables is where there are read-only auto-calculated cells which contain the sum of the write-able elements of the side-tables (e.g. **POT2 - Chi-Square Test for Proportions in Multiple Categories**).

When an out or range error occurs, a red ⊗ symbol will appear on the left-hand side of the affected cell. Placing the mouse over the cell will provide a tooltip which gives a brief summary of the allowable values in the cell. An example of this is shown in Figure 2.4.

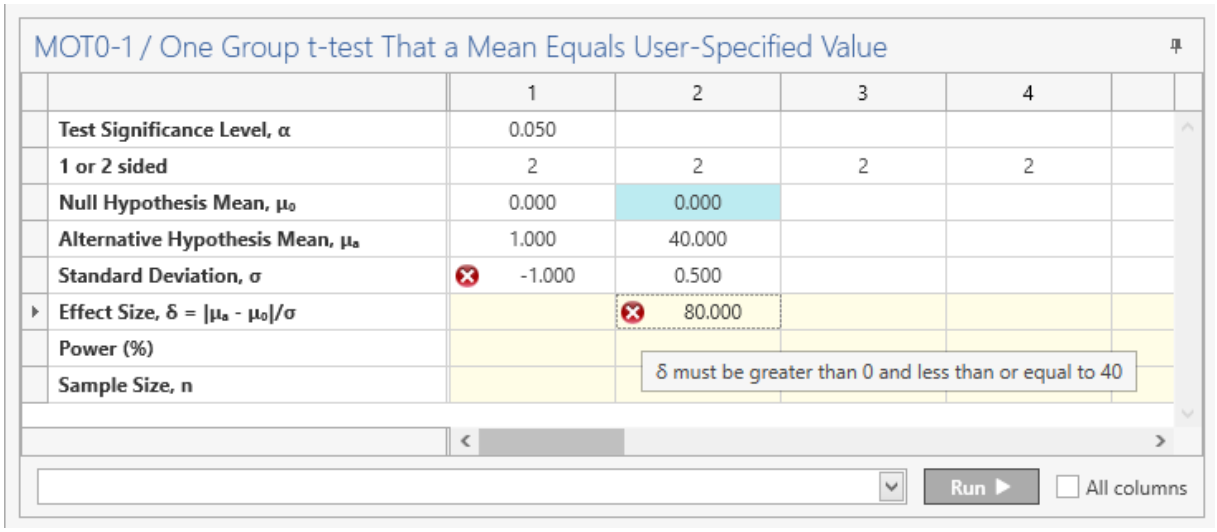


Figure 2.4: Out of Range Error Example

While an out of range error is present in a design table column, no solver activation can occur in that column. In a side-table, an out of range error will prevent the side-table from being able to Compute or Transfer values.

2.2.2 Solver Errors

Solver errors occur when a solver cannot find a solution for the given inputs. This is most common when the design parameter inputs were too extreme (e.g. leading to the solver algorithm outputting an infinity or NA) or when the solver reached a numerical limit (e.g. too wide array search leading to memory overflow). These errors indicate that either there is no correct result for the design parameters provided or that the correct solver result was too extreme to be found by nQuery's solver algorithm. (e.g. <1E-10)

When a solver error occurs, the affected cell will be highlighted in red. If you hover the mouse over the affected cell, a brief description of the error will be given.

An example is given in Figure 2.5 where the population size is too low causing there to be no legitimate output for the Lgamma function due to there being no value for the adjusted sample size which would achieve 80% power.

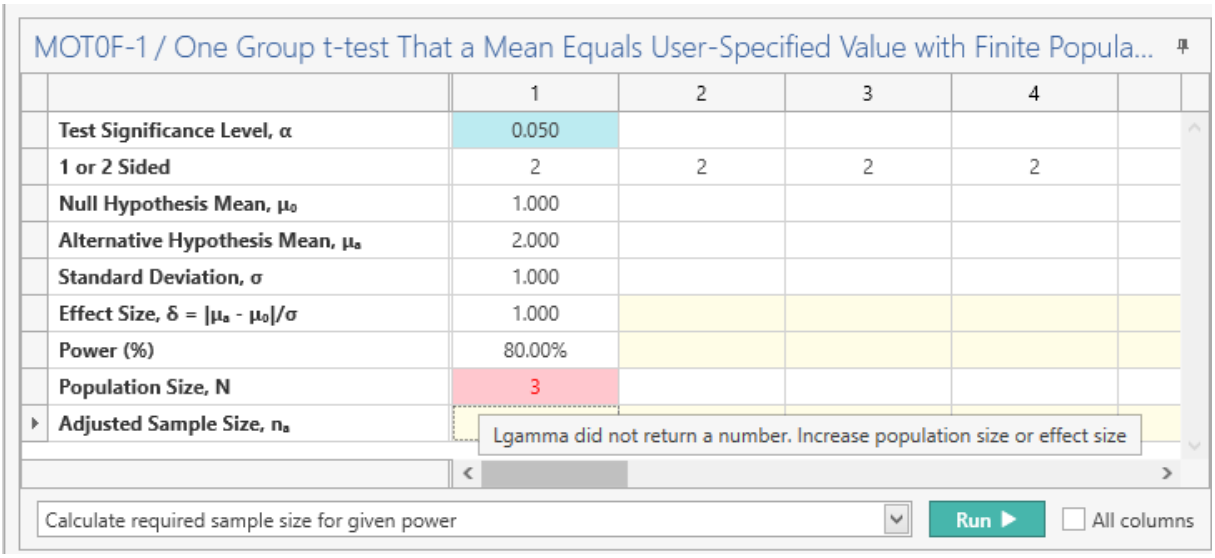


Figure 2.5: Solver Error Example

2.2.3 Solver Warnings

Solver warnings occur when a solver result is given but there are issues which would cause concern over the veracity of the result given. The two major categories of solver warnings are **Rounding Warnings** and **Assumption Warnings**.

1. **Rounding Warnings:** These occur if the solver output was rounded due to being too extreme originally.
2. **Assumption Warnings:** These occur if an underlying assumption of study design is not met by the current design parameters.

Examples of rounding warnings include nQuery rounding the sample size up to two when it was below two and rounding the power down to 99% when it was greater than 99%.

Examples of assumption warnings include the minimum cell count being too low for chi-square tests and the normal approximation not holding when the population size and sample size are too similar when the finite population adjustment is being used.

When a solver warning occurs, the background is clear and the solver answer value is red. Unlike Solver Errors, Solver Warnings do not prevent the user from generating a solver result but they do provide additional context to prevent over-interpretation of a questionable sample size or power calculation.

This is illustrated in Figure 2.6 where column one has a "Calculate power" solver warning for the minimum cell count being low and the column two has a "Calculate power" solver warning that the power was rounded down to 99% due to being "unrealistically" high. As per the errors above, the specific warning is viewable by placing your cursor over the affected cell(s).

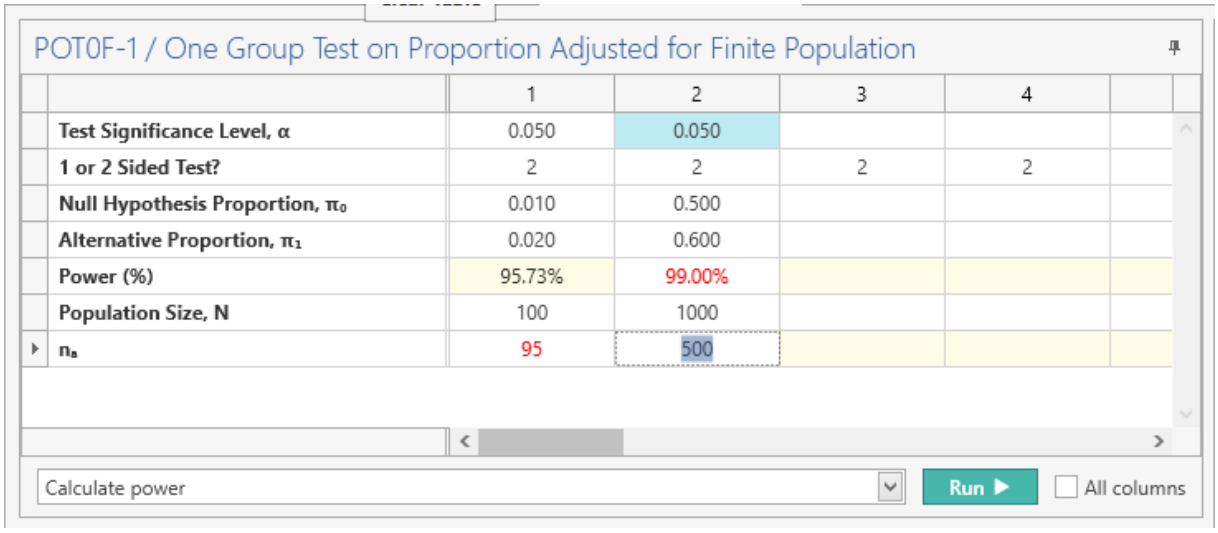


Figure 2.6: Solver Warning Example

2.2.4 Application Logging

When nQuery opens a table or encounters an error, these are logged automatically by nQuery. If you want to track errors in the application or asked to provide additional information to the nQuery Technical Support Team then these logs can be useful. An example is given in Figure 2.7.

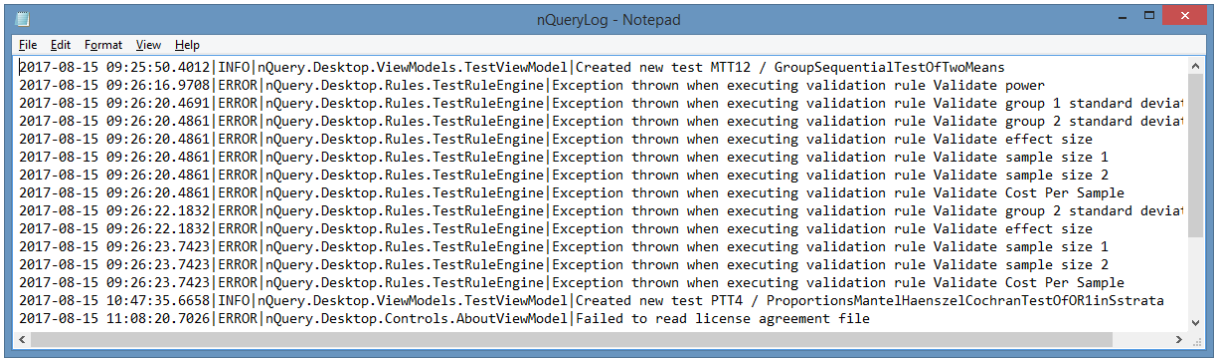


Figure 2.7: nQuery Log Example

By default, these logs are saved in "C:/Users/<Username>/AppData/Roaming/nQuery/Logs" - where <Username> is the name of the Windows account associated with the nQuery

installation. The save location for the Log can be changed in the Options menu (see section 2.3).

2.3 Options Menu

The **Options** menu gives the user the ability to change a number of nQuery features to reflect a users preferences for the software.

The **Options** menu can be opened by selected *Options* item from the **File** menu in the top-left of the nQuery software.

2.3.1 Application-Wide Options

The application-wide options are shown in Figure 2.8 with their default settings.

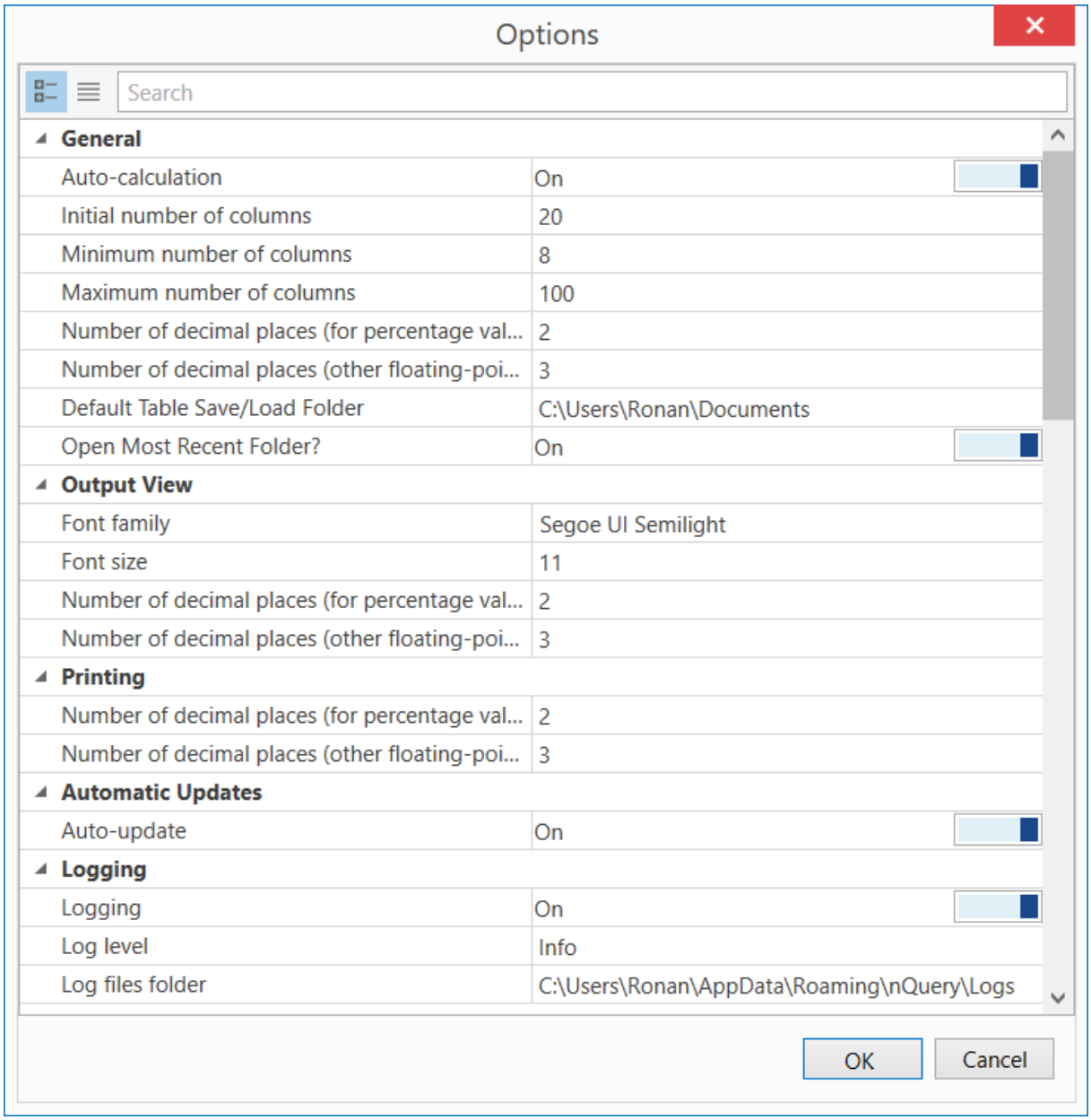


Figure 2.8: Application Options Menu

There are three main categories of application-wide settings. These are named and described below:

1. **General Settings:** Determine number of columns shown in design tables, number of decimals shown in design table cells and save/load folder default locations. Following fields available:
    a) **Auto-calculation:** Toggle whether solvers are activated automatically if column is filled appropriately. If disabled, solvers are only activated via the Run button - *Default: On*
    b) **Initial number of columns:** Set the number of columns included in a design table when opened initially - *Default: 20*
    c) **Minimum number of columns:** Set the minimum number of columns in a

design table. Resets to this value if the number of Specify Multiple Factors combinations is less than this value - *Default: 8*

d) **Maximum number of columns:** Set the maximum number of columns in a design table. Resets to this value if the number of Specify Multiple Factors combinations is more than this value - *Default: 100*

e) **Number of decimal places (for percentages):** Set number of decimals displayed for percentage rows in tables e.g. power - *Default: 2*

f) **Number of decimal places (other floating-point values)**: Set number of decimals displayed for all non-percentage rows in tables e.g. means, proportions, effect size - *Default: 3*

g) **Default Table Save/Load Folder:** Default folder shown in Save/Open windows in nQuery - *Default: C:\Users\<Username>\Documents*

h) **Open Most Recent Folder?:** Toggle for whether to show folder most recently used to save or open an nQuery table file (.nqt) - *Default: On*

2. **Output View:** Determine fonts and number of decimals shown in Output statements. Following fields available:

a) **Font Family**: Select the font family used in the Output window text - *Default: Segoe UI Semilight*

b) **Font Size:** Select the font size used in the Output window text - *Default: 11*

c) **Number of decimal places (for percentages):** Set number of decimals displayed for percentage rows in output statement e.g. power - *Default: 2*

d) **Number of decimal places (other floating-point values):** Set number of decimals displayed for all non-percentage rows in output statement e.g. means, proportions, effect size - *Default: 3*

3. **Printing:** Determine number of decimals shown in Print Preview. Following fields available:

a) **Number of decimal places (for percentages):** Set number of decimals displayed for percentage rows in print preview e.g. power - *Default: 2*

b) **Number of decimal places (other floating-point values):** Set number of decimals displayed for all non-percentage rows in output statement e.g. means, proportions, effect size - *Default: 3*

4. **Automatic Updates:** Determine if software should automatically alert user if software update is available. Following field available:

a) **Auto-update:** Select if software should prompt user to install update if available on software start-up - *Default: On*

5. **Logging:** Determine if nQuery log should be generated, which information to log and location to save log files. Following fields available:

a) **Logging:** Toggle whether logging occurs - *Default: On*

b) **Log Level:** Change the level of event logged by nQuery. Options are Trace, Debug, Info, Warning, Error - *Default: Info*

c) **Log Files Folder:** Specify file location where log file is saved *Default: C:\Users\<Username>*

2.3.2 Chart (Plotting) Options

This section contains options to edit all default options for plots. The plot options are discussed in details in section 1.9 and are editable within each plot individually.

These options are shown in Figure 2.9 with their default settings.

Chart	
Legend Visible	Off
Multiple Column Legend Visible	On
Legend Border Color	#00FFFFFF
Legend Horizontal Position	RightOutside
Legend Vertical Position	Center
Title Visible	On
Title Font	Segoe UI
Title Color	Black
Title Font Size	21
Title Bold	Off
Title Italic	Off
Subtitle Visible	On
Subtitle Font	Segoe UI
Subtitle Color	#FFA9A9A9
Subtitle Font Size	16
Subtitle Bold	Off
Subtitle Italic	Off
X-Axis Title Visible	On
X-Axis Title Font	Segoe UI
X-Axis Title Color	Black
X-Axis Font Size	16
X-Axis Bold	Off
X-Axis Italic	Off
Y-Axis Title Visible	On
Y-Axis Title Font	Segoe UI
Y-Axis Title Color	Black
Y-Axis Font Size	16
Y-Axis Bold	Off
Y-Axis Italic	Off
X-Axis Gridlines Visible	Off
Y-Axis Gridlines Visible	Off
Marker Style	Circle
Marker size	6
Series Palette	Grayscale

Figure 2.9: Plot Options

The options for Chart (plotting) are as follows:

1. **Legend Visible:** Toggle if legend is shown for single column plots. - *Default: Off*
2. **Multiple Column Legend Visible:** Toggle if legend is shown for multiple column plots. *Default: On*
3. **Legend Border Color:** Select color of legend border - either hex number of color name will be displayed. Selecting this option will open the color picker interface, select **More Colors** to manually select color - *Default: #00FFFFFF (Transparent White)*
4. **Legend Horizontal Position:** Combination of horizontal location of legend (Left, Right, Center) and if legend is inside or outside of plot frame (Outside, Inside) - *Default: Right Outside*
5. **Legend Vertical Position:** Combination of vertical location of legend (Top, Bottom, Center) and if legend is inside or outside of plot frame (Outside, Inside) - *Default: Center*
6. **Title Visible:** Toggle if main plot title is shown. *Default: On*
7. **Title Font:** Select font for main plot title. The dropdown will preview each font style. *Default: Segoe UI*
8. **Title Color:** Select color of main plot title - either hex number of color name will be displayed. Selecting this option will open the color picker interface, select **More Colors** to manually select color - *Default: Black*
9. **Title Font Size:** Select size of font for main plot title. *Default: 21*
10. **Title Bold:** Toggle if main plot title font is bolded. *Default: Off*
11. **Title Italic** Toggle if main plot title font is italicized. *Default: Off*
12. **Subtitle Visible:** Toggle if main plot subtitle is shown. Subtitles (title text which appears below main plot title) are primarily used in nQuery Predict plots. *Default: On*
13. **Subtitle Font:** Select font for main plot subtitle. The dropdown will preview each font style. *Default: Segoe UI*
14. **Subtitle Color:** Select color of main plot subtitle - either hex number of color name will be displayed. Selecting this option will open the color picker interface, select **More Colors** to manually select color - *Default: Grey (#FFA9A9A9)*
15. **Subtitle Font Size:** Select size of font for main plot subtitle. *Default: 16*
16. **Subtitle Bold:** Toggle if main plot subtitle font is bolded. *Default: Off*
17. **Subtitle Italic** Toggle if main plot subtitle font is italicized. *Default: Off*
18. **X-axis Title Visible:** Toggle if X-axis plot title is shown. *Default: On*
19. **X-axis Title Font:** Select font for X-axis plot title. The dropdown will preview each font style. *Default: Segoe UI*
20. **X-axis Title Color:** Select color of X-axis plot title - either hex number of color name will be displayed. Selecting this option will open the color picker interface, select **More Colors** to manually select color - *Default: Black*

21. **X-axis Title Font Size:** Select size of font for X-axis plot title. *Default: 16*
22. **X-axis Title Bold:** Toggle if X-axis plot title font is bolded. *Default: Off*
23. **X-axis Title Italic** Toggle if X-axis plot title font is italicized. *Default: Off*
24. **Y-axis Title Visible:** Toggle if Y-axis plot title is shown. *Default: On*
25. **Y-axis Title Font:** Select font for Y-axis plot title. The dropdown will preview each font style. *Default: Segoe UI*
26. **Y-axis Title Color:** Select color of Y-axis plot title - either hex number of color name will be displayed. Selecting this option will open the color picker interface, select **More Colors** to manually select color - *Default: Black*
27. **Y-axis Title Font Size:** Select size of font for Y-axis plot title. *Default: 16*
28. **Y-axis Title Bold:** Toggle if Y-axis plot title font is bolded. *Default: Off*
29. **Y-axis Title Italic** Toggle if Y-axis plot title font is italicized. *Default: Off*
30. **X-axis Gridlines Visible:** Toggle if X-axis gridlines are displayed. These are major and minor gridlines. *Default: Off*
31. **Y-axis Gridlines Visible:** Toggle if Y-axis gridlines are displayed. These are major and minor gridlines. *Default: Off*
32. **Marker Style:** Select shape for markers for points charted in plot. Select from Hidden, Circle, Cross, Polygon, Ring, Square, Star, Triangle. *Default: Circle*
33. **Marker Size:** Select size for markers for points charted in plot. *Default: 6*
34. **Series Palatte:** Select color palette used for color(s) of lines and markers in plots. See `https://docs.devexpress.com/WPF/400728/common-concepts/themes/palettes#predefined-palettes` for details on the available palettes *Default: Grayscale*

2.3.3 nQuery Predict Options (nQuery Advanced Expert only)

This section contains the options for nQuery Predict. These options are shown in Figure 2.10 with their default settings. More detail on nQuery Predict can be found in chapter 11.

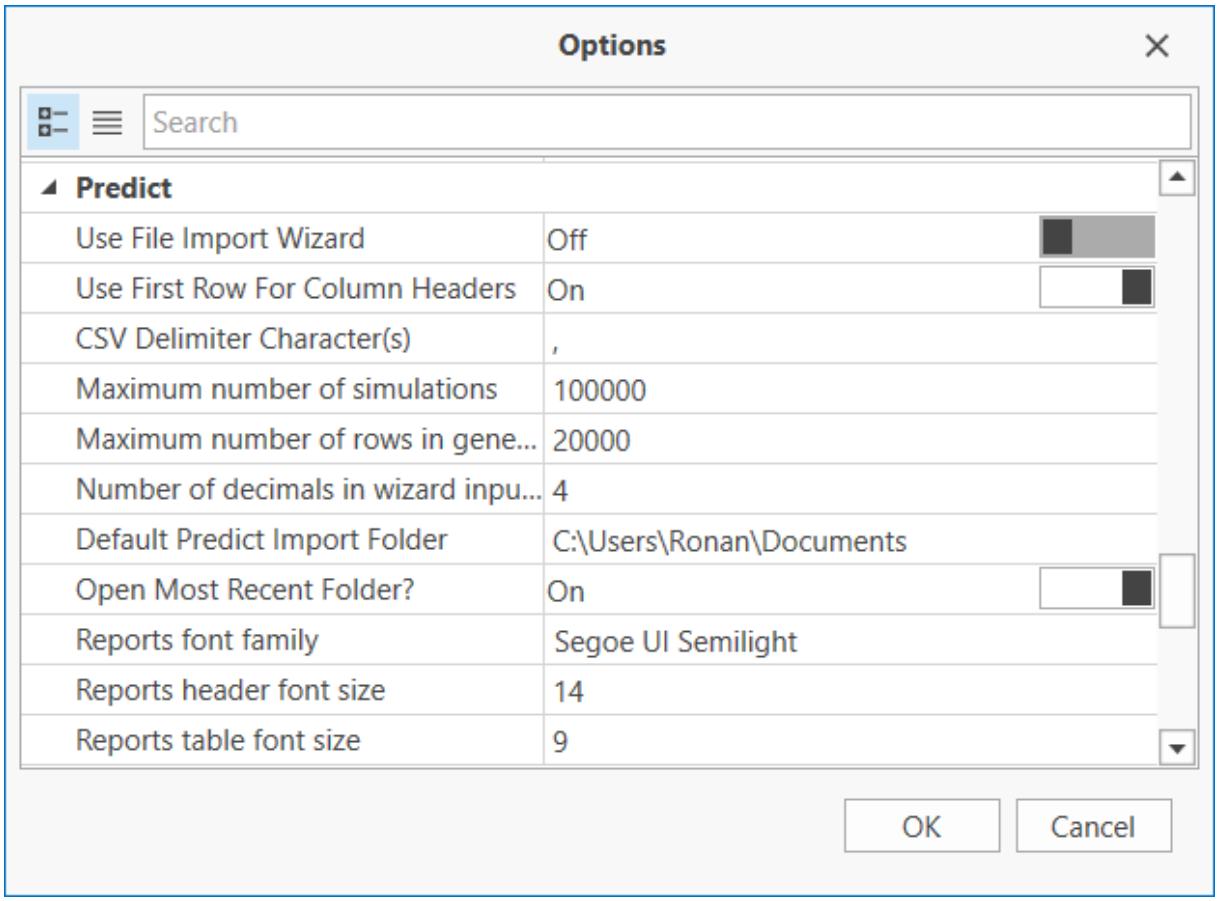


Figure 2.10: nQuery Predict Options

The options for nQuery Predict are as follows:

1. **Use File Import Wizard:** Toggle if nQuery Predict should use "advanced" file import wizard. The advanced file import wizard will provide option to specify whether to use the first row for column headers and csv delimiter character at file import. The "simple" file import wizard used when this option is off will assume those options equal the values specified here in the Options menu *Default: Off*
2. **Use First Row for Column Headers:** Toggle if first row of imported datasets should be assigned as the column headers *Default: On*
3. **CSV Delimiter Character(s):** Enter delimiter between entries in imported CSV files *Default: , (Comma)*
4. **Maximum Number of Simulations:** Maximum number of simulations allowed in nQuery Predict workspace. Note this option will also apply to the spreadsheet outputs of the Randomization List and Group Sequential Design Simulator tools. *Default: 100000*
5. **Maximum Number of Rows in Generated Reports:** Maximum number of rows displayed in generated spreadsheet reports. nQuery Predict will generate up to this amount of rows in the report, the remaining rows, if any, will not be included. Note this option will also apply to the spreadsheet outputs of the Randomization List and Group Sequential Design Simulator tools. *Default: 20000*

6. **Number of decimals in wizard input fields:** Number of decimal places displayed in nQuery Predict numeric input fields *Default: 4*
7. **Default Predict Import Folder:** Default folder displayed when importing datasets *Default: C:\Users\<UserName>\Documents*
8. **Open Most Recent Folder?:** Open most recently used folder in nQuery Predict workspace when importing datasets *Default: On*
9. **Reports Font Family:** Font used in nQuery Predict Reports *Default: Segoe UI Semilight*
10. **Reports Header Font Size**: Font size of headers in nQuery Predict Reports *Default: 14*
11. **Reports Table Font Size:** Font size of values in tables within nQuery Predict Reports *Default: 9*

2.3.4 Randomization List Options

This section contains the options for **Randomization List** tool, see chapter 6. These options are shown in Figure 2.11 with their default settings. Note that these settings also apply to the **Group Sequential Report** feature in the GSTX series of tables.

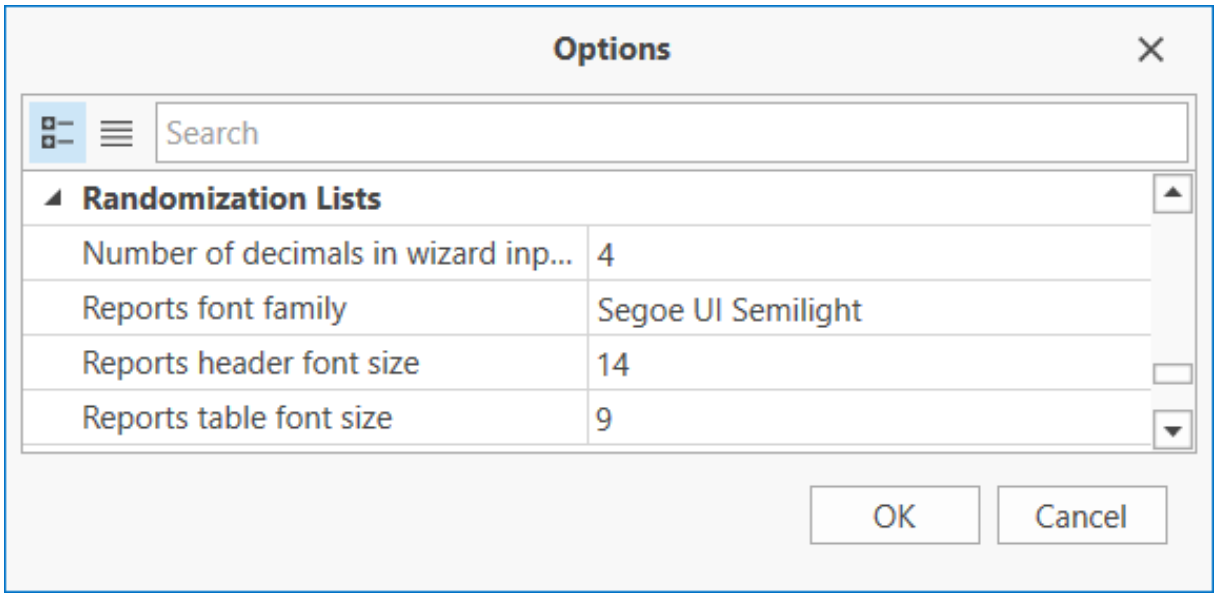


Figure 2.11: Randomization List Options

The options for the **Randomization List** are as follows:

1. **Number of decimals in wizard input fields:** Number of decimal places displayed in numeric input fields *Default: 4*
2. **Reports Font Family:** Font used in Reports *Default: Segoe UI Semilight*
3. **Reports Header Font Size**: Font size of headers in Reports *Default: 14*
4. **Reports Table Font Size:** Font size of values in tables within Reports *Default: 9*

2.3.5 Group Sequential Report Options (nQuery Advanced Pro only)

This section contains the options for the **Group Sequential Report** in the GST series of group sequential tables - chapter 7 covers the GST series of tables, subsection 7.3.4 covers the **Group Sequential Report** specifically. These options are shown in Figure 2.12 with their default settings

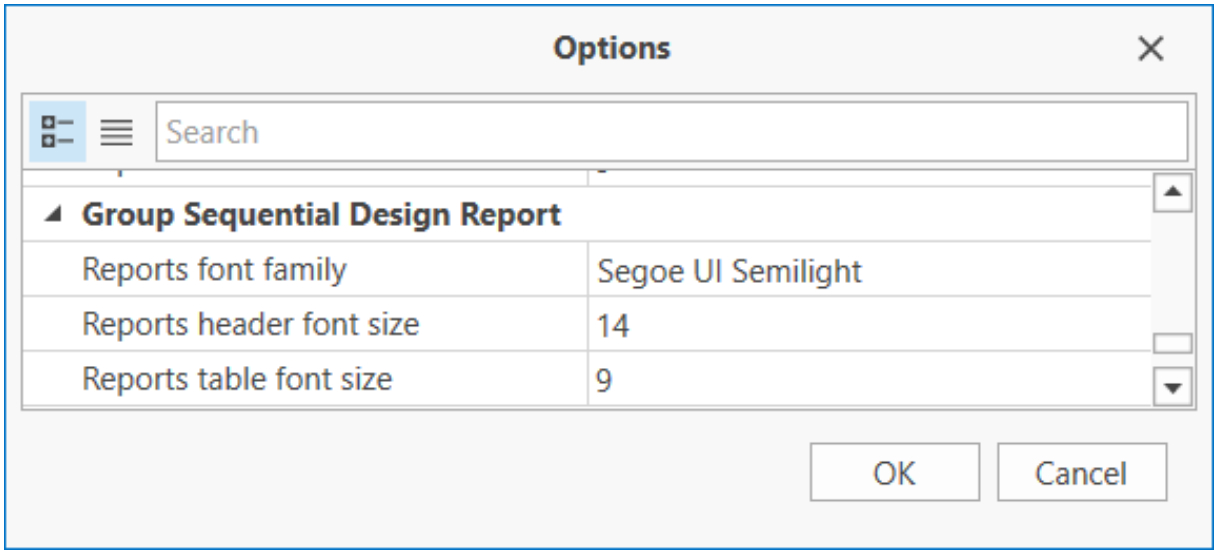


Figure 2.12: Group Sequential Report Options

The options for the **Group Sequential Design Simulator** are as follows:

1. **Reports Font Family:** Font used in Group Sequential Report *Default: Segoe UI Semilight*
2. **Reports Header Font Size**: Font size of headers in Group Sequential Report *Default: 14*
3. **Reports Table Font Size:** Font size of values in tables within Group Sequential Report *Default: 9*

2.3.6 Group Sequential Simulation Options (nQuery Advanced Pro only)

This section contains the options for Group Sequential Simulation tool. This tool is available from the GSTX series of group sequential tables or from the **Group Sequential Design Simulation** option from the **Assistants** file menu. These options are shown in Figure 2.13 with their default settings.

More detail on Group Sequential Design and the Group Sequential Design Simulator, can be found in chapter 8 and chapter 7.

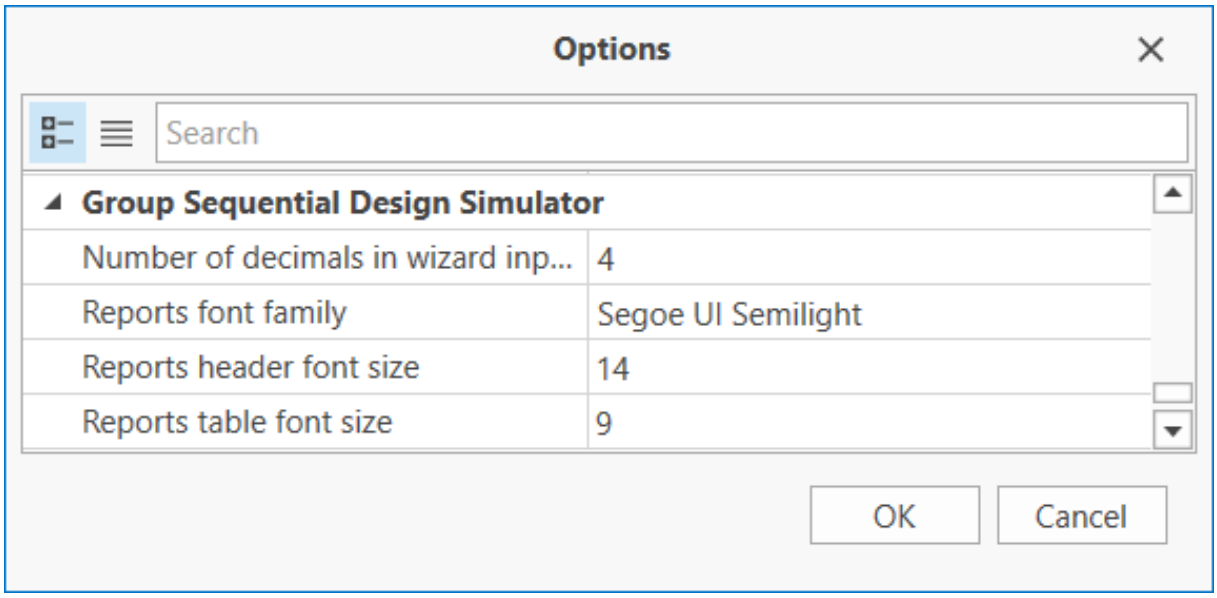


Figure 2.13: Group Sequential Design Simulator Options

The options for the **Group Sequential Design Simulator** are as follows:

1. **Number of decimals in wizard input fields:** Number of decimal places displayed in Group Sequential Design Simulator numeric input fields *Default: 4*
2. **Reports Font Family:** Font used in Group Sequential Design Simulator Reports *Default: Segoe UI Semilight*
3. **Reports Header Font Size**: Font size of headers in Group Sequential Design Simulator Reports *Default: 14*
4. **Reports Table Font Size:** Font size of values in tables within Group Sequential Design Simulator Reports *Default: 9*

2.3.7 Per-Table Options

Some of the General Settings options can be changed on a per design table basis.

To achieve this, select the arrow to the left of **Tables** under the **Per-Table Configuration Settings** field found at the end of the Options menu window. Then select the arrow to the right of table code name of interest. An example of this is shown in Figure 2.14

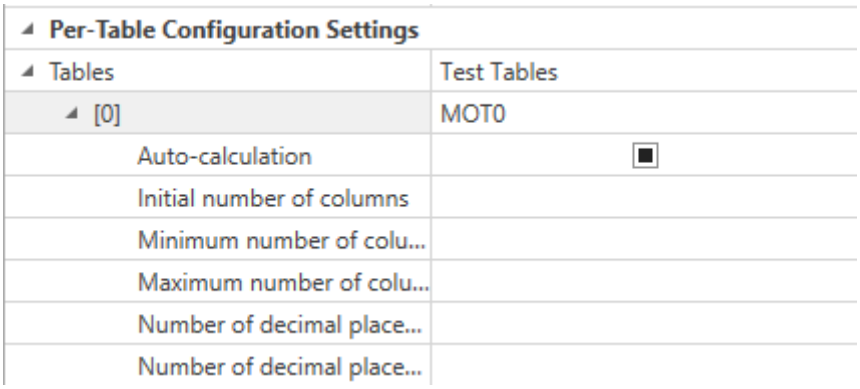


Figure 2.14: Per-Table Options Menu Example

The user can then edit the Auto-calculation, Initial number of columns, minimum number of columns, maximum number of columns, Number of decimal places (percentages) and Number of decimal places (double) as per the General Settings fields described above. Unless manually edited, the same settings and defaults for a specific design table are used as per **General Settings** i.e. General Setting used if leave that field empty.

2.4 Print and Report Options

nQuery provides printing options for the design tables and other table outputs.

2.4.1 Print Table

To Print the contents of the table, select either the **Print** option under the **File** menu or from the tool bar. This will display the default Windows print screen where you can edit the printer used, the printer preferences, the pages printed and number of copies printed.

2.4.1.1 Print Preview

To have nQuery generate a Print Preview, select either **Print Preview** option under the **File** menu or from the tool bar. This will display a Print Preview screen with an example shown in Figure 2.15.

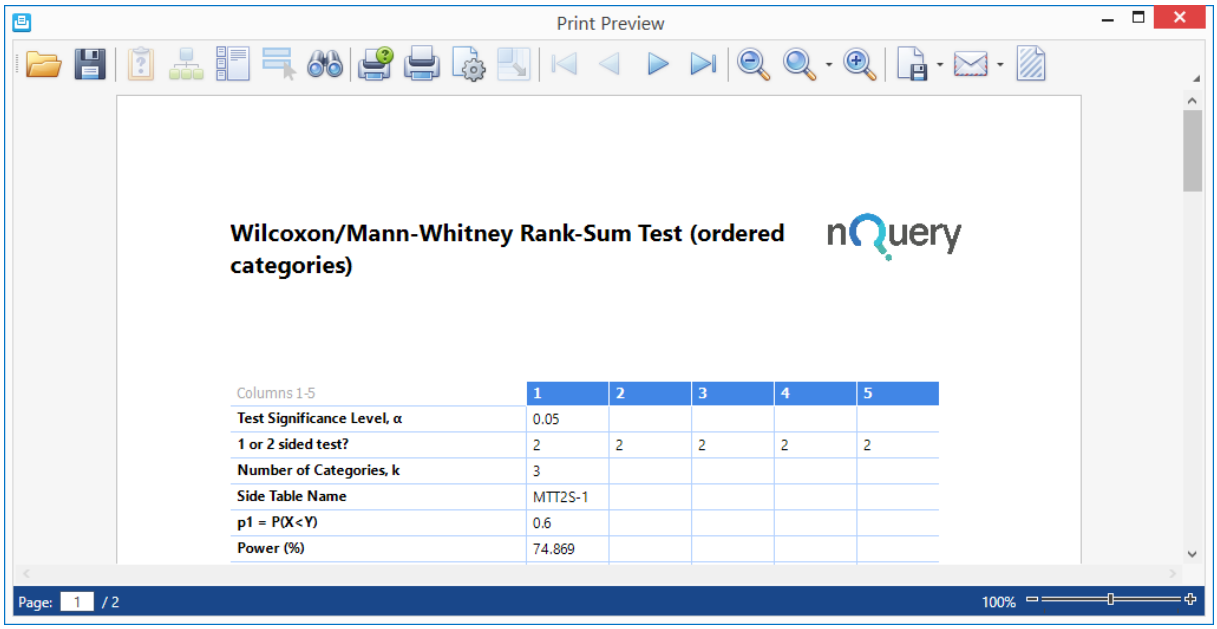


Figure 2.15: Print Preview Example

The toolbar at the top of the Print Preview screen gives options to open, save, search, print, quick print, adjust settings, page up, page down, first page, last page, zoom, zoom in, zoom out, export, send or watermark. A hand tool is also available from the right-click context menu.

2.4.2 Other Print Options

Print options are available for the following table outputs: Plots, Output Statement.

To print plots, use the Print option in the right-click context menu used within a plot.

To print the output statement, use the Print button in the bottom-right of the Output window or in the right-click context menu.

2.4.3 Report

nQuery provides a report function which allows users to summarise the results for specific design table column in a print-ready format.

To open a report for a specific column, select that column by clicking the column name bar above the column. Then right-click the column and select the **Report** option at the bottom of the context menu or select **Report** from the **Assistants** file menu. This will open a column report which will include a summary of the design parameter values in that column and the output statement for that column if a solver is active.

The report will be opened in a Print Preview style window and has the same options and functionality described in subsubsection 2.4.1.1. An example of report is shown in Figure 2.16.

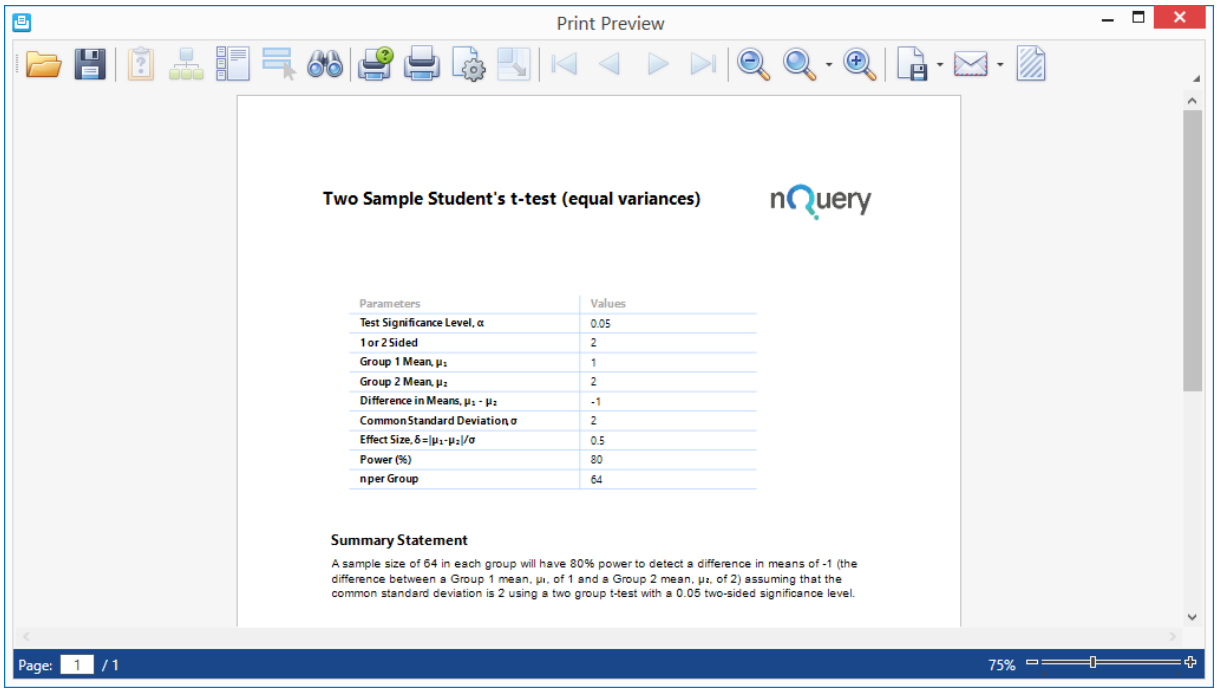


Figure 2.16: Report Example

2.5 Other Topics

2.5.1 Design Table Context Menu and Shortcuts

Within an nQuery design table when a cell or cells is selected, right-clicking will open a context menu for those cells. In nQuery when a cell or multiple cells are selected, the context menu will contain options for Copy, Cut, Paste, Select All, Fill Right, Clear and Copy Table.

Many shortcuts for standard Windows commands (e.g. Ctrl+C for Copy, Ctrl+V for Paste) are used in nQuery. These shortcuts are displayed to the right of the name within the file menus and context menus where appropriate.

If a full column is selected either by dragging over all the cells in a column or by clicking the column title bar, selecting Clear will reset the solver in the column. It also opens a Report option which is described in subsection 2.4.3.

To select multiple entries in a design table, select a cell and then hold down the Shift key (to select all cells between the first and second selected cells) or Ctrl key (to select multiple individual cells) and select another cell.

2.5.2 Design Table Drop-downs

In some nQuery design tables, a row is a drop-down menu rather than a numeric input. To select a value from this drop-down, select the relevant cell and click the downwards arrow on the right-hand side of the cell. This will display the full set of options available

for that row. The help card will provide a description of the solver drop-down options, their meaning and usually a Suggestion for this option.

Where all options for a drop down are numeric, the numeric input can be inputted directly. One example of this class of drop-down menu is for "1 or 2 Sided Test?" or "1 or 2 Sided Interval?" rows. In these rows, you have the option to either enter 1 or 2 directly into the cell or use the drop-down menu as above.

These rows are treated differently in the Specify Multiple Factors tool and the Plot User Selected rows tool to other rows. In the Specify Multiple Factors tool, these rows will have a drop-down menu similar to design table drop-down. In Plot User Selected rows, these rows will not be available as an option in the X-axis drop-down. To plot the effect of changing the options in these cells, fill multiple columns with all other values fixed and then apply the relevant plotting method to all the relevant columns in the same plot.

2.5.3 Customising Table Layout

2.5.3.1 Changing Window Size and Docking

In nQuery, the default size and positioning of each window and element is editable by user to create the layout which best suits their needs. There are two main elements which can be edited: windows and tabs.

Manipulating nQuery Windows Windows are the primary user interface unit of an nQuery design table. By default the three windows displayed are the design table window (top-left), the Output/Specify Multiple Factors window (bottom-left) and the Help/Notes window (right). If a plot or plots are created, the Plot window can be manipulated in the same fashion.

There are two main actions that can be applied to a window: docking/undocking and resizing.

- Docking/Undocking

To move a window, click and drag the window bar at the top of the window of interest. This bar will contain the name of the tab currently open in that window (e.g. Help, Output etc.). While the window is being dragged, two options are given for that window: dock the window or undock the window.

To dock the window, drag the cursor while the window is selected to a "docking square" and nQuery will highlight in blue where the window will be docked. Four edge docking squares will be available on the centre left, right, top and bottom of the nQuery window which will place the current element to the left/right/above/below all other nQuery windows. In addition, the "current" nQuery window over which the cursor is placed will contain the relational docking squares. The centre square will combine the current window and the docking window into a single window with all of their tabs combined. The other squares will place the docking window to the left/right/above/below the current window .

To undock the window, drag the cursor away from the "docking squares" and to the undocked placement of choice.

In both cases, when the desired placement is achieved let go of the left mouse button (or other "clicking" method) and the window will appear in the desired place. An example of the docking process "in action" for the Output window where it is being placed between the MTT0 Design Table and Help windows is given in Figure 2.17. The effect of this placement (after resizing) is shown in Figure 2.18.

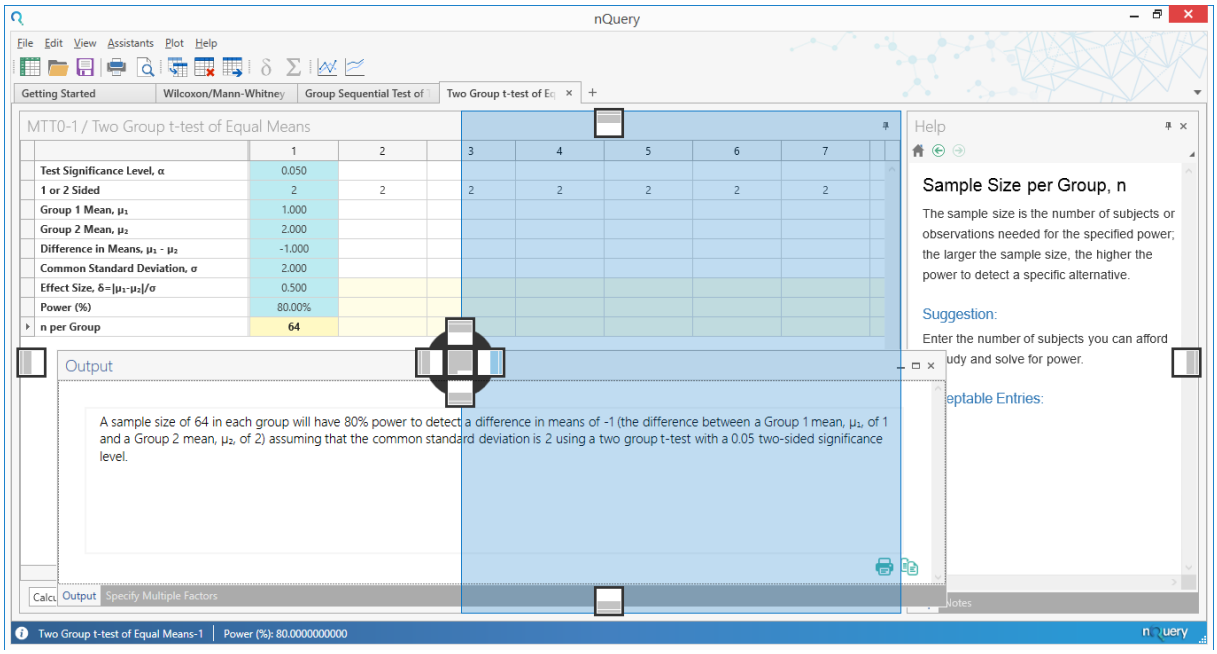


Figure 2.17: nQuery Window Docking Example

- Resizing

To resize a window, place the cursor at the edge of the nQuery window of interest. The mouse cursor will change to a ↔ symbol. Then hold down the left mouse button and drag the cursor left/right (for a vertical edge) or up/down (for a horizontal edge) until the window is the desired size. Note that elements in the table will dynamically update to show how they will look for a given window size. An example of the output statement being resized after the docking example above is shown in Figure 2.18.

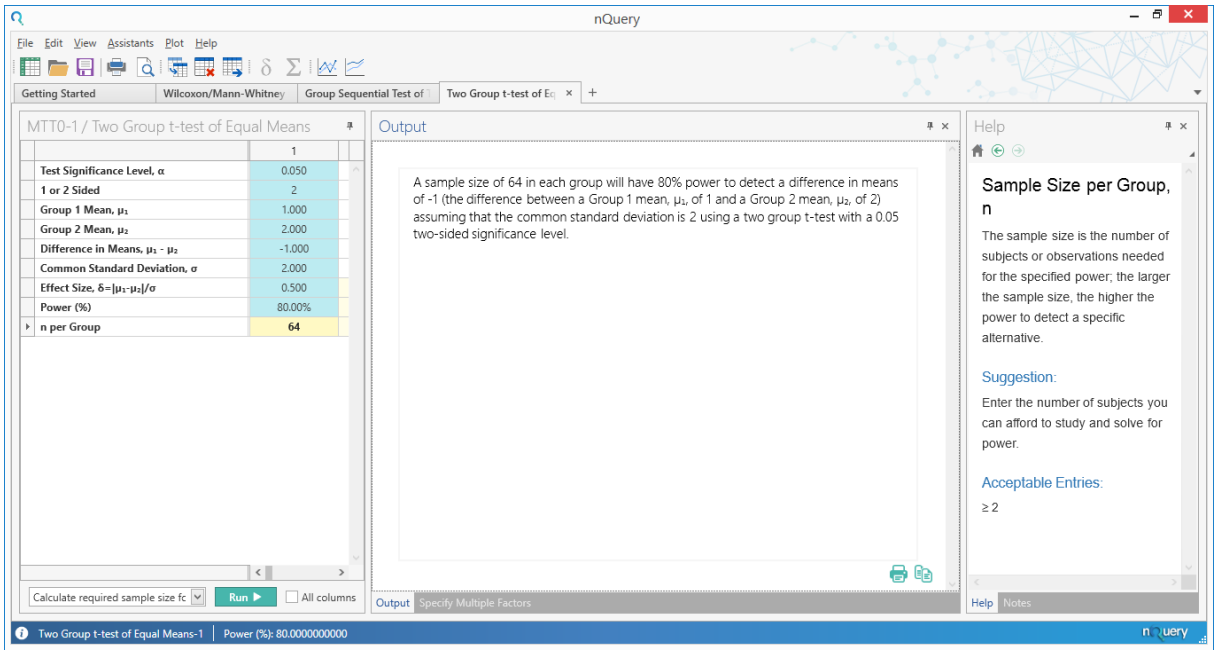


Figure 2.18: nQuery Window Resizing Example

Manipulating Window Tabs Window tabs have a single applicable operation: docking/undocking. This process works similarly to undocking/docking a window. For tabs, the window element which is clicked and dragged is the tab bar name rather than the window name. The tab names are found in the grey tab bar at the bottom of an nQuery window. When a tab is being dragged, the same options are available as for a window. The three main actions are to undock the tab, place the tab relative to the other windows or dock the tab into another window.

To undock, drag the select tab away from any of the docking squares and leave. When a tab is undocked, it will become an nQuery window.

To place relative to the other windows, select on of the left/right/up/down docking squares and place in the desired position which will be previewed in blue by hovering over a docking square while dragging.

To dock the tab into another window, drag the cursor over the window of interest and select the centre docking square in the middle of the current window.

An example where the Output tab is currently being moved and where the Notes tab has been moved into the main design table window is shown in Figure 2.19.

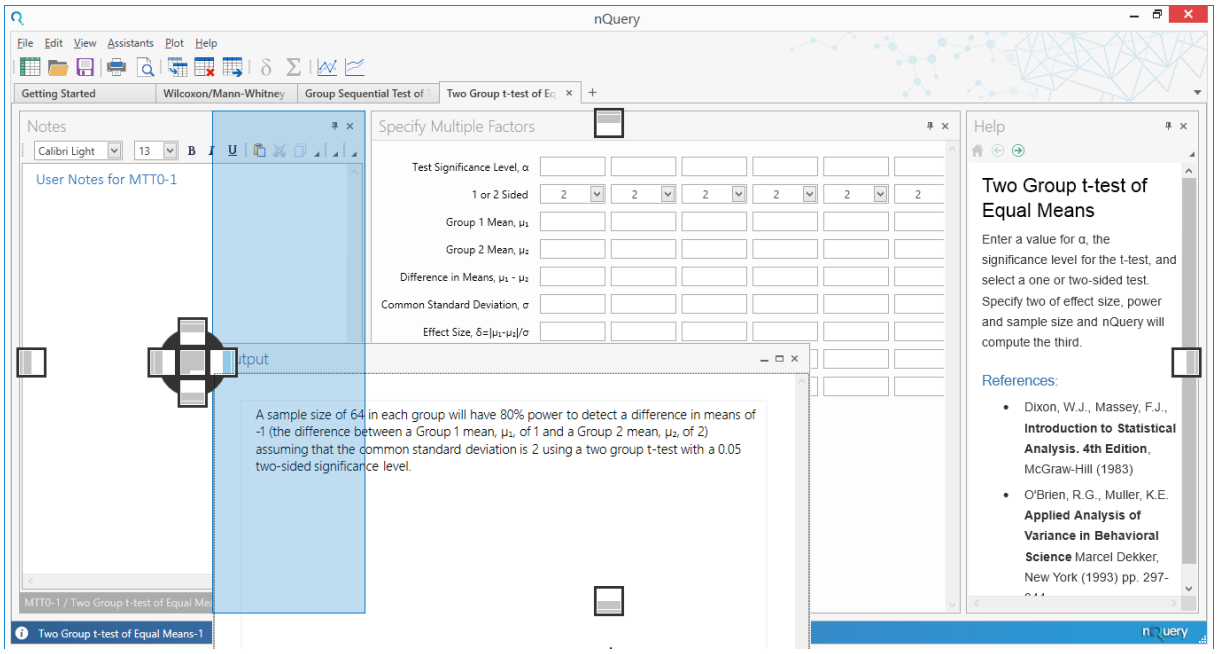


Figure 2.19: nQuery Tab Docking Example

Note that you can also drag tab names within the tab bar to place it relative to the other tab names in the same click and drag fashion.

The user can also close or open table elements by selecting these from the View file menu.

2.5.3.2 Editing Column Names

nQuery provides the user the ability to change a column name. To change a column name, double-click the number in the column title bar above the column cells. The number will appear in a white square and will now be editable. Replace the number with the desired column name and this name will then be displayed in the design table. An example of a design table with changed column names was shown in Figure 2.2.

Note that these column names will be reflected automatically in the Legend of plots involving that include the renamed columns.

3 Advanced nQuery Assistants

3.1 Design Table Side-Tables

Side-tables provide table specific tools which allow users to calculate design parameters based on additional information which is commonly known or used in a particular design type. This section will go over the three primary types of side-tables: Effect Size Side-Tables, Covariance Matrix Side-Tables and Mandatory Side-Tables

3.1.1 Compute Effect Size Side-Table

For an introduction in how to open and use effect size side-tables, see subsection 1.7.4. In this section, we will briefly summarise the process of opening the side-table, using the side-table and cover some additional information not included in subsection 1.7.4.

3.1.1.1 Opening an Effect Size Side-Table

There are three main routes to open an effect size side-table: using the "Compute Effect Size" option in the Assistants menu, using the Compute Effect Size button  in the menu bar or by selecting the cell(s) in design table which are transferred from that side-table. Column cells which are the transfer target for an Effect Size side-table will be indicated in the cell's Help Card by its "Aid" section.

When a side-table is opened for a column, it will appear below the main analysis table in the same window as the Output and Specify Multiple Factors tools.

For each column in which a side-table is opened, a unique side-table will open associated with that selected column. The names of these side-tables are found in the tab bar at the bottom of the side-table window.

The most common template for a side-table name is [Table Code]S-[Column Number]. For example, opening a side-table in MGT0 (One Way Analysis of Variance) for column one will open a side-table named "MGT0S-1". Note there are some exceptions e.g. Looks-[Column Number] for Group Sequential Design.

Note that users can edit and transfer from other column side-tables into that column by selecting them in the tab menu at the bottom of the side-table window.

3.1.1.2 Using an Effect Size Side-Table

For a specific example of an effect size being used, see subsection 1.7.4. The format for an effect size side-table will be unique depending on the design table being used. For

guidance on using a specific side-table refer to the help materials, in particular the Home Card and Help Card "Aid" sections of relevant cells.

In general, the effect size side-table works by the user fully specifying the required cells in the table.

When the minimum amount of information required in a side-table is completed, the "Compute" button in the upper-left of the side-table window will become active (un-greyed). Selecting the Compute button will calculate the design parameter(s) which will be transferred to the main table and other parameters of interest in certain design tables.

After the Compute button is used, the "Transfer" button (right of the Compute button) will become active and when selected this will transfer the relevant design parameters into the associated column in the main design table.

Note that some tables will not contain a "Compute" and/or "Transfer" button. Where the Compute button is missing, nQuery will automatically calculate the required outputs in the side-table. Where the Transfer button is missing, nQuery will automatically transfer the required side-table outputs to main table when the side-table is completed.

To return the side-table to its original state, use the "Clear" button (to the right of the Transfer button) to remove all user entries, read-only entries and computed values from the side-table.

Using the right-click context menu gives access to same edit tools and shortcuts as the main table (see subsection 2.5.1).

An example of an effect size side-table is shown in Figure 3.1.

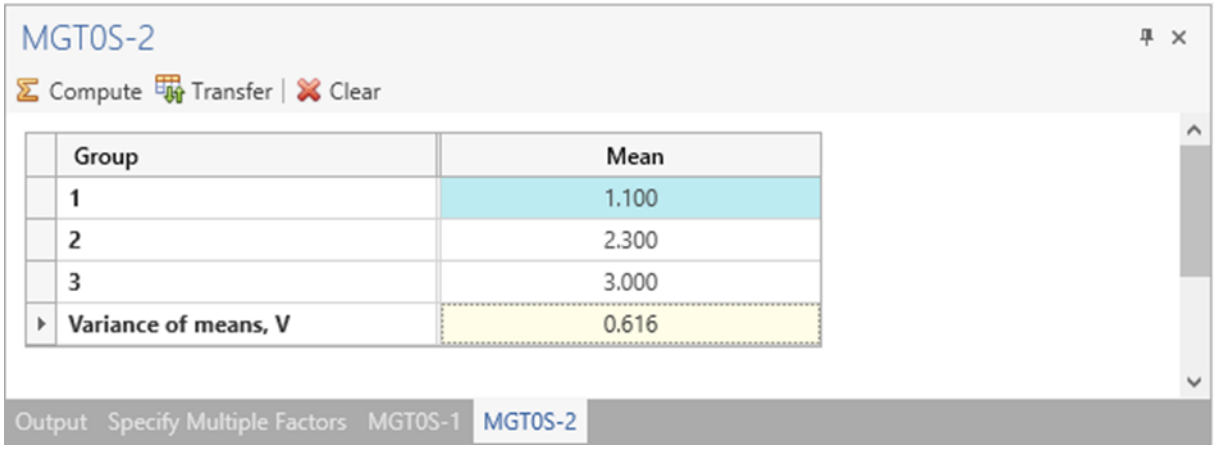


Figure 3.1: Effect Size Side-Table Example

3.1.1.3 Closing an Effect Size Side-Table

To close a specific effect size side-table, use the "x" in the top-right of the effect size side-table window. You can also hide the side-table using the pin symbol in the top-right or by right-clicking on the tab menu name.

3.1.2 Specify Covariance Matrix Side-Table

The Specify Covariance Matrix side-table provides a convenient method to calculate the error and Greenhouse-Geisser correction terms for the Repeated Measures ANOVA tables which use the Greenhouse-Geisser approximation in nQuery. These are MOT4 and MTT3.

Note that a small number of other tables use this option as generic way to open a second side-table where required.

3.1.2.1 Opening an Effect Size Side-Table

There are three main routes to open an Specify Covariance Matrix side-table: using the "Specify Covariance Matrix" option in the Assistants menu, using the Specify Covariance Matrix button  in the menu bar or by selecting the cell(s) in design table which are transferred from the side-table. These are the "error-term", sphericity and bias term rows. This will be indicated in the relevant cell's Help Card by its "Aid" section.

As per the effect size side-tables, when a covariance matrix side-table is opened for a column, it will appear below the main analysis table in the same window as the Output and Specify Multiple Factors tools.

For each column in which a side-table is opened, a unique covariance matrix side-table will open associated with that selected column. The names of these side-tables are found in the tab bar at the bottom of the side-table window. The template for a side-table name is [Table Code]C-[Column Number]. For example, opening a covariance matrix side-table in MOT4 (One Way Repeated Measures ANOVA (Greenhouse Geisser Approximation) for column one will open a side-table named "MOT4C-1".

Note that users can edit and transfer from other column side-tables (effect size or covariance matrix) into that column by selecting them in the tab menu at the bottom of the side-table window.

3.1.2.2 Using a Specify Covariance Matrix Side-Table

There are two modes for filling the Specify Covariance Matrix side-table: the Specify Standard Deviations and Correlations mode and the Specify Full Covariance Matrix mode. To switch between the modes, use arrow on the right of the mode drop-down to the right of the "Transfer" button at the top of the side-table window. This drop-down is shown in Figure 3.2.

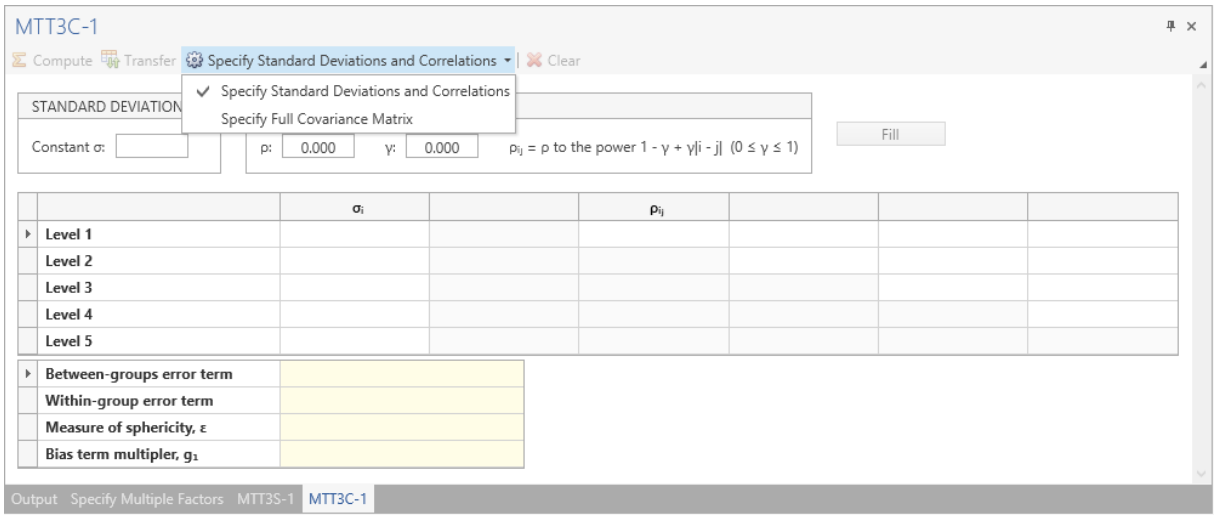


Figure 3.2: Specify Covariance Matrix Mode Drop-down Example

Specify Standard Deviations and Correlations Mode The Specify Standard Deviations and Correlations mode has two primary methods to activate the side-table: using the Constant Standard Deviations and Correlation Pattern shortcuts or directly filling the σ_i and ρ_{ij} table entries.

Note that changes made in one mode will affect the table values given in the other mode.

1) Constant Standard Deviations and Correlation Pattern

To use the Constant Standard Deviations and Correlation Patterns shortcuts you need to fill three inputs: the common standard deviation σ, the correlation ρ and the pattern term γ.

The common standard deviation value will fill σ_i in the table below with the same common standard deviation values. This value must be greater than zero.

The correlation will be the value included in the first diagonal of the ρ_{ij} table below and will adjusted downwards by the pattern term as you rightwards in the ρ_{ij} table. This value must be between 0 and 1

The pattern term defines the adjustment applied to the correlation as you move rightwards within the ρ_{ij} table. The formula for this adjustment is given the table and is $1 - \gamma + \gamma|i - j|$ where $|i - j|$ is the absolute distance between the first cell in the row in the ρ_{ij} and the cell of interest. This value must be between 0 and 1.

The common standard deviation will assign a common standard for the measurements at each measurement level and the correlation and pattern terms will represent the correlation between measurements taken on a subject at a given "measurement distance". For example, the 2nd column cell in row 1 of the ρ_{ij} table represents the average correlation between the 1st and 3rd measurement for a subject.

To transfer the relevant σ_i and ρ_{ij} values for the specified values given in the Shortcuts menu, select the "Fill" button to the right of the shortcuts menus. This will activate the Compute button which will calculate the relevant error-terms, bias and sphericity and activate the Transfer button. Selecting Transfer will place these values in the associated main design table column.

To use a compound symmetry (CS) model, set the constant correlation to the desired value and set the pattern term to zero. In the CS matrix, the correlation between measurements is assumed to be constant regardless of the distance between measurements.

To use an autoregressive(1) (AR(1)) model, set the correlation at the desired value (this will be the "distance 1" correlation) and set the pattern term to one. In the AR(1) matrix, the correlation between measurements is assumed to decay via an AR(1) process as the distance between measurement increases.

To achieve a pattern where the correlation does decay but slower than the AR(1) model, set the correlation at the desired value (this will be the "distance 1" correlation) and set the pattern term to between zero and one.

An example of using the AR(1) model computed using the shortcuts method is shown in Figure 3.3.

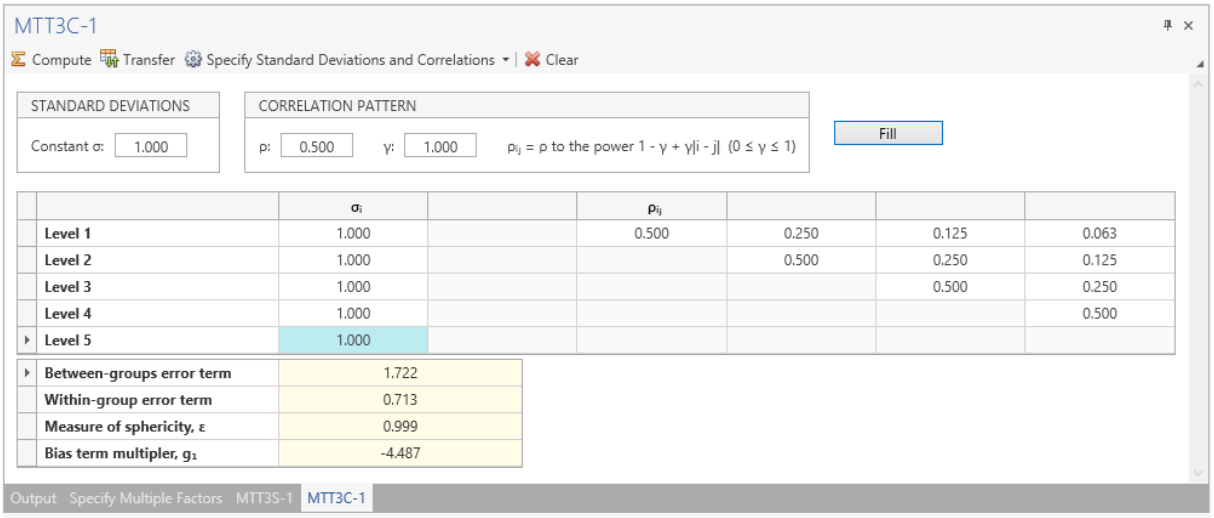


Figure 3.3: Specify Covariance Matrix SD + Correlation Example

2) Directly Filling Table

In addition to using the shortcuts method, you can fill the σ_i and ρ_{ij} in the table directly. This can be done with a blank table or the values can be edited from a shortcuts generated template. This gives the user a large amount of flexibility to set the table to their specifications. Once all σ_i and ρ_{ij} cells are filled, this will activate the Compute button which will calculate the relevant error-terms, bias and sphericity and activate the Transfer button. Selecting Transfer will place these values in the associated main design table column.

An example where we edited from the Figure 3.3 template to have the individual level standard deviations vary and the distance 4 (i.e. between measurement 1 and 5) correlation equal to zero is shown in Figure 3.4.

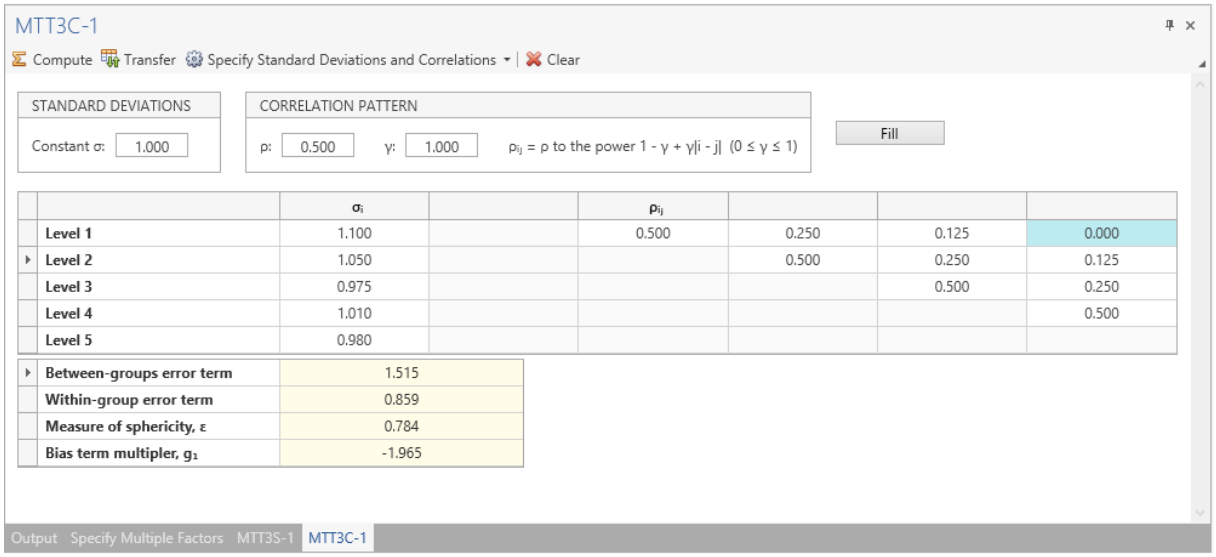


Figure 3.4: Specify Covariance Matrix Manual SD + Correlation Example

Specify Full Covariance Matrix mode The Specify Full Covariance mode works similarly to directly filling the standard deviations and correlations table. However, the covariance matrix is entered directly in this case. In the covariance matrix, the main diagonal elements are equal to within-measurement level variance and off-diagonal elements represent the covariance between main diagonal element level and the measurement at that distance (e.g. the third column entry in row one equals the average covariance between the first level subject measurement and the third level subject measurement).

There are two main methods to fill the covariance matrix: automatically fill using Constant Standard Deviations and Correlation Pattern mode or manually fill.

As noted at the start of this section, if the standard deviations and correlations table has been filled (either using the shortcuts menu or manually) in the other mode then the Covariance Matrix will be filled in this mode. Alternatively, you can fill or edit the covariance matrix manually to the study's specifications. Once all elements are filled in the covariance matrix, this will activate the Compute button which will calculate the relevant error-terms, bias and sphericity and activate the Transfer button. Selecting Transfer will place these values in the associated main design table column.

An example of an Specify Covariance Matrix side-table computed using the Specify Full Covariance Matrix mode is shown in Figure 3.5.

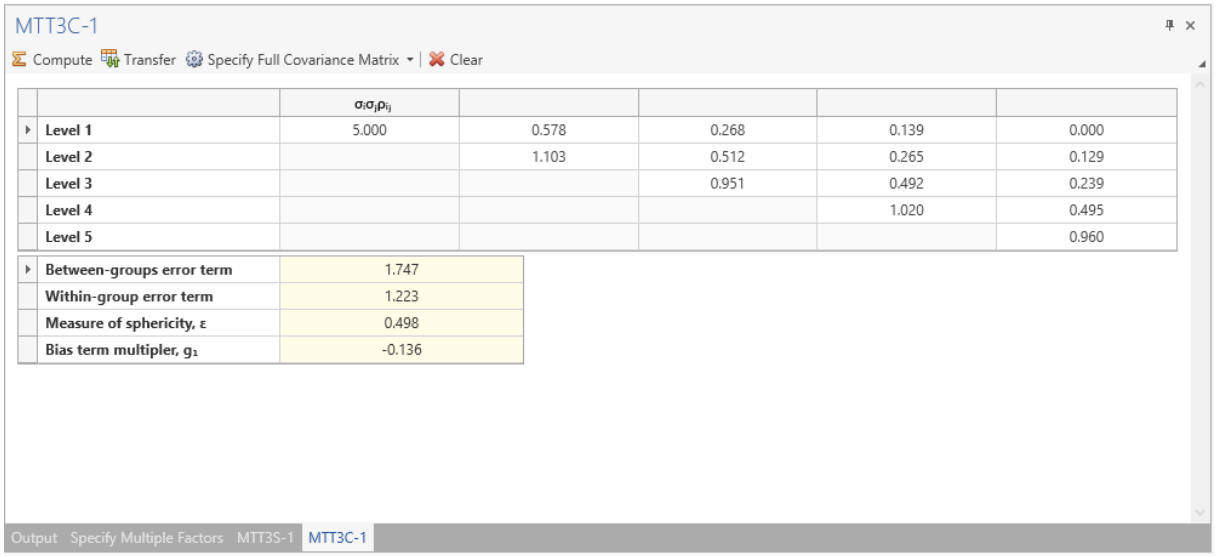


Figure 3.5: Specify Covariance Matrix Matrix Example

3.1.2.3 Closing a Covariance Matrix Side-Table

To close a specific covariance matrix side-table, use the "x" in the top-right of the effect size side-table window. You can also hide the side-table using the pin symbol in the top-right or by right-clicking on the tab menu name.

3.1.3 Mandatory Side-Tables

In the majority of nQuery design tables which use side-tables, the side-table is optional. In these cases, the role of the side-table is to provide a method for users to derive required design parameters based on other information they may have access to.

In a minority of nQuery design tables, the side-table is mandatory. In these cases, the inputs in the side-table(s) are used directly by the solvers of that table. The following is a list of examples where the table has a mandatory side-table(s) (Table Codes in Brackets):

- Group Sequential Tests (Spending Function, Haybittle-Peto, Wang-Tsiatis, Unified Family, Custom Boundaries) (GST0, GST1, GST2) (Discussed in chapter 7)
- Group Sequential Tests (Lan-DeMets only) (Means: MOT26, MTT12, MTE32; Incidence Rates/Counts: MTT40, MTT42; Proportions: POT8, POT13, PTT12; Survival: STT12, STT15, STT23, STT25) (Discussed in chapter 9)
- Multiple Comparison Procedure - Modeling (MCP-Mod) (MGT5, MGT7, MGT8, MGT9, PGT3) (Discussed in chapter 10)
- Blinded Sample Size Re-estimation for Overdispersed Poisson Counts (MTT47)
- Multi-Arm Multi-Stage (MAMS) Group Sequential Tests (MGT6, PGT4)
- Potvin 2-Stage Bioequivalence Design (MTE36)
- Bayesian Assurance using Custom Prior (MOT25, MTT21, POT7, PTT13, STT14)
- Stepped-Wedge Cluster Randomized Designs (CRT16, CRT17, CRT18)

- Multivariate Analysis of Variance (MANOVA) (MGT3)
- Mantel-Haenszel (Cochran) Test (PTT4, PTT4CC, PTT4U, PTT44, PTE22)
- Wilcoxon/Mann-Whitney Rank-Sum Test (Ordered Categories) (MTT2, MTT2U)
- Stratified Win Ratio (PTT42)
- Log-Rank Test, User Specified Survival Rates, Accrual, Dropouts (STT22, STT24, STT37, STT38)
- Log-Rank Test, User Specified Survival Rates, Accrual, Dropouts (Simulation) (STT3, STT3U)
- Maximum Combination Linear Rank Tests (STT33, STE11, STE13)
- Two Sample Stratified Log-Rank Test (STT31)
- Test for Polychotomous Kappa (AOT15)

From this list, all except MGT3 and the Group Sequential (see chapter 9) tables, use the same instructions as for the Effect Size side-tables above to open the side-table. In each of these design tables except MGT3 and the group sequential tables, there is a row named "Side Table Name" which will also open the side-table for a column automatically (assuming all side-table opening conditions are met).

In MGT3, there are three separate side-tables per column and these are opened by selecting the Factor Level Table, Means Matrix and Covariance Matrix read-only cells in a column. In the group sequential tables, selecting any cell in a column will open the Looks side-table.

The side-tables are the same between MTT2/MTT2U, PTT4/PTT4cc, STT3/STT3U, the Bayesian Assurance custom prior tables (MOT25/POT7 etc.) and the group sequential tables (MTT12/PTT12 etc.). These side-tables operate the same as optional side-tables except they do not have Compute/Transfer buttons. For mandatory side-tables when the table is filled sufficiently to be used in a solver, the name of the side-table in "Side Table Name" row (or MGT3 equivalent) will go from grey to black. The table otherwise will operate as per any other design table.

Note that Looks side-table for the group sequential tables does not require any editing to be active and is by default read-only. It is only required to be edited if the Information Times or Spending Function rows are set to "User Specified". See the help for the group sequential details for further details.

If a side-table has been completed in any column, you can automatically use that side-table in another column by selecting the relevant side-table name from the drop-down options in that column's "Side Table Name" row.

An example of a mandatory side-table being used in MTT2 is shown in Figure 3.6.

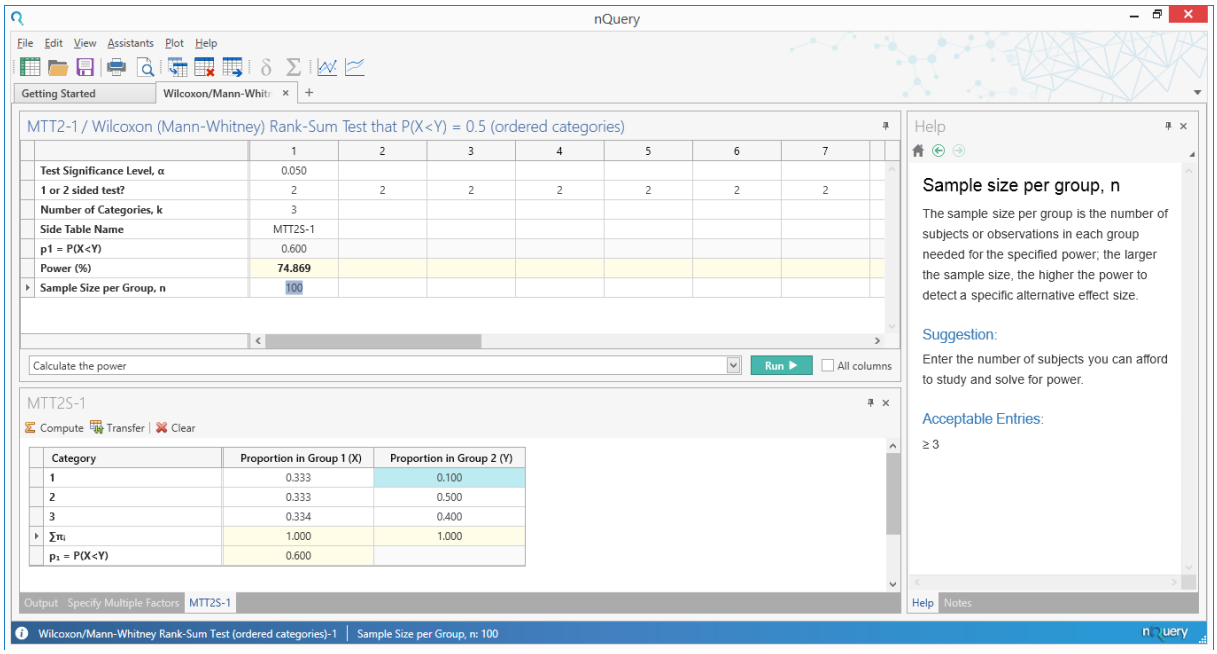


Figure 3.6: MTT2 Mandatory Side-Table Example

3.2 Compute Standard Deviation Assistants

nQuery provides a number of assistants which allow a user to derive the standard deviation for a study based on other parameters or data which the user has.

To access these assistants, select the "Standard Deviation" option from the Assistants file menu. This will open a radio button list menu containing the standard deviation assistants. Select an assistant radio button and select OK to open the relevant assistant.

There are 10 standard deviations (SD) assistants available in nQuery. These are (with a brief description):

1. From Standard Error: Derive SD from sample size (n) and standard error
2. For SD1 and SD2 (pooled SD): Derive pooled SD from group 1 and 2 standard deviations (SD1/SD2) and sample sizes (n1/n2)
3. From Range: Derive SD from range (using maximum and minimum optionally to derive range) and sample size, n
4. From Percentile: Derive the SD from the percentile and the difference in upper and lower percentile values (using upper and lower values optionally).
5. From Coefficient of Variation: Derive the log-scale SD and mean from the coefficient of variation and observed mean respectively
6. From Upper Confidence Limit: Derive the upper limit of the SD from the sample size, observed standard deviation and confidence level.
7. From SD1, SD2, Correlation: Derive the SD for the differences from the first condition SD, the second condition SD and the correlation
8. For Cluster Sampling: Derive the "cluster" SD from the between-cluster and within-cluster variances, the intra-cluster correlation and subjects per cluster.

9. For specified x values: Derive the SD from a set of x data values. See section 3.3
10. Of residuals: Derive the SD of the residuals and the dependent (Y) variable from the regression coefficient, correlation coefficient and independent (X) variable SD.

All of these assistants work in the same or similar way as nQuery design tables except for the "For specified x values" option. Use the guide given in chapter 1 and the individual Home and help cards provided for guidance on how to use each table.

Options 1 - 4 provide alternative methods to derive a standard deviation for one or two sample independent means test and Option 6 provides the alternative estimate for the standard deviation by using the upper confidence limit . Option 5, 7, 8 and 10 provide help to derive the adjusted standard deviation for specific designs or testing methods. Option 5 would be used if the analysis will be of the log-transformed data, Option 7 would be used for paired means testing or analysis, Option 8 would be used if the study will use cluster randomisation and Option 10 is used if the analysis is using linear regression.

3.3 Data Entry Assistant

nQuery provides a data entry assistant to allow users to derive commonly used design parameters based on data which may be available to the user.

The Data Entry Assistant has three main components: the Data Entry table, the Transformation menu and the Insert Values menu.

3.3.1 Data Entry Table

The data entry table is the main table on the left-hand side of the Data Entry Assistant. It consists of 20 columns and 500 rows. Each column corresponds to a data set and each row corresponds to an individual subject's data value in that column's data set.

As a user fills a column, four commonly used design parameters will be derived for the data set. These are the sample size (N), the mean, the sample standard deviation and population standard deviation, $\sigma(x)$. The difference between the sample and populations standard deviations is the denominator in the estimate for each is N-1 and N respectively.

3.3.2 Transformations Menu

The transformations menu gives the option to create a new column containing the transformed values for an entered data set. Transformations are commonly used when data is non-normal but has a distribution which would be amenable to being transformed into a normally distributed data using a common transformation.

The Transformations menu is found to the right of the Data Entry table and can be opened by selecting the Transformations tab at the top of the menu window.

The three transformations are a square root transformation (Sqrt(X)), a base 10 log transformation (log10(X)) and the natural log transformation (ln(X)). In addition, you can conduct these transformations to the data with a fixed value (A) added to each data

value before transformation. In this case, the user is required to enter a value of A in the menu.

To use the transformations menu, select the relevant column in the data entry table, select the transformation required, enter a value for A if a (X+A) transformation is selected and select "Add".

This will generate the transformed data (with summary statistics) in the next empty column to the right of the selected data entry column. The column title will include the name of the transformation and the column transformed and any transformed columns will be highlighted in orange.

3.3.3 Insert Values Menu

The insert values menu gives the option to create a number column using an evenly spaced number of data values in a specified range. This can be useful to generate a large dataset easily.

The insert values menu is found to the right of the Data Entry table and can be opened by selecting the Insert Values tab at the top of the menu window.

To generate a column using the insert values menu, specify a From value and To value in the relevant cells. These correspond to the minimum and maximum values of the range of interest respectively.

The user can then activate either the Specify Increment or Specify num. values option by selecting the radio button to the left of each option.

If the Specify Increment option is activated, the entered value will be increments in which the data will increase going from the "From" to the "To" value. For example, if From = 0 and To = 10 then Specify Increment = 2 will give the five values of [0, 2, 4, 6, 8].

If the Specify num. values option is activated, the entered value will be the number of data values which will be taken between the "From" and "To" value. For example, if From = 0 and To = 10 then Specify num. values = 5 will give the five values of [0, 2.5, 5, 7.5, 10].

Once the required values are entered for "From", "To" and "Specify Increment"/"Specify num. values", select "Execute" and that data will be generated on the currently selected Data Entry Table cell.

An example of Data Entry table using the above options is shown in Figure 3.7.

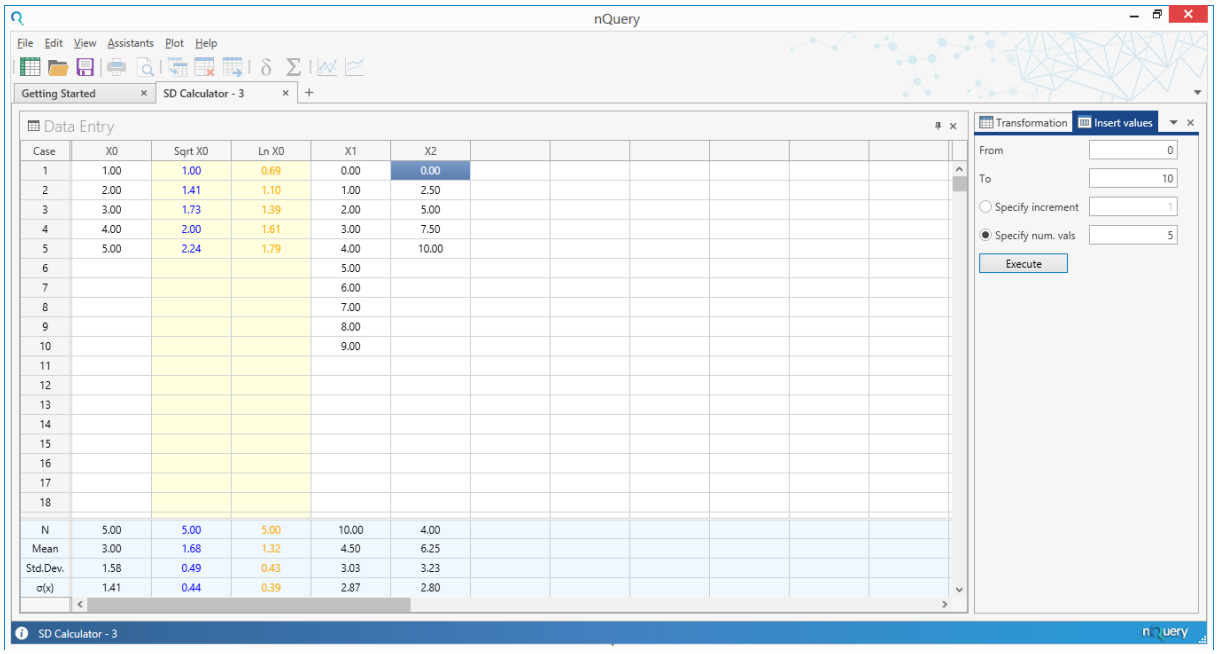


Figure 3.7: Data Entry Assistant Example

In column 1 is a user entered set of values (X0), in column 2 is Sqrt(X) transformed data for column 1, in column 3 is ln(X+1) (i.e. A=1 with natural log transform) transformed data for column, in column 4 is Insert Values menu data generated with From = 0, To = 10, Specify Increment = 1 and in column 5 is Insert Values menu data generated with From = 0, To = 10, Specify num. values = 5.

3.4 Cumulative Distribution Function Assistants

nQuery provides access to the most commonly used cumulative and inverse cumulative distribution functions used by the nQuery solver algorithms. To open a table for a specific statistical distribution, select Distribution Function from the Assistants file menu. This will open a radio button menu of the available statistical distributions. To open a distribution table, select the relevant radio button to the left of the distribution name and select "OK".

There are distribution assistants provided for the following statistical distributions:

1. z (Gaussian/Normal)
2. t (Central)
3. t (Non-central)
4. χ^2(Central) *(Chi-Square)*
5. χ^2(Non-central) *(Chi-Square)*
6. F (Central)
7. F (Non-central)
8. Cumulative binomial

The distribution tables work the same as standard nQuery design tables with the solvers being for the cumulative probability of P(X<x_p) (all tables), the percentile test statistic (e.g. F_p, t_p) (all tables except cumulative binomial) and the non-centrality parameter (non-central tables only).

3.5 Survival Parameter Conversion Assistant

The survival parameter conversion assistant provides a tool to convert between the three most commonly used survival parameters for an exponential survival curve.

STT00-1 / Conversion to alternate rates for exponential survival curves

	1	2	3
Time t			
Group 1 Proportion π_1 at Time t			
Group 1 Median Survival, med_1			
Group 1 Exponential Parameter, λ_1			
Group 2 Proportion π_2 at Time t			
Group 2 Median Survival, med_2			
Group 2 Exponential Parameter, λ_2			
Hazard Ratio, $h=\ln(\pi_1)/\ln(\pi_2)=med_2/med$			

Figure 3.8: Survival Parameter Converter

The three parameterizations available are the proportion surviving at time t, the median survival and the exponential parameter. In the survival parameter conversion assistant, the three survival parameters can be specified for a two group design individually for each group. In addition, there are rows for the Time t and the Hazard ratio. The Time t is required to calculate the proportion surviving at time t from the median survival or exponential parameter and vice-versa. The hazard ratio is calculated after the median survival/exponential parameter are specified in each group.

Note that the exponential parameter will automatically calculate the median survival when specified and vice-versa in each group.

Many nQuery survival tables (e.g. STT2, STT6) contain an Effect Size side-table based on this assistant but where this is not present the Survival Parameter Conversion Assistant is available.

3.6 Posterior Error Rate Calculator Assistant

The Posterior Error Rate Calculator is an assistant which allows conversion between frequentist Type I (Significance Level) and II (1 - Power) errors and Bayesian False Positive (β^*) and False Negative (α^*) errors given a prior probability against the null hypothesis,

H0. This is based on theory from [Lee and Zelen, 2000]. The Posterior Error Rate Calculator is shown in Figure 3.9.

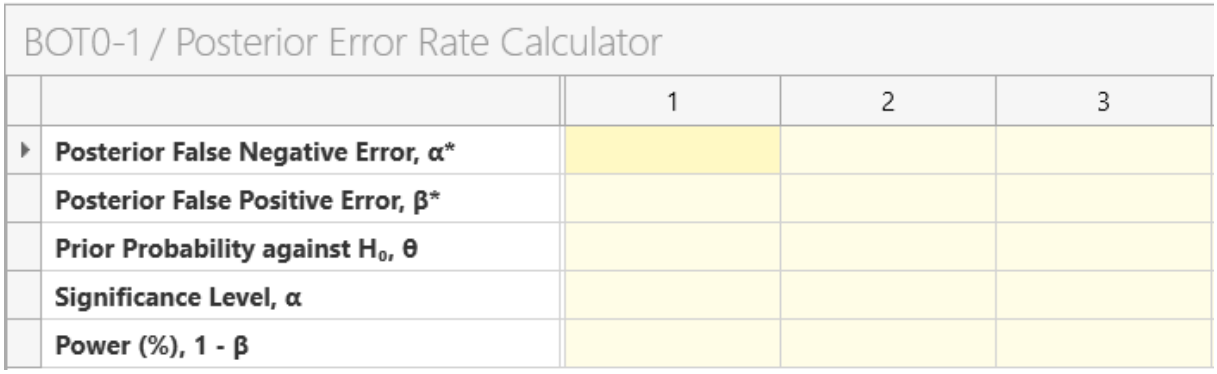


Figure 3.9: Posterior Error Rate Calculator

The Posterior Error Rate Calculator can be used to calculate any two of the Posterior False Negative Error, Posterior False Positive Error, Prior Probability against H_0, Significance Level or Power given all three other inputs are given in a column.

This completes the general user guidance for using nQuery for sample size and power calculations. What follows is a series of chapters dedicated to specialized topics where additional guidance and background will assist in using the referenced features and design tables.

Note: Posterior Error Rate Calculator Assistant is currently only available for users with an nQuery Advanced Plus license. Active packages are displayed in the Packages section in the Home tab. To purchase additional packages, see `www.statsols.com`.

4 nQuery Qualification Tools

nQuery provides automated qualification scripts to quickly allow a user to verify that their nQuery application is installed and operating to the manufacturers specifications. nQuery specifically has two separate tools for installation qualification (IQ) and operation qualification (OQ) to assist you in verifying nQuery in regulatory industries.

Note that operational and performance qualification (PQ) are considered interchangeable based on our correspondence with the relevant stakeholders. However, you may wish to perform within-application testing for PQ purposes.

4.1 Installation Qualification (IQ) Tool

The nQuery IQ tool assists you in demonstrating that nQuery has been installed and maintained to the manufacturer's specifications. nQuery IQ verifies the integrity of each file in the nQuery 8 system and provides the user a set of reports detailing the results.

The nQuery Installation Qualification (IQ) Tool validates an nQuery installation by verifying that each installed file is correct with a report generated detailing all file results. This determination is made using the SHA-1 algorithm to create a hash value for each file. This thus checks that each file is present and that its integrity has been maintained.

Important: IQ validation represents the expected state of the system as it is at the time an installation is completed. If changes are made to the original files subsequently then these may show as failed when IQ is run on the system at a later date.

4.1.1 Running nQuery IQ

To run nQuery IQ, select "Installation Qualification" from the Help file menu. This will automatically run the nQuery.Tools.InstallationQualification.exe application (found in your installation folder, default of C:/Program Files (x86)/Statistical Solutions Ltd/nQuery) and output a HTML report which will display the results automatically in the machine's default HTML viewer (e.g. default internet browser).

4.1.2 nQuery IQ Results

The IQ report file will automatically be saved on the machine when the IQ tool runs. It will be saved to the C:\Users\<User Account>\AppData\Local\nQuery\Reports folder where <User Account> is the named User which currently logged into on the machine. An example of an IQ report is shown in Figure 4.1.

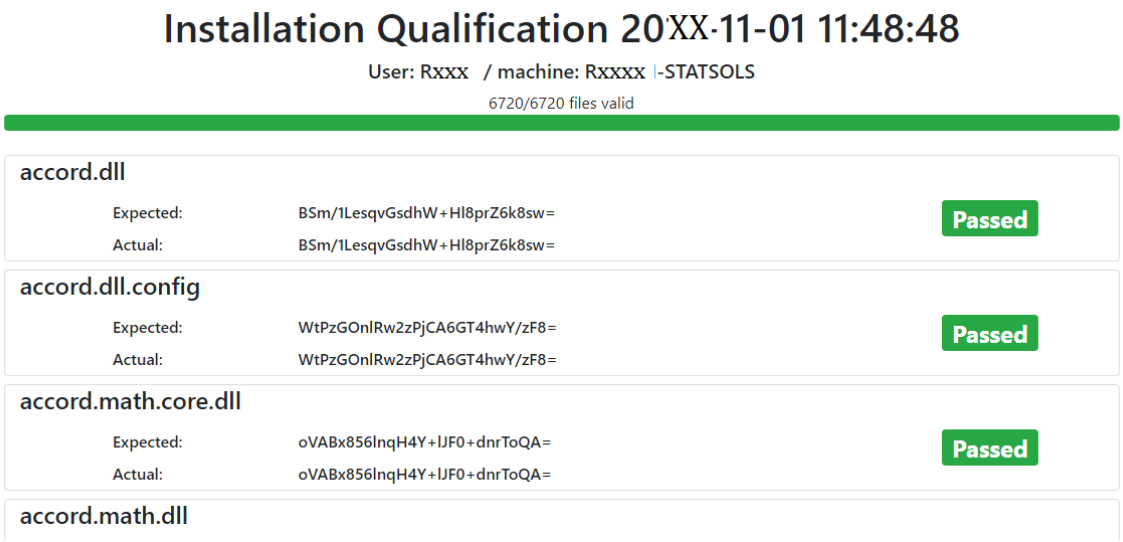


Figure 4.1: Installation Qualification Report Example

4.2 Operational Qualification (OQ) Tool

The nQuery OQ tool assists you in demonstrating that nQuery 8 is operational. nQuery 8 uses the nQuery solver functions over each design table for a set of validated design parameter inputs and will execute, process, and report the solver results.

Note that the files used for OQ are available in the TestData folder in your installation folder (default is C:/Program Files (x86)/Statistical Solutions Ltd/nQuery)

Important: All nQuery results have been validated exactly against the results from nQuery + nTerim 4.0 and the original validation documentation and references. All results should be identical to nQuery + nTerim 4.0 except for simulation tables. There are slight difference with simulation tables due to an upgraded random number generator being used in nQuery. For those tables a 5% precision rule was used for validation. Results were also compared to EAST 6.5, PASS 2021 and SAS 9.4 Proc Power where the same or similar methods were implemented in those software for a design table.

4.2.1 Running nQuery OQ

To run nQuery OQ, select "Operational Qualification" from the Help file menu. This will open the OQ Validation Tool menu which is shown in Figure 4.2.

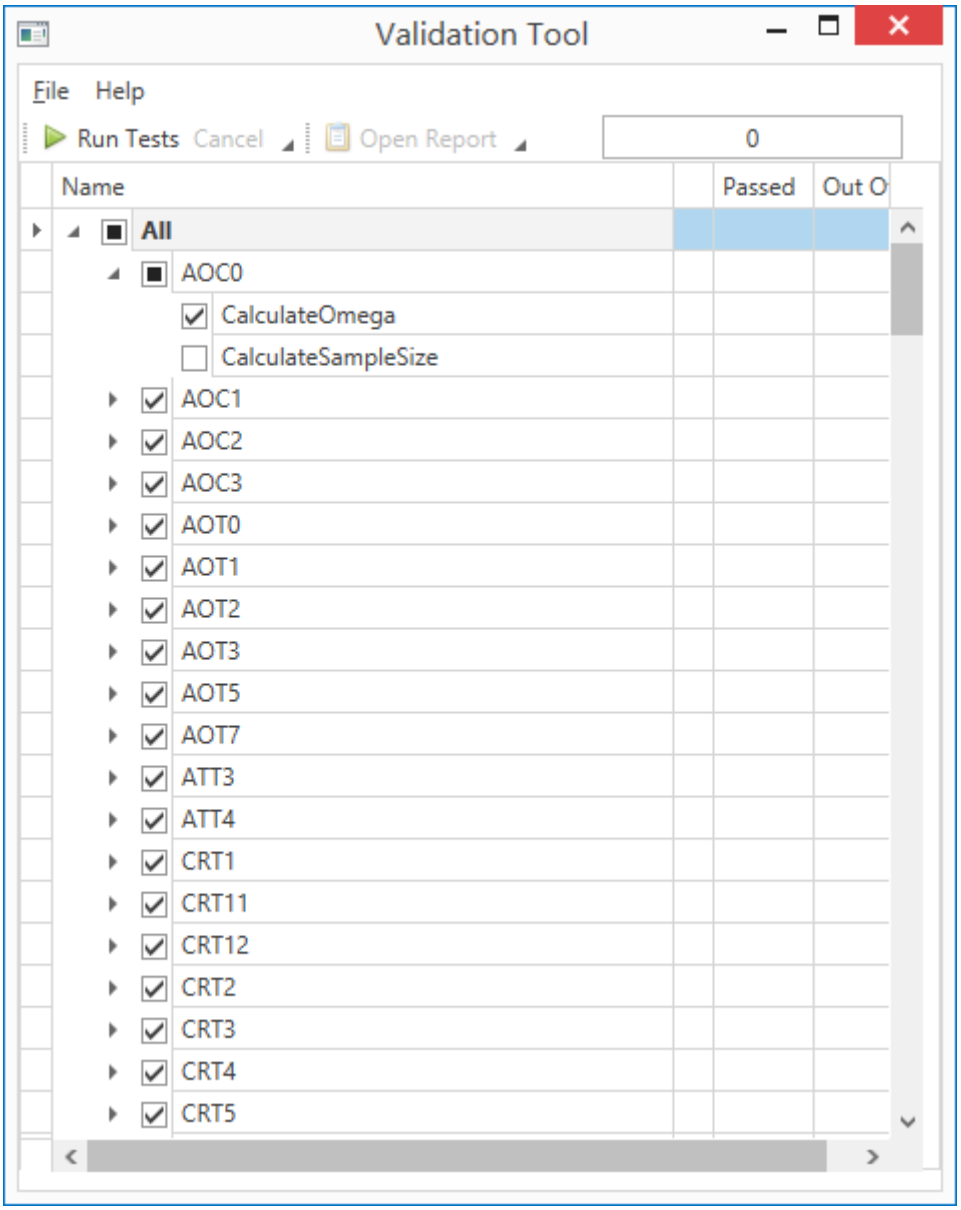


Figure 4.2: Operational Qualification Tool

The nQuery OQ window provides a list of all of the nQuery design tables by code (AOT1, MTE1 etc.) and has a three level menu hierarchy: All Tables, Per Table, Per Solver. Selecting the arrow ▶ to the left of the "All" option at the top of the menu will open and collapse the per-table options. Selecting the arrow ▶ to the left of a table code option will open and collapse the solver options for that table.

For all options, the user can include or exclude a table or solver by selecting or de-selecting the check-box to the left of that option. Selection is indicated with a tick icon.

Note that the tables selected by default will depend on when the OQ tool is opened. If the OQ tool is opened on the Getting Started tab or when no tab is open then all tables will be selected by default. If the OQ tool is opened on a specific design table then only that table will be selected by default.

Note that a small number of shortcuts are available for the OQ tool. Select the Help file menu item to see these.

Once the user has selected the tables which will be qualified, select the "Run Tests" button in the window menu bar. Note that since the nQuery testing data is specifically designed to include extreme values to test robustness that some tests may take some time to run. If the user wishes to stop qualification before it is finished, select the "Cancel" button in the menu bar.

As the OQ tool progresses, each item in the menu will show the Qualification results per-feature as it is completed in the columns to the right of the code-name.

The first column will show a tick symbol if the feature has passed and an "x" symbol if it has failed. The next "Passed" column will show the number of passed individual table/solver tests. The final "Out of" column will display the total number of tests ran for that individual table/solver tests. If a table/solver passes then the tests passed should equal the total number of tests.

A progress bar in the menu bar will display the total number of tables tests and indicate overall progress by the amount of the bar filled.

An example of the OQ tool in progress is shown in Figure 4.3.

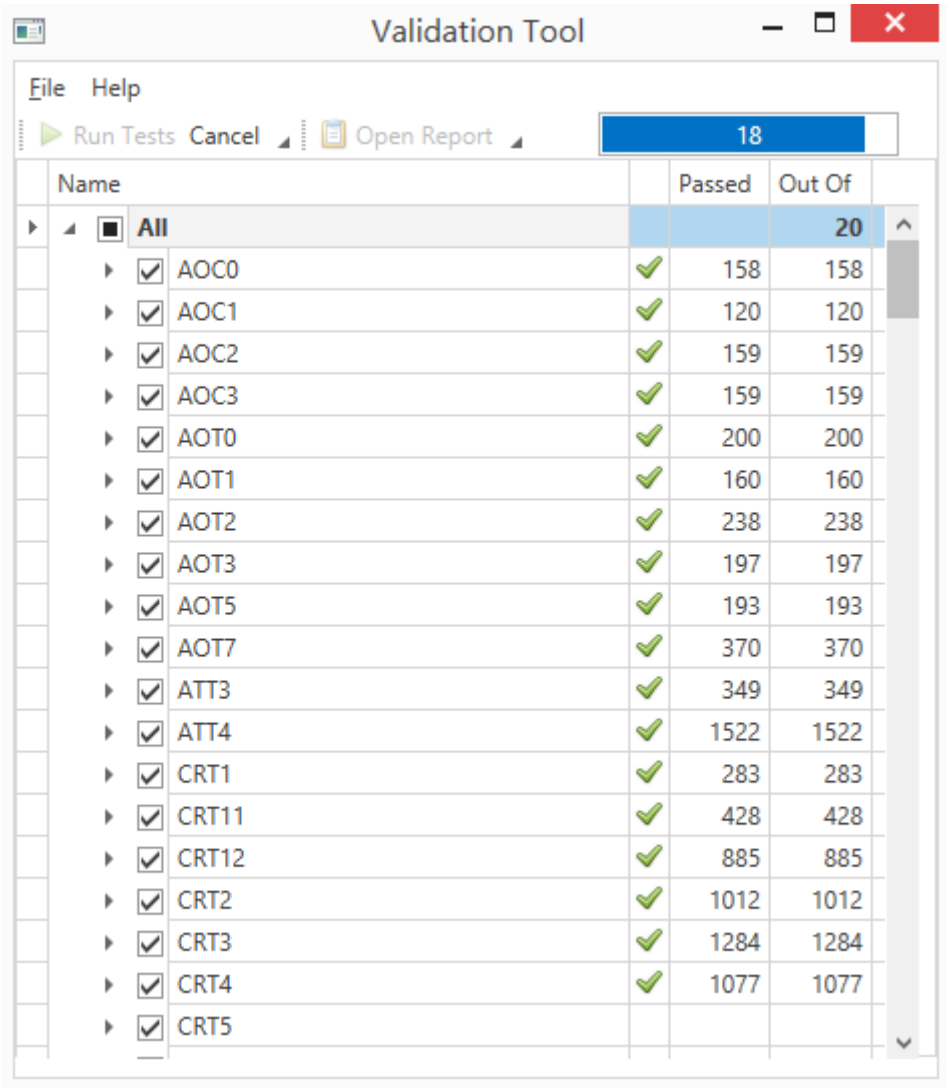


Figure 4.3: Operational Qualification Tool - In Progress

4.2.2 nQuery OQ Results

To view the full report of the OQ results, select the "Open Report" option in the menu bar. This will automatically output a HTML report which will display the results automatically in the machine's default HTML viewer. This will often be the users default internet browser.

To OQ report file will automatically be saved on the machine when a "Open Report" is used. It will be saved to the C:\Users\<User Account>\AppData\Local\nQuery\Reports folder where <User Account> is the named User which currently logged into on the machine. Alternatively, you can save a report to an alternative folder using the "Save as" option in the File menu of the OQ window.

If OQ report is opened in a supported application, the structure of the report will be as follows:

At the start, the report will contain the time and date the tests were run, the number of passed design table tests and the time taken for testing.

Within the report, there will be an individual report for each design table test run. These will show the table code, table name, an indication whether the table passed overall, the time taken to test that table and the number of passed tests for that table.

Within each design table report, there will be a report for each solver in that design table. This will show the solver name, an indication whether the table solver passed overall, the time taken to test that table and the number of passed table solver tests. When shown within a browser, it allows a user to see the individual design parameters used for each test applied to a solver. To open these, select the "Details" option to the right of the solver name. An example an OQ report with a Details menu open is shown in Figure 4.4.

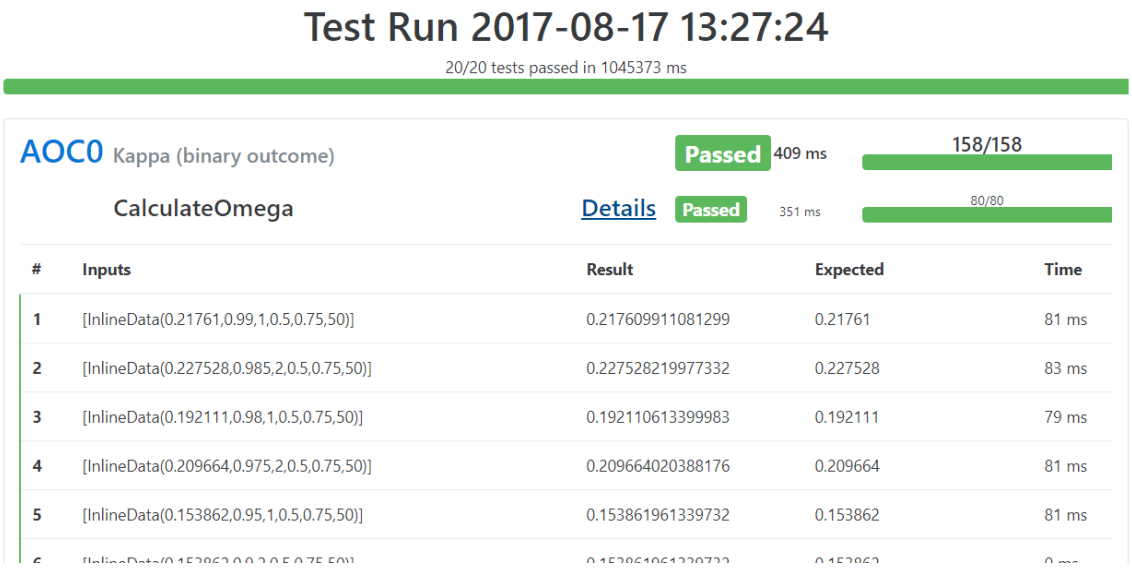


Figure 4.4: Operational Qualification Tool Report

5 nQuery Updates and Licensing

5.1 Renewing a License

Important: Internet Access is required to renew nQuery using the Activation key. If you need to renew offline, please use the "Web Registration" option in the bottom-right of the Product Activation dialog to obtain a License key on an internet enabled device or if still unable to renew your software, contact support@statsols.com or login to your online account

To renew an nQuery License, select the Activate/Renew License option from the Help menu. This will open the Product Activation dialog. Enter your provided nQuery Activation Key in the Activation Key field. This is shown in Figure 5.1.

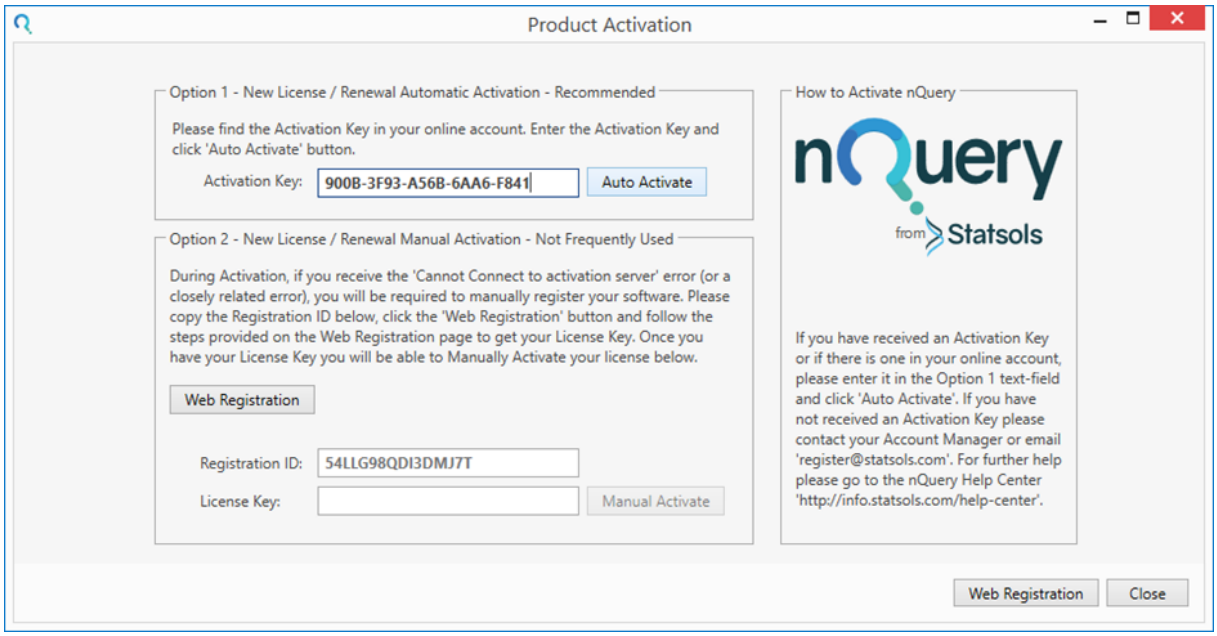


Figure 5.1: Renewal Example

If you have issues you can contact support@statsols.com or login to your online account and create a support ticket for fastest response.

5.2 Activating an Add-on Module

Important: Internet Access is required to add an Add-on module nQuery. If you need to add a module offline, please contact support@statsols.com or login to your online account

To purchase an add-on module, either use the link provided in the Getting Started screen or visit the Statsols website at www.statsols.com

To activate an add-on module, select the Enable Modules option in the Help file menu. The Enable Modules dialog box should open. This is shown in Figure 5.2.

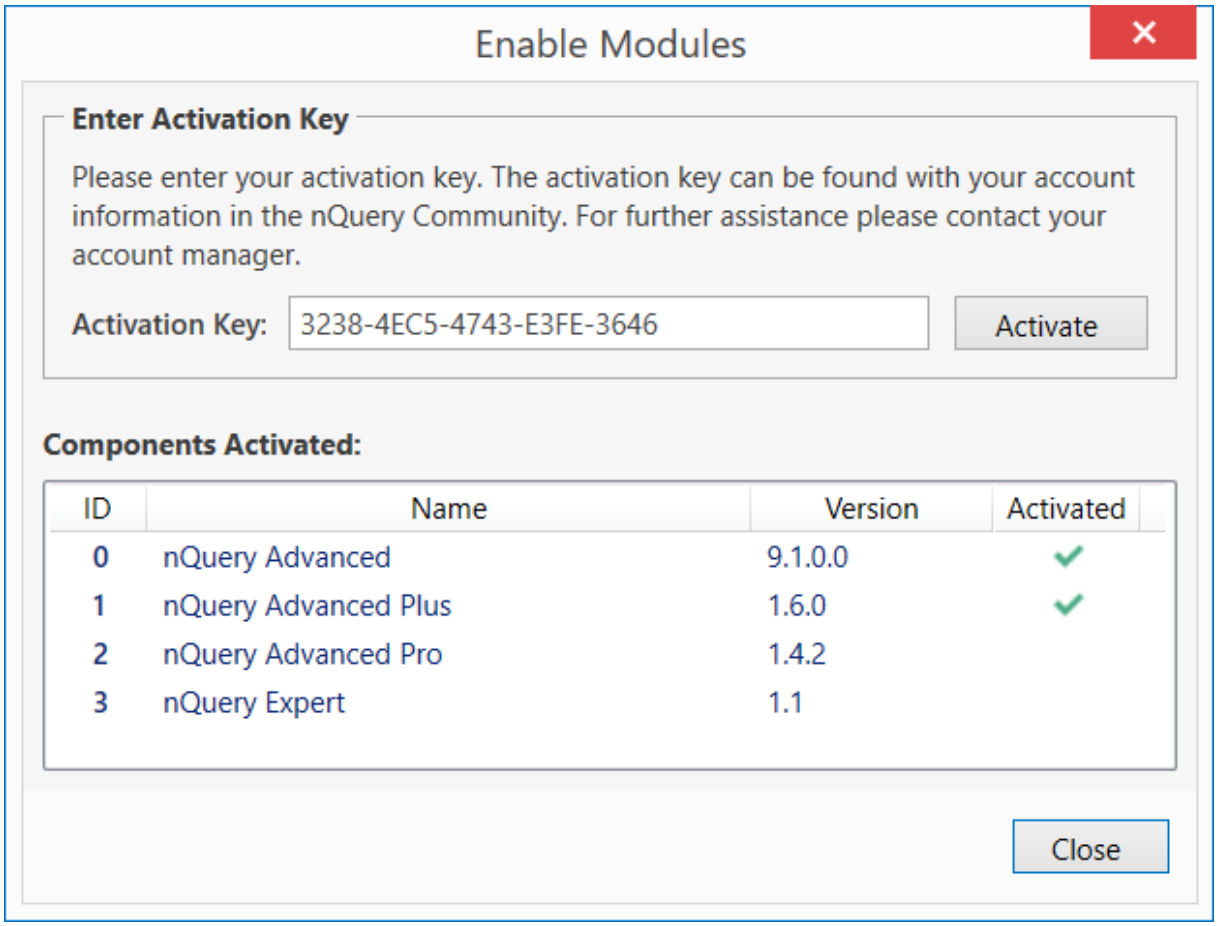


Figure 5.2: Module Activation Screen

If you have used a valid nQuery Activation Key in nQuery before, this key will appear in the Activation Key area. Otherwise, you will need to enter the key provided by Statsols.

To activate the module, click "Activate". The Components Activated area will refresh after a couple of seconds and the nQuery Module(s) should have a tick in the Activated column for the selected module(s) .

All tables in the module(s) will be enabled in nQuery Advanced

If you have issues you can contact support@statsols.com or login to your online account and create a support ticket for fastest response.

5.3 Checking for Software Updates

Important: Internet Access is required to update nQuery. If you want to manually update, please contact support@statsols.com or login to your online account

5.3.1 Checking for Updates

nQuery provides automated tools to allow the user to upgrade their nQuery application to the latest version. There are two methods to update your nQuery application: using the Help menu option or using the system tray option.

To select the Help menu option, open the Help file menu and select "Check for Updates". To use the system tray option, find the Update Statsols - nQuery system tray item, right-click and select "Open Updater".

If there are no updates, these will open the Update Statsols - nQuery dialog which will say that no upgrades are available.

If updates are available, a prompt will open asking the user if they wish to upgrade. An example of this prompt is shown in Figure 5.3.

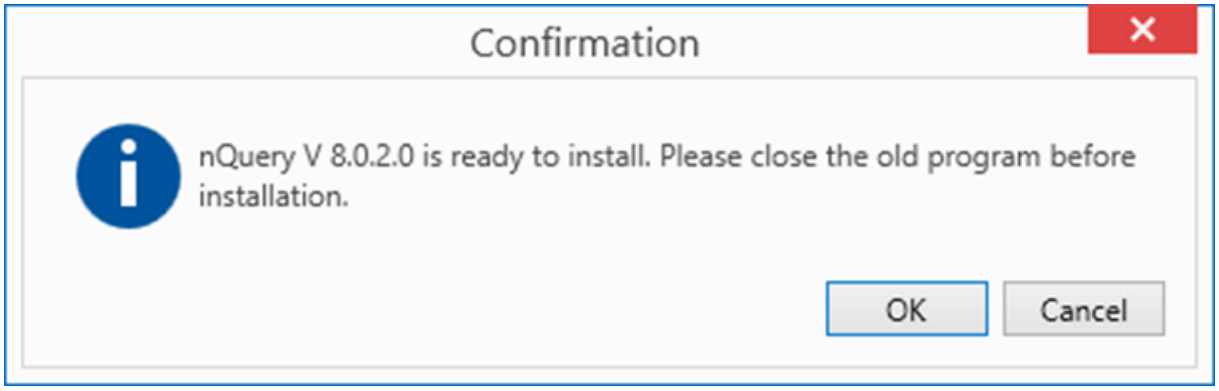


Figure 5.3: Update Prompt Example

Select OK to install the update or Cancel to close this dialog. If you select OK, the Update Statsols - nQuery dialog will appear and show the download progress. When downloading is completed, the Figure 5.3 dialog will appear again. Select OK and this will close any currently open versions of nQuery. An install screen will automatically appear and update your nQuery application. On completion, your nQuery application will be updated and can be used again.

6 nQuery Randomization Lists

Randomization lists is an nQuery tool which can be used to generate a sequence of random assignments of subjects to multiple treatment groups. Subjects can be randomized into up to 25 different treatment groups and can be stratified on up to 500 different centers and on up to 2 stratification factors, each with up to 25 different levels.

Randomization involves random assignment of subjects to receive either experimental treatment(s) or a control. Randomization forms a critical component of Randomized Controlled Trials (RCTs), which are considered the gold standard for evaluating the causal relationship between an intervention/treatment and a clinical outcome. Randomization is needed for several reasons. Firstly, because it provides a basis for the standard methods of statistical analysis by ensuring that the subjects assigned to the different treatment groups should not differ in any systematic way. Hence, the two different treatment groups should essentially become interchangeable, which will allow an estimate to be made of the reliability of the treatment effect. The second reason for randomization is that randomization forms one of the principal statistical elements that allows one to claim that a study is unbiased, particularly with regard to selection bias. Selection bias refers to bias that can be introduced by selecting particular patients to receive a particular treatment, which could influence the results. In a RCT, this can occur if the physician or subject can guess or predict the treatment being assigned by examining previous assignments. Using a randomization algorithm to generate a list of assignments will help to minimize any discernable pattern in assignments, making it unlikely if not impossible for assignments to be predicted.

6.1 Randomization Algorithms

Seven algorithms exist in nQuery for generating randomization lists. These vary in several respects and some algorithms may be more suitable than others for different scenarios. These algorithms are Block Randomization, Complete (Simple) Randomization, Efron's Biased Coin Randomization, Smith's Randomization, Wei's Urn Randomization, Random Sorting and Random Sorting using Maximum Allowable Deviation. Further inforrmation on all algorithms (except for Random Sorting and Random Sorting using Maximum Allowable Deviation) can be found in [Pocock, 1983] and [Rosenberger and Lachin, 2016].

In this section, we seek to give a high-level understanding of the various algorithms that can be used for generating randomization lists in nQuery, which should provide users with information allowing them to make a decision on which algorithm may be most suitable in their scenario. More information on the workings of each algorithm, including detailed descriptions of the parameters required for each can be found in the **Randomization Lists Setup** subsection (subsection 6.2.3).

Before examining the properties of each algorithm, we will first define some notation. Let N be the sample size which is to be randomized into the various treatment groups and

let G be the number of treatment groups. Let n_i be the target sample size for each of the treatment groups and let a_i be the actual sample size in each treatment group after randomization has concluded. Note that the actual sample sizes may differ slightly from the target sample sizes due to the way in which some algorithms operate and also due to the inputs specified by the user in particular scenarios. Thus,

$$N = \sum_{i=1}^{G} n_i = \sum_{i=1}^{G} a_i$$

Let R_i be the target allocation ratio for each treatment group. These can then be calculated as

$$R_i = \frac{n_i}{N}$$

Let p_{ij} denote the probability of subject j being assigned to treatment group i and let $n_i[j]$ be the sample size in treatment group i after the j^{th} subject has been assigned.

It is also important to note that when the list is stratified with centers and/or additional stratification factors, a stratified randomization will be performed. Stratified randomization involves subjects first being divided into various strata based on the user entered centers/stratification factors and a separate randomization sequence taking place within each strata in order to ensure an ideal balance between subjects from each strata in each treatment group. The algorithms described in the following section will be applied individually for each strata if stratification is used. As stratified randomization will prevent imbalance of known risk factors, it will aid in improving power of trials when stratified factors have a large effect on the outcome, particularly in cases with low sample size.

6.1.1 Block Randomization

Block or Permuted Block Randomization is one of the most commonly used forms of randomization. Block Randomization can be used for multiple treatment groups where the groups are allowed to have different allocation ratios. It involves subjects being assigned in randomized blocks rather than each subject being randomized and assigned individually. The algorithm works as follows. The minimum block size, B_{min} is calculated as

$$B_{min} = \sum_{i=1}^{G} R_i$$

Where the R_i values are the target allocation ratios. Because the minimum block size is the sum of the target allocation ratios, the desired allocation ratios will be preserved within each block. The user provides at least one block size multiplier value (here denoted as M_b), which are multiplied by the minimum block size value to get the actual block sizes (denoted B_b) that subjects will be assigned using.

$$B_b = B_{min} \times M_b$$

To properly elucidate to the reader the concept of assigning subjects in blocks, consider the following example. A researcher wishes to randomize 30 subjects into 3 different treatment groups: Treatment A, Treatment B and Treatment C. As the researcher wishes to achieve an equal sample size in each of the treatment groups, the target allocation ratios are set to 1:1:1 and as a result, B_{min}= 3. The researcher wishes to use block multiplier values of 1,2 and 3 to ensure that a diverse number of blocks sizes are used for assigning subjects. As a result, subjects will be assigned using block sizes of 3, 6 and 9. Take the example of a block size of 3 being used for one particular set of assignments. Subjects can be randomized in a block size of 3 as follows:

ABC,ACB,BAC,BCA,CAB,CBA

Note that no matter which block is chosen, the target allocations will always be preserved. This is true regardless of which block size is used.

The block size to be used at each step can be chosen from the possible block sizes in several different ways by the user. Subjects will be assigned in blocks in this way until the target sample size is met.

Block randomization will ensure that the proportion of total sample size in each treatment group at the end of the randomization equals the targetted values. It will also ensure that the desired balance in assignments to the different treatment groups is maintained throughout the course of assignments. Once at least two different block sizes are used, it will be very difficult for researchers or subjects to predict assignments which will help to minimize selection bias. For these reasons, block randomization is generally the recommended form of the randomization to use.

6.1.2 Complete (Simple) Randomization

Complete or Simple Randomization is the most basic form of randomization. The probability of assignment to treatment group i is calculated for each subject as

$$p_i = \frac{R_i}{\sum_{i=1}^{G} R_i}$$

Each subject is then randomly assigned to a treatment group using these probabilities. In the case of two treatment groups with equal allocation ratios, this algorithm will be equivalent to assigning subjects using a coin toss.

The algorithm does not ensure that the actual sample size in each of the treatment groups will meet the target sample size, and there may be imbalances in the numbers assigned to each group as the trial progresses. For these reasons, this algorithm is not recommended when maintaining the desired balance between the treatment groups is important.

This algorithm also has an option for a user to search for a list in which all actual sample sizes equal the target sample sizes. If the user selects this option, the algorithm will be repeated until a randomization list is found in which the actual group sample sizes equal the target sample sizes, or until a maximum number of iterations is exceeded.

6.1.3 Efron's Biased Coin Randomization

Efron's Biased Coin Randomization is a variation on complete randomization which can only be used for assigning subjects to two treatment groups with equal allocation ratios. This algorithm simulates a coin toss for assigning subjects to the two treatment groups with an added feature to improve the degree of balance achieved between the two treatment groups, both throughout the trial and at the end. If the two groups have the same sample size at any stage throughout the assignment process, the probability of assignment to either group is 0.5. However, if the sample sizes of the two groups are currently unequal, the probability of assignment to the group which has less subjects is set to a constant probability p (called "Efron's p"), where $0.5 < p \leq 1$. The probability of assignment of subject j to group 1 is given as

$$p_{1j} = \begin{cases} 0.5 & n_1[j] = n_2[j] \\ p & n_1[j] < n_2[j] \\ 1-p & n_1[j] > n_2[j] \end{cases}$$

The algorithm works by assigning subjects to the two treatment groups using the above probabilities, where $p_{2j} = 1 - p_{1j}$. This algorithm is outlined in [Efron, 1971].

The algorithm does not ensure that the actual sample size in each of the treatment groups will meet the target sample size, and there may be imbalances in the numbers assigned to each group as the trial progresses. However, there will tend to be a much higher degree of balance between the treatment groups when compared with the same scenario performed using complete randomization.

This algorithm also has an option for a user to search for a list in which all actual sample sizes equal the target sample sizes. If the user selects this option, the algorithm will be repeated until a randomization list is found in which the actual group sample sizes equal the target sample sizes, or until a maximum number of iterations is exceeded.

6.1.4 Smith's Randomization

Smith's Randomization is a variation on complete randomization which can only be used for assigning subjects to two treatment groups with equal allocation ratios. Similarly to Efron's Biased Coin, this algorithm simulates a coin toss for assigning subjects to the two treatment groups with an added feature to improve the degree of balance achieved between the number of subjects assigned to the two treatment groups, both throughtout the trial and at the end. The user enters a value for parameter ρ (known as "Smith's Exponent"), where $\rho > 0$ and the probability of assignment of subject j to group 1 is defined as

$$p_{1j} = \frac{n_2[j-1]^\rho}{n_1[j-1]^\rho + n_2[j-1]^\rho}$$

The algorithm works by assigning subjects to the two treatment groups using the above probabilities, where $p_{2j} = 1 - p_{1j}$.

The algorithm does not ensure that the actual sample size in each of the treatment groups will meet the target sample size, and there may be imbalances in the numbers assigned to

each group as the trial progresses. However, there will tend to be a much higher degree of balance between the treatment groups when compared with the same scenario performed using complete randomization.

This algorithm also has an option for a user to search for a list in which all actual sample sizes equal the target sample sizes. If the user selects this option, the algorithm will be repeated until a randomization list is found in which the actual group sample sizes equal the target sample sizes, or until a maximum number of iterations is exceeded.

6.1.5 Wei's Urn Randomization

Wei's Urn Randomization is an adaptive randomization algorithm which can be used for multiple groups with equal allocation ratios. The algorithm involves simulating a scenario where each group begins with several balls in an urn, with the initial number of balls belonging to each group known as Wei's A, where $A \geq 0$. The algorithm begins by drawing a ball at random and the subject is assigned to the group which corresponds to that ball and the ball is placed back in the urn. Following this, a number of balls are added for all groups besides the group which was just drawn, with the number of new balls being added for the other groups being known as Wei's B, where $B \geq 1$. A ball is drawn again and the subjects are assigned in this way until the target sample size is met. The algorithm is outlined in [Wei, 1978].

The algorithm does not ensure that the actual sample size in each of the treatment groups will meet the target sample size, and there may be imbalances in the numbers assigned to each group as the trial progresses. However, there will tend to be a much higher degree of balance between the treatment groups when compared with the same scenario performed using complete randomization.

This algorithm also has an option for a user to search for a list in which all actual sample sizes equal the target sample sizes. If the user selects this option, the algorithm will be repeated until a randomization list is found in which the actual group sample sizes equal the target sample sizes, or until a maximum number of iterations is exceeded.

6.1.6 Random Sorting

The Random Sorting algorithm can be used for any number of treatment groups and unequal allocation ratios between treatment groups are allowed. This algorithm involves assigning each subject a random real number between 0 and 1. The subjects are then ordered ascendingly according to these random numbers and are assigned in this order. For example, consider a sample size of 30 being assigned to 3 treatment groups with equal allocation ratios. Each subject is assigned a number and then ordered according to these numbers. The first 10 in the ordered list will be assigned to the first group, the second 10 to the second group and the final 10 to the third group.

For non-complex cases this algorithm will generally maintain balance in treatment assignments at the end. However, it is not guaranteed that balance will be maintained between the numbers assigned to the different groups throughout the course of the trial. For complex cases involving stratified randomization or diverse group sample size targets, this algorithm may fail to work as intended, as the cohort to be randomized at each stage

may not be divisible by the allocation ratios. For these reasons, the algorithm is generally not recommended.

6.1.7 Random Sorting using Maximum Allowable Deviation

Random sorting using Maximum Allowable Deviation is a variation on the Random Sorting algorithm described previously. Subjects are allocated randomly using the same method as Random Sorting, but the deviation from the target sample size in each group is calculated after each subject is assigned as

$$\begin{aligned} \%Deviation_{ij} &= \left| \frac{n_i[j] - E(n_i[j])}{n_i} \right| \times 100 \\ &= \left| \frac{n_i[j] - j(p_i)}{n_i} \right| \times 100 \end{aligned}$$

where i is the treatment group, j is the number of subjects currently assigned and $p_i = \frac{R_i}{\sum R_i}$.

If any of the deviation values are greater than the user entered maximum deviation value, the generated list is deleted and the randomization restarts. This process will continue until an ideal list is found in which all deviations are less than the maximum deviation value, or until a user entered maximum number of iterations is exceeded.

For example, consider a scenario in which 60 subjects are being assigned to two treatments groups with equal allocation ratios, with a maximum allowable deviation value of 5%. Suppose that after 15 assignments, that 6 subjects are assigned to the first treatment group and 9 subjects assigned to the second treatment group. At this stage, the percentage deviation in the first group is $\left|(\frac{6-15(0.5)}{30})\right| \times 100 = 5\%$ and the percentage deviation in the second group is $\left|(\frac{8-15(0.5)}{30})\right| \times 100 = 1.6667\%$. As both deviation values do not exceed the the maximum allowable deviation value, the algorithm will continue assigning subjects. Assume that the next subject is assigned to the second treatment group. Then percentage deviation values for the two groups will be $\left|(\frac{6-16(0.5)}{30})\right| \times 100 = 6.6667\%$ and $\left|(\frac{8-16(0.5)}{30})\right| \times 100 = 3.3333\%$. Since the deviation value in the first group now exceeds the maximum allowable deviation, the current list will be deleted and the process will begin again. This will continue until an ideal list is found, or until a maximum number of iterations value is exceeded.

For non-complex cases this algorithm will generally maintain balance in treatment assignments at the end and depending on the value inputted for the maximum allowable deviation, will generally maintain a greater deal of balance as the trial progresses when compared with the random sorting algorithm. For complex cases involving stratified randomization or diverse group sample size targets, this algorithm may fail to work as intended, as the cohort to be randomized at each stage may not be divisible by the allocation ratios. For these reasons, the algorithm is generally not recommended.

6.2 nQuery Randomization Lists Demonstration

This section will demonstrate how to generate valid randomization lists using the nQuery Randomization Lists tool. This demonstration will be split into the following subsections

1. Creating an nQuery Randomization Lists Workspace (subsection 6.2.1)
2. nQuery Randomization Lists Workspace Layout (subsection 6.2.2)
3. Randomization Lists Setup (subsection 6.2.3)
4. Results Output Summary (Randomization List/Output) (subsection 6.2.4)
5. Block Randomization Demonstration (subsection 6.2.5)
6. Block Randomization with Stratification Demonstration (subsection 6.2.6)
7. Complete Randomization Demonstration (subsection 6.2.7)
8. Other Features (subsection 6.2.8)

Creating an nQuery Randomization Lists Workspace (subsection 6.2.1) gives an overview of how to create a new nQuery Randomization Lists Workspace.

nQuery Randomization Lists Workspace Layout (subsection 6.2.2) gives an overview on the layout of an nQuery Randomization Lists Workspace and how this workspace can be navigated through.

Randomization Lists Setup (subsection 6.2.3) gives an overview of the various stages of the **Setup** required for generating a valid randomization list, as well as a detailed description of the parameters required for each possible scenario.

Results Output Summary (subsection 6.2.4) gives a high-level overview of the outputs from randomization lists tool, including the **Randomization List** and **Randomization List Summary** available.

Block Randomization Demonstration (subsection 6.2.5) gives an overview of how to generate a valid randomization list for the most common and recommended randomization algorithm, Block Randomization.

Block Randomization with Stratification Demonstration (subsection 6.2.6) gives an overview of how to generate a valid randomization list for Block Randomization when stratification also occurs upon enrollment center and 2 additional stratification factors.

Complete Randomization Demonstration (subsection 6.2.7) gives an overview of how to generate a valid randomization list for the Complete Randomization algorithm.

Other Features (subsection 6.2.8) gives an overview of other features of nQuery Randomization Lists, including information on how to save, export and load Workspaces.

The first 2 subsections and last subsection are common across all randomization algorithms. There will be differences in the remaining subheadings, due to the alternate algorithms and differing options available throughout the **Setup**.

6.2.1 Creating an nQuery Randomization Lists Workspace

The nQuery Randomization Lists Workspace is a tab in which the user will setup, run and view the results of their randomization list generation. To create a new nQuery

Randomization Lists Workspace, the user can select the **Create Randomization List** button in the top-left Home quadrant (1) or select the **Create Randomization Lists** option in the dropdown list from the **Assistants** menu at the top of the software window (2). This can be seen in Figure 6.1.

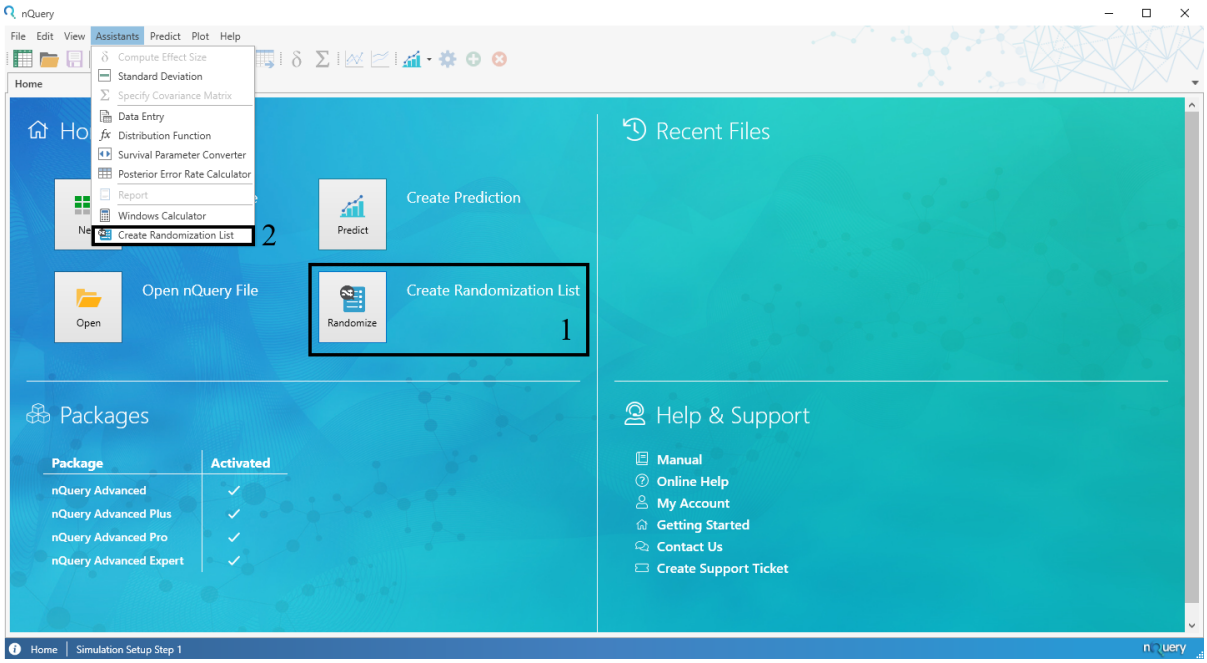


Figure 6.1: nQuery Randomization Lists Workspace Creation Options

6.2.2 nQuery Randomization Lists Workspace Layout

6.2.2.1 nQuery Randomization Lists Workspace Layout Overview

An nQuery Randomization Lists Workspace will consist of three primary user interface elements: the workspace navigation bar (1), the Main Display Window (2), and the Help Window (3). These are numbered in Figure 6.2.

The Workspace Navigation Bar (1) is used to navigate to a specific element (**Setup**, **Report**) of the current nQuery Randomization Workspace at any time. Elements are organized under headers with an example header (**Setup)** highlighted as per 1A in Figure 6.2. A specific element can be selected from under a given header. Header elements can be opened and collapsed by selecting the header name. In Figure 6.2, the **Select randomization algorithm** element can be selected from the **Setup** header. More options will become available under the **Setup** header once the user progresses through the relevant steps. Once the user procedes through all steps, a **Report** header will become available. The **Report** header will contain two elements; **Randomization List** and **Randomization List Summary**.

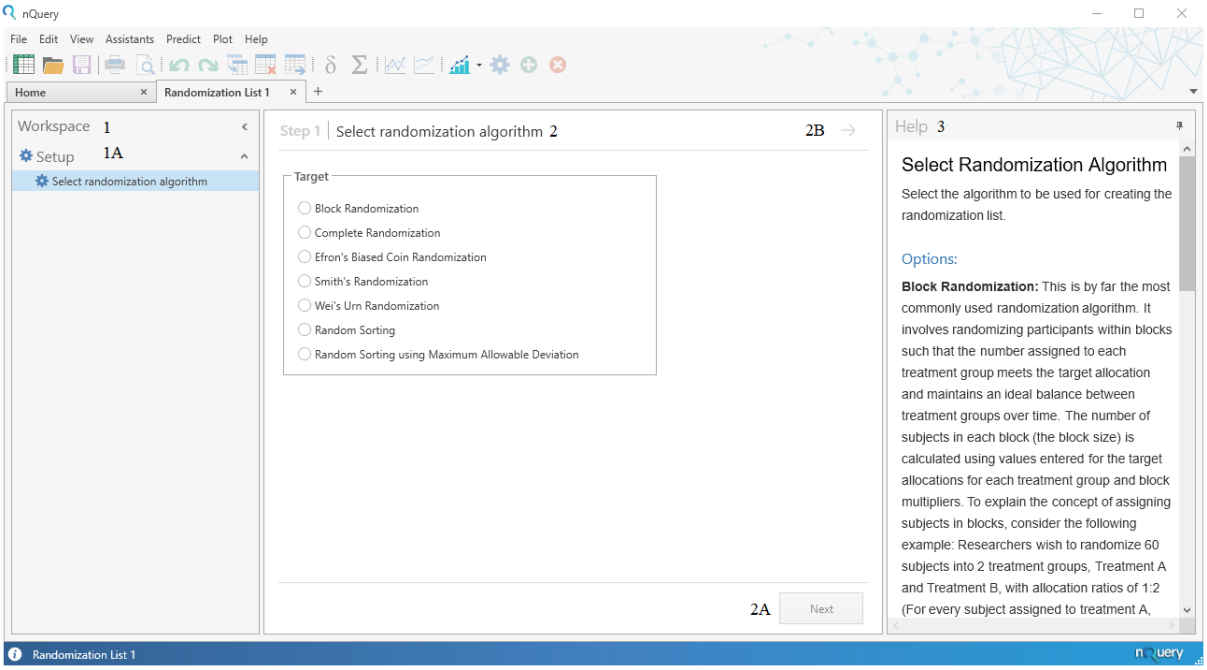


Figure 6.2: New nQuery Randomization Lists Workspace

The Main Display Window (2) displays the current element selected and is where the user can input values and view results. During the **Setup** stage, the user can select the Next button (2A) or Right-Arrow buttons (2B) to move to the next step (note subsequent **Setup** steps will have a corresponding adjacent Back and Left-Arrow buttons to go back to the prior step) and users can select and enter values in the main fields (e.g. for the current **Select randomization algorithm** step, the randomization algorithm can be selected using radio buttons). Details on what is displayed in the Main Display Window for a given element will be shown in the sections below.

The Help Window (3) provides context and guidance on all of the elements currently displayed in the Main Display Window. The Help will include definitions, context, suggested values and tips.

6.2.2.2 Editing the nQuery Randomization Lists Workspace Layout

There are three primary ways to change the default layout of an nQuery Randomization Lists Workspace: collapsing the Workspace Navigation Bar, unpinning the Help Window and changing the width of the Main Display Window.

To collapse the Workspace Navigation Bar, select the ‹ button to the right of the main "Workspace" header at the top-right of the Workspace Navigation Bar. When the Workspace Navigation Bar is collapsed, elements can be shown and selected by clicking the named bar (name will be the same as the current element shown in the Main Display Window) on the left-hand side of the nQuery Randomization Lists Workspace. To expand the Workspace Navigation Bar, select the › button at the top of the named bar on the left-hand side.

To unpin the Help window, select the 📌 button on the right of Help Window header in the top-right. When the Help Window is unpinned, the Help Window will not be

displayed unless the cursor is placed over the Help section in the top-right of the nQuery Randomization Lists Workspace after which the Help Window will be displayed until a different element is selected in the nQuery Randomization Lists Workspace. To repin the Help Window, select the button when the Help Window is open.

To change the width of the Main Display Window, move the cursor over the lefthand edge (if the Workspace Navigation Bar is not collapsed) or right-hand edge (if the Help Window is displayed) of the Main Display Window until the cursor changes to a two-way arrow (↔) and click and drag the cursor to change the Main Display Window width.

An example workspace where the Workspace Navigation Bar is collapsed and Help Window is unpinned and unselected is shown in Figure 6.3, with the user interface items referenced above highlighted in yellow.

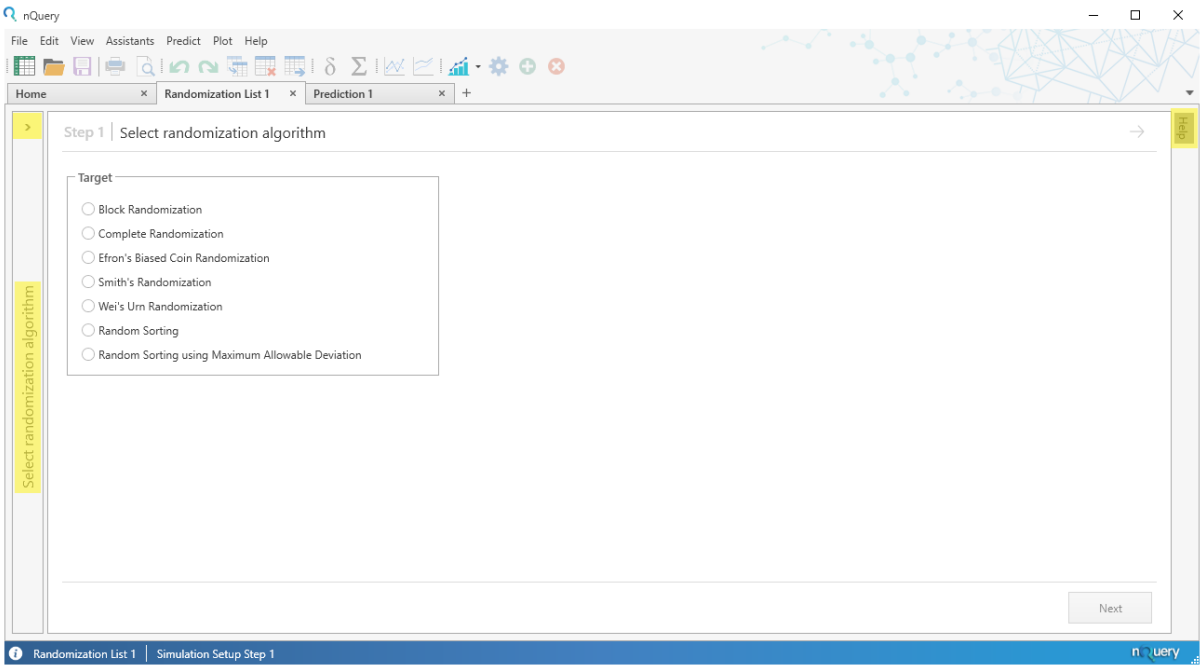


Figure 6.3: Collapsed nQuery Randomization Lists Workspace

6.2.3 Randomization Lists Setup

The section will describe how the user can move through the various stages in the **Setup** in order to generate a valid randomization list. This will include detailed discussions of the parameters required in each step. The **Setup** process is divided into five steps. These are:

1. Select randomization algorithm
2. Specify Parameters for [Chosen algorithm]
3. Specify target sample size
4. Specify Centers/Stratification Factors
5. Randomization list options

The **Select randomization algorithm** subsection will provide information on how a randomization algorithm can be selected.

The **Specify Parameters for [Chosen Algorithm]** subsections will provide information on how to correctly specify the parameters needed for each particular algorithm. As each algorithm requires different parameters, this step will be different depending on which algorithm the user chooses in **Step 1**. The discussion of **Step 2** for the various algorithms will be discussed in different subsections. Within each subsection, a detailed description of the parameters for each algorithm will be given.

The **Specify target sample size** subsection will provide information on how to specify a value for the target sample size and correctly provide information on the treatment groups that subjects will be randomized into.

The **Specify Centers/Stratification Factors** subsection will provide information on how the user can stratify subjects based on center of enrollment and/or on up to two different stratification factors. Note however, that this is an optional step which can be skipped if the user does not wish to conduct a stratified randomization.

The **Randomization list options** subsection will provide information on extra options that are available when generating the randomization list.

6.2.3.1 Step 1 - Select randomization algorithm

The **Select randomization algorithm** is the first step of the **Setup** stage for the randomization list generation in nQuery. The **Select randomization algorithm** step selects the specific algorithm which will be used for generating the randomization list. The **Select randomization algorithm** step in the nQuery Randomization Lists workspace is shown in Figure 6.4.

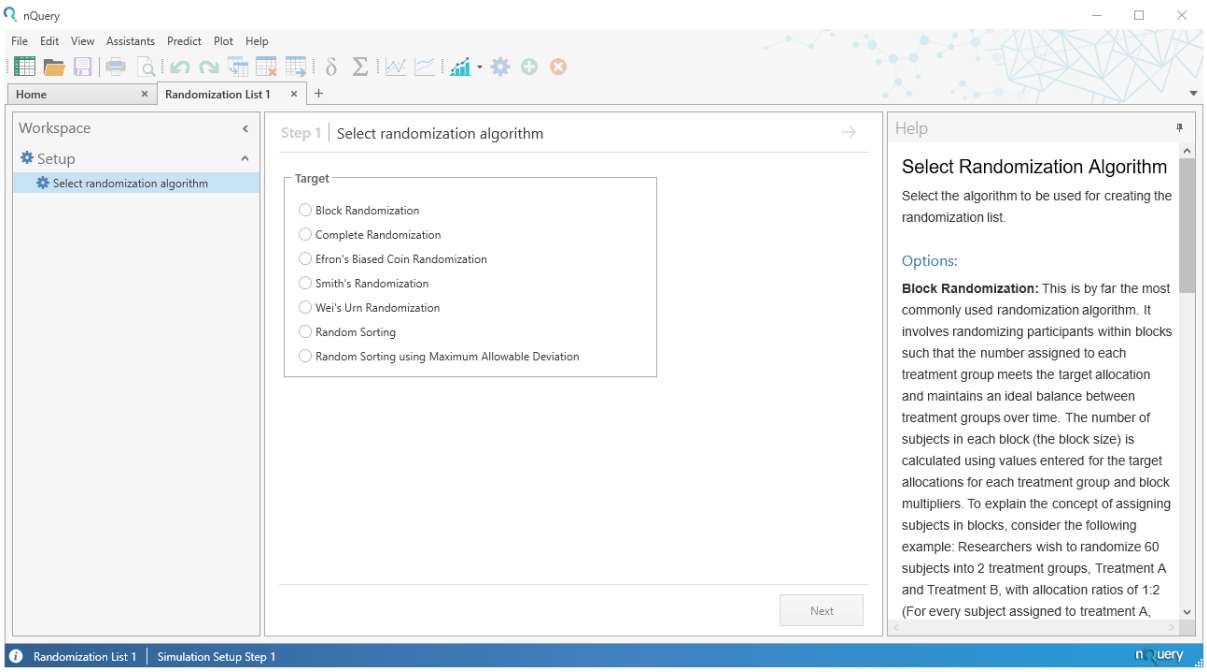


Figure 6.4: Overview of the Select randomization algorithm Step

The appropriate randomization list algorithm can be chosen by clicking the radio button to the left of the desired option. Information on available algorithms can be found in section 6.1 or else in the Help Card section on the right-hand side of the nQuery Randomization Lists Workspace.

Once a randomization algorithm is chosen, the **Next** button in the bottom-right of the Main window will be enabled. Clicking on this will move the user onto the next **Step 2** in the Setup.

6.2.3.2 Step 2 - Select Parameters for Block Randomization

An overview of the options for the **Selecting Parameters for Block Randomization** step can be seen in Figure 6.5. This step will involve chosing a number of block multiplier values to use. Then in the block multiplier table, the user can then enter the values for each of the block multipliers. The user must also choose whether to use Random, Equal or Custom Block Subject Allocation. If the user chooses Custom, a table will appear in which the user should enter allocation ratios which determine the proportion of subjects that the algorithm aims to assign using each block size. The user should also enter whether they wish to constrain the block allocation in order to minimize sample size and whether they wish specify information about block size and block ID in the output.

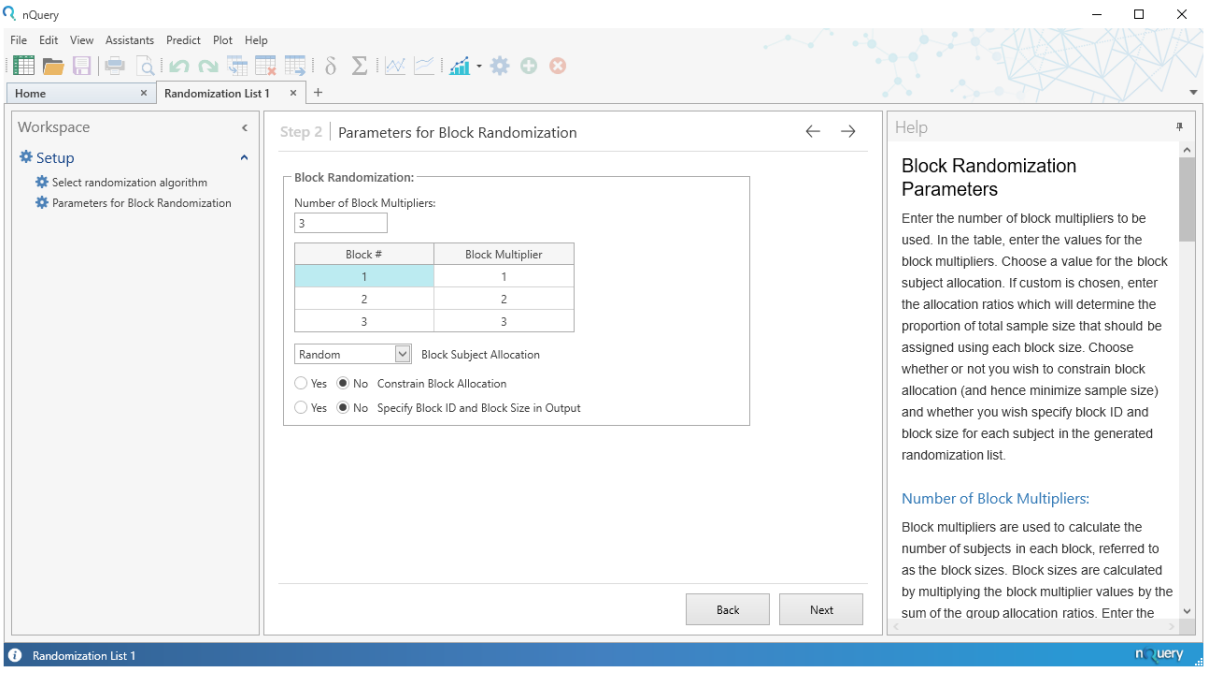


Figure 6.5: Overview of the Parameters for Block Randomization Step

Block Randomization Parameters

- **Number of Block Multipliers:** Enter an integer between 1 and 10 for the number of block multipliers. It is recommended that at least 2 block multiplier values are used to decrease the likelihood that future assignments can be determined from previous assignments. Once a value is entered for the number of block multipliers, the **Block Multiplier Table** will update to have the same number of rows as

the value entered for the number of block multipliers. The default value of 3 is recommended if the user does not have any strong preference on the number of block multipliers to be used.

- **Block Multiplier Table:** In this table the user will enter the block multiplier values used for the calculation of the block sizes. Each row corresponds to one block multiplier. Block multiplier values can be entered in the second column and must take the value of integers. These values will be multiplied by the sum of the target allocation ratios (target allocation ratios are described in the **Specify target sample size** step) in order to determine the actual block size values that will be used for the randomization. If the user decides to use 3 block multiplier values, values of 1,2 and 3 would be good choice for the block multipliers.
- **Block Subject Allocation:** This value determines the approximate proportion of the total sample size that should be assigned using each block size. Three options are available: "Random", "Equal" or "Custom". If Random is chosen, the size of the block at each step will be chosen at random from the possible block sizes. If Equal is chosen, the algorithm will attempt to assign subjects in such a way that approximately equal proportions are assigned using each of the possible block sizes. If Custom is chosen, the **Custom Block Subject Allocation Table** will become visible to the user below this field. An example of this table being present within the step window is provided in Figure 6.6.

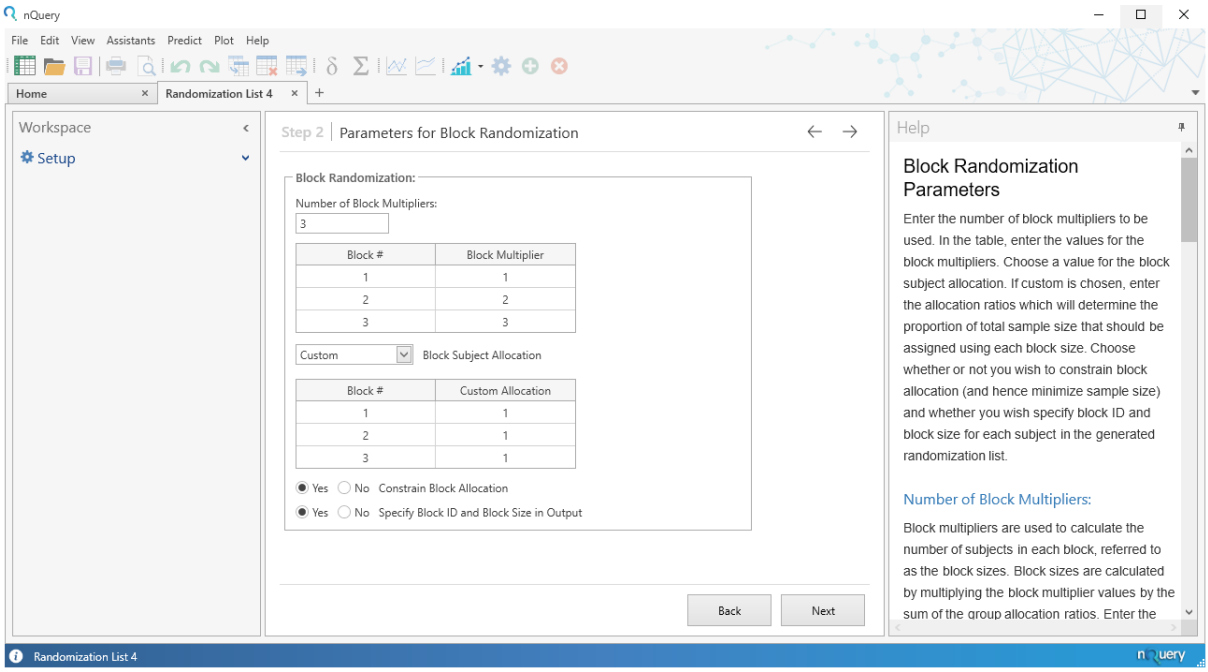


Figure 6.6: Parameters for Block Randomization Step with Custom Block Subject Allocation Table

- **Custom Block Subject Allocation Table:** This table will be visible if the user has set the **Block Subject Allocation** field to "Custom". This table will have the same number of rows as the value entered for the number of block multipliers, with each row corresponding to one block size. Enter the custom block subject allocations for each block size in the **Custom Allocation** column. For example, consider a scenario where a researcher wishes to use three block multiplier values (and hence

three block sizes). They desire that approximately 2 subjects are assigned using the first block size for every 1 subject that is assigned with the second block size and 1 subject assigned with the third block size. In this scenario, in the **Custom Allocation** column, they would enter 2,1 and 1 in each of the rows.

- **Constrain Block Allocation:** In certain scenarios for Block Randomization, the actual sample size will be larger than the target sample size. As subjects are assigned in blocks, it is possible for the target sample size to be exceeded. Consider an example where a sample size of 100 is being randomized into three different treatment groups with equal allocation ratios. Hence the minimum block size is 3. Assume further that 2 block multiplier values of 1 and 2 are being used, which yield actual block sizes of 3 and 6. Subjects will be assigned using these block sizes until the target sample size is met. Assume that after many random assignments, 99 subjects have been assigned. For the final assignment, a block size of 3 or 6 can be used, which will bring the actual sample size over the target sample size of 100 to 102 or 105 respectively. If **Constrain Block Allocation** is set to "Yes", the algorithm will override the value specified for **Block Subject Allocation** and choose the block size which will minimize the actual sample size for the final assignment, i.e., in the aforementioned example, the block sizse of 3 will be chosen for the final assignment, regardless of the option chosen for **Block Subject Allocation**
- **Specify Block ID and Block Size in Output:** If "Yes" is selected for this option, information on the block that each subject was assigned with and that block's block size will be provided in the generated randomization list.

6.2.3.3 Step 2 - Select Parameters for Complete Randomization

Step 2 in the case where Complete Randomization is used as the randomization algorithm will involve specifying **Parameters for Complete Randomization.** The **Step 2** Setup window can be seen below in Figure 6.7.

For Complete Randomization, this step will involve choosing whether the subject wishes to search for a list in which actual group sample sizes equal the target sample sizes. The default window for Complete Randomization can be seen in Figure 6.7.

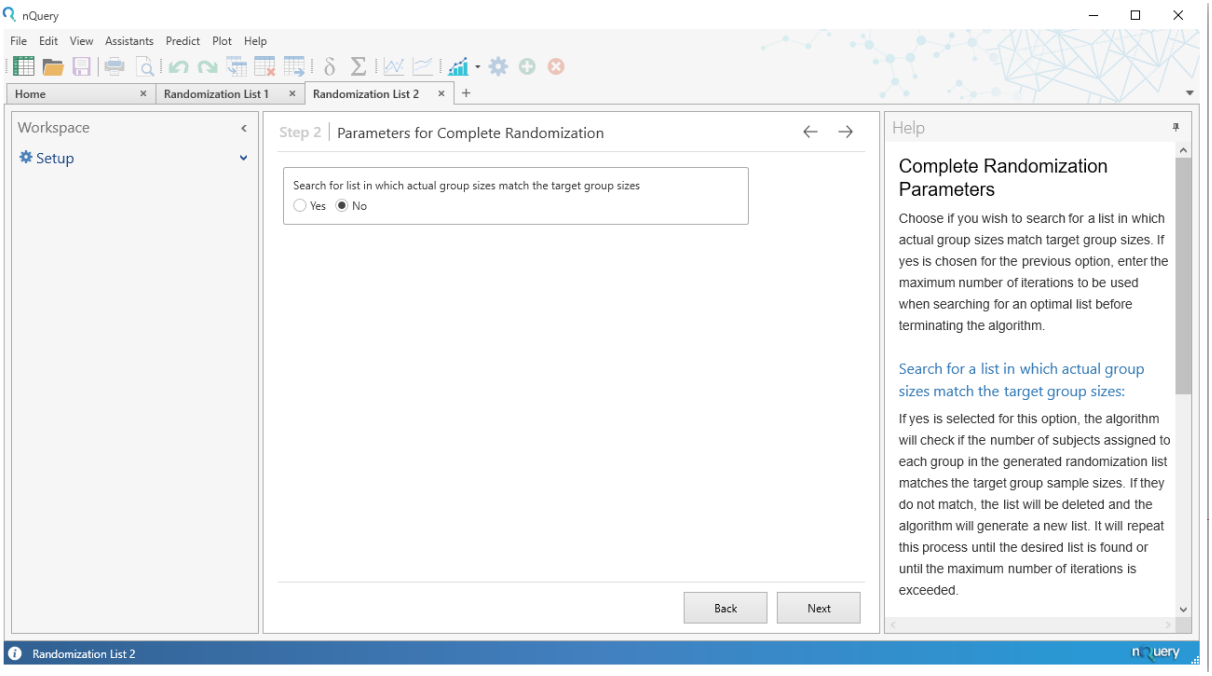


Figure 6.7: Overview of the Parameters for Complete Randomization Step

Complete Randomization Parameters

- **Search for list in which actual group sizes match the target group sizes:** Unlike Block Randomization, the proportion of total sample size in each treatment group for Complete Randomization may not equal the targetted values. This option gives the ability for the user to search for a list in which the proportion of the total sample size in each group equals the values calculated using the target allocation ratios which are specified in **Step 3.** If the user wishes to search for a list in which the actual group sizes match the target group sizes, they should set the radio button to "Yes". If "Yes" is selected for this option, a new Maximum number of iterations when search for list in which actual group sizes match the target group sizes field will become visible. This field is shown in Figure 6.8.

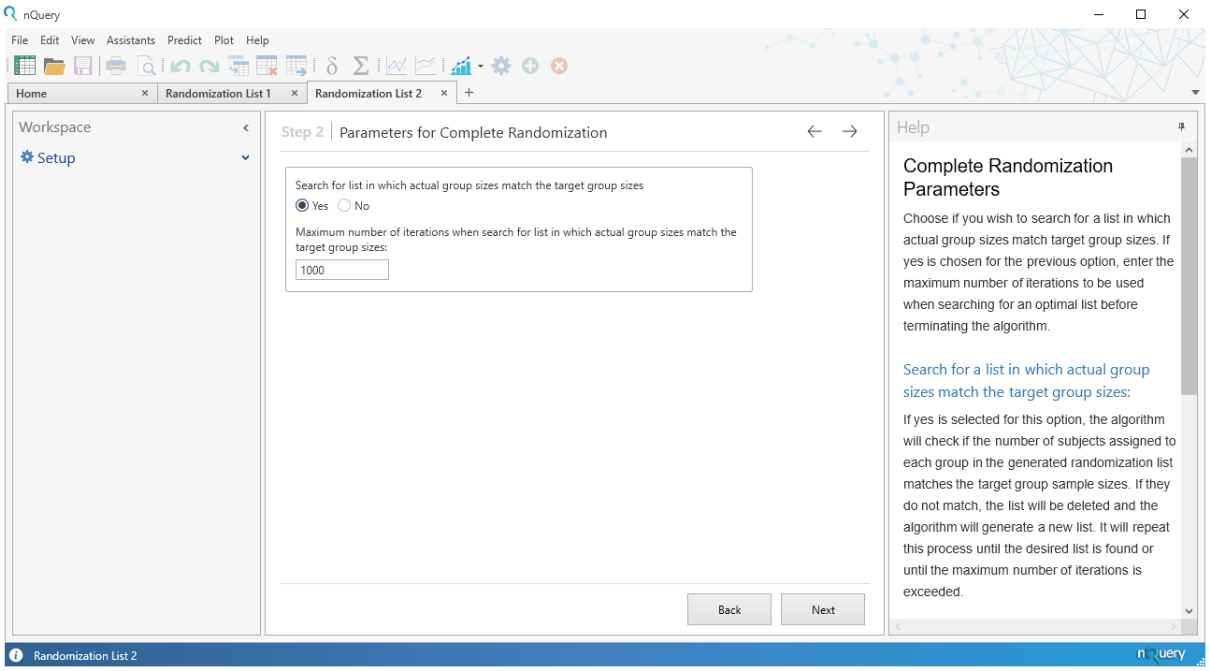


Figure 6.8: Parameters for Complete Randomization Step when searching for a list in which actual group sizes match target group sizes

- **Maximum Number of iterations when searching for list in which actual group sizes match the target group sizes:** This parameter controls the maximum number of iterations that are to be used when searching for a list in which actual group sizes match the target group sizes. In some scenarios, it may be impossible or take an unreasonably large amount of time in order to find an ideal list. In these cases, the algorithm will terminate after a certain number of attempts, which is specified by this parameter. Enter an integer greater than 0 for this value. A default value of 1000 is used. This value will generally find an ideal list if possible, while not wastefully searching for an ideal list that is unlikely or impossible to generate.

6.2.3.4 Step 2 - Select Parameters for Efron's Biased Coin Randomization

Step 2 in the case where Efron's Biased Coin Randomization is used as the randomization algorithm will involve specifying **Parameters for Efron's Biased Coin Randomization. Step 2** will involve choosing a value for the Efron's p parameter and choosing whether the user wishes to search for a list in which actual group sample sizes equal the target sample sizes. If the user does wish to search for a list in which actual group sample sizes equal the target group sample sizes, an additional maximum number of iterations parameter will be required. The default window for Efron's Biased Coin Randomization can be seen in Figure 6.9.

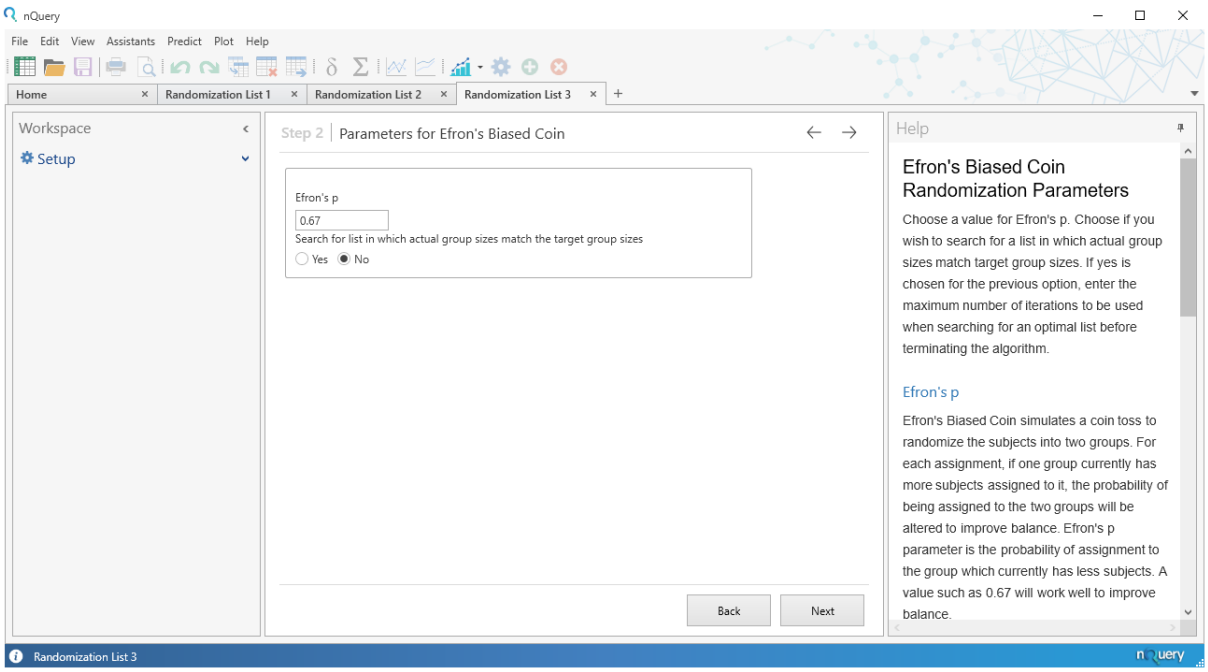


Figure 6.9: Overview of the Parameters for Efron's Biased Coin Randomization Step

Efron's Biased Coin Randomization Parameters

- **Efron's p:** Efron's Biased Coin simulates a coin toss to randomize subjects into the two groups. For each assignment, if one group currently has less subjects assigned to it, this group has an increased probability of being selected for the next assignment. This increased probability is Efron's P. Efron's P can take real values of $0.5 < p \leq 1$. The default value of 0.67 was recommended by Efron (1971) for improving balance without making assignments too predictable.
- **Search for list in which actual group sizes match the target group sizes:** Unlike Block Randomization, the proportion of total sample size in each treatment group for Efron's Biased Coin Randomization may not equal the targetted values. This option gives the ability for the user to search for a list in which the proportion of the total sample size in each group equals the values calculated using the target allocation ratios which are specified in **Step 3.** If the user wishes to search for a list in which the actual group sizes match the target group sizes, they should set the radio button to Yes. If Yes is selected for this option, a new field will open for the maximum number of iterations to be used in the search. This field is shown in Figure 6.10.

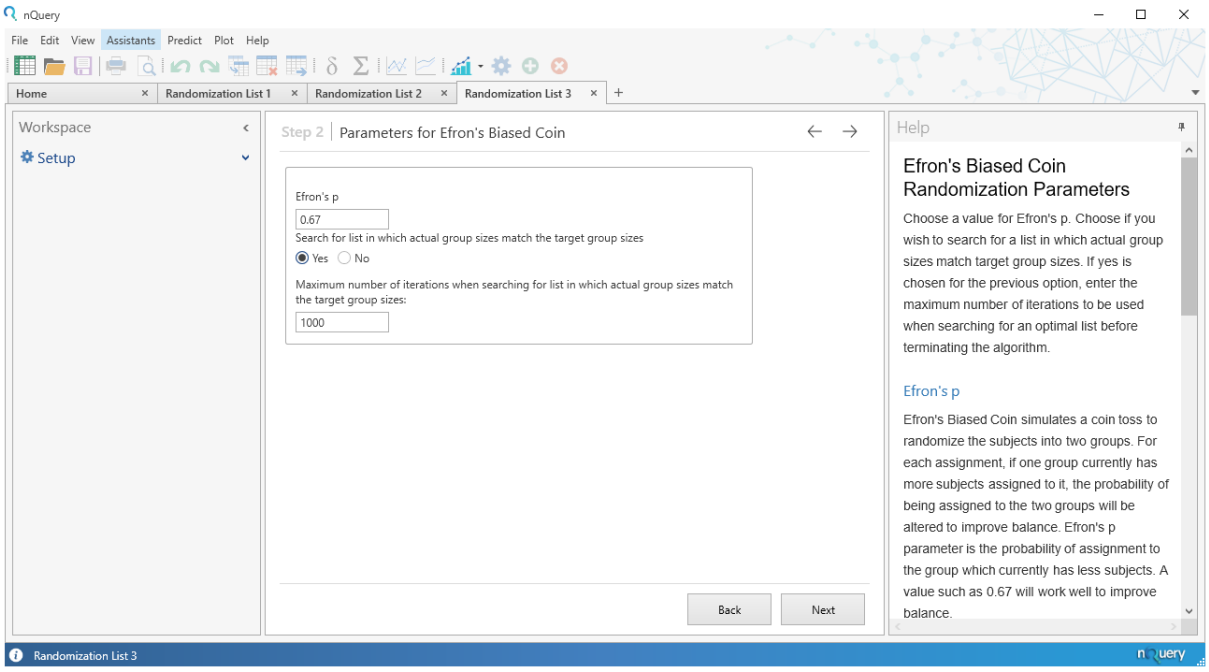


Figure 6.10: Parameters for Efron's Biased Coin Randomization Step when searching for a list in which actual group sizes match target group sizes

- **Maximum Number of iterations when searching for list in which actual group sizes match the target group sizes:** This parameter controls the maximum number of iterations that are to be used when searching for a list in which actual group sizes match the target group sizes. In some scenarios, it may be impossible or take an unreasonably large amount of time in order to find an list. In these cases, the algorithm will terminate after a certain number of attempts, which is specified by this parameter. Enter an integer greater than 0 for this value. A default value of 1000 is used. This value will generally find an ideal list if possible, while not wastefully searching for an ideal list that is unlikely or impossible to generate.

6.2.3.5 Step 2 - Select Parameters for Smith's Randomization

For **Smith's Randomization, Step 2** will involve choosing a value for the Smith's Exponent parameter and choosing whether the user wishes to search for a list in which actual group sample sizes equal the target sample sizes. If the user does wish to search for a list in which actual group sample sizes equal the target group sample sizes, an additional maximum number of iterations parameter will be required. The default **Step 2** window for Smith's Randomization is provided in Figure 6.11.

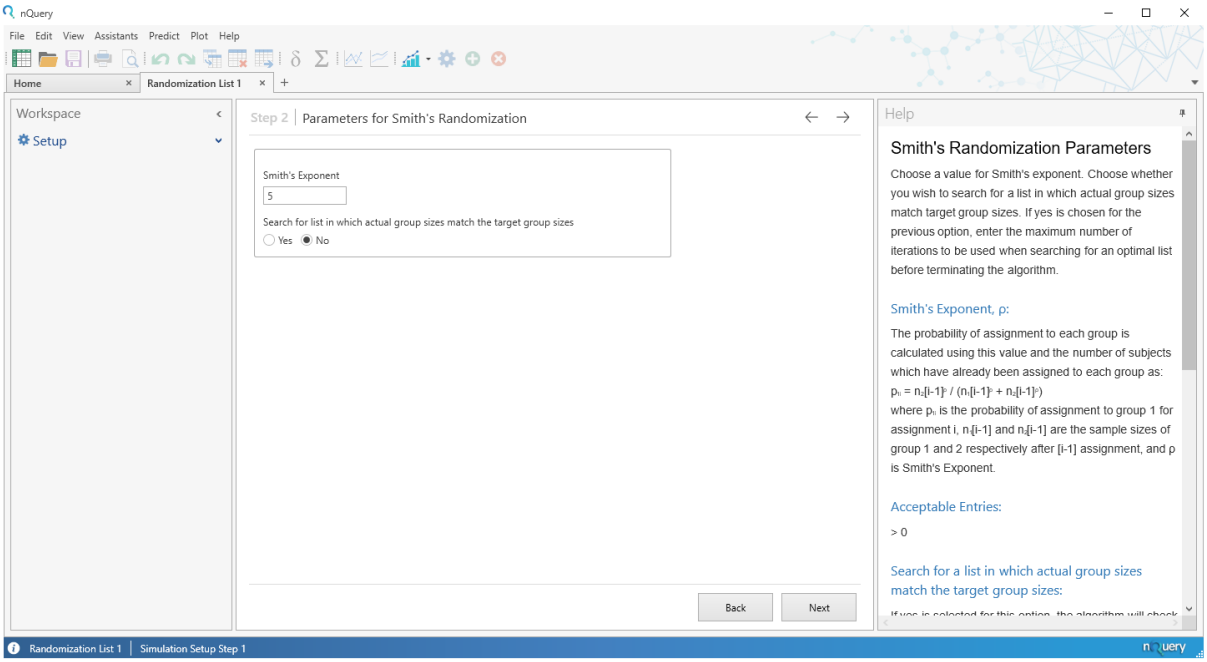


Figure 6.11: Overview of the Parameters for Smith's Randomization Step

Smith's Randomization Parameters

- **Smith's Exponent:** Smith's Randomization simulates a coin toss to randomize subjects into the two groups. For each assignment, if one group currently has less subjects assigned to it, the group with less subjects assigned to it has an increased probability of being selected for the next assignment. This increased probability is calculated using Smith's Exponent (see subsection 6.1.4 for further information on how this value is calculated). Smith's Exponent can take any real value greater than 0. A default value of 5 is generally recommended for improving balance without making assignments too predictable.
- **Search for list in which actual group sizes match the target group sizes:** Unlike Block Randomization, the proportion of total sample size in each treatment group for Smith's Randomization may not equal the targetted values. This option gives the ability for the user to search for a list in which the proportion of the total sample size in each group equals the values calculated using the target allocation ratios which are specified in Step 3. If the user wishes to search for a list in which the actual group sizes match the target group sizes, they should set the radio button to Yes. If Yes is selected for this option, a new field will open for the maximum number of iterations to be used in the search. This field is shown in Figure 6.12.

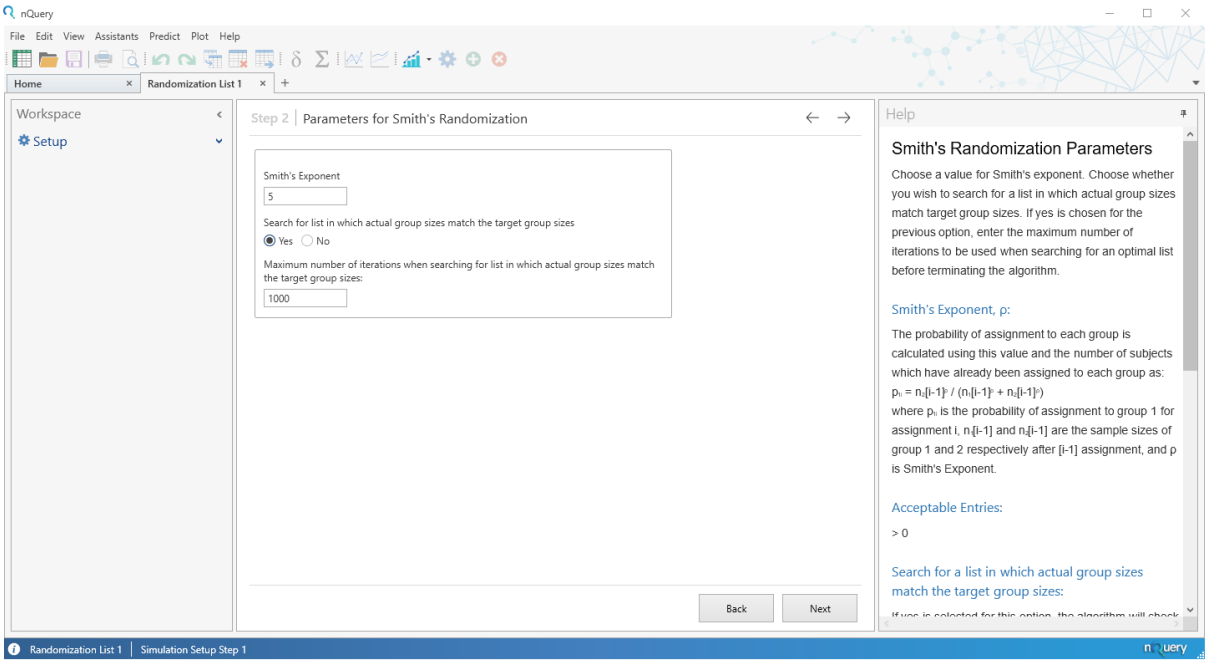


Figure 6.12: Parameters for Smith's Randomization Step when searching for a list in which actual group sizes match target group sizes

- **Maximum Number of iterations when searching for list in which actual group sizes match the target group sizes:** This parameter controls the maximum number of iterations that are to be used when searching for a list in which actual group sizes match the target group sizes. In some scenarios, it may be impossible or take an unreasonably large amount of time in order to find an list. In these cases, the algorithm will terminate after a certain number of attempts, which is specified by this parameter. Enter an integer greater than 0 for this value. A default value of 1000 is used. This value will generally find an ideal list if possible, while not wastefully searching for an ideal list that is unlikely or impossible to generate.

6.2.3.6 Step 2 - Select Parameters for Wei's Urn Randomization

For **Wei's Urn Randomization, Step 2** will involve choosing a value for the Wei's A and Wei's B parameters and choosing whether the user wishes to search for a list in which actual group sample sizes equal the target sample sizes. If the user does wish to search for a list in which actual group sample sizes equal the target group sample sizes, an additional maximum number of iterations parameter will be required. The default **Step 2** window for Wei's Randomization is provided in Figure 6.13.

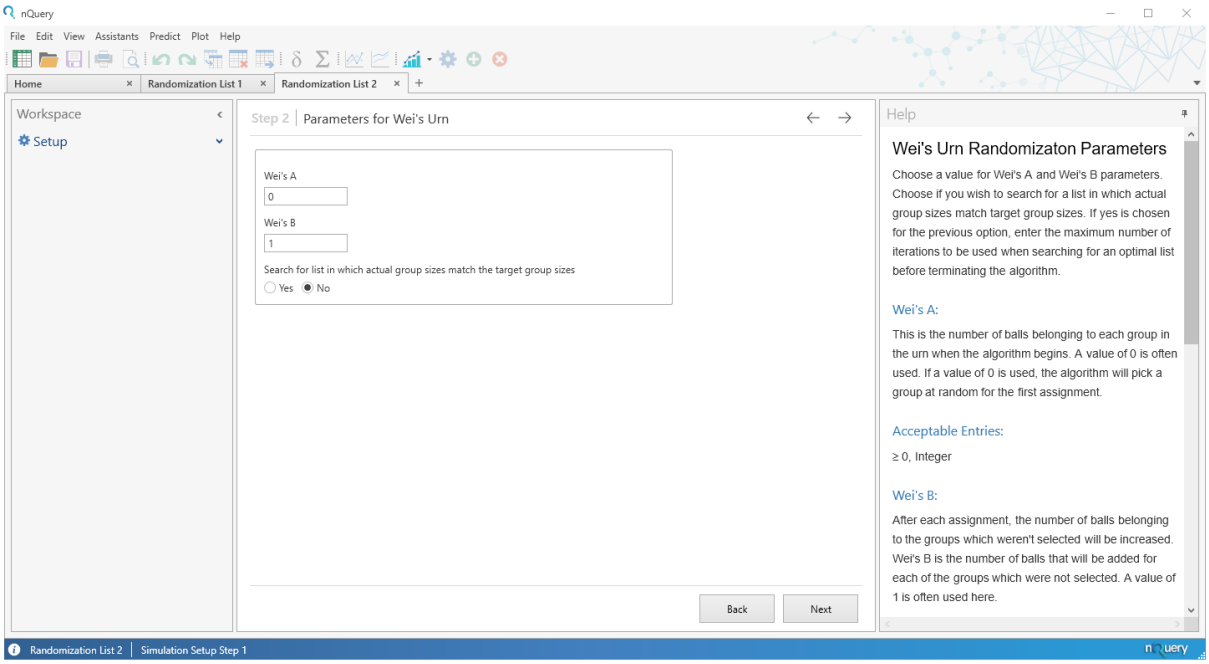


Figure 6.13: Parameters for Wei's Urn Randomization Step

Wei's Urn Randomization Parameters

- **Wei's A:** Wei's A controls the number of balls belonging to each group in the simulated urn at onset. Wei's A can take integer values greater than or equal to 0. A value of 0 is often used.
- **Wei's B:** Wei's B controls the number of balls that are added to the urn for each group that were not the previous selection. Wei's B can take integer values greater than or equal to 1. A value of 1 is often used.
- **Search for list in which actual group sizes match the target group sizes:** This option gives the ability for the user to search for a list in which the proportion of the total sample size in each group equals the values calculated using the target allocation ratios which are specified in **Step 3**. If the user wishes to search for a list in which the actual group sizes match the target group sizes, they should set the radio button to Yes. If Yes is selected for this option, a new field will open for the maximum number of iterations to be used in the search. This field is shown in Figure 6.14.

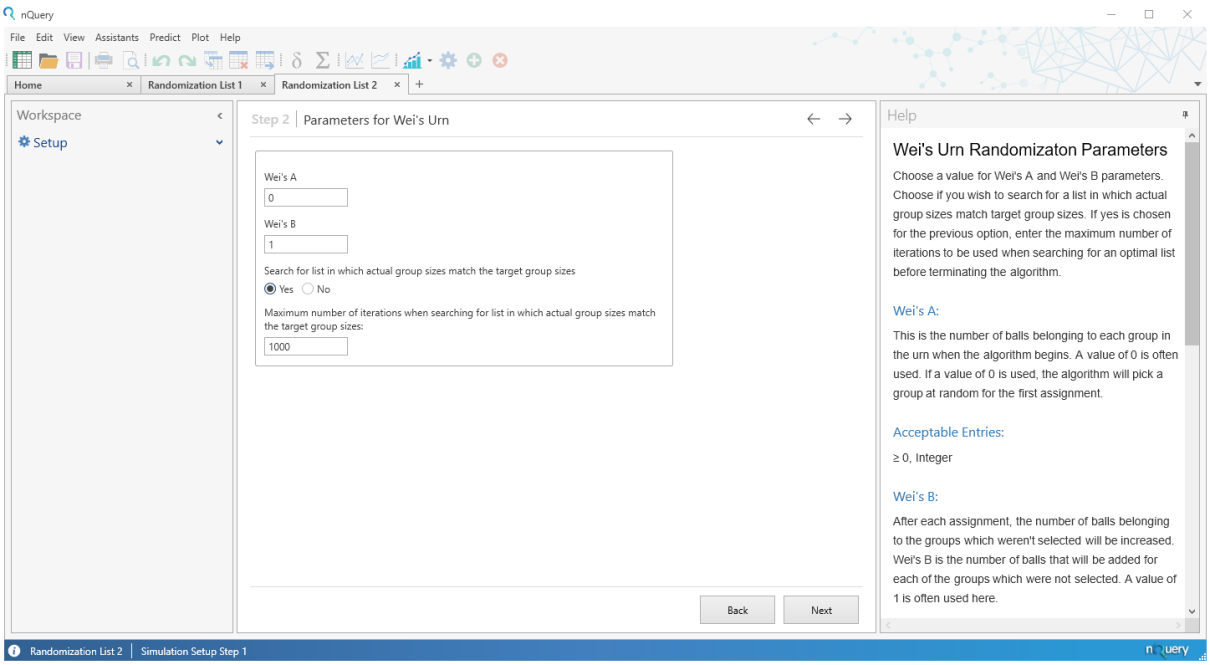


Figure 6.14: Selecting Parameters for Wei's Urn Randomization when searching for a list in which actual group sizes match target group sizes

- **Maximum Number of iterations when searching for list in which actual group sizes match the target group sizes:** This parameter controls the maximum number of iterations that are to be used when searching for a list in which actual group sizes match the target group sizes. In some scenarios, it may be impossible or take an unreasonably large amount of time in order to find an list. In these cases, the algorithm will terminate after a certain number of attempts, which is specified by this parameter. Enter an integer greater than 0 for this value. A default value of 1000 is used. This value will generally find an ideal list if possible, while not wastefully searching for an ideal list that is unlikely or impossible to generate.

6.2.3.7 Step 2 - Select Parameters for Random Sorting

For **Random Sorting,** no algorithm specific parameters are required. As such, **Step 2** is skipped for the **Random Sorting** algorithm. The **Step 2** window for **Random Sorting** is provided in Figure 6.13.

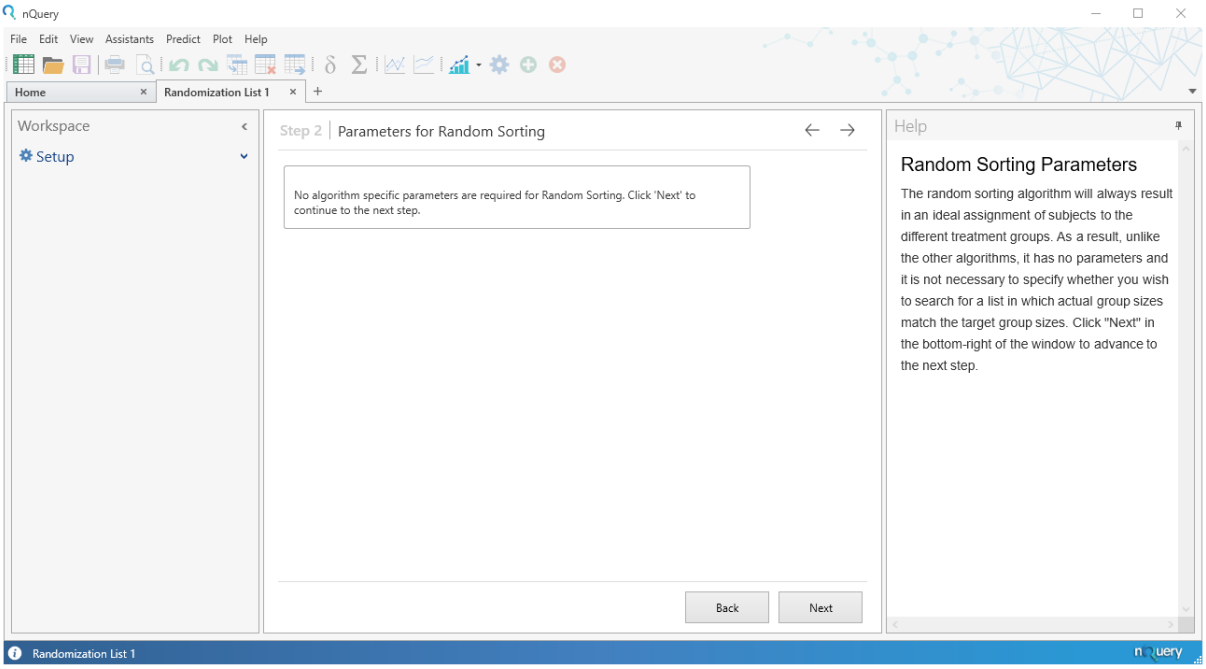


Figure 6.15: Overview of the Parameters for Random Sorting Step

6.2.3.8 Step 2 - Select Parameters for Random Sorting using Maximum Allowable Deviation

For **Random Sorting using Maximum Allowable Deviation, Step 2** will involve choosing a value for the Maximum Allowable Percentage Deviation and the Maximum number of iterations to use when conducting a search. The default **Step 2** window for **Random Sorting using Maximum Allowable Deviation** is displayed in Figure 6.16.

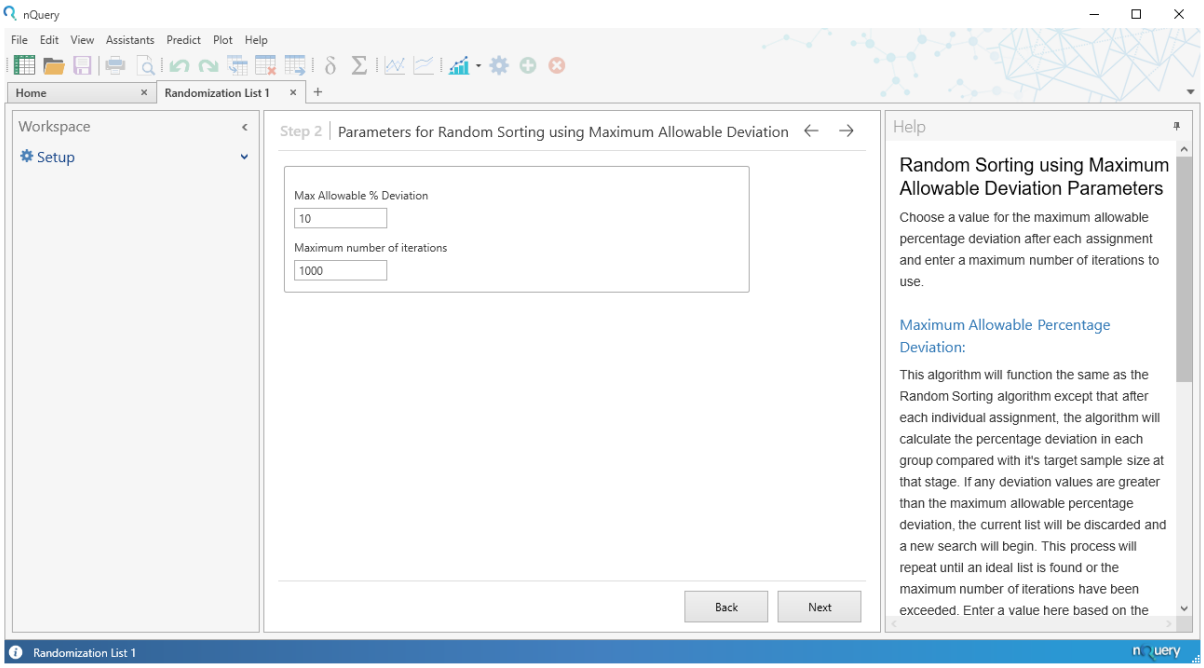


Figure 6.16: Overview of the Parameters for Random Sorting using Maximum Allowable Deviation Step

Random Sorting using Maximum Allowable Deviation Parameters

- **Max Allowable % Deviation:** Enter the maximum allowable percentage deviation. If the percentage deviation in any group at any stage during the randomization process exceeds this value, the randomization list will be deleted and the search will begin again. This field takes real values between 0 and 100.
- **Maximum number of iterations:** Enter the maximum number of times that the algorithm may restart the randomization process if a group deviation value exceeds the max allowable deviation. A value of 1000 is recommended. This cell takes integer values greater than 0.

6.2.3.9 Step 3 - Specify target sample size

Specify target sample size is the third step in the Randomization Lists **Setup**. This step involves specifying the target sample size that is to be randomized into the various treatment groups and specifying information on the treatment groups. An overview of **Step 3** can be seen in Figure 6.17.

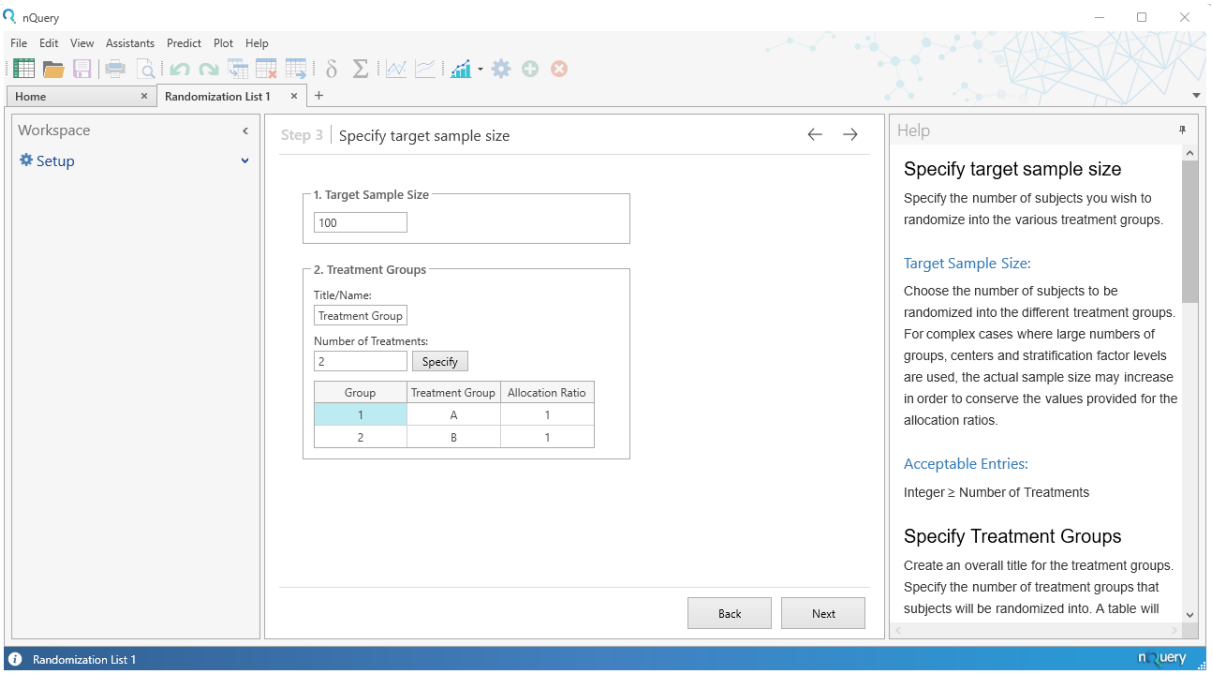


Figure 6.17: Overview of the Specify target sample size Step

Target Sample Size Parameters

- **Target Sample Size:** Enter the target number of subjects that you desire to randomize into the various treatment groups. Note that the actual sample size may be larger than this value in some scenarios. Enter an integer value greater than or equal to 2 in this field.

Treatment Groups Parameters

- **Title/Name:** Enter a general title that will be used for the treatment groups. For example, you could enter "Treatment", "Dose" or "Group". This field takes text values.
- **Number of Treatments:** Enter the number of treatment groups that you wish to randomize subjects into. This field can take integer values between 2 and 25. When the value for this is altered, the number of rows in the **Specify Treatment Group Information** table will change to this value and the values in the table will reset. Clicking the "Specify" button on the right will hide the **Specify Treatment Group Information** table.
- **Specify Treatment Group Information Table:** The Specify Treatment Group Information table allows the user to enter the required information for the treatment groups that subjects are randomized into. The **Specify Treatment Group Information Table** will have three columns.
  - **Group:** This column will contain the sequential order of the groups. These values are not editable by the user.
  - **Treatment Group:** This column will have the heading "Treatment Group" by default, but will take on whatever value the user inputs previously in the **Title/Name** field. The values in this column will represent the name or label that is applied to each treatment group. The groups will by default be labelled

alphabetically. The user can edit these values by clicking on the desired cell and entering new values. These cells take text entries.

– **Allocation Ratio:** This column gives the user the ability to enter an allocation ratio for each treatment group. The allocation ratio will determine how the sample size will be ideally split between the treatment groups. For example, with three groups with allocation ratios of 1,2 and 1, the algorithm will aim to randomize 25% of the sample size in groups 1 and 3 and 50% of the sample size in group 2. These values will be one by default, but can be changed to any integer value.

Note that for the Efron's Biased Coin Randomization, Smith's Randomization and Wei's Urn Randomization Algorithms there is an additional constraint that the allocation ratios for the treatment groups must be equal. If the user attempts to enter unequal allocation ratios for these scenarios, an acceptable entries error will be thrown in the **Allocation Ratio** column of the **Specify Treatment Group Information Table.**

For the readers benefit, an example of a more complex set of inputs for **Step 3** than the default case is provided in Figure 6.18.

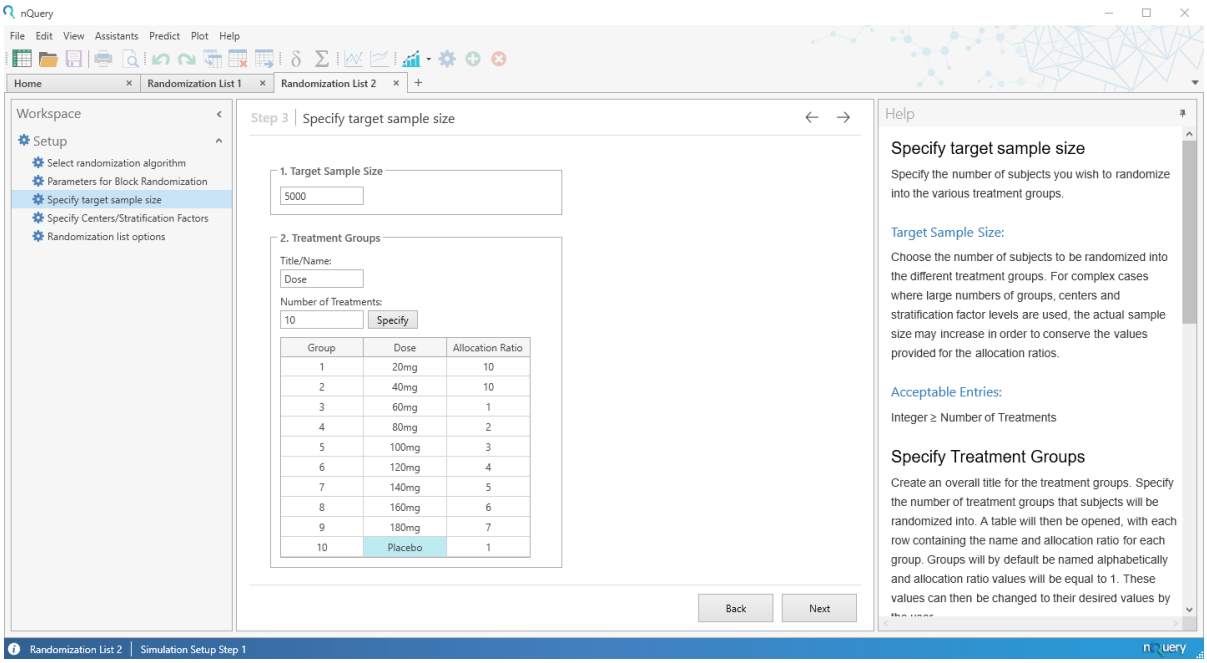


Figure 6.18: Example of Specify target sample size Step for a complex case

6.2.3.10 Step 4 - Specify Centers/Stratification Factors

Step 4 in the **Setup** involves **Specifying Centers/Stratification Factors**. This is an optional step and can be skipped directly by clicking the "Next" button in the bottom-right if the user does not wish to stratify on Centers/Stratification Factors. An overview of the options for this step can be seen in Figure 6.19.

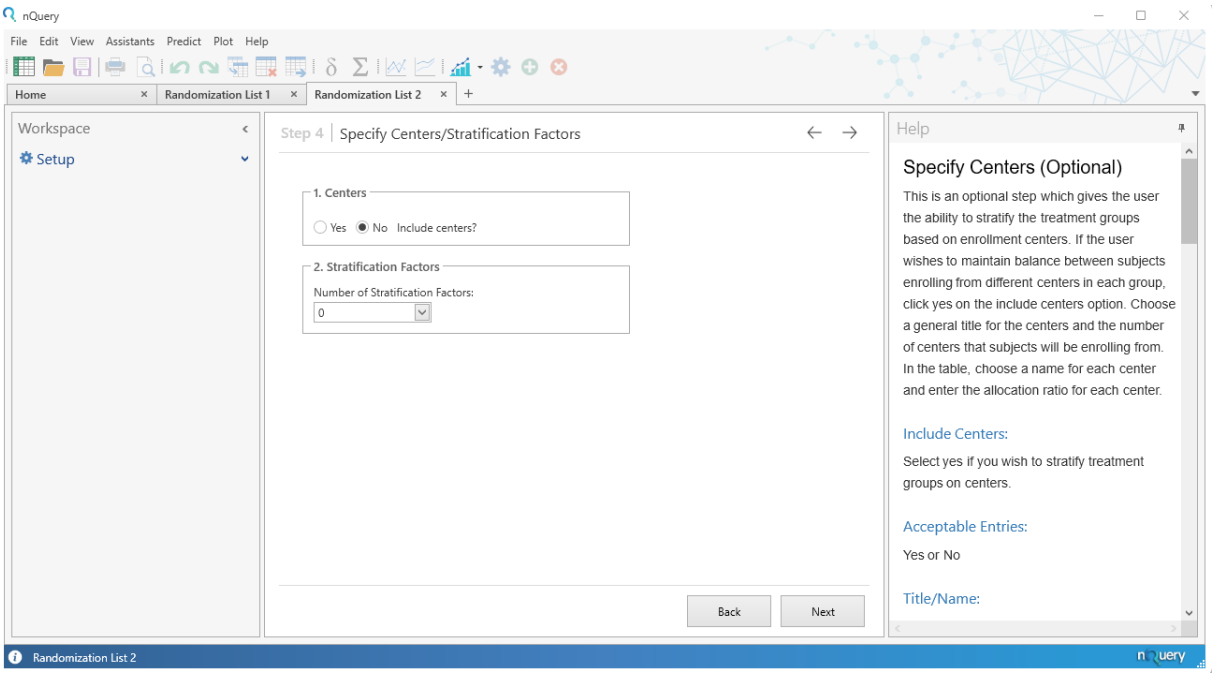


Figure 6.19: Overview of the Specify Centers/Stratification Factors Step

Centers Parameters

- **Include Centers:** Select whether you wish to stratify upon centers. If "Yes" is selected for this option, the **Specify Centers Information** table will appear as as shown in Figure 6.20.

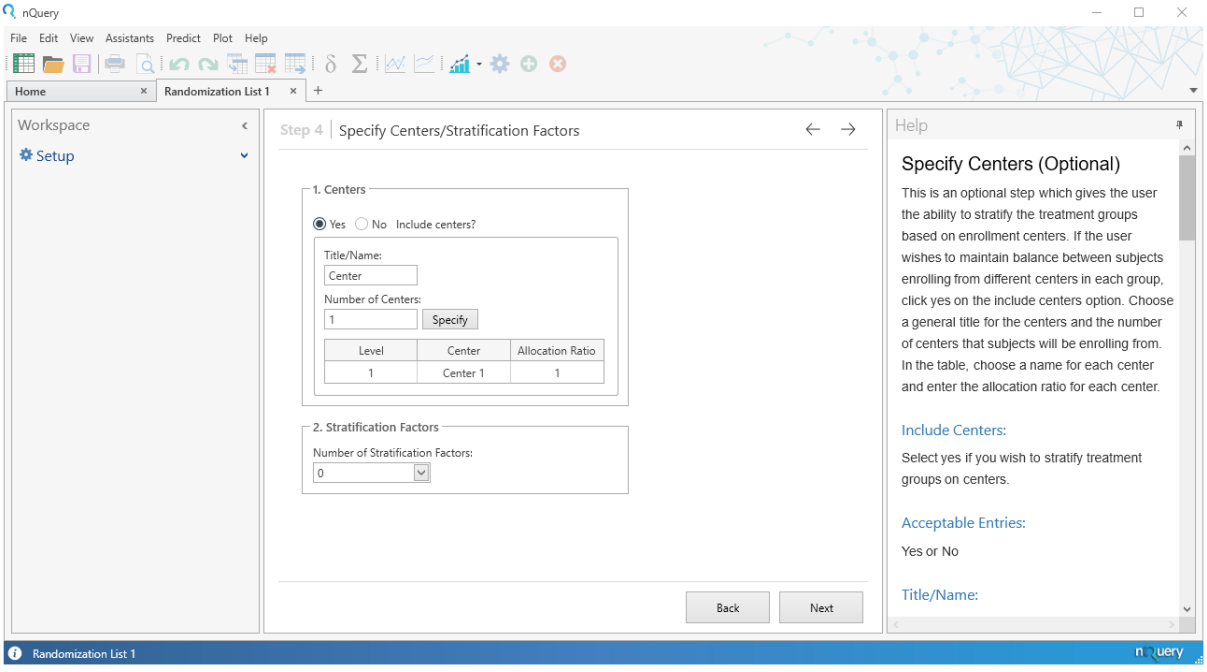


Figure 6.20: Specifying Center Information

- **Title/Name:** Enter a general title that will be used for the centers. For example, you could enter "Center", "Enrollment Center" or "Site". This field accepts text

values.

- **Number of Centers:** Enter the number of centers that you wish subjects to be drawn from. This field can take values between 2 and 500. When the value for this is altered, the number of rows in the **Specify Center Information Table** will change to this value and the values in the table will reset. Clicking the "Specify" button on the right will hide the **Specify Center Information Table**.
- **Specify Center Information Table:** The Specify Center Information table allows the user to enter the required information for the centers. The **Specify Center Information Table** will have three columns.
  - **Level:** This column will contain the sequential order of the centers. These values are not editable by the user.
  - **Center:** This column will have the heading "Center" by default, but will take whatever value the user inputs previously in the **Title/Name** field. The values in this column will represent the name or label that is applied to each center. These values will by default be Center 1, Center 2 and so on. The user can edit these values by clicking on the desired cell and entering new values. These cells take text entries.
  - **Allocation Ratio:** This column gives the user the ability to enter an allocation ratio for each center. The allocation ratio will determine how the sample size within each group will be ideally split between the centers. For example, with 3 centers with allocation ratios of 2,1 and 1, the algorithm will aim to have 50% of the sample size of each treatment group coming from the first center and 25% from the second and third centers respectively. These values will be one by default, but can be changed to any integer value.

An example of the **Specify Center Information Table** with values inputted is shown in Figure 6.21.

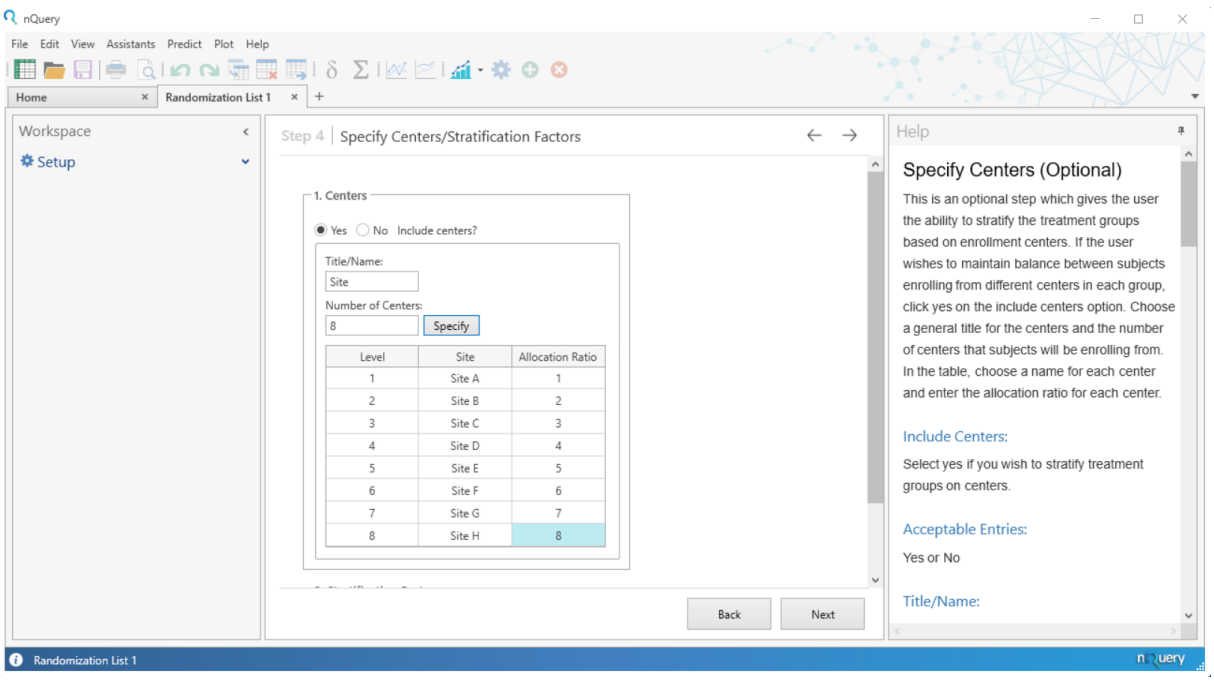


Figure 6.21: Specifying Center Information Table Example

If the user wishes to stratify upon other stratification factors, they can do so in the **Stratification Factors** section. The parameters used for both Factor 1 and Factor 2 are identical, so the following discussion of parameters will be the same for both factors.

Stratification Factors Parameters

- **Number of Stratification Factors:** Enter the number of factors that you wish for subjects to be stratified on. Subjects can be stratified on up to 2 different factors. Once a value is entered for the **Number of Stratification Factors,** the required inputs for Factor 1 (and Factor 2 if **Number of Stratification Factors** value is set equal to 2) will appear in the **Stratification Factors** section. The default **Step 5** window when one and two factors are used can be seen in Figure 6.22 and Figure 6.23 respectively.

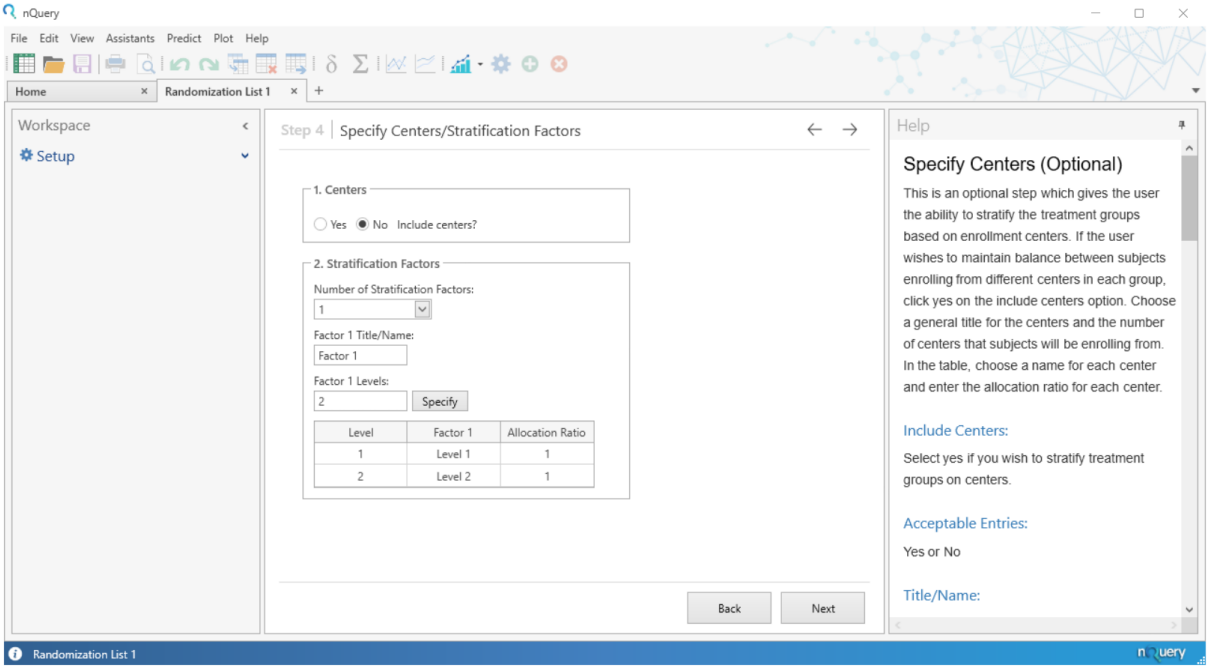


Figure 6.22: Specify Centers/Stratification Factors Step when Number of Stratification Factors equals 1

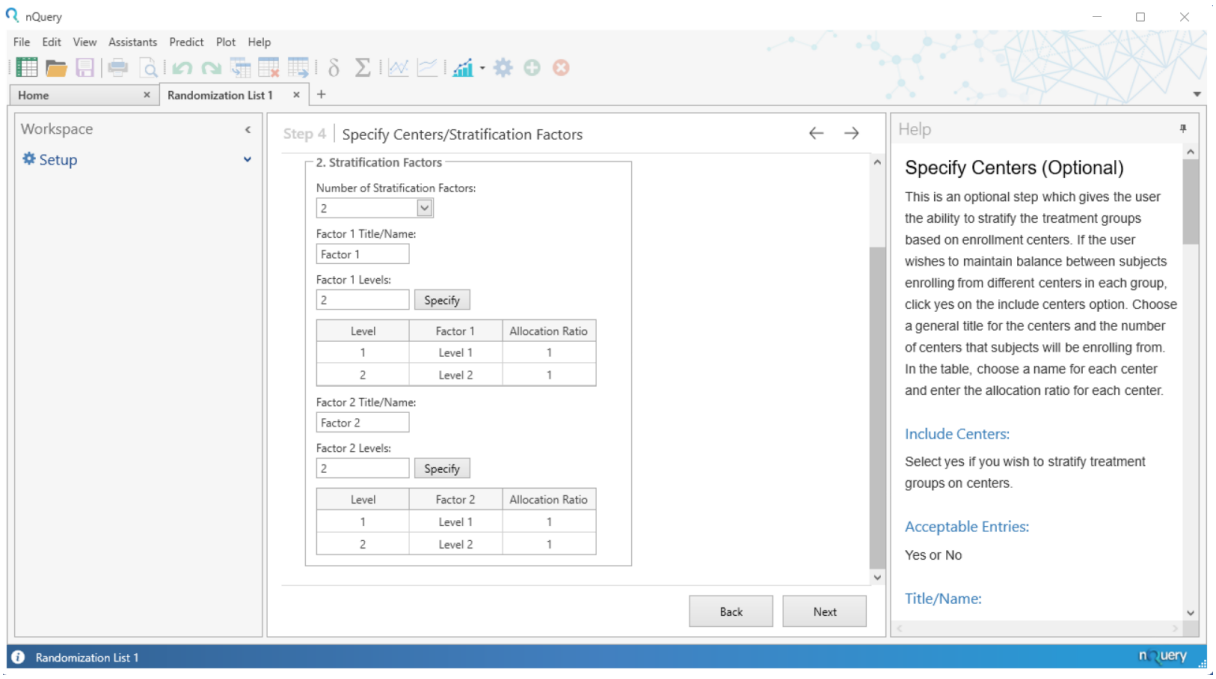


Figure 6.23: Specify Centers/Stratification Factors Step when Number of Stratification Factors equals 2

- **Title/Name:** Enter a general title that will be used for the stratification factor. For example, you could enter "Smoking Status", "Age" or "BMI". This field accepts text values.
- **Number of Levels:** Enter the number of levels within the stratification factor. This field can take values between 2 and 25. When the value for this is altered, the number of rows in the **Specify Factor Information Table** will change to this value and the values in the table will reset. Clicking the **Specify** button on the right will hide the **Specify Factor Information Table**. Clicking the **Specify** button will make the table reappear.
- **Specify Factor Information Table:** The Specify Factor Information Table allows the user to enter the required information for the stratification factor(s). The **Specify Factor Information Table** will have three columns.
  - **Level:** This column will contain the sequential order of the levels within the factor. These values are not editable by the user.
  - **Factor:** This column will have the heading "Factor" by default, but will take whatever value the user inputs previously in the **Title/Name** field. The values in this column will represent the name or label that is applied to each level within the factor. These values will by default be Level 1, Level 2 and so on. The user can edit these values by clicking on the desired cell and entering new values. These cells take text entries.
  - **Allocation Ratio:** This column gives the user the ability to enter an allocation ratio for each level of the factor. The allocation ratio will determine how the sample size within each group (if stratification is not used)/center (if only stratification on centers is used)/factor 1 (if stratification on centers and/or a stratification factor is used) will be ideally split between the levels of the factor. These values will be one by default, but can be changed to any integer value.

An example where the inputs of the **Specify Centers/Stratification Factors** step is filled for two stratification factors, where one stratification factor is smoking status and the other stratification factor is age is displayed in Figure 6.24.

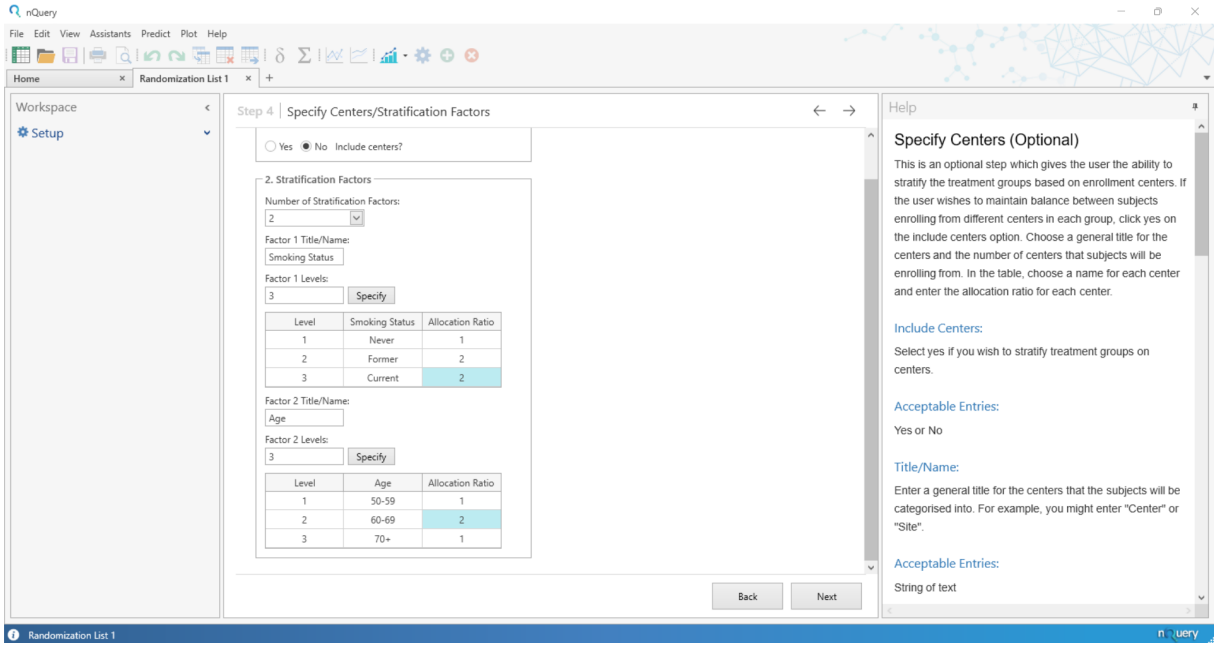


Figure 6.24: Specify Centers/Stratification Factors Step when Two Stratification Factors are used Example

6.2.3.11 Step 5 - Randomization List Options

Step 5 in the **Setup** involves specifying two final options for the randomization list. An overview of the options for this step can be seen in Figure 6.25.

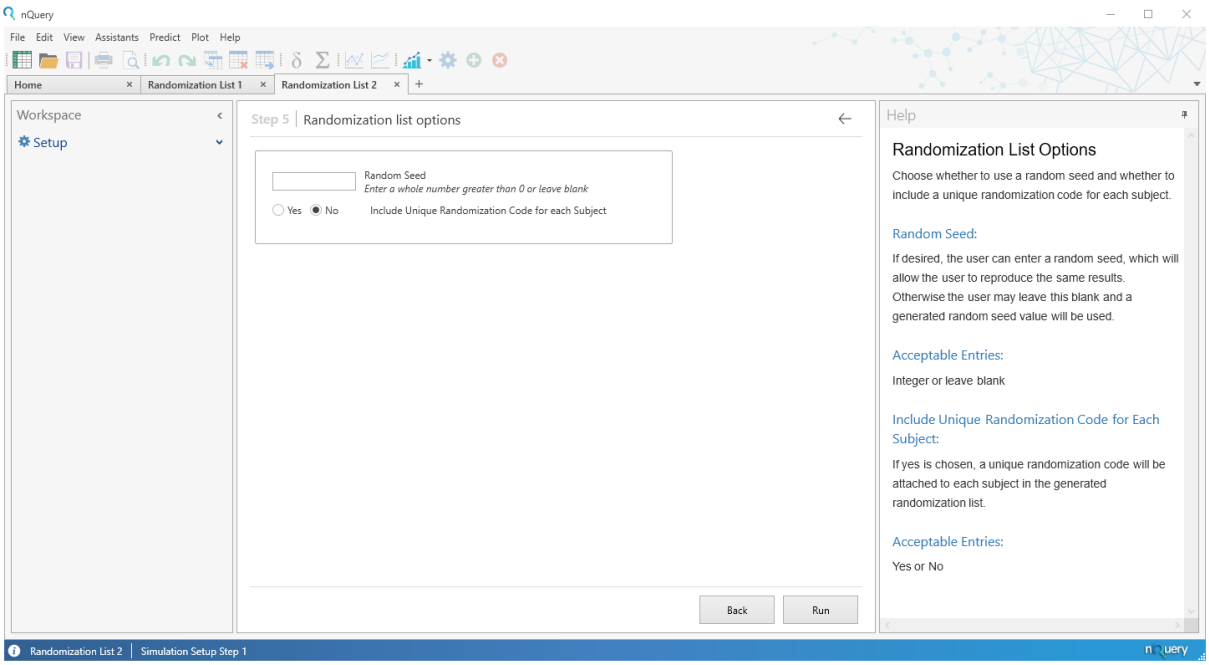


Figure 6.25: Overview of the Randomization list options Step

Randomization List Options

- **Random Seed:** This is the numeric seed that will be used for random number generation. Using the same random seed value will ensure that the same random sequence will be generated with each run of the algorithm and the output will not change. This is often useful for replicating results. If the user wishes to replicate their results, they can enter an integer value in this field. If the user chooses not to enter a random seed value, one will be randomly generated. The value for the random seed will be displayed in the **Output Summary** for the user, regardless if it is randomly generated or not.
- **Include Unique Randomization Code for each Subject:** Setting this option to "Yes" will include a unique code for each subject in the randomization list. This information may be helpful in blinding the study, by allowing the information about treatments, blocks and strata corresponding to each unique randomization code to be retained.

6.2.4 Results Output Summary

Once the **Randomization Lists Setup** procedure has been carried out, the output results section will become available to the user. A separate **Reports** section will be listed in the **Workspace** area on the left hand-side of the screen. This can be seen in Figure 6.26.

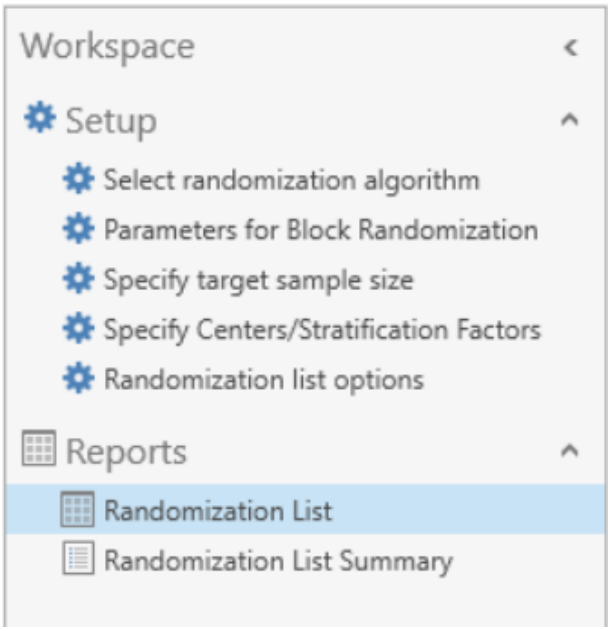


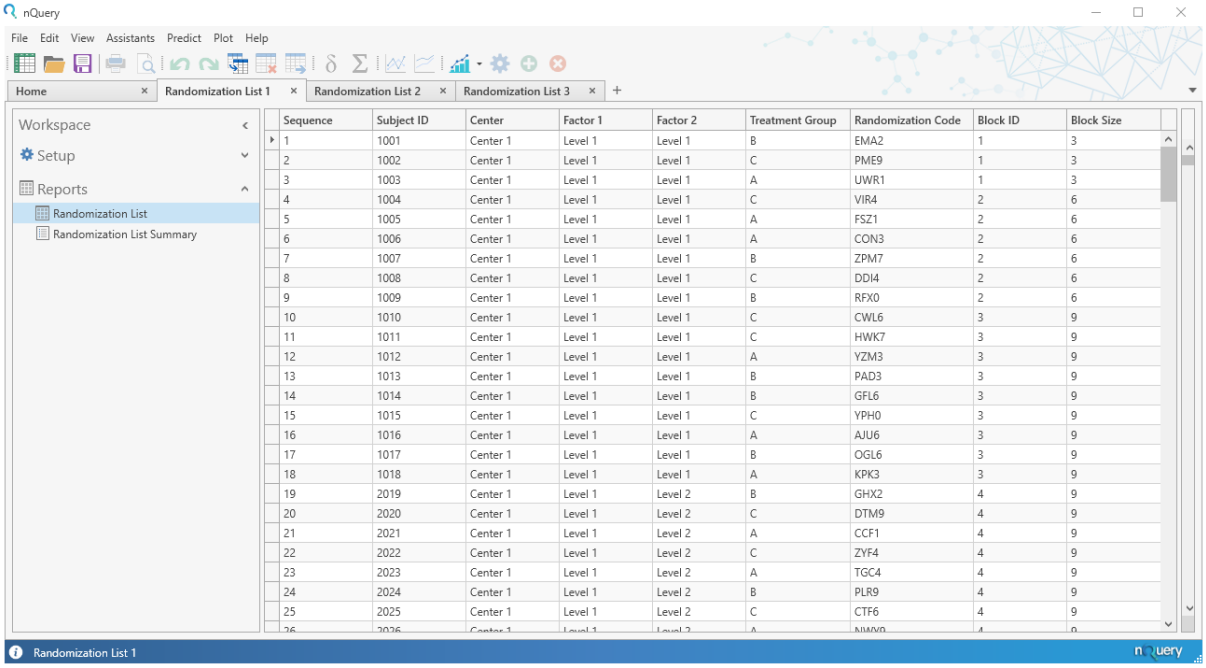
Figure 6.26: nQuery Workspace with Reports Section Included

The **Reports** section has two further sub-headings: **Randomization List** and **Randomization List Summary.** **Randomization List** will display the generated randomization list and **Randomization List Summary** will display summary information on the inputs and results of the generated randomization list. The user can navigate

between the steps in the setup and these two steps by clicking on the desired step. Similarly to the Setup steps, a help card will be provided on the right-hand side of the screen which will provide additional information and advice to the user.

6.2.4.1 Randomization List

The **Randomization List** item in the **Reports** section will display the randomization list that is generated using the inputs provided in the **Setup**. The randomization list will contain the randomization information for each subject and will be displayed in a spreadsheet format. These values are not editable. An example of a generated randomization list can be seen in Figure 6.27.



Sequence	Subject ID	Center	Factor 1	Factor 2	Treatment Group	Randomization Code	Block ID	Block Size
1	1001	Center 1	Level 1	Level 1	B	EMA2	1	3
2	1002	Center 1	Level 1	Level 1	C	PME9	1	3
3	1003	Center 1	Level 1	Level 1	A	UWR1	1	3
4	1004	Center 1	Level 1	Level 1	C	VIR4	2	6
5	1005	Center 1	Level 1	Level 1	A	FSZ1	2	6
6	1006	Center 1	Level 1	Level 1	A	CON3	2	6
7	1007	Center 1	Level 1	Level 1	B	ZPM7	2	6
8	1008	Center 1	Level 1	Level 1	C	DDI4	2	6
9	1009	Center 1	Level 1	Level 1	B	RFX0	2	6
10	1010	Center 1	Level 1	Level 1	C	CWL6	3	9
11	1011	Center 1	Level 1	Level 1	C	HWK7	3	9
12	1012	Center 1	Level 1	Level 1	A	YZM3	3	9
13	1013	Center 1	Level 1	Level 1	B	PAD3	3	9
14	1014	Center 1	Level 1	Level 1	B	GFL6	3	9
15	1015	Center 1	Level 1	Level 1	C	YPH0	3	9
16	1016	Center 1	Level 1	Level 1	A	AJU6	3	9
17	1017	Center 1	Level 1	Level 1	B	OGL6	3	9
18	1018	Center 1	Level 1	Level 1	A	KPK3	3	9
19	2019	Center 1	Level 1	Level 2	B	GHX2	4	9
20	2020	Center 1	Level 1	Level 2	C	DTM9	4	9
21	2021	Center 1	Level 1	Level 2	A	CCF1	4	9
22	2022	Center 1	Level 1	Level 2	C	ZYF4	4	9
23	2023	Center 1	Level 1	Level 2	A	TGC4	4	9
24	2024	Center 1	Level 1	Level 2	B	PLR9	4	9
25	2025	Center 1	Level 1	Level 2	C	CTF6	4	9

Figure 6.27: An example of a generated randomization list in nQuery

Each row in the randomization list will represent one subject. Each row will contain the subjects position in the sequence of assignment, a subject ID and the treatment group that the subject is assigned to. Depending on choice of options in the **Setup** stage, there may be several other columns specifying which center, factor 1 level and factor 2 level each subject is drawn from. A unique randomization code may also be included for each subject and information on the block ID and block size that each subject was assigned using may also be displayed if block randomization is used.

Mandatory Column Headings

- **Sequence:** The sequence column contains the position of each subject in the randomization sequence. These will be integer values.
- **Subject ID:** This column will contain a unique identification number for each subject. For each stratum, the lead number will increase by 1.
- **Treatment Group:** This column will take on the value specified in "Title/name" field in the **Specify target sample size** step of the **Setup**, which by default will

be "Treatment Group". This column will contain the group each subejct has been assigned to. The values in this column will be the group names that were entered by the user in the **Specify Treatment Group Information** of the **Specify target sample size** step of the **Setup**.

Non-Mandatory Column Headings

- **Center:** This column will only be present in the randomization list if the user has chosen to stratify upon center. This column will take on the heading specified in "Title/name" field in the **Centers** section (this will by default be "Center") of the **Specify Centers/Stratification Factors** step of the setup. In this column, the center that each subject in the randomization sequence is drawn from will be specified. Values in this column will take the values which were specified for center names in the **Specify Center Information Table** of the **Specify Centers/Stratification Factors** step of the **Setup**.
- **Factor 1:** This column will only be present in the randomization list if the user has chosen to stratify upon at least one stratification factor. This column will take on the heading specified in "Title/name" field for the first stratification factor in the **Stratification Factors** section (this will by default be "Factor 1") of the **Specify Centers/Stratification Factors** step of the **Setup**. In this column, the factor 1 level that each subject in the randomization sequence is drawn from will be specified. Values in this column will take the values which were specified for factor 1 levels in the **Specify Factor 1 Information Table** of the **Specify Centers/Stratification Factors** step of the **Setup**.
- **Factor 2:** This column will only be present in the randomization list if the user has chosen to stratify upon two stratification factors. This column will take on the heading specified in "Title/name" field for the second stratification factor in the **Stratification Factors** section (this will by default be "Factor 2") of the **Specify Centers/Stratification Factors** step of the **Setup**. In this column, the factor 2 level that each subject in the randomization sequence is drawn from will be specified. Values in this column will take the values which were specified for factor 2 levels in the **Specify Factor 2 Information Table** of the **Specify Centers/Stratification Factors** step of the setup.
- **Randomization Code:** The **Randomization list options** step of the **Setup** gives the user the option to include a unique randomization code for each subject. If this option is set to "Yes", the Randomization Code column will be included in the randomization list, with each subject being assigned a unique code consisting of three letters and a number between 0 and 9.
- **Block ID:** This column is only available if Block Randomization is used as the randomization algorithm and will be included if the user sets the **Specify Block ID and Block Size in Output** option to "Yes" in the **Parameters for Block Randomization** step of the **Setup**. This column will display the sequential order of blocks that each subject was assigned using.
- **Block Size:** This column is only available if Block Randomization is used as the randomization algorithm and will be included if the user sets the **Specify Block ID and Block Size in Output** option to "Yes" in the **Parameters for Block Randomization** step of the **Setup**. This column will display the size of the block that each subject was assigned using.

6.2.4.2 Randomization List Summary

This section will provide a description of the **Randomization List Summary** and the tools available to explore and edit this report. Multiple examples of the **Randomization List Summary** report are also provided in the demonstrations in later sections (subsection 6.2.5, subsection 6.2.6 and subsection 6.2.7).

The **Randomization List Summary** report can be divided into 5 parts:

- Input Summary
- Output Summary
- Algorithm Summary (Will not be present if **Random Sorting** is used as the randomization algorithm)
- Groups
- Strata (Will only be present if a stratified randomization is conducted)

The **Input Summary** and the **Algorithm Summary** sections will give summary information on the inputs that were used in the **Setup** phase to generate the current randomization list. The **Output Summary**, **Groups** and **Strata** sections will give summary information on the generated randomization list. An example **Randomization List Summary** report displayed in an nQuery Randomization Lists Workspace is shown in Figure 6.28.

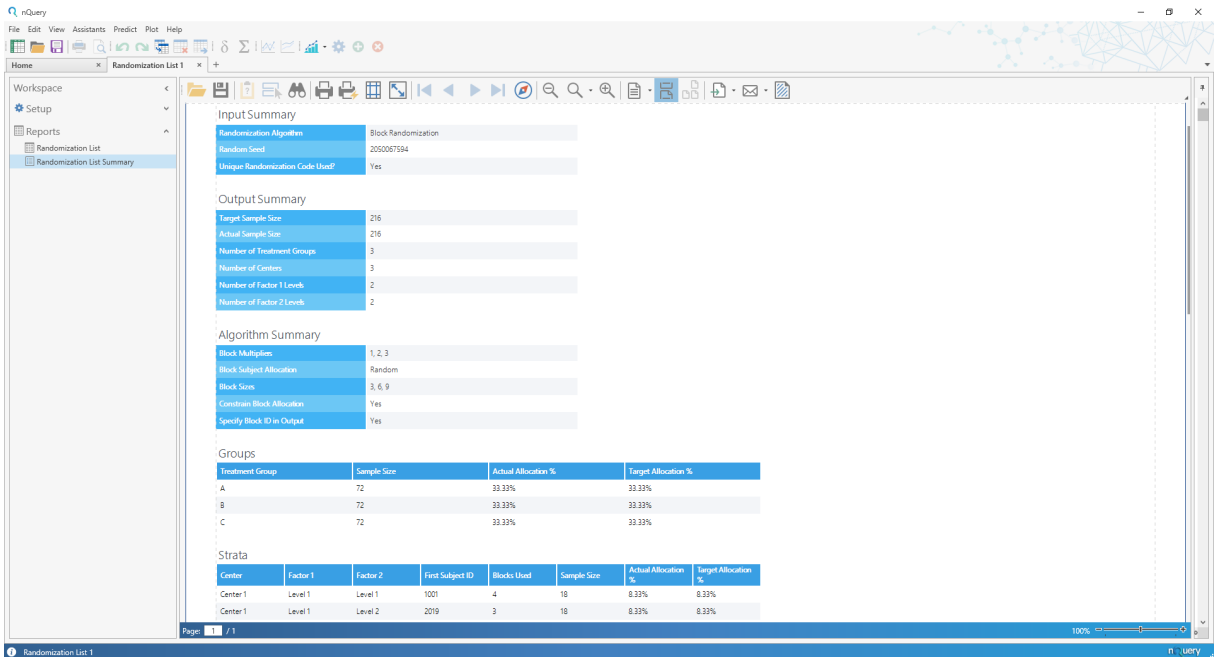


Figure 6.28: Randomization List Summary Report Example

The **Input Summary** section is shown for all randomization lists and provides a high-level summary of the target randomization list and it's inputs. The **Input Summary** provides a summary of the **Randomization Algorithm** (Block Randomization, Complete Randomization, Efron's Biased Coin Randomization, Smith's Randomization, Wei's Urn Randomization, Random Sorting, Random Sorting using Maximum Allowable Deviation), **Random Seed** (User inputted or generated random seed value) and **Unique**

Randomization Code Used? (Yes/No). Examples of the **Input Summary** section are provided in Figure 6.29.

Input Summary

Randomization Algorithm	Complete Randomization
Random Seed	621354167
Unique Randomization Code Used?	No

Input Summary

Randomization Algorithm	Block Randomization
Random Seed	1
Unique Randomization Code Used?	No

Input Summary

Randomization Algorithm	Smith's Randomization
Random Seed	881759496
Unique Randomization Code Used?	Yes

Figure 6.29: Input Summary Section Examples

The **Output Summary** section is provided for all randomization lists and provides a summary of the sample size information for the randomization list alongside information on the number of treatment groups subjects were randomized into and the strata subjects are drawn from. The **Output Summary** provides the **Target Sample Size** that was specified by the user in the output, as well as the **Actual Sample Size** of the generated list. The **Number of Treatment Groups** in the generated list will be shown, alongside the **Number of Centers** subjects are drawn from and the **Number of Factor 1 Levels** and **Number of Factor 2 Levels** that subjects are stratified upon. Note that if the user does not stratify upon center or other stratification factors, nQuery will assume that subjects are all drawn from the same center or stratification factor level, and as such the displayed value for these fields will be 1. Examples of the **Output Summary** sections are provided in Figure 6.30.

Output Summary

Target Sample Size	1000
Actual Sample Size	1005
Number of Treatment Groups	5
Number of Centers	3
Number of Factor 1 Levels	1
Number of Factor 2 Levels	1

Output Summary

Target Sample Size	216
Actual Sample Size	216
Number of Treatment Groups	3
Number of Centers	3
Number of Factor 1 Levels	2
Number of Factor 2 Levels	2

Output Summary

Target Sample Size	100
Actual Sample Size	100
Number of Treatment Groups	2
Number of Centers	1
Number of Factor 1 Levels	1
Number of Factor 2 Levels	1

Figure 6.30: Output Summary Section Examples

The **Algorithm Summary** section will provide summary information on the parameters that were used for the chosen randomization algorithm. As different algorithms will require different parameters, this section will differ depending on choice of algorithm. When **Block Randomization** is used as the randomizaiton algorithm, this section will contain 5 items. These are the **Block Multipliers** that were used, the **Block Subject Allocation** (Random/Equal/Custom), the **Block Sizes** (calculated using the block multipliers and treatment allocation ratios) that were used, the **Constrain Block Allocation** value (Yes/No) and the **Specify Block Info in Output** (Yes/No) value. An example of the **Algorithm Summary** section when **Block Randomization** is used is provided in Figure 6.31.

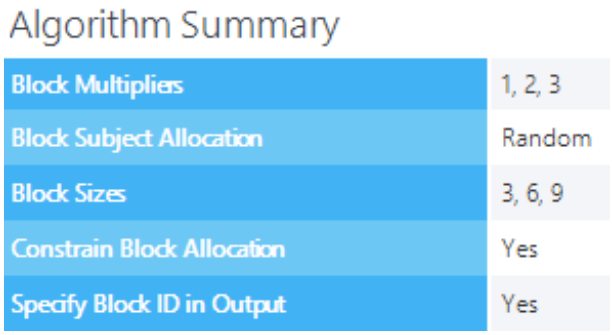


Figure 6.31: Algorithm Summary Section for Block Randomization Example

When **Complete Randomization** is used as the randomization algorithm, the **Algorithm Summary** section can take on two possible forms. In **Step 2** of the **Setup,** if **Search for list in which actual group sizes match the target group sizes** is set to "No", the **Algorithm Summary** will display one value, **Match Group Sizes** as No. An example of this is shown in part A of Figure 6.32. If however, in **Step 2** of the **Setup,** the **Search for list in which actual group sizes match the target group sizes** is set to "Yes", the value entered for the **Maximum number of iterations when search for list in which actual group sizes match the target group sizes** will also be displayed in the **Algorithm Summary** section in a row named **Maximum Iterations**. An example of this is shown in part B of Figure 6.32.

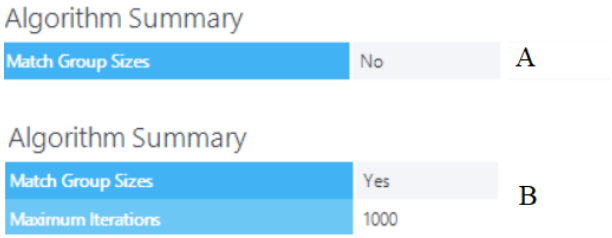


Figure 6.32: Algorithm Summary Section for Complete Randomization

When **Efron's Biased Coin Randomization** is used as the randomization algorithm, the **Algorithm Summary** section can take on two possible forms. Both forms will display the value entered In **Step 2** of the **Setup** for the **Efron's p** parameter. In **Step 2,** if **Search for list in which actual group sizes match the target group sizes**

is set to "No", the **Algorithm Summary** will display also display this in the **Match Group Sizes** row as No. An example of this is shown in part A of Figure 6.33. If however, in **Step 2** of the **Setup,** the **Search for list in which actual group sizes match the target group sizes** is set to "Yes", the value entered for the **Maximum number of iterations when search for list in which actual group sizes match the target group sizes** will also be displayed in the **Algorithm Summary** section in the **Maximum Iterations** row. An example of this is shown in part B of Figure 6.33.

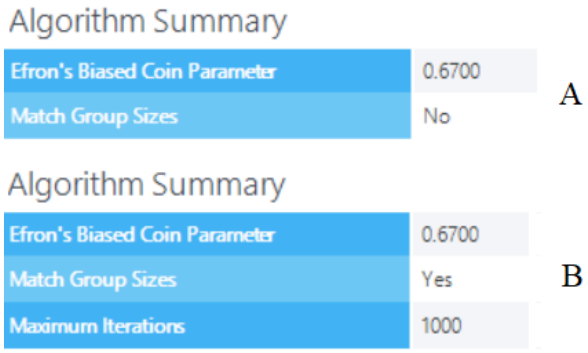


Figure 6.33: Algorithm Summary Section for Efron's Biased Coin Randomization

When **Smith's Randomization** is used as the randomization algorithm, the **Algorithm Summary** section can take on two possible forms. Both forms will display the value entered In **Step 2** of the **Setup** for the **Smith's Exponent** parameter. In **Step 2,** if **Search for list in which actual group sizes match the target group sizes** is set to "No", the **Algorithm Summary** will display also display this in the **Match Group Sizes** row as No. An example of this is shown in part A of Figure 6.34. If however, in **Step 2** of the **Setup,** the **Search for list in which actual group sizes match the target group sizes** is set to "Yes", the value entered for the **Maximum number of iterations when search for list in which actual group sizes match the target group sizes** will also be displayed in the **Algorithm Summary** section in the **Maximum Iterations** row. An example of this is shown in part B of Figure 6.34.

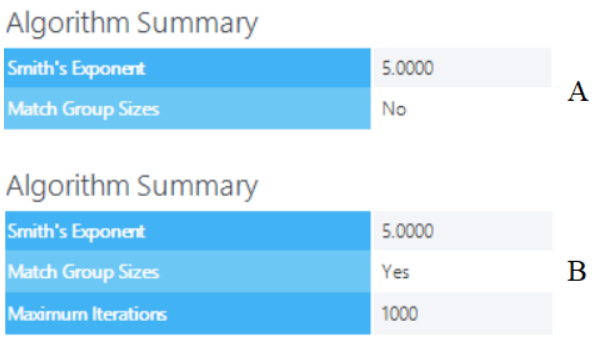


Figure 6.34: Algorithm Summary Section for Smith's Randomization

When **Wei's Urn** is used as the randomization algorithm, the **Algorithm Summary** section can take on two possible forms. Both forms will display the values entered In **Step 2** of the **Setup** for the **Wei's A** and **Wei's B** parameters. In **Step 2,** if **Search for**

list in which actual group sizes match the target group sizes is set to "No", the **Algorithm Summary** will display also display this in the **Match Group Sizes** row as No. An example of this is shown in part A of Figure 6.35. If however, in **Step 2** of the **Setup,** the **Search for list in which actual group sizes match the target group sizes** is set to "Yes", the value entered for the **Maximum number of iterations when search for list in which actual group sizes match the target group sizes** will also be displayed in the **Algorithm Summary** section in the **Maximum Iterations** row. An example of this is shown in part B of Figure 6.35.

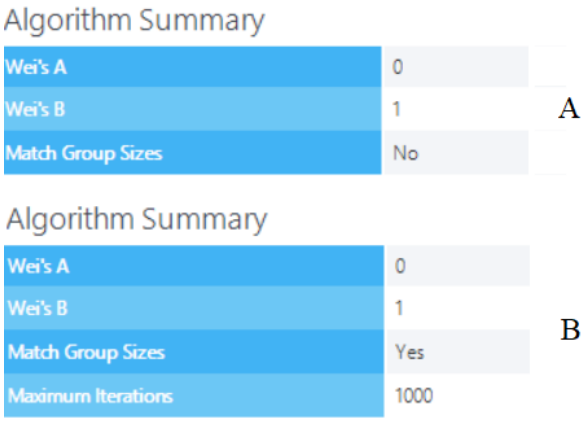


Figure 6.35: Algorithm Summary Section for Wei's Urn

When **Random Sorting** is used as the randomization algorithm, the **Algorithm Summary** section will not be present, as the **Random Sorting** algorithm does not require and parameters.

When **Random Sorting using Maximum Allowable Deviation** is used as the randomization algorithm, the **Algorithm Summary** section will display the values entered In **Step 2** of the **Setup** for the **Max Allowable % Deviation** and **Maximum number of iterations** parameters. This **Algorithm Summary** section for this algorithm is displayed in Figure 6.36.

Figure 6.36: Algorithm Summary Section for Random Sorting using Maximum Allowable Deviation

The **Groups** section contains a table with four columns; the **Treatment Group** column (this will alternatively be the value entered **Title/Name** field in **Step 2** of the **Setup**), the **Sample Size** column, the **Actual Allocation %** column and the **Target Allocation %** column. The **Treatment Group** column will display the names of each of the treatment groups which were entered in the **Specify Treatment Group Information Table** in **Step 2**. The **Sample Size** column will display the number of subjects which

were randomized into each group. The **Actual Allocation %** will display the percentage of the actual total sample size that each group makes up. The **Target Allocation %** will display the target percentage allocation that is calculated using the **Target Sample Size** and **Allocation Ratio** values that are entered in **Step 2** of the **Setup**. An example of the **Groups** section when three groups are used is provided in Figure 6.37.

Groups

Treatment Group	Sample Size	Actual Allocation %	Target Allocation %
A	36	35.29%	33.33%
B	35	34.31%	33.33%
C	31	30.39%	33.33%

Figure 6.37: Groups Section Example

The **Strata** section will only be available to the user if a stratified randomization is performed, i.e., if the list is stratified on at least one center and/or at least one stratification factor. The **Strata** section contains a table which displays summary information on the number of subjects in each strata. In total, the number of rows in the **Strata** table will be equal to **Number of Centers** x **Number of Factor 1 Levels** x **Number of Factor 2 Levels** which are entered in the **Specify Centers/Stratification Factors** step**.** These values are equal to 1 if they are not specified by the user. The number of columns in the **Strata** table will depend on inputs used in the **Setup**. If subjects are stratified upon center, there will be a **Center** column (this column will alternatively be named whatever value is inputted by the user in the **Title/Name** field of the **Center** section of **Specify Centers/Stratification Factors** step). The **Center** column will display the center value of each strata. If subjects are stratified upon stratification factors, there will additionally be a column for each factor. The **Factor** columns (these columns will alternatively be named whatever value is inputted by the user in the **Title/Name** field of the corresponding **Factor** section of **Specify Centers/Stratification Factors** step) will display the level of each factor for that strata. The **First Subject ID** column will display the ID of the first subject in that strata. If **Block Randomization** is used as the randomization algorithm, there will also be a **Blocks Used** column, which will display the number of blocks that were used to randomize subjects in that strata. The **Sample Size** column will display the number of subjects in each strata. The **Actual Allocation %** column will display the percentage of the total sample size that is made up of subjects from each strata. The **Target Allocation %** will display the target percentage of subjects in each strata calculated using the **Target Sample Size** and **Allocation Ratio** values from the **Specify Centers/Stratification Factors** step. An example of the **Strata** section when the list is stratified on three centers, two factor 1 levels and two factor 2 levels is provided in Figure 6.38.

Strata

Center	Factor 1	Factor 2	First Subject ID	Blocks Used	Sample Size	Actual Allocation %	Target Allocation %
Center 1	Level 1	Level 1	1001	3	12	8.45%	8.33%
Center 1	Level 1	Level 2	2013	3	10	7.04%	8.33%
Center 1	Level 2	Level 1	3023	3	14	9.86%	8.33%
Center 1	Level 2	Level 2	4037	3	14	9.86%	8.33%
Center 2	Level 1	Level 1	5001	2	12	8.45%	8.33%
Center 2	Level 1	Level 2	6013	3	10	7.04%	8.33%
Center 2	Level 2	Level 1	7023	3	14	9.86%	8.33%
Center 2	Level 2	Level 2	8037	3	12	8.45%	8.33%
Center 3	Level 1	Level 1	9001	3	10	7.04%	8.33%
Center 3	Level 1	Level 2	10011	2	10	7.04%	8.33%
Center 3	Level 2	Level 1	11021	3	14	9.86%	8.33%
Center 3	Level 2	Level 2	12035	2	10	7.04%	8.33%

Figure 6.38: Groups Section Example

Randomization List Summary Toolbar In nQuery Randomziation List, the **Randomization List Summary** has a toolbar which allows the user to edit, save, print and export a report. The toolbar options available for nQuery Randomization List Summary Report is shown in Figure 6.39.

Figure 6.39: Report Toolbar

These options are defined as follows:

1. Open: Open another nQuery Randomization Lists Report (.prnx)
2. Save: Save current nQuery Randomization Lists Report (.prnx)
3. Help: Unused
4. URL: Unused
5. Search: Search for text in current report. Select 14 to remove
6. Print: Open Print menu for current report
7. Quick Print: Print report using system defaults
8. Page Setup: Open Page Setup window to edit page size, orientation and margin sizes
9. Scale: Open Scale window to rescale size of report text by percentage or page size
10. First Page: Return to first page if report has multiple pages
11. Page Up: Go up one page if report has multiple pages
12. Page Down: Go down one page if report has multiple pages

13. Last Page: Go to last page if report has multiple pages
14. Navigation Pane: Open and close Navigation Pane. Contains Pages list and Search Results window
15. Zoom Out: Zoom out report by one increment
16. Zoom: Change the current zoom from list of options
17. Zoom In: Zoom in report by one increment
18. Page Layout: Set out how multiple pages are displayed (Single Page, Two Pages, Wrap Around)
19. Continuous Scolling: Enable or disable continuous scrolling in report
20. Show Cover Page: Show cover page
21. Export: Export report as other file type. Select arrow to see list in-report or select icon to open Export window
22. Send: Send report as email in export file type using system default email client.
23. Watermark: Add watermark to result using Watermark menu

The Export option can be used to save the report in the following file formats: PDF, HTML, MHT, RDF, DOCX, XLS, XLSX, CSV, Plain Text File (TXT), Image File (PNG, JPEG, BMP, GIF, EMF, WMF, TIFF).

6.2.5 Block Randomization Demonstration

In this section we will demonstrate an example of how **Block Randomization** can be used to generate a valid randomization list for a basic example where stratification is not used. Consider a scenario where researchers wishes to randomize 120 subjects into three different treatment groups. In these three groups, subejcts will receive a 40mg dose, an 80mg dose and a placebo dose of a particular drug. After investigating the various randomization algorithms that can be used, the researchers decide that they will use **Block Randomization** to generate the randomization list. Subjects will not be stratified upon center of enrollment or any other stratification factors. Subjects will be assigned to the three treatment groups using equal allocation ratios, i.e., the desired sample size is the same for the three groups.

In order to generate the desired randomization list, the researchers open a new nQuery Randomization Lists Workspace in order to begin the **Setup**. For information on how to open and navigate through the Workspace, see subsection 6.2.1 and subsection 6.2.2. The first step in the **Setup** will be the **Select Randomization algorithm** step. From the list of possible options in the **Target** section, the researchers will select the **Block Randomization** option. An example of selecting the **Block Randomization** algorithm can be seen in Figure 6.40.

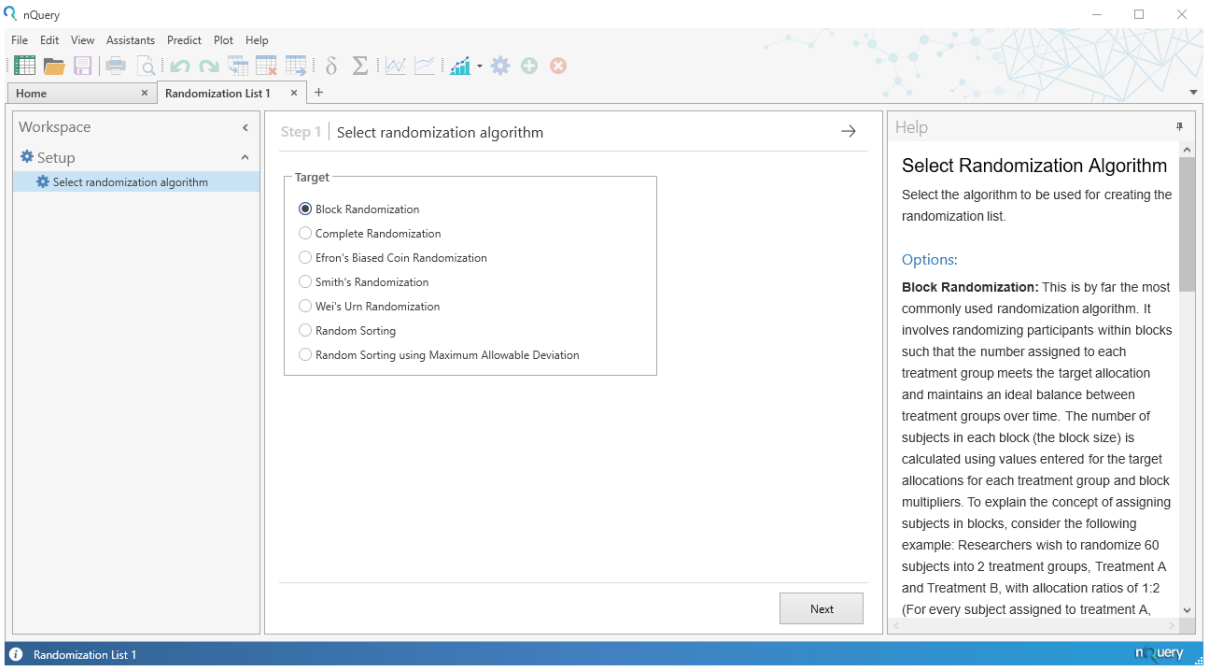


Figure 6.40: Selecting Block Randomization in Step 1 of Setup

The second step in the setup is the **Parameters for Block Randomization** step. After consideration, the researchers have identified that for the **Number of Block Multpliers** value they will choose 3 (the default). Then for the actual **Block Multiplier** values, they will use values of 1,2 and 3 (the default). For **Block Subject Allocation,** they will choose Random. They will also choose Yes for both the **Constrain Block Allocation** and **Specify Block ID and Block Size in Output.** The researchers have identified that using 3 block multiplier values of 1,2 and 3 (the default values) will be ideal for generating the desired the randomization list by ensuring that there is minimal oppurtunities for selection bias to occur. An example of these values being selected for the **Parameters for Block Randomization** step of the **Setup** is provided in Figure 6.41.

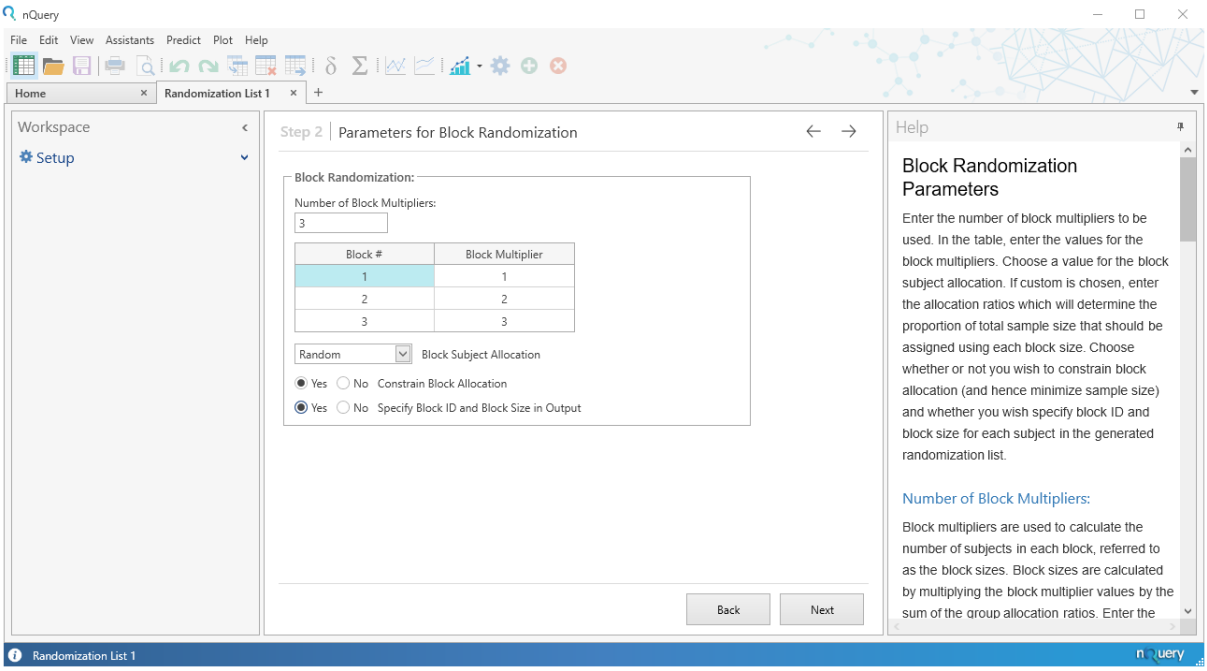


Figure 6.41: Specifying Block Randomization Parameters in Step 2 of Setup

The third step in the **Setup** is **Specify target sample size**. As previously stated, the researchers wish to randomly assign 120 subjects into 3 different treatment groups with equal sample sizes. Subjects in the treatment groups will receive a 40mg dose, a 80mg dose and a placebo respectively. In **Step 3**, the reserchers set the **Target Sample Size** value to 120. Then in the **Treatment Groups** section, the researchers keep the value in the **Title/Name** field as Treatment Group. Following this, the value in the **Number of Treatments** field is changed to 3. When the value of 3 is entered, the **Specify Treatment Group Information Table** will update to include a third row for entering information for the third group. In the **Treatment Group** column of the **Specify Treatment Group Information Table,** the researchers change the values in each of the rows to "40mg", "80mg" and "Placebo" respectively. No changes are made in the **Allocation Ratio** column, as the researchers will be using the default allocation ratio values of 1,1 and 1. An example of the **Specify target sample size** step with these inputs entered is provided in Figure 6.42.

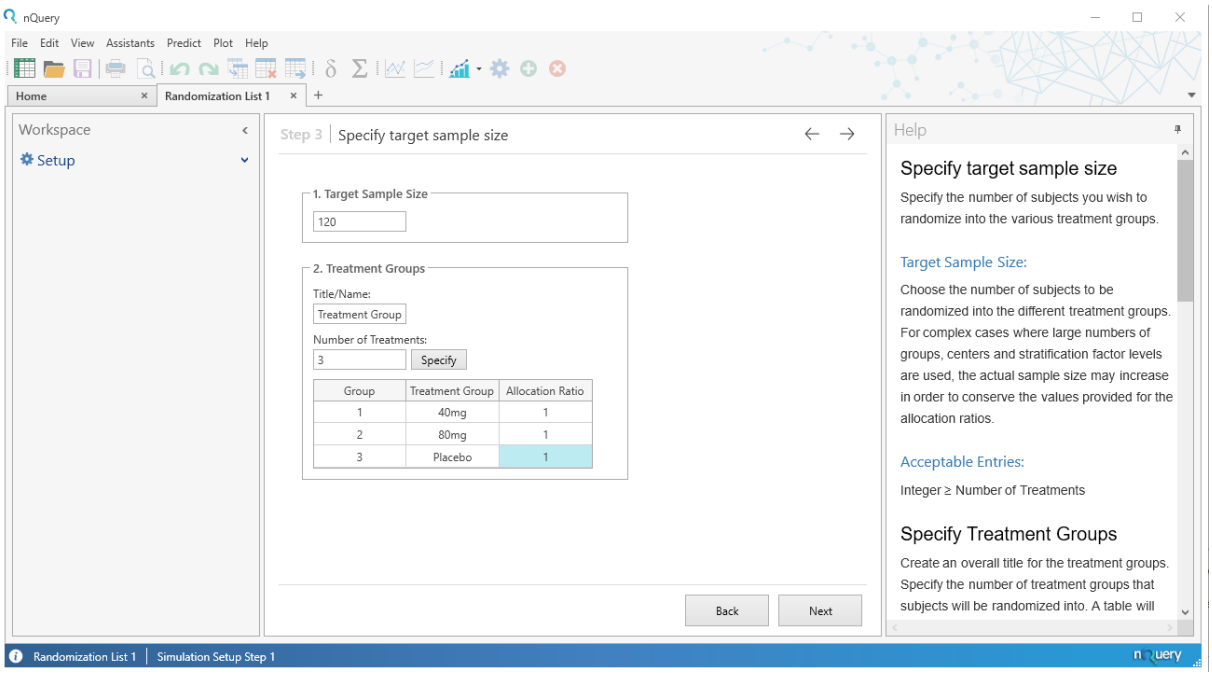


Figure 6.42: Specifying Target Sample Size and Treatment Group Information in Step 3 of Setup

The fourth step in the **Setup** is the **Specify Centers/Stratification Factors** step. Since the researchers will not be stratifying on center or any other stratification factors, no options need to be changed for this step. As such, in the **Centers** section, the option for **Include Centers?** can be left as No and in the **Stratification Factors** section, the **Number of Stratification Factors** option can be left as 0. An example of the **Specify Centers/Stratification Factors** step with these inputs entered is provided in Figure 6.43.

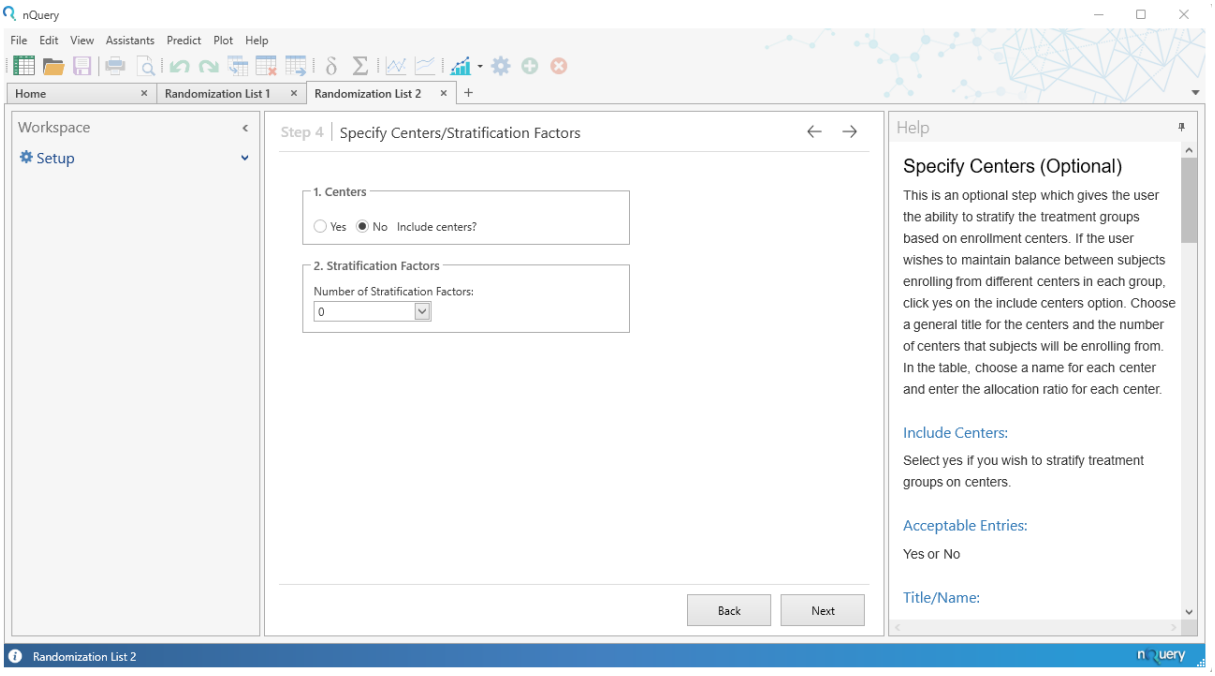


Figure 6.43: Specifying Centers/Stratificiation Factors in Step 4 of Setup

The fifth (and final) step in the **Setup** is the **Randomization list options** step. For reproducibility, the researchers will use a value of 10 for the **Random Seed** option. They also desire a unique randomization code to be attached to each subject, so they will set the **Include Unique Randomization Code for each Subject** option to Yes. An example of the **Randomization List options** with these options selected is provided in Figure 6.44.

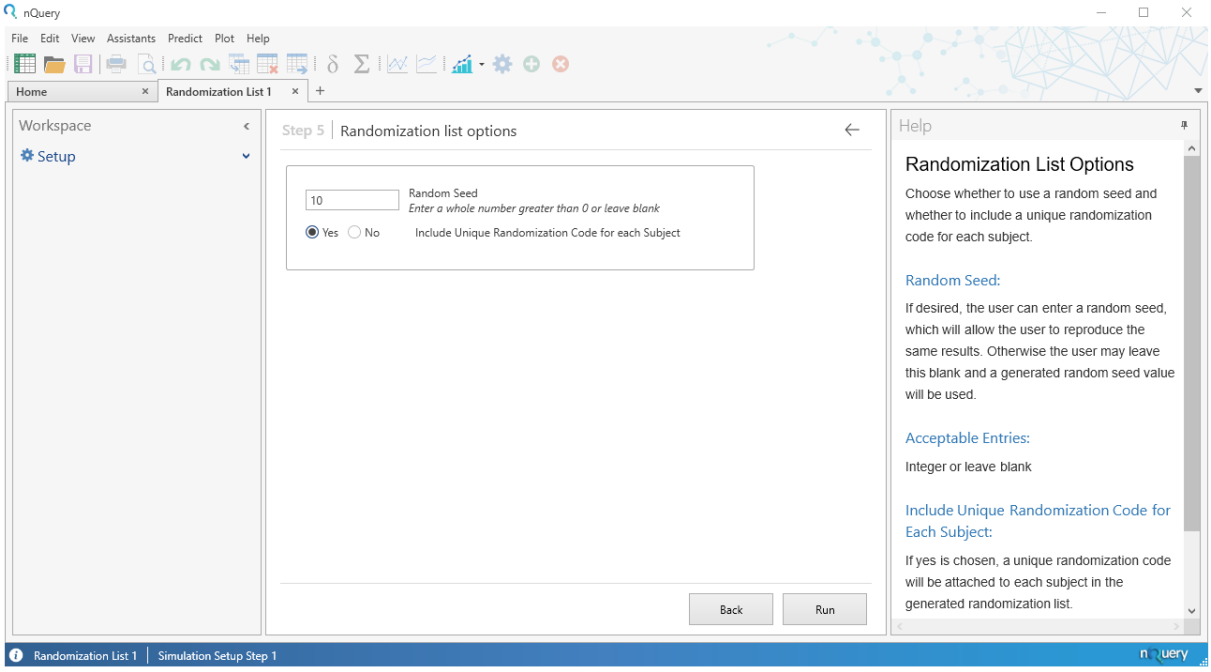


Figure 6.44: Specifying Randomization List Options in Step 5 of Setup

Once the **Setup** has been performed, the **Reports** section in the nQuery Randomization Lists Workspace will become available. Within this **Reports** section there will be two items, **Randomization List** and **Randomization List Summary. Randomization List** will contain the generated randomization list, which can be seen in Figure 6.45.

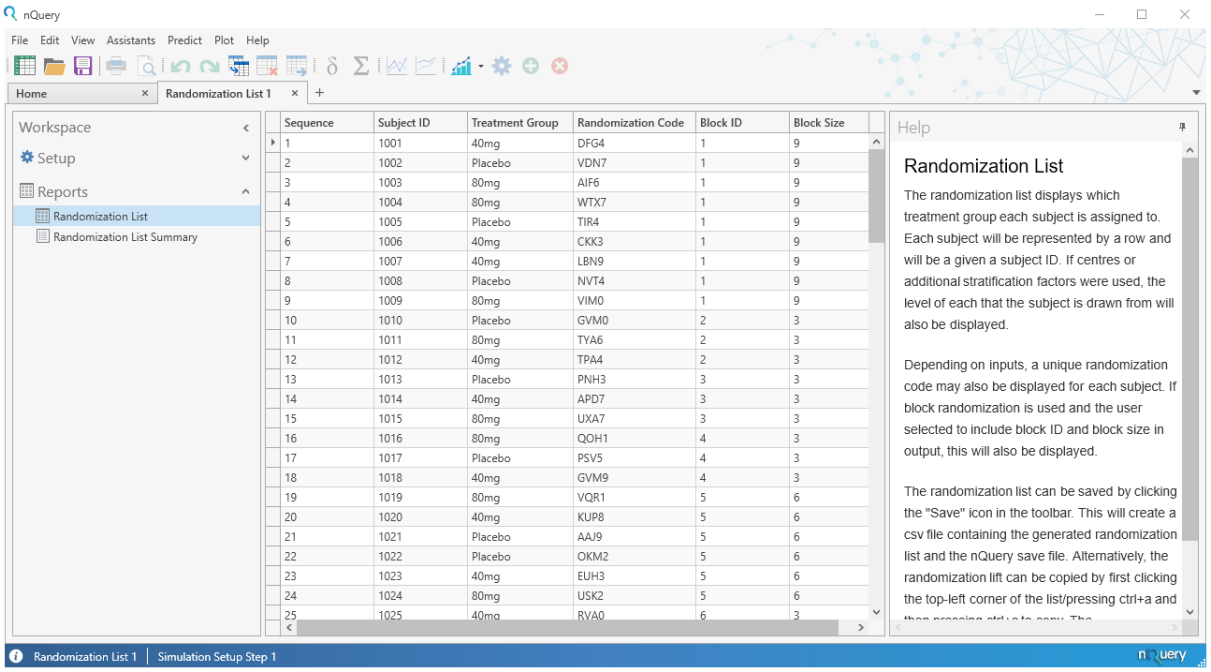


Figure 6.45: Generated Randomization List in Block Randomization Demonstration

Randomization List Summary will contain the summary information on the inputs and results of the generated randomization list. The **Randomization List Summary** can be seen in Figure 6.46.

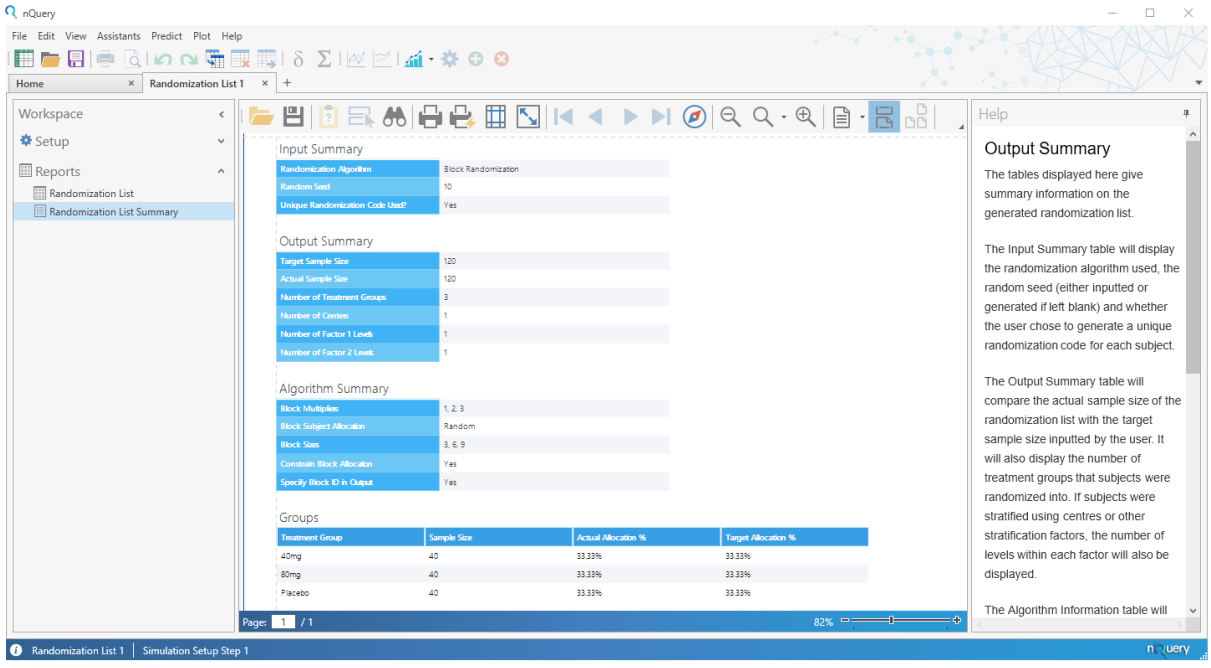


Figure 6.46: Randomization List Summary for Block Randomization Demonstration

6.2.6 Block Randomization with Stratification Demonstration

In this section we will perform a demonstration in which **Block Randomization** is used to generate a valid randomization list for a more complex example where stratification is desired. Consider a scenario where researchers wish to randomize 540 subjects into five different treatment groups. These five groups will be named A through E respectively. After investigating the various randomization algorithms that can be used, the researchers decide that **Block Randomization** will be the most appropriate in this scenario. A stratified randomization will be performed, with subjects being stratified on center of enrollment, as well as on two stratification factors, Age and Smoking Status. Subjects will be drawn from 6 centers. For each subject drawn from the last four centers, the researchers desire 2 subjects from the first 2 centers each. For the Age stratification factor, subjects will be drawn from three cohorts, those under 40, those between 40 and 60 and those greater than 60. Twice as many subjects will be drawn from the age cohort between 40 and 60 when compared with the other two age cohorts. For the Smoking Status stratification factor, subjects will be drawn from three cohorts, those who never smoked, former smokers and current smokers. For every subject drawn from the never smoked cohort, two will be drawn from the current smoker and former smoker cohorts.

In order to generate the desired randomization list, the researcher will open a new nQuery Randomization Lists Workspace in order to begin the **Setup**. For information on how to open and navigate through a Workspace, see subsection 6.2.1 and subsection 6.2.2. The first step in the **Setup** is the **Select Randomization algorithm** step. From the list of possible options in the **Target** section, the researcher will select the **Block Randomization** option. An example of the **Block Randomization** algorithm being selected is provided in Figure 6.47.

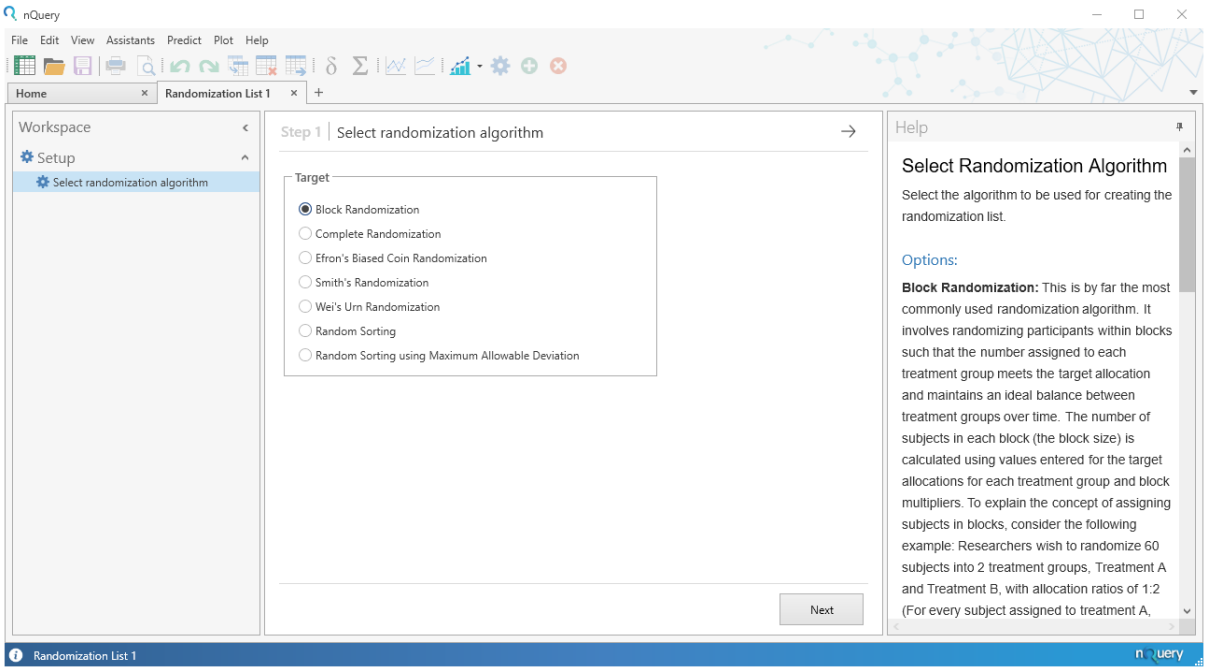


Figure 6.47: Select Randomization Algorithm Step in Demonstration of Block Randomization with Stratification

The second step in the **Setup** is the **Parameters for Block Randomization** step.

After consideration, the researchers decide they will set the **Number of Block Multipliers** to 3 and will set the corresponding **Block Mulitplier** column values in the **Block Multiplier Table** to 1,2 and 3, as these values will ensure that there is a low level of assignment predictability. They will set the **Block Subject Allocation** value to Random. As they wish to ensure that the actual sample size of the generated randomization list is minimized, they will set **Constrain Block Allocation** to Yes. They will also set **Specify Block ID and Block Size in Output** to Yes, as they will find it helpful having information on the blocks used in the output. The **Parameters for Block Randomization** step with these inputs is provided in Figure 6.48.

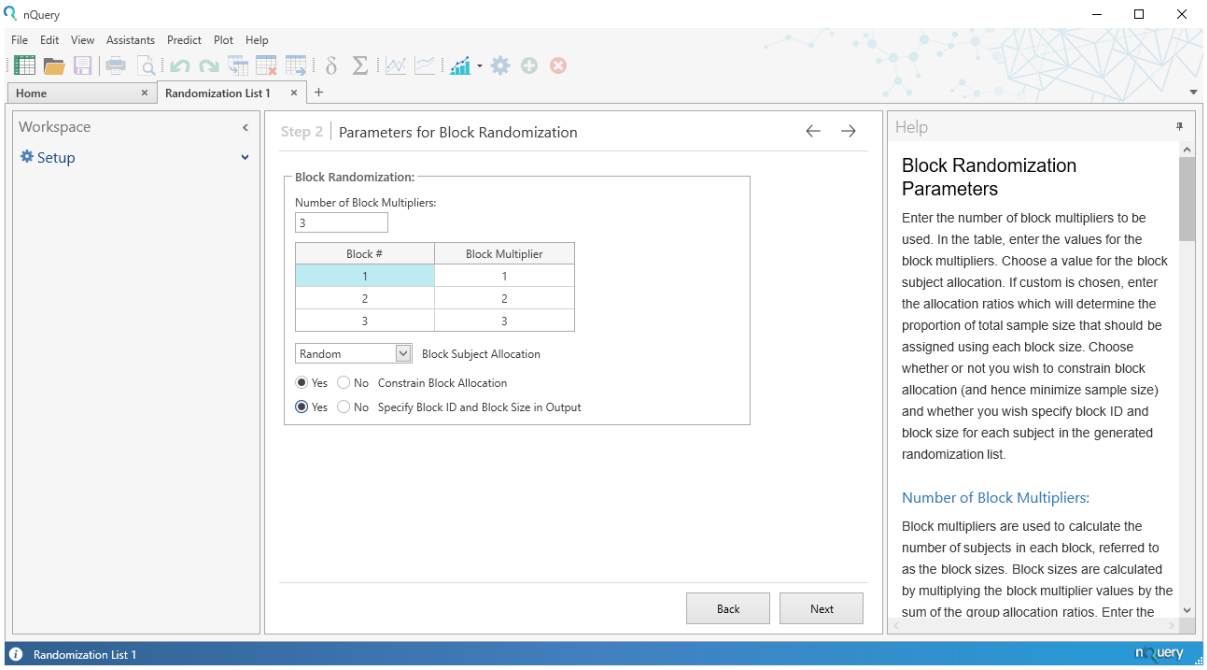


Figure 6.48: Parameters for Block Randomization step in Block Randomization with Stratification Demonstration

The third step in the **Setup** is the **Specify target sample size** step. As stated previously, the researchers wish to randomly assign 540 subjects into 5 different treatment groups with allocation ratios of (2,2,1,1,1). These groups will be named A through E respectively. In the **Target Sample Size** section, the researchers should enter 500 in the field. In the **Treatment Groups** section, the researchers will keep the default of value of "Treatment Group" in the **Title/Name** field. The value in the **Number of Treatments** field is changed to 5. When the value of 5 is entered, the **Specify Treatment Group Information Table** will update to include 5 rows for entering the required information for each of the groups. In the **Treatment Group** column of the **Specify Treatment Group Information Table**, the researchers change the values in each of these rows to "A", "B", "C", "D", "E". In the **Allocation Ratio** column, the values are changed to 2,2,1,1,1. An example of the **Specify target sample size** step with these inputs is provided in Figure 6.49.

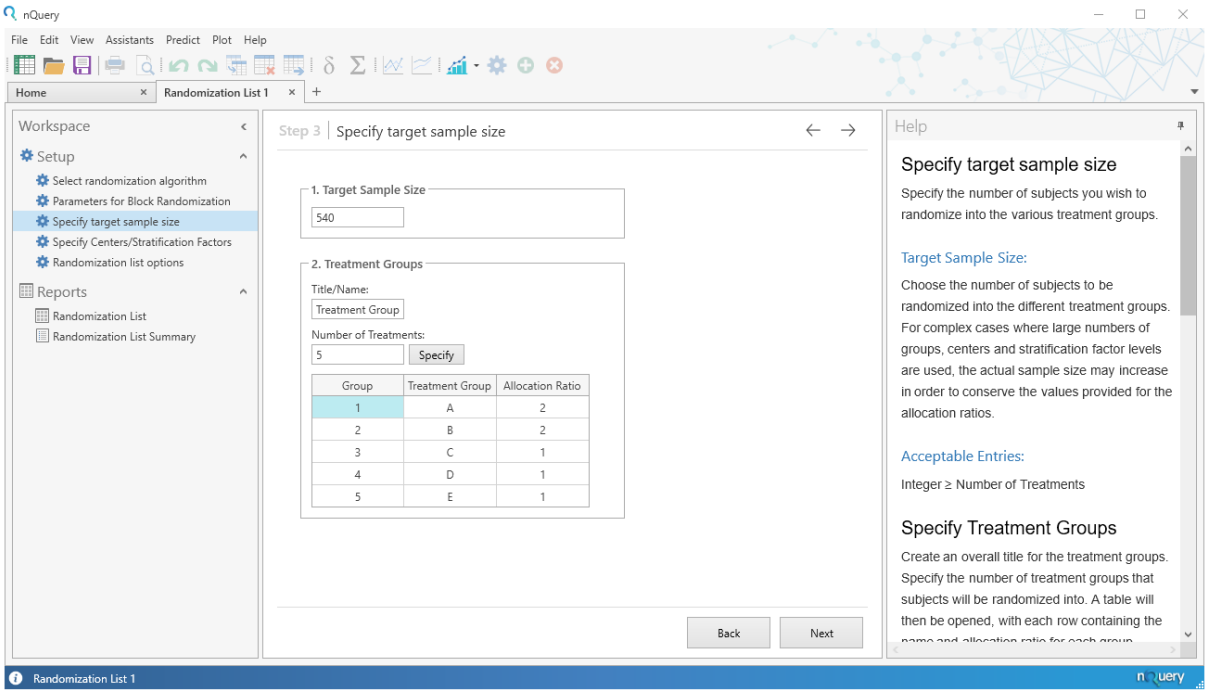


Figure 6.49: Specify target sample size Step for Block Randomization with Stratification Demonstration

The fourth step in the **Setup** is the **Specify Centers/Stratification Factors** step. First they examine the **Centers** section**.** As the researchers wish to stratify upon center, they set the **Include Centers?** option to Yes. They leave the **Title/Name** field as "Center". As they wish to draw subjects from six centers, they change the **Number of Centers** value to 6. When this value is changed, the **Specify Center Information Table** will update to include 6 rows. The researchers leave the center names in the **Center** column as the default values. They change the values in the **Allocation Ratio** column to 2,2,1,1,1,1. The **Centers** section of **Step 4** with these inputs is provided in Figure 6.50.

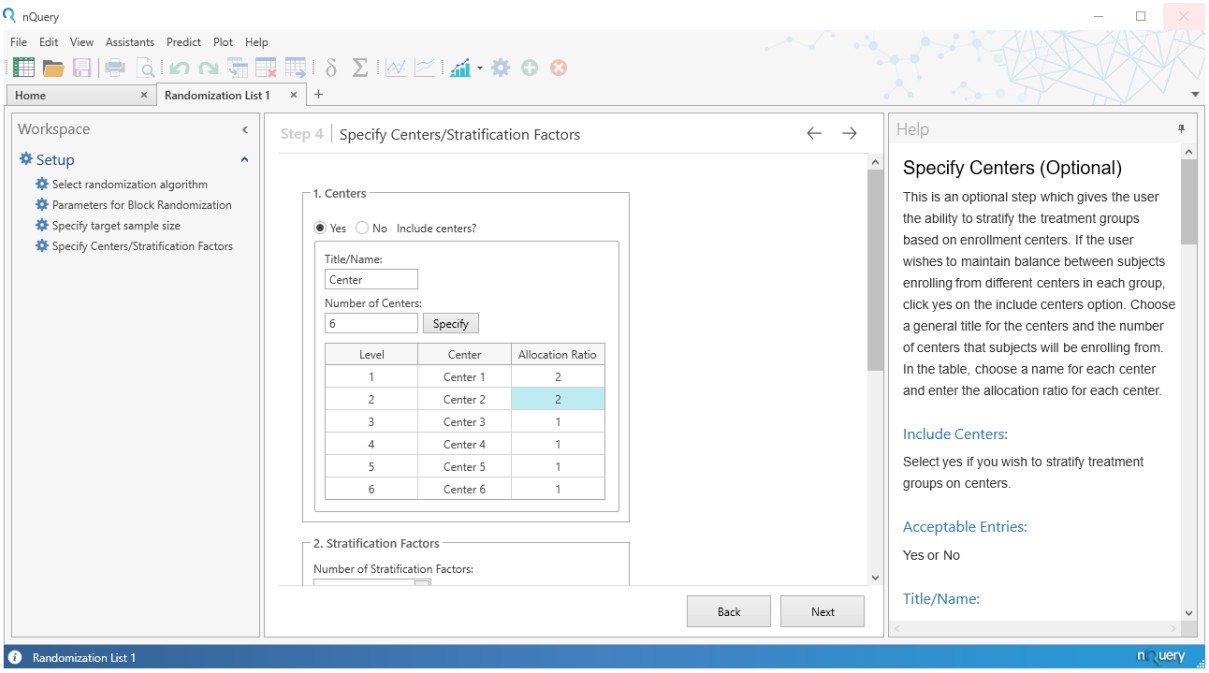


Figure 6.50: Centers section of Specify Centers/Stratification Factors Step for Block Randomization with Stratification Demonstration

Now the researchers will examine the **Stratification Factors** section. As they wish to stratify subjects upon two stratification factors, they change the **Number of Stratification Factors** value to 2. They then change the **Factor 1 Title/Name** value to Age and change the **Factor 1 Levels** value to 3. In the **Specify Factor 1 Information Table**, they change the values in the **Age** column to <40, 40-60 and >60. In the **Allocation Ratio** column, they change the values to 1,2,1. Following this, they set the **Factor 2 Title/Name** value to Smoking Status and change the **Factor 2 Levels** value to 3. In the **Specify Factor 2 Information Table**, they change the values in the **Smoking Status** column to Never, Former and Current. They will change the values in the **Allocation Ratio** column to 1,2 and 2. The **Stratification Factors** section of **Step 4** with these inputs in provided in Figure 6.51.

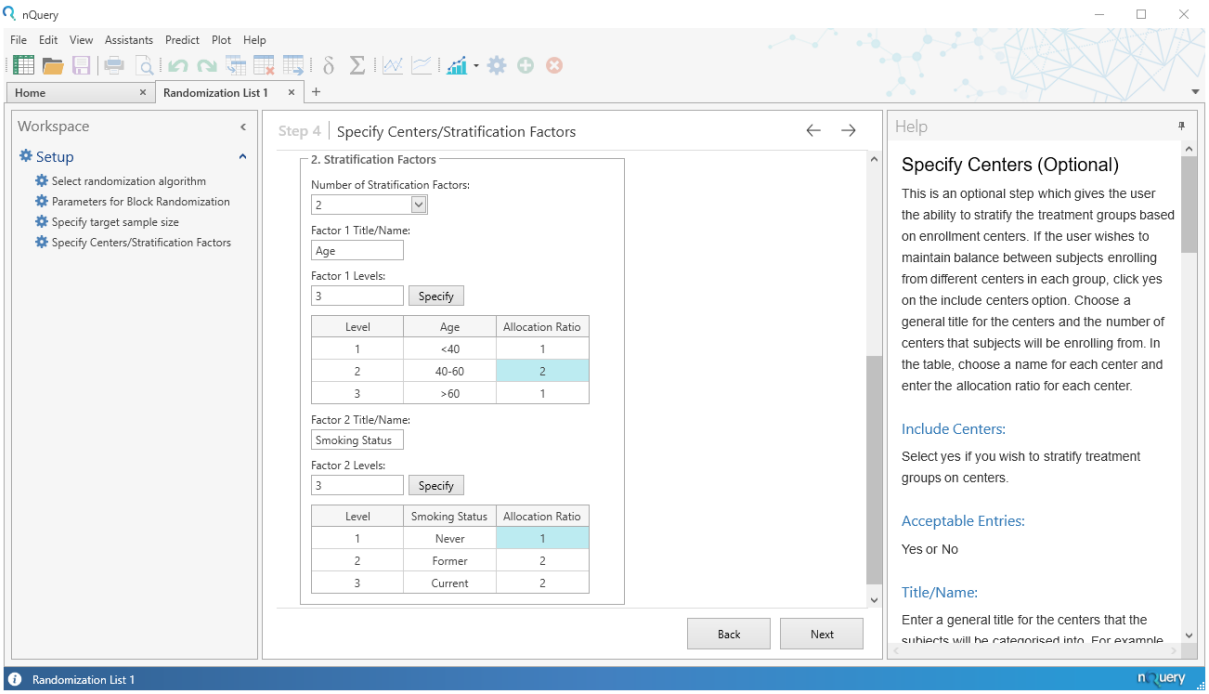


Figure 6.51: Stratification Factors section of Specify Centers/Stratification Factors Step for Block Randomization with Stratification Demonstration

The fifth step in the **Setup** is the **Randomization list options** step. The researchers enter a value of 100 for the **Random Seed**, so that the results can be easily reproduced. They also set the **Include Unique Randomization Code for each Subject** value to Yes, as this may be helpful for blinding purposes.

Once the **Setup** has been performed, the **Reports** section in the nQuery Randomization Lists Workspace will become available. Within this **Reports** section there will be two options, **Randomization List** and **Randomization List Summary. Randomization List** will contain the generated randomization list, which can be seen in Figure 6.52.

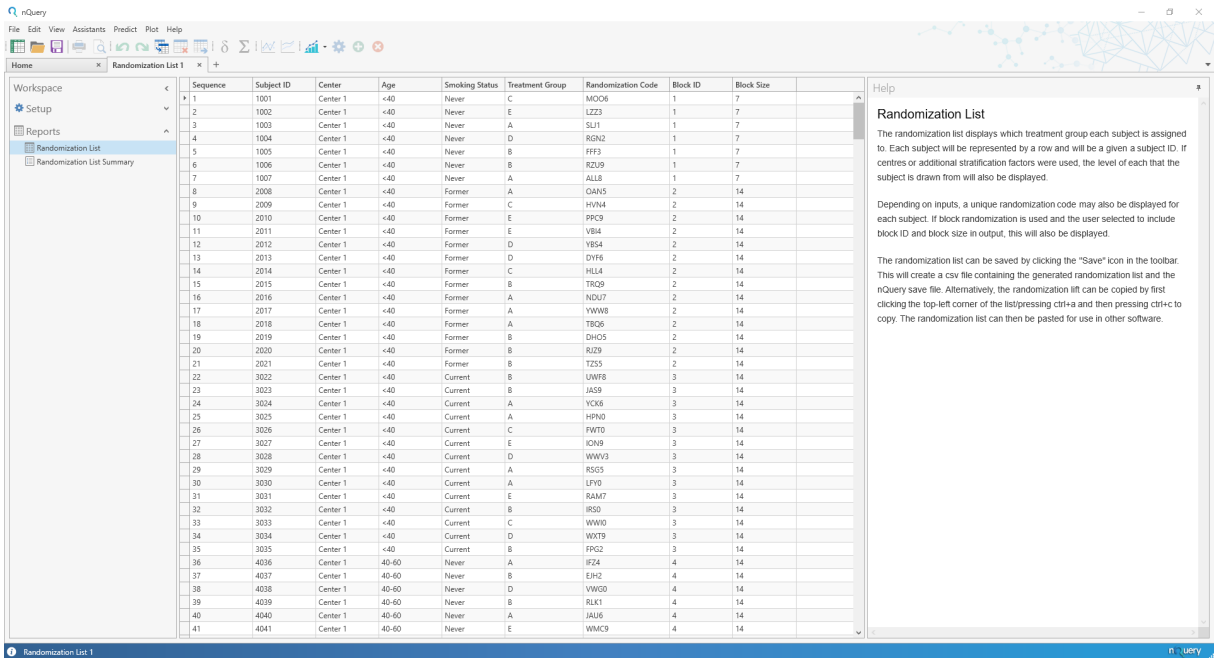


Figure 6.52: Generated Randomization List in Block Randomization with Stratification Demonstration

Randomization List Summary will contain the summary information on the inputs and results of the generated randomization list. The **Randomization List Summary** can be seen in Figure 6.53 and Figure 6.54.

Input Summary

Randomization Algorithm	Block Randomization
Random Seed	100
Unique Randomization Code Used?	Yes

Output Summary

Target Sample Size	540
Actual Sample Size	588
Number of Treatment Groups	5
Number of Centers	6
Number of Factor 1 Levels	3
Number of Factor 2 Levels	3

Algorithm Summary

Block Multipliers	1, 2, 3
Block Subject Allocation	Random
Block Sizes	7, 14, 21
Constrain Block Allocation	Yes
Specify Block ID in Output	Yes

Groups

Treatment Group	Sample Size	Actual Allocation %	Target Allocation %
A	168	28.57%	28.57%
B	168	28.57%	28.57%
C	84	14.29%	14.29%
D	84	14.29%	14.29%
E	84	14.29%	14.29%

Figure 6.53: Part 1 of Randomization List Summary for Block Randomization with Stratification Demonstration

Strata

Center	Age	Smoking Status	First Subject ID	Blocks Used	Sample Size	Actual Allocation %	Target Allocation %
Center 1	<40	Never	1001	1	7	1.19%	1.25%
Center 1	<40	Former	2008	1	14	2.38%	2.50%
Center 1	<40	Current	3022	1	14	2.38%	2.50%
Center 1	40-60	Never	4036	1	14	2.38%	2.50%
Center 1	40-60	Former	5050	2	28	4.76%	5.00%
Center 1	40-60	Current	6078	2	28	4.76%	5.00%
Center 1	>60	Never	7106	1	7	1.19%	1.25%
Center 1	>60	Former	8113	1	14	2.38%	2.50%
Center 1	>60	Current	9127	1	14	2.38%	2.50%
Center 2	<40	Never	10001	1	7	1.19%	1.25%
Center 2	<40	Former	11008	1	14	2.38%	2.50%
Center 2	<40	Current	12022	1	14	2.38%	2.50%
Center 2	40-60	Never	13036	1	14	2.38%	2.50%
Center 2	40-60	Former	14050	2	28	4.76%	5.00%
Center 2	40-60	Current	15078	2	28	4.76%	5.00%
Center 2	>60	Never	16106	1	7	1.19%	1.25%
Center 2	>60	Former	17113	1	14	2.38%	2.50%
Center 2	>60	Current	18127	1	14	2.38%	2.50%
Center 3	<40	Never	19001	1	7	1.19%	0.63%
Center 3	<40	Former	20008	1	7	1.19%	1.25%
Center 3	<40	Current	21015	1	7	1.19%	1.25%
Center 3	40-60	Never	22022	1	7	1.19%	1.25%
Center 3	40-60	Former	23029	1	14	2.38%	2.50%
Center 3	40-60	Current	24043	1	14	2.38%	2.50%
Center 3	>60	Never	25057	1	7	1.19%	0.63%
Center 3	>60	Former	26064	1	7	1.19%	1.25%
Center 3	>60	Current	27071	1	7	1.19%	1.25%
Center 4	<40	Never	28001	1	7	1.19%	0.63%
Center 4	<40	Former	29008	1	7	1.19%	1.25%
Center 4	<40	Current	30015	1	7	1.19%	1.25%

Figure 6.54: Part 2 of Randomization List Summary for Block Randomization with Stratification Demonstration

6.2.7 Complete Randomization Demonstration

In this section, a demonstration will be performed in which **Complete Randomization** is used to generate a valid randomization list. Consider a scenario where researchers wish to randomize 3000 subjects into three different treatment groups, which will be called Group 1, Group 2 and Group 3. They wish to have an approximately equal sample size in each group. Due to the relatively large sample size, the researchers decide that **Complete Randomization** will be sufficient as it is not overly important that the desired sample sizes in each group are met exactly. A stratified randomization will not be performed.

In order to generate the desired randomization list, the researchers open a new nQuery Randomization Lists Workspace in order to begin the **Setup**. For information on how to open and navigate through a Workspace, see subsection 6.2.1 and subsection 6.2.2. The first step in the **Setup** is the **Select Randomization algorithm** step. From the list of possible options in the **Target** section, the researcher will select the **Complete**

Randomization option. An example of the **Complete Randomization** algorithm being selected is provided in Figure 6.55.

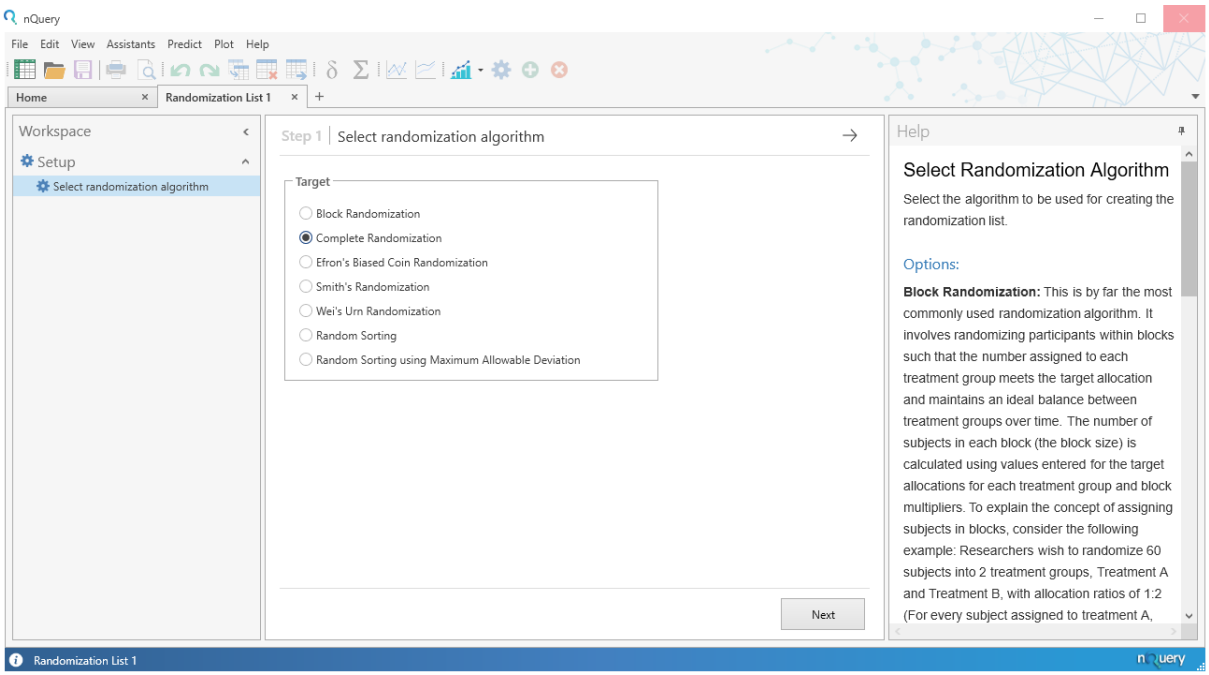


Figure 6.55: Select randomization algorithm Step in Complete Randomization Demonstration

The second step in the **Setup** is the **Parameters for Complete Randomization** step. After consideration, the researchers decide that they will not utilize the ability to **Search for a list in which actual group sizes match the target group sizes**. As a result, no options need to be changed for this step. An example of the **Step 2** window for this demonstration can be seen in Figure 6.56.

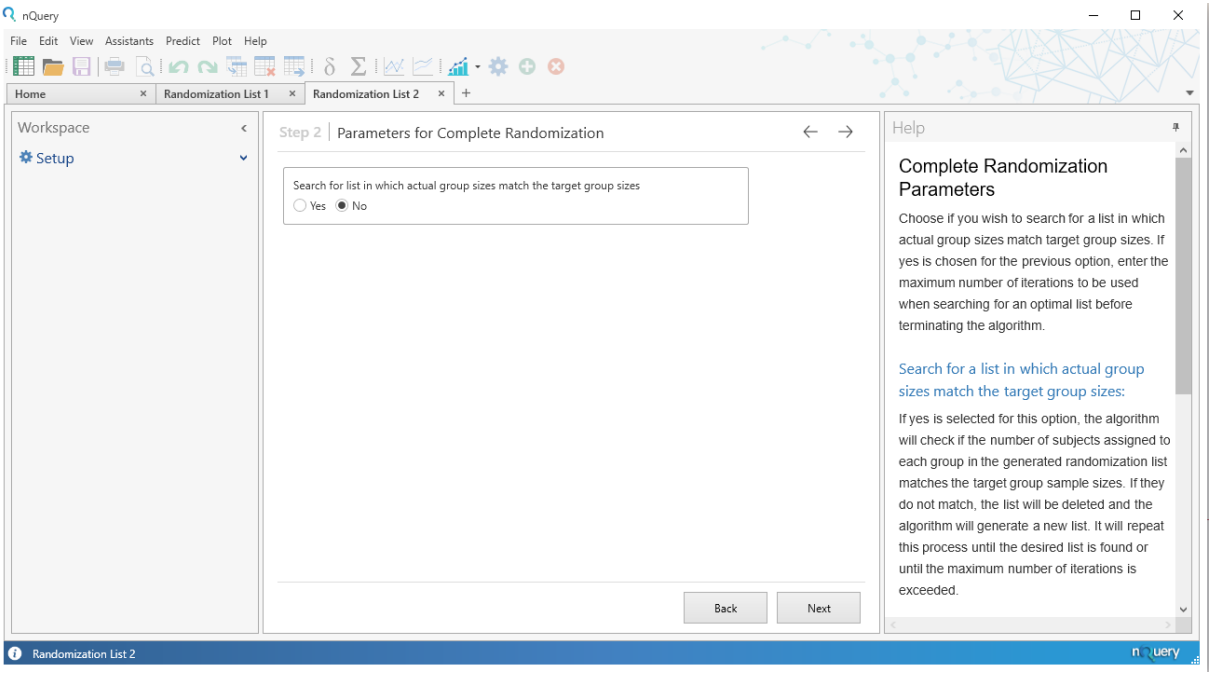


Figure 6.56: Parameters for Complete Randomization Step in Complete Randomization Demonstration

The third step in the **Setup** is the **Specify target sample size** step. As the researchers wish to randomize 3000 subjects, they enter 3000 in the **Target Sample Size** section. In the **Treatment Groups** section, the researchers leave the value in the **Title/Name** field as the default value of Treatment Group. They change the value in the **Number of Treatments** field to 3. As a result, the **Specify Treatment Group Information Table** will update to have three rows. In the **Treatment Group** column of the table, they set the names of the treatment groups to "Treatment 1", "Treatment 2" and "Treatment 3". As they wish to have an approximately equal sample size in each group, they will leave the values in the **Allocation Ratio** column as the default values of 1,1,1. An example of the **Step 3** window with these values inputted can be seen in Figure 6.57.

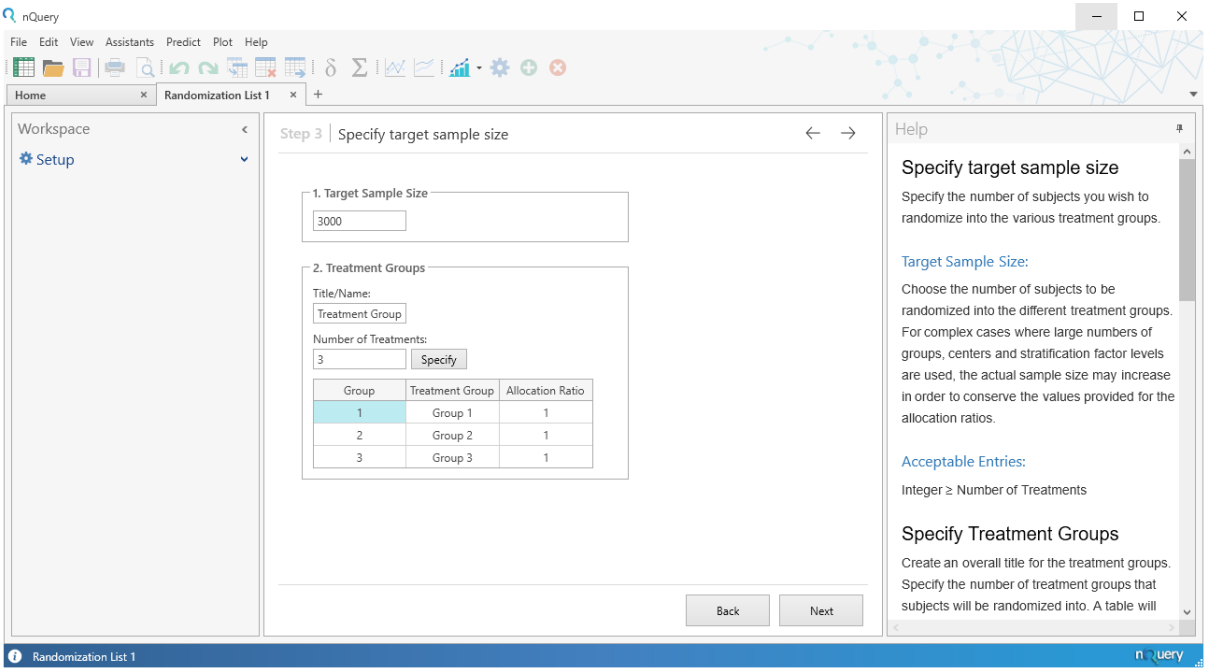


Figure 6.57: Specify target sample size step for Complete Randomization Demonstration

The fourth step in the **Setup** is the **Specify Centers/Stratification Factors** step. As the researchers have decided that they will not be conducting a stratified randomization, this step can be skipped and no options need to be changed. An example of the **Step 4** window with these values inputted can be seen in Figure 6.58.

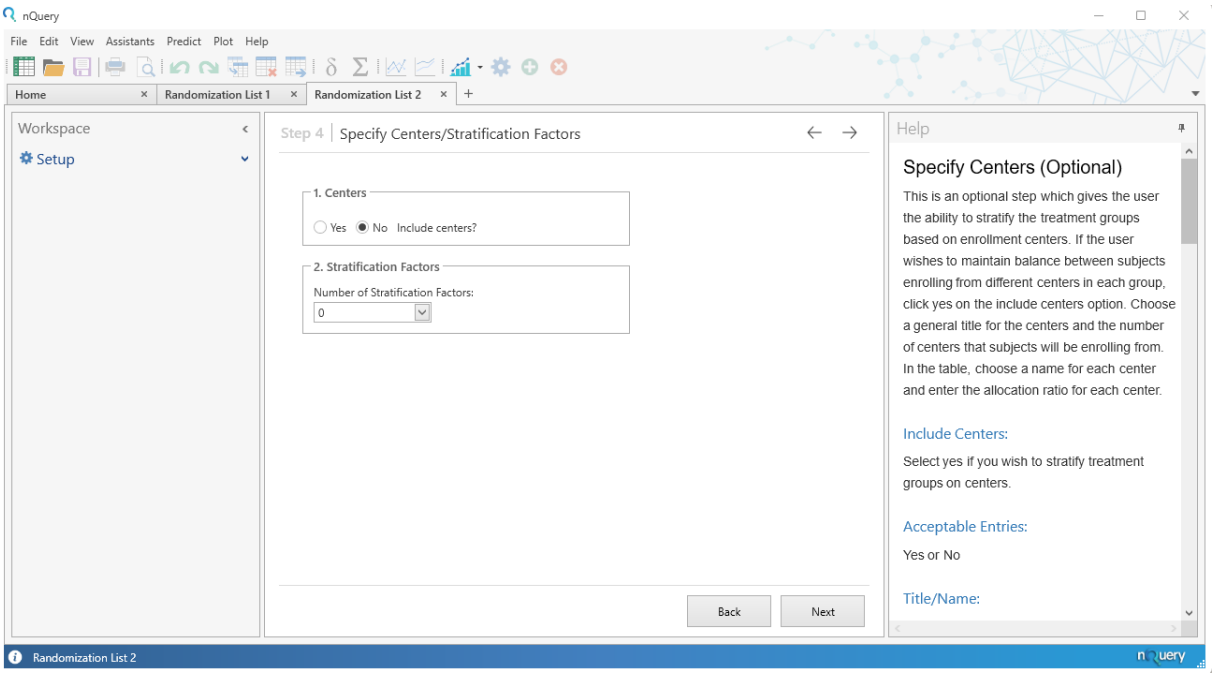


Figure 6.58: Specify Centers/Stratification Factors Step in Complete Randomization Demonstration

The fifth step in the **Setup** is the **Randomization list options** step. The reseachers decide that for reproducibility purposes, they wish to use a **Random Seed** value of

100. They also decide that for blinding purposes, they will set the **Include Unique Randomization Code for each Subject** to "Yes" so that each subject obtains a unique randomization code. The **Step 5** window with these options selected can be seen in Figure 6.59.

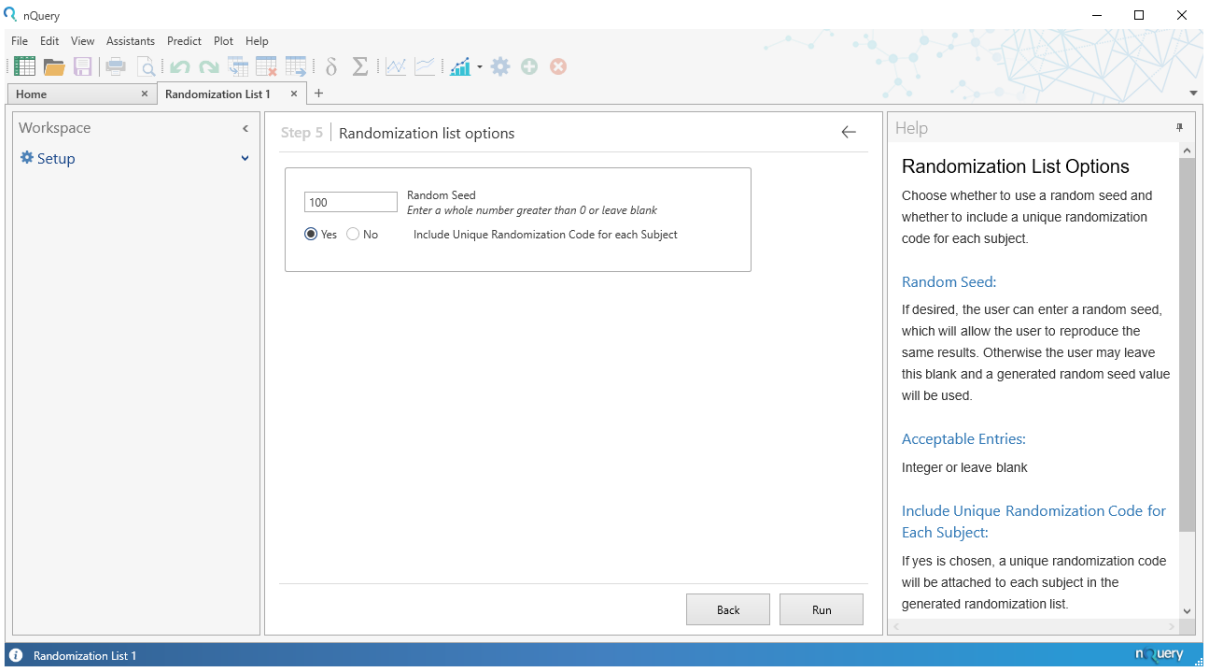


Figure 6.59: Randomization list options Step in Complete Randomization Demonstration

Once the **Setup** has been performed, the **Reports** section in the nQuery Randomization Lists Workspace will become available. Within this **Reports** section there will be two options, **Randomization List** and **Randomization List Summary. Randomization List** will contain the generated randomization list, which can be seen in Figure 6.60.

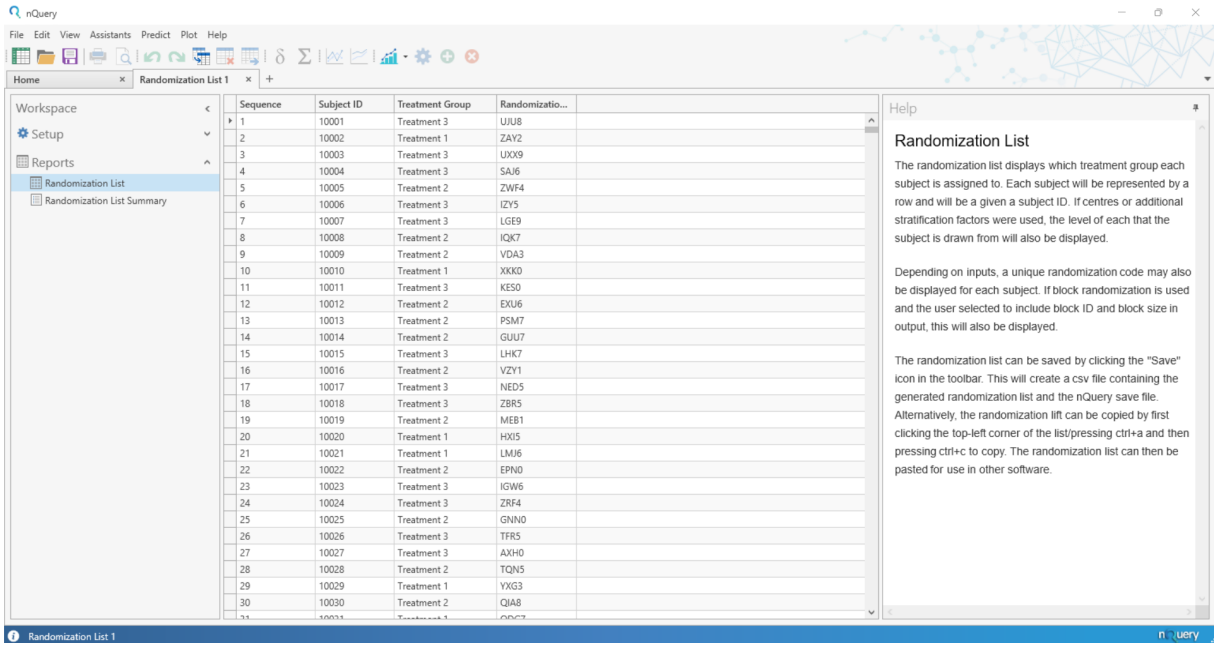


Figure 6.60: Generated Randomization List in Complete Randomization Demonstration

Randomization List Summary will contain the summary information on the inputs and results of the generated randomization list. The **Randomization List Summary** can be seen in Figure 6.61.

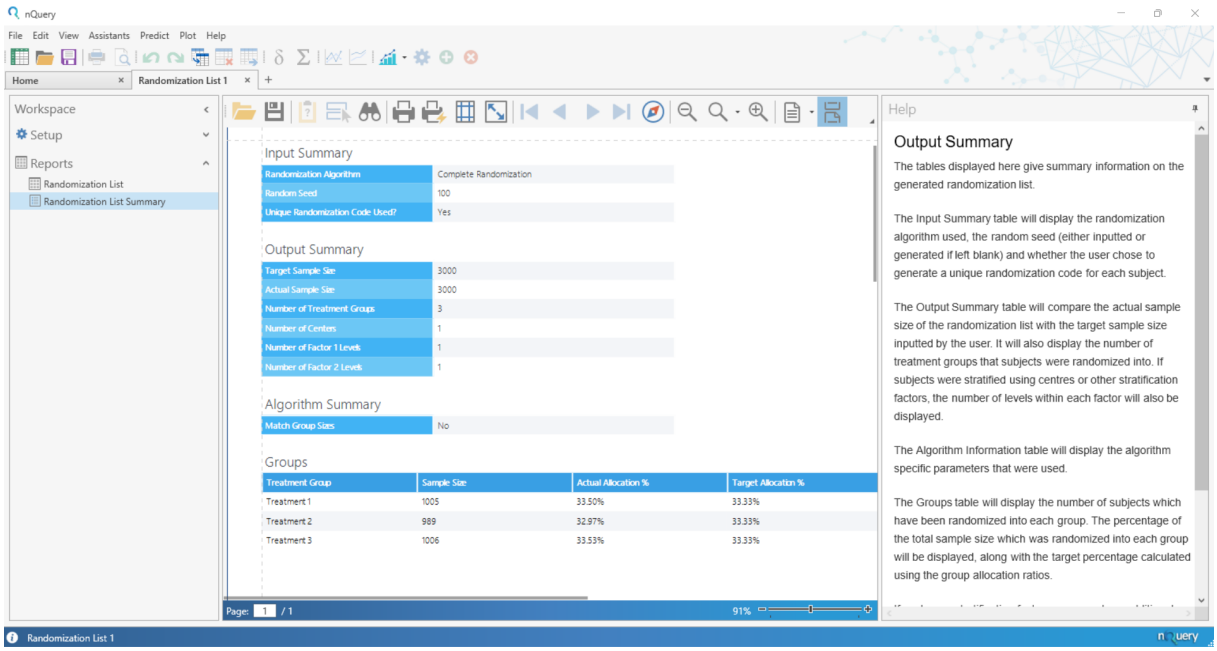


Figure 6.61: Randomization List Summary for Complete Randomization Demonstration

6.2.8 Other Features

6.2.8.1 Saving and Exporting a Workspace

nQuery provides the file format of **.nqrl** to save and export an nQuery Randomization Lists Workspace. To save an nQuery Randomization Lists Workspace, select **Save** from the File Menu or select the **Save** icon from the toolbar or use the **CTRL+S** keyboard shortcut. This will open the **Save Workspace** window which is shown in Figure 6.62.

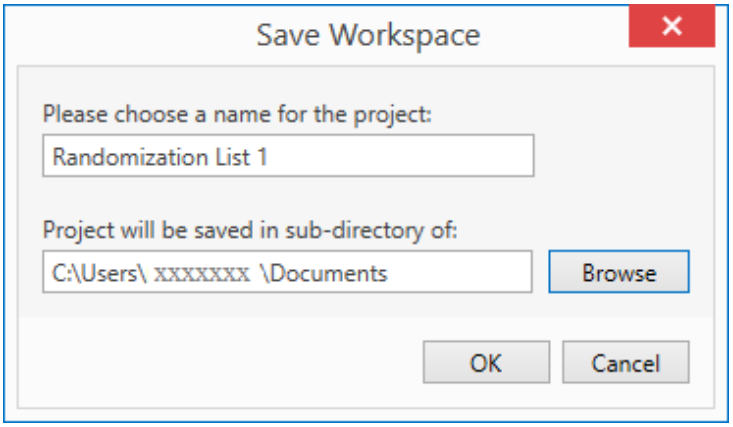


Figure 6.62: Save Workspace Window

The **Save Workspace** window allows the user to specify the name of the .nqrl file in the **Please choose a name for the project** field and the location to save the .nqrl file in the **Project will be saved in sub-directory of** field. The user can also edit the **Project will be saved in sub-directory of** using the Browse button, which will open the **Browse for Folder** window. To save the project, select the OK button.

When a project is saved, a folder with the **Please choose a name for the project:**name will be present in the folder specified in the **Project will be saved in sub-directory of** field. This project folder will contain the .nqrl file. If a randomization list has been fully generated in the current workspace, the project folder will also contain this generated randomization list in **.csv** format.

After an nQuery Workspace is saved, if a change is made to the workspace the user can save over the prior save using the Save options (see above) or save a separate version using Save As from the File menu.

To open a saved .nqrl file, select the file in Windows Explorer or find the file from the Open Menu which can be selected from the File Menu, the toolbar icon or **CTRL+O** keyboard shortcut. Opening a .nqrl file works as for other nQuery file types (see subsection 1.7.5).

6.2.8.2 Exporting a Generated Randomization List Comma Separated Variable file

Two options exist for exporting a generated randomization list comma separated variable (csv) file. The first is saving and exporting the nQuery Randomization List Workspace (see Figure 6.62). In the generated folder, there will be a file containing the generated randomization list in **.csv** format. This file will take the name of the value entered for

the **Please choose a name for the project** field in the **Save Workplace** step. An example of this file in the save folder is displayed in Figure 6.63.

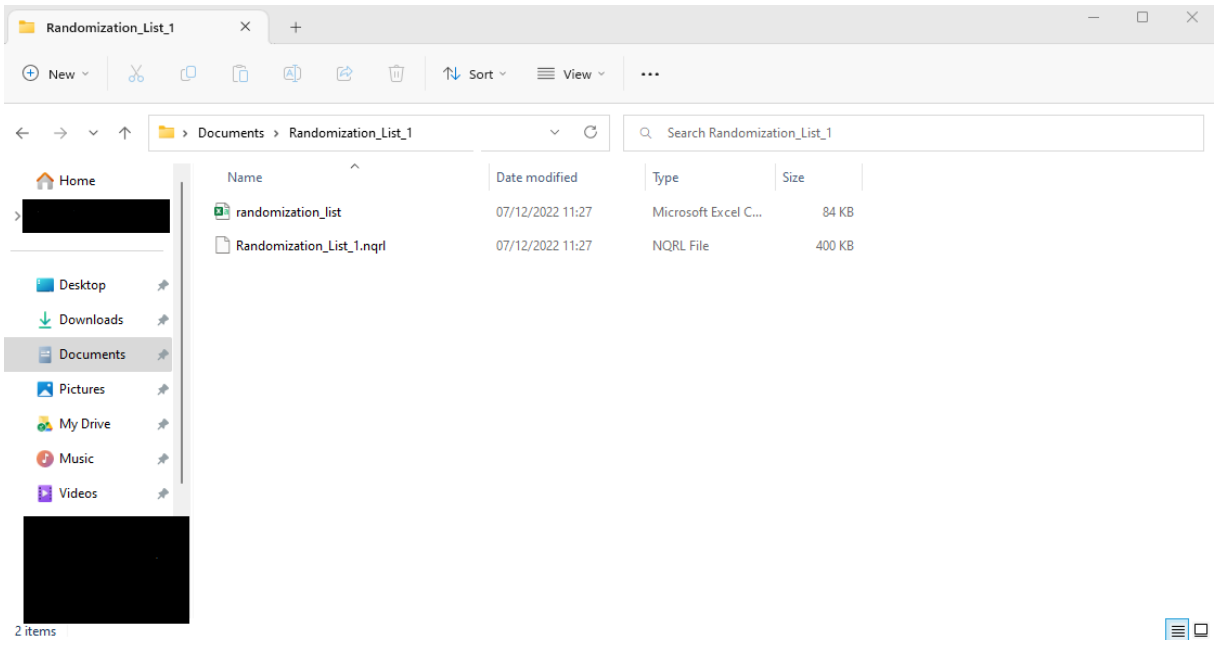


Figure 6.63: Example of an nQuery Randomization Lists Save Folder

The generated randomization list can also be copied to the Windows clipboard directly from the nQuery Randomization Lists Workspace. To do this, the **Randomization List** report in the **Reports** section must be open. To select the entire randomization list, the user can use the keyboard shortcut **CTRL+A** or can click the empty top-left cell of the **Randomization List** window. Alternatively, particular rows can be selected by clicking the empty cell to the left of a row, holding the **SHIFT** keyboard button and then clicking the empty cell to the left of another row. Once the **Randomization List** is selected in this way, the user can use the keyboard shortcut **CTRL+C** to copy the information to the clipboard. This information can then be pasted in **.csv** format into relevant software by using the right-click and paste option or by using the keyboard shortcut **CTRL+V**.

7 Group Sequential Design (Spending Function, Haybittle-Peto, Wang-Tsiatis, Unified Family, Custom Boundaries Tables)

This chapter only provides information on the ***Group Sequential Design (Spending Function, Haybittle-Peto, Wang-Tsiatis, Unified Family, Custom Boundaries)*** *series of tables and the associated* ***Group Sequential Simulator Tool***

For information on the ***Group Sequential Design (Lan-DeMets Spending Function Only)*** *tables and their associated* ***Interim Monitoring & Unblinded Sample Size Re-estimation*** *tools, please refer to chapter 9.*

For reference the Spending Function, Haybittle-Peto, Wang-Tsiatis, Unified Family, Custom Boundaries tables are the GSTX series of tables including GST0 (Information-Based), GST1 (Two Means), GST2 (Two Proportions), GST3 (Two Survival - Event-Driven or Fixed Follow-up, Piecewise Survival, Accrual %)

The Lan-DeMets Spending Function Only tables are MTT12 (Two Means), MTT40 (Two Poisson), MTT42 (Two Negative Binomial), MTE32 (Two Means Non-inferiority), MOT26 (One Mean), PTT12 (Two Proportions), POT8 (One Proportion - Alternative Variance), POT13 (One Proportion - Null Variance), STT12 (Two Survival - Fixed Follow-up, Constant Hazard), STT15 (Two Survival - Event-Driven, Constant Hazard), STT23 (Two Survival - Event-Driven, Piecewise Survival, Accrual Rates), STT25 (Two Survival - Event-Driven, Piecewise Survival, Accrual %). The associated Interim Monitoring & Unblinded Sample Size Re-estimation tables are MTT25 (Two Means - linked with MTT12), PTT21 (Two Proportion - linked with PTT12) and STT17 (Two Survival - linked with STT12, STT15, STT23, STT25)

7.1 Introduction

This chapter will cover the statistical theory behind the **Group Sequential Design (Spending Function, Haybittle-Peto, Wang-Tsiatis, Unified Family, Custom Boundaries)** series of **GSTX** tables and will give detailed description of how to design a group sequential trial in nQuery using these tables. It will also summarize the theory and user interface of the **Group Sequential Design Simulator** tool.

The Group Sequential Design and Group Sequential Design Simulator features will only be available to users if an nQuery Advanced Pro license is active. Active packages are displayed in the Packages section on the Home tab. To purchase additional packages, see `www.statsols.com`.

7.2 Group Sequential Design Theory

This section will provide an overview of the statistical theory of group sequential design. It will cover the following aspects:

- **Group Sequential Design Theory Overview:** Group Sequential Design definition and statistical background
- **Numerical Algorithm for Group Sequential Exit Probabilities:** Summary of theory for deriving required group sequential boundaries based on specified interim exit probabilities
- **Calculating Power/Maximum Information:** How to find power or maximum information for specific group sequential design
- **Different Boundary Calculation Methods:** Overview and statistical background on difference group sequential design boundary methods
- **Endpoint/Design Specific Sample Size Determination:** Overview and statistical background on determining sample size for group sequential designs for specific endpoints and designs

For further detail on the statistical theory of group sequential design, nQuery recommends the following books:

- Group Sequential Methods with Applications to Clinical Trials, Jennison, C. and Turnbull, B. W. (1999) [Jennison and Turnbull, 1999]
- Group Sequential and Confirmatory Adaptive Designs in Clinical Trials, Wassmer, G. and Brannath, W. (2016) [Wassmer and Brannath, 2016].

7.2.1 Group Sequential Design Theory Overview

Group Sequential Designs are the most common type of adaptive design in confirmatory clinical trials. Group sequential designs allow for a trial to be stop early at an interim analysis if there is sufficiently strong evidence at the interim analysis that the trial would accept or fail to accept the null hypothesis while maintaining the desired overall Type I (α) and Type II (β) error across all analyses.

In the clinical trial setting, the number of and the timing of the interim analyses are typically pre-specified with trials stopping early based on whether the evidence is strong enough to stop early based on a proposed treatment being effective (e.g. mean difference > 0 - by clinically significant amount) or ineffective/futile (e.g. mean difference $= 0$) based on interim analysis. Given the long nature of most clinical trials, group sequential designs offer a significant opportunity to get effective treatments to patients faster and reduce clinical trial costs.

Stopping early when there is strong evidence for a proposed treatment being effective at an interim analysis is called **stopping for efficacy.** This will occur when the test statistic crosses the **efficacy boundary** at a given interim analysis.

Stopping early when there is strong evidence against a proposed treatment being effective at an interim analysis is called **stopping for futility.** This will occur when the test statistic crosses the **futility boundary** at a given interim analysis.

The majority of group sequential designs are based on extending a fixed term trial (i.e. a trial where analysis occurs after all subjects have been followed up) to include interim analyses.[1] Naively testing a hypothesis multiple times during a trial can lead to substantial Type I error inflation. For example, five equally spaced interim analysis without adjustment can lead to an inflation of the Type I error from 0.05 to 0.142 [Armitage et al., 1969].

The adjustment for multiple interim analyses is conceptually similar to adjusting for multiple comparisons generally. However, there are significant efficiencies due to the correlated nature of interim analyses (since each interim analysis's data will contain the same data as from all earlier interim analyses) which substantially reduces the required information (sample size) compared to naively applying standard multiple comparison methods such as the Bonferonni adjustment to each interim analysis.

Multiple group sequential design methods have been proposed to calculate interim analysis boundaries that control the overall Type I error while also allowing control other operating characeteristics as the probability of exiting early at each given look or the average sample size. The different boundary calculation methods available in nQuery will be covered in detail in subsection 7.2.4. However, all these methods take advantage of this correlated nature of interim analyses and an overview of this theory is provided below as per Jennison and Turnbull [Jennison and Turnbull, 1999].

7.2.1.1 Group Sequential Assumptions

Let θ denote the effect difference between the treatment and control arms of a two arm trial. For example, θ may be the mean difference if comparing means or the (log) hazard ratio for survival analysis.

Assume there are a maximum of K analyses in the trial, which is to say K–1 interim analyses.

Denote the standardized test statistics from each analysis by Z_k, where the interim analysis look number $k = 1, 2, \ldots, K-1, K$. We will assume that the per-look standardized test statistics $(Z_1, Z_2, \ldots, Z_{K-1}, Z_K)$ have a *canonical joint distribution* conditional on the (Fisher) information levels $(I_1, I_2, \ldots, I_{K-1}, I_K)$ at each look if they satisfy the following properties:

1. $(Z_1, Z_2, \ldots Z_{K-1}, Z_K)$ are multivariate normal
2. $E(Z_k) = \theta\sqrt{I_k}$, $k = 1, 2, \ldots, K-1, K$
3. $Cov(Z_{k_1}, Z_{k_2}) = \sqrt{\frac{I_{k_1}}{I_{k_2}}}$, $1 \leq k_1 \leq k_2 \leq K$

I_K represents the maximum amount of statistical (Fisher) information that can be gained from the trial at the final analysis. We will denote this *maximum information* as I_{max}.

For each analysis in the trial we obtain an *information fraction*, t_k, where $t_k = I_k / I_{max}$. For most scenarios considered here this information fraction will be proportional to the fraction of subjects which have had follow-up i.e. proportional to fraction of total sample

[1] Note that there are also group sequential methods based on discretizing continuous monitoring tests such as the sequential probability ratio test (SPRT) [Wald and Wolfowitz, 1948, Wald, 1992] - see for example the triangular test proposals of Whitehead [Whitehead and Brunier, 1990, Whitehead, 1997] or many Bayesian sequential designs [Zhou and Ji, 2023].

size for two means/proportions, proportional to fraction of total events for time-to-event analysis (under proportional hazards).

At each of these information fractions we assume that one can obtain an efficient estimate of the true treatment effect, $\hat{\theta}(t_k)$, and a consistent estimate of the variance of this estimate, $Var\left(\hat{\theta}(t_k)\right)$. Maximum likelihood estimators, produced by most standard statistical software packages for example, will be efficient estimators. Given sufficient sample size, we can also assume:

$$I_k \approx \frac{1}{Var\left(\hat{\theta}(t_k)\right)}.$$

Suppose we wish to test the hypothesis $H_0 : \theta = \theta_0$. Then, assuming all the above, the standardized test statistics are given by the following:

$$Z_k = \frac{(\hat{\theta}(t_k) - \theta_0)}{\sqrt{Var\left(\hat{\theta}(t_k)\right)}} = (\hat{\theta}(t_k) - \theta_0)\sqrt{I_k}$$

We can therefore show [Scharfstein et al., 1997] that these Z_k are then asymptotically multivariate normal where:

1. $\eta = (\theta - \theta_0)\sqrt{I_{max}}$
2. $E(Z_k) = \eta\sqrt{t_k}$, $k = 1, 2, \ldots, K-1, K$
3. $Var(Z_k) = 1$
4. $Cov(Z_{k_1}, Z_{k_2}) = \sqrt{\frac{I_{k_1}}{I_{k_2}}}$, $1 \leq k_1 \leq k_2 \leq K$

where η is usually referred to as the *drift parameter*. The term "drift" is used in relation to this being the drift of the Brownian motion process for the independent increments [Lan and Zucker, 1993].

For inequality testing θ_0 will equal zero while for non-inferiority testing this will equal the non-inferiority margin.

Derivation of the group sequential theory above for the standarized test statistic scale can also be found in some resources on other statistic scales. The most common statistics used are the score statistic $\left(S_k = \hat{\theta} I_k\right)$, the interim treatment effect $\left(\hat{\theta}_k\right)$ and the B-score $\left(Z\sqrt{t_k}\right)$ [Lan and Wittes, 1988] - note the B-score is not used directly in nQuery at present but is included for completeness. The equivalent distributional assumptions for the various scales are:

- $Z_k \sim N(\theta\sqrt{I_k}, 1)$, $COV(Z_{k_1}, Z_{k_2}) = \sqrt{\frac{I_{k_1}}{I_{k_2}}}$
- $\hat{\theta}_k \sim N(\theta, I_k^{-1})$, $COV(\hat{\theta}_{k_1}, \hat{\theta}_{k_2}) = I_{k_2}^{-1}$
- $S_k \sim N(\theta I_k, I_k)$, $COV(S_{k_1}, S_{k_2}) = I_{k_1} \Rightarrow COV(S_{k_i} - S_{k_i-1}, S_{k_j} - S_{k_j-1}) = 0$, $i \neq j$
- $B_k \sim N(\eta\sqrt{t_k}, t_k)$, $COV(B_{k_1}, B_{k_2}) = t_{k_1} \Rightarrow COV(B_{k_i}, B_{k_j} - B_{k_i}) = 0, i < j$

Conversions between the standardized test statistic and the treatment effect, score statistic and p-value scale are discussed in subsubsection 7.2.4.5.

An important assumption for the above group sequential theory to hold is the *independent increments assumption* - where it assumed there is no dependence between the information, I_k, and the standardized test statistics $(Z_1, Z_2, \ldots Z_{k-1})$ at each prior look - This is

equivalent to following assumption being true for the score statistics/increments:

$$COV(S_{k_i} - S_{k_i-1}, S_{k_j} - S_{k_j-1}) = 0$$

This assumption will hold for a wide variety of statistical models (as shown in subsection 7.2.5) but could be violated in presence of adaptive pooling/treatment assignment [Jennison and Turnbull, 1999] or for weighted linear-rank statistics such as the Gehan statistic for time-to-event analysis [Proschan et al., 2006] for example.

Assuming the *independent increments assumption* holds, the exit probability for an arbitrary set of boundaries can be found for any specified treatment effect via an efficient recursive integration algorithm. This algorithm will be discussed next.

7.2.2 Numerical Algorithm for Group Sequential Exit Probabilities

One of the main calculations required in order to define group sequential boundaries is to calculate the probabilities of a given set of group sequential boundaries being crossed (*the exit probability*). A numerical integration algorithm is required for this purpose.

The numerical integration algorithm theory is based on the work of Armitage, McPherson and others [Armitage et al., 1969, McPherson and Armitage, 1971] and is summarized in Chapter 19 of Jennison and Turnbull (1999).

The computational implementation of the recursive intergration in nQuery is based on the "ld98" Fortran code developed by Reboussin et al. [Reboussin et al., 2000] and is available at `https://biostat.wiscweb.wisc.edu/resources/software/`.

A detailed breakdown of the integration and the computational aspects are provided in the resources above but a high level overview is provided below. We will focus on the one-sided testing scenario for the following however Jenison & Turnbull [Jennison and Turnbull, 1999] discusses how the below methods can be extended to the 2-sided case.

Using the same notation as in subsubsection 7.2.1.1, we will now define the *information difference* as $\Delta_k = I_k - I_{k-1}, k = 2, 3, \ldots, K$.

It follows that for $Z_1 \sim N(\theta\sqrt{I_1}, 1)$ and $Z_k\sqrt{I_k} - Z_{k-1}\sqrt{I_{k-1}} \sim N(\theta\Delta_k, \Delta_k)$, for each $k = 2, 3, \ldots, K$.

Denote at each interim look, the efficacy boundaries as b_k and the futility boundaries as a_k for $k = 1, 2, \ldots, K$. We can then denote the probability that an efficacy bound is crossed at a given analysis as the following:

$$\psi_k\left(a_1, b_1, \ldots, a_k, b_k; \theta\right) = Pr_\theta\left\{a_1 < Z_1 < b_1, \ldots, a_{k-1} < Z_{k-1} < b_{_{k-1}}, Z_k > b_k\right\}$$

and the probability that a futility bound is crossed at a given look is:

$$\xi_k\left(a_1, b_1, \ldots, a_k, b_k; \theta\right) = Pr_\theta\left\{a_1 < Z_1 < b_1, \ldots, a_{k-1} < Z_{k-1} < b_{_{k-1}}, Z_k < a_k\right\}$$

These probabilities can be calculated under any specified value for θ.

In subsection 7.2.3, these functions will allow us to calculate the per-look and overall Type I and Type II errors. For the 1-sided case discussed here, note the final efficacy and futility boundaries will be set to be equal ($b_K = a_K$).

The density of the first standardized test statistic Z_1 will equal $f_1(z_1;\theta) = \phi(z_1 - \theta\sqrt{I_1})$ where ϕ is the probability density function of the standard normal distribution.

Given $Z_k\sqrt{I_k} - Z_{k-1}\sqrt{I_{k-1}} \sim N(\theta\Delta_k, \Delta_k)$, it follows for $K > 2$ that the conditional density of Z_k given $Z_1 = z_1, \ldots, Z_{k-1} = z_{k-1}$ depends only on z_{k-1} and will equal

$$f_k(z_{k-1}; z_k, \theta) = \frac{\sqrt{I_k}}{\sqrt{\Delta_k}}\phi\left(\frac{z_k\sqrt{I_k} - z_{k-1}\sqrt{I_{k-1}} - \theta\Delta_k}{\sqrt{\Delta_k}}\right)$$

Based on this we can see the conditional density depends only on the data accrued between the current look and the immediately prior look. Hence ψ_k has the following integral form:

$$\psi_k\left(a_1, b_1, ..., a_k, b_k; \theta\right) = \int_{a_1}^{b_1} ... \int_{a_{k-1}}^{b_{k-1}} \int_{b_k}^{\infty} f_1(z_1;\theta) f_2(z_2;\theta) \ldots f_k(z_{k-1}; z_k, \theta) dz_k \ldots dz_1$$

We can replace the final integral $\int_{b_k}^{\infty} (z_{k-1}; z_k, \theta) dz_k$ with the following function:

$$e_{k-1}(z_{k-1}, b_k; \theta) = \Phi\left(\frac{z_k\sqrt{I_k} - b_k\sqrt{I_{k-1}} + \theta\Delta_k}{\sqrt{\Delta_k}}\right)$$

where Φ is cumulative distribution function of the standard normal distribution. $\xi_k\left(a_1, b_1, \ldots, a_k, b_k; \theta\right)$ can also be re-written in a similar manner.

Rather than calculating the multivariate normal integral directly, the recursive integral formula of Armitage, McPherson & Rowe (1969) [Armitage et al., 1969] can be applied to significantly reduce the complexity. Their method allows the direct calculation of the probability of exiting from looks 1 to k_1 in turn, which reduces the probability calculation to a series of one-way integrals for the per-look exit probability $p(k, z, \theta)$. The formulae are as follows:

$$p(k, z, \theta) = \begin{cases} g_k(z;\theta) & z \notin C_k \\ 0 & z \in C_k \end{cases}$$

$$g_1(z;\theta) = \phi(z - \theta\sqrt{I_1})$$

$$g_k(z;\theta) = \int_{C_{k-1}} g_{k-1}(u;\theta)\frac{\sqrt{I_k}}{\sqrt{\Delta_k}}\phi\left(\frac{z\sqrt{I_k} - u\sqrt{I_{k-1}} - \theta\Delta_k}{\sqrt{\Delta_k}}\right) du$$

where C_i is the *continuation region* for a given look i.e. the values for the standardized test statistic where the trial would continue to the next look[2]. This would be the region between our futility bound (a) and efficacy bound (b) in our example above.

Note that this formulation based on the standardized test statistic is taken from Jennison and Turnbull (1999) [Jennison and Turnbull, 1999] - the original Armitage, McPherson & Rowe derivation used the score statistic scale.

[2]Replace z with z_1 in the second equation and replace z with z_k and u with z_{k-1} for comparability with the other formulae related to boundary construction

Based on the above we can re-write out integral for $\psi_k\left(a_1, b_1, ..., a_k, b_k; \theta\right)$ as follows:

$$\int_{b_k}^{\infty} g_k(z_k;\theta)dz_k$$

$$\Rightarrow \int_{a_{k-1}}^{b_{k-1}} \int_{b_k}^{\infty} g_{k-1}(z_{k-1};\theta) f_k(z_{k-1}; z_k, \theta)dz_k dz_{k-1}$$

$$\Rightarrow \int_{a_{k-1}}^{b_{k-1}} g_{k-1}(z_{k-1};\theta) e_{k-1}(z_{k-1}; b_k, \theta)dz_{k-1}$$

This integral can be evaluated via a quadrature procedure. While standard numerical integration functions are now widely available in standard software packages (e.g. integrate in R), a short summary of the integration procedure as described by Jennison and Turnbull [Jennison and Turnbull, 1999] is provided. This numerical integration function is the basis of the widely used and adapted "ld98" FORTRAN code by Reboussin et al [Reboussin et al., 2000] for finding group sequential bounds.

Jennison and Turnbull show in several steps that the integral for $\psi_k\left(a_1, b_1, ..., a_k, b_k; \theta\right)$ can be approximated by the following summation:

$$\sum_{i_{k-1}=1}^{m_{k-1}} h_{k-1}\left(i_{k-1};\theta\right) e_{k-1}\left(z_{k-1}\left(i_{k-1}\right), b_k, \theta\right)$$

$$h_1(i_1;\theta) = w_1(i_1) f_1(z_1(i_1);\theta)$$

$$h_k(i_k;\theta) = \sum_{i_{k-1}=1}^{m_{k-1}} h_{k-1}(i_{k-1};\theta) w_k(i_k) f_k(z_{k-1}(i_{k-1}); b_k, \theta)$$

where the m is the number of discrete points included to approximate the integral, i represents the index of each point and w_k is the weight assigned to each point. m is set equal to $12r-3$ where r is a user-specified value, see subsection 7.3.7. The gridpoints and weights for indefinite integrals are selected to have two thirds of the probability density within 3 standard deviations of the mean and the remaining one third in the tails. For definite integrals, values outside the bounds are trimmed and re-assigned appropriately within the integral space. See Chapter 19 of Jennison and Turnbull for further details on how weights are specifically calculated.

The above calculations are easily extensible to the case of 1-sided efficacy only designs, 1-sided futility only designs and 2-sided efficacy only designs by replacing the relevant limits for integration described above with infinity or the upper/lower efficacy bounds. Extension of the above to 2-sided futility bounds is more complicated due to the disjoint continuation region and adjusting for overlapping futility boundaries which is common at earlier looks.

Note that nQuery adjusts for overlapping futility boundaries by setting both the upper and lower boundary equal to θ_0 and then re-assigns the unused β error proportionally to the future looks to calculate the remaining futility boundaries - this is equivalent to BETAOVERLAP = TRUE in SAS PROC SEQDESIGN for example. Options implemented in other software are to ignore the overlapping boundaries (BETAOVERLAP =

FALSE) allowing the beta error to be spent regardless or to re-calculate the boundaries as if those futility looks were originally planned to be skipped - skipping looks in nQuery is discussed in subsection 7.3.2.

7.2.3 Calculating Error Rates/Maximum Information

Given a 1-sided analysis with a given set of efficacy and futility boundaries, the definitions for the Type I (false positive) and Type II (false negative) error rates are as follows:

For the total Type I (α) error, set $\theta = \theta_0$ (e.g. 0 for inequalty hypothesis for mean difference) and find boundaries such that the following holds:

$$\alpha = \sum_{k=1}^{K} Pr_0 \left\{ a_1 < Z_1 < b_1, \ldots, a_{K-1} < Z_{k-1} < b_{k-1}, Z_k > b_k \right\}$$

For the total Type II (β) error, set $\theta = \theta_1$ (e.g. the specified mean difference) and find boundaries such that the following holds

$$\beta = \sum_{k=1}^{K} Pr_{\theta_1} \left\{ a_1 < Z_1 < b_1, \ldots, a_{k-1} < Z_{k-1} < b_{k-1}, Z_k < a_k \right\}$$

By definition at the final analysis a decision for or against the null hypothesis is made and therefore for 1-sided testing the final efficacy bound, b_K, and final futility boundary, a_K, are forced to be equal at the final analysis.

Note $1-\beta$ is the statistical power (true positive rate). The statistical power is the typical output of interest in clinical trial design under the alternative hypothesis and will equal:

$$Power\,(1-\beta) = \sum_{k=1}^{K} Pr_{\theta_1} \left\{ a_1 < Z_1 < b_1, \ldots, a_{k-1} < Z_{k-1} < b_{k-1}, Z_k > b_k \right\}$$

The cumulative Type I or Type II error (stop at or before current look) at a given look k can be found by assessing the same probability up to look k instead of the final look K used above for the total error rates - the components being summed are equivalent to the incremental (stop at current look only) Type I/Type II errors. This is used directly for the error spending function approach where the per-look cumulative error rates (α_k, β_k) are used to calculate the group sequential boundaries sequentially - see subsubsection 7.2.4.1.

Therefore given a set of boundaries and known maximum information, the Type I and Type II error can be calculated using the methods described in subsection 7.2.2. The Type I error will correspond to the *Test Significance Level*. 1 - Type II error will correspond to the *Power* of the test.

For clinical trial design, the primary interest is calculating a set of boundaries which have the desired value for trial-level parameters $(\alpha, 1-\beta, I_{max})$ and, if defined explicity, per-look exit probabilities for efficacy (α_k) and/or futility (β_k).

In practice, the interest is in either calculating the power $(1-\beta)$ for a given maximum (Fisher) information (I_{max}) or the maximum information for a given power while controlling for the overall Type I error - increasing the maximum information will increase

the power. As maximum information increases proportionally with the sample size (or events for time-to-event analysis), this corresponds to the objective of a standard sample size determination to find the appropriate sample size to power a trial to the desired level (e.g. 80%, 90%). Note that it is also common to see these calculations done in terms of the (alternative hypothesis) drift parameter η discussed in subsubsection 7.2.1.1 which equals $(\theta - \theta_0)\sqrt{I_{max}}$

In this section, the focus will be on the calculations which use the maximum information directly - this corresponds to the calculations available in the design table **GST0 - Information-Based Group Sequential Design**. The conversions required from maximum information to the sample size (or events) for the specific endpoints and designs available in nQuery are covered in subsection 7.2.5. Given an appropriate definition for the treatment effect (θ) and maximum information (I_{max}) that GST0 can be used to construct boundaries for any given clinical trial design.

The calculation of the boundaries will depend on the choice of boundary calculation method (see subsection 7.2.4) and (if present) whether the futility boundaries are non-binding or binding.

To calculate the Maximum Information (I_{max}), assume a target type II error rate (1-Power) has been specified. Then iterate over different values for I_{max} and in conjunction with the efficacy boundaries and/or futility boundaries, found via their respective group sequential boundary calculation method, find the value for I_{max} which satisfies the type II error/statistical power constraint(s) using the ψ_k, ξ_k functions above.

To calculate the Power, assume our Maximum Information (I_{max}) has been specified. Then iterate over different values of the Power (or β) and for each iteration calculate the futility boundaries via the specified futility boundary calculation method until the final futility boundary produced matches the final efficacy boundary found via the selected efficacy boundary calculation method. For efficacy-only designs, the $\psi_k\left(a_1, b_1, \ldots, a_k, b_k; \theta_1\right)$ function can be evaluated directly for the specified I_{max} and efficacy boundaries found via the selected efficacy boundary calculation method.

Non-binding futility boundaries are futility boundaries where if the futility boundary is crossed and the trial continues to future analyses, the Type I error rate will not be inflated by the choice to continue. In the non-binding case, the relevant efficacy boundaries are calculated first via the chosen efficacy boundary calculation method to satisfy the target type I error constraint. The futility boundaries are then calculated to ensure the desired futility exit probabilties given the pre-calculated efficacy boundary. For a futility-only design, the efficacy bound will only be defined at the final analysis and will equal to standard normal quantile function assessed at $1 - \alpha$, e.g. 1.96 for $\alpha = 0.025$.

Binding futility boundaries are futility boundaries where if the futility boundary is crossed and the trial continues into subsequent analyses the Type I error rate will be inflated. Therefore, it is highly recommended that the trial be stopped if a **Binding** futility boundary is crossed. In the binding case, the efficacy and futility boundaries are calculated simultaneously to fulfil the respective Type I and Type II error constraints.

Non-binding futility boundaries are the far more popular choice in clinical trials.

Note that for 2-sided design, nQuery assumes symmetrical efficacy and/or futility bounds and the lower bound will be set equal the upper bound times -1 by the search algorithm.

Standard root-finding algorithms such as the Brent algorithm [Brent, 1971] are appropriate for most of the search algorithms above. A robust bi-section based method is required

for finding the power in the presence of futility boundaries when finding the final futility boundary such that the final efficacy and futility boundary are equal.

7.2.3.1 Inflation Factor

For a given group sequential design, the relative efficiency of that group sequential design if it reached the final analysis and the equivalent fixed term design can be calculated. This is known as the **Inflation Factor** (IF). This inflation factor can be used to calculate the information (i.e. sample size) increase required to convert a fixed term trial to a given group sequential design or provide context on the maximum possible inefficiency of a given group sequential design compared to an equivalent fixed term trial.

Tables of inflation factors are provided by Jennison and Turnbull [Jennison and Turnbull, 1999] for a wide variety of group sequential designs as the inflation factor was considered convenient to calculate the sample size required for a group sequential design by multiplying the calculated sample size for a fixed term trial by the appropriate inflation factor. Its calculation is as follows:

The drift parameter is a function of the number of looks, Type I error, Type II error and the group sequential boundaries (i.e. $K, \alpha, \beta, b_k, a_k$). Given the definition of the drift parameter $\left(\eta = \theta\sqrt{I_{max}}\right)$ then re-arrangment implies that $I_{max} = \left(\frac{\eta}{\theta}\right)^2$. For the Information-Based design, the information required for an equivalent (1-sided) fixed term trial will equal:

$$I_{Fixed} = \left(\frac{Z_\alpha + Z_\beta}{\theta}\right)^2$$

Given this definition and the drift parameter, the inflation factor (IF) equals:

$$I_{max} = \left(\frac{\eta}{\theta}\right)^2 \left(\frac{Z_\alpha + Z_\beta}{Z_\alpha + Z_\beta}\right)^2$$

$$\Rightarrow I_{max} = \left(\frac{Z_\alpha + Z_\beta}{\theta}\right)^2 \left(\frac{\eta}{Z_\alpha + Z_\beta}\right)^2$$

$$\Rightarrow I_{max} = I_{Fixed}\left(\frac{\eta}{Z_\alpha + Z_\beta}\right)^2 \Rightarrow \frac{I_{max}}{I_{Fixed}} = \left(\frac{\eta}{Z_\alpha + Z_\beta}\right)^2 = IF$$

7.2.4 Boundary Calculation Methods (Group Sequential Design Types)

Multiple proposals have been developed for the calculation of group sequential boundaries. These methods have different strengths and weaknesses with there often being a trade-off between flexibility and complexity. The following methods for group sequential boundary calculation are available in nQuery:

- Lan-DeMets Spending Function

- Haybittle-Peto (p-value) Boundaries
- Wang-Tsiatis/Pampallona-Tsiatis
- Unified Family
- Custom Boundaries

Note that not all these methods are mutually compatible with each other. For a summary of which methods are compatible in nQuery see subsubsection 7.3.1.1

An overview of each of these methods is provided below.

7.2.4.1 Lan-DeMets Spending Function

The Lan-DeMets error spending function method is the most widely used method to generate group sequential boundaries in confirmatory clinical trials.

The *error spending function* concept was introduced by Lan & DeMets [Gordon Lan and DeMets, 1983, Demets and Lan, 1994] for constructing efficacy boundaries by "spending" a proportion of the total Type I α error at each analysis. This method was extended to spending the Type II β error for the construction of futility boundaries [Pampallona et al., 1995, Pampallona et al., 2001, Chang et al., 1998]. Alpha and beta spending functions work functionally the same.

The *Efficacy Spending Function* is used to generate efficacy boundaries which spends a certain amount of the total type I error (α) at each look. In practical terms, the Type I error is the probability of crossing the efficacy boundary under the null hypothesis ($\theta = \theta_0$) at any interim analysis or at the final analysis. α_k will be used to indicate the interim cumulative Type I error exit probability (i.e. the probability of stopping early for efficacy up to and including the current look under the null hypothesis) "spent" at look k.

The *Futility Spending Function* is used to generate futility boundaries which spends a certain amount of the total type II error (β) at each look. In practical terms, the Type II error is the probability of crossing the futility boundary under the alternative hypothesis ($\theta = \theta_1$) [3] at any interim analysis or at the final analysis. β_k will be used to indicate the interim cumulative Type II error exit probability (i.e. the probability of stopping early for futility up to and including the current look under the alternative hypothesis) "spent" at look k.

The spending function method has the advantage of significant flexibility compared to other group sequential methods. The error spending approach allows full control over the desired desired interim (cumulative) error exit probabilities $(\alpha_1, \alpha_2 \ldots, \alpha_{K-1}\alpha, \beta_1, \beta_2 \ldots, \beta_{K-1}, \beta)$ at each look while maintaining the overall desired error rates (α, β) . The error spending approach also does not require equally spaced pre-specified interim analyses - this had been a constraint of earlier group sequential proposals such as the Pocock and O'Brien-Fleming sequential designs [Pocock, 1977, O'Brien and Fleming, 1979]. This flexibility extends to the analysis stage where the error spending boundaries can be easily adjusted for extra interim analyses or for when the interim analysis timing diverges from the originally planned information time.

[3] note that θ and θ_1 may be used interchangeably for the alternative hypothesis treatment effect below.

The only rules the spending functions must satisfy are that the cumulative error spent at each look must be non-decreasing and that the error spent at the start of the trial equals zero and the error spent at the final analysis equals the desired total error level (α, β).

After the full spending sequence of errors has been determined by the spending function then the group sequential boundaries are calculated in sequence (e.g. b_1 then $b_2 \ldots b_{K-1}$ then b_K for efficacy boundaries) to have the appropriate interim exit probability using the ψ_k (exit probability function for efficacy bounds) or ξ_k (exit probability function for futility bounds) function via a search algorithm as described in subsection 7.2.2. Note that the exit probability functions referenced above output the incremental exit probability (i.e. the probability of exiting at that specific look) rather than cumulative exit probability provided by the spending function. The interim probability can be found by substracting the cumulative exit probability at the prior look from the cumulative exit probability at the current look e.g. $(\alpha_k - \alpha_{k-1})$.

As noted in subsection 7.2.3, for non-binding futility boundaries the efficacy boundaries are calculated first and then futility boundaries are found that have the appropriate β_k errors based on the fixed efficacy boundary while for binding futility boundaries the efficacy and futility boundaries are determined simultaneously.

Due to the flexiblity of spending functions, a wide variety of spending function have been proposed in the literature. The following error spending functions are included in nQuery:

- O'Brien-Fleming
- Pocock
- Hwang-Shih-DeCani
- Power Family
- 2-Parameter Family (Logistic, Normal, Cauchy)
- Exponential
- Beta
- t-distribution
- User Defined

Different spending functions have differing levels of flexibility with less flexible methods typically selected for having a good balance of statistical power and low average sample size [Viele, 2023]. More flexible methods allow for more fine control over the error spending but can easily lead to an inefficient group sequential design. Therefore, the first four less flexible options (O'Brien-Fleming, Pocock, Hwang-Shih-DeCani, Power Family) continue to be the most widely used spending functions in practice. In clinical trials, the efficacy spending function will tend to be conservative (low probability of early exit e.g. O'Brien-Fleming) while futility spending functions will tend to be more aggressive (higher probability of early exit e.g. Pocock).

The alpha spending function $(\varepsilon(t_k, \alpha, p_i))$ will use at least the total α error (i.e. test significance level) and information time (t_k) to generate the cumulative Type I error spent at look k bur some spending functions will require one or more additional parameter(s) (p_i) - details on these spending function specific parameters are provided below. For futility boundaries, replace α with the total β error (i.e. $1 - Power$) for the beta spending function. These formulae assume a support for the information time (t_k) of $[0, 1]$.

A brief overview of each spending function available in nQuery is provided below:

O'Brien-Fleming The **O'Brien-Fleming spending function** was proposed by Lan & DeMets [Gordon Lan and DeMets, 1983]. It generates boundaries, using the total error and information time alone, that are similar (but not identical! - see subsubsection 7.2.4.3 for details on how to generate the original O'Brien-Fleming boundaries) to those from the O'Brien-Fleming sequential design [O'Brien and Fleming, 1979].

The O'Brien-Fleming spending function has the following form for both 1-sided efficacy and futility boundaries and 2-sided futility boundaries:

$$\varepsilon\left(t_k, \alpha\right) = 2\left(1 - \varphi\left(\frac{Z_{1-\alpha/2}}{\sqrt{t_k}}\right)\right)$$

For the 2-sided efficacy boundaries, the O'Brien-Fleming spending function has the following form:

$$\varepsilon\left(t_k, \alpha\right) = 4\left(1 - \varphi\left(\frac{Z_{1-\alpha/4}}{\sqrt{t_k}}\right)\right)$$

Note that some software uses the second equation for 2-sided futility boundaries. However, this is believed to be incorrect [Wassmer, 2023] despite providing an allowable sequence of β_k.

This is a widely used "conservative" spending function where a small amount of error is spent at earlier look. This means a lower probability of early exit but that the final boundary is closer to an equivalent fixed term analysis.

Pocock The **Pocock spending function** was proposed by Lan & DeMets [Gordon Lan and DeMets, 1983]. It generates boundaries, using the total error and information time alone, that are similar (but not identical! - see subsubsection 7.2.4.3 for details on how to generate the original Pocock boundaries) to those from the Pocock sequential design [Pocock, 1977].

The Pocock spending function has the following form:

$$\varepsilon\left(t_k, \alpha\right) = \alpha \ln\left\{1 + (e-1)\, t_k\right\}$$

This is a widely used "aggressive" spending function where a larger amount of error is spent at earlier look - the original Pocock proposal had the same p-value efficacy threshold at each look. This means a higher probability of early exit but that the final boundary is further from an equivalent fixed term analysis.

Hwang-Shih-DeCani The **Hwang-Shih-DeCani spending function** was proposed by Hwang, Shih and DeCani [Hwang et al., 1990]. It is also commonly referred to as the Gamma spending function as it requires the specification of the gamma (γ) parameter, alongside the total error and information time, to generate boundaries.

The Hwang-Shih-DeCani (Gamma) spending function has the following form:

$$\varepsilon\left(t_k, \alpha, \gamma\right) = \begin{cases} \alpha\frac{\left(1-e^{-\gamma t_k}\right)}{\left(1-e^{-\gamma}\right)} & \gamma \neq 0 \\ \alpha t_k & \gamma = 0 \end{cases}$$

This is a widely used flexible spending function where the gamma parameter will determine the error spending pattern.

Negative values will generate a convex spending function where conservatism increases for lower values. Positive values will generate a concave spending function where high values will increase the agressiveness. $\gamma = 0$ spends the error linearly so can be used to generate the **Linear spending function** where $\alpha_k = t_k$. $\gamma = 1$ generates boundaries similar to **Pocock**. $\gamma = -4$ generates boundaries similar to **O'Brien-Fleming.**

While γ can take on any value, nQuery restricts the gamma (γ) parameter to values less than or equal to 3 to prevent unreasonable boundaries being generated.

Power Family The **Power Family spending function** was proposed by Kim and DeMets [Kim and Demets, 1987] and generalized by Jennison and Turnbull [Jennison and Turnbull, 1999]. It is also commonly referred to as the Kim-DeMets spending function or the rho spending function as it requires the specification of the power (ρ) parameter, alongside the total error and information time, to generate boundaries.

The Power Family (Kim-DeMets) spending function has the following form:

$$\varepsilon\left(t_k, \alpha, \rho\right) = \alpha t_k^{\rho}$$

Higher values of ρ generate increasingly conservative boundaries. $\rho = 1$ generates boundaries similar to **Pocock**. $\rho = 3$ generates boundaries similar to **O'Brien-Fleming**.

The power rho (ρ) parameter must be greater than zero.

2-Parameter Family (Logistic, Normal, Cauchy) The **2-Parameter Family spending function(s)** are a series of flexible spending functions based on parametric distributions proposed by Keaven Anderson [Anderson and Clark, 2010] and implemented for several distributions in Anderson's R package gsDesign [Anderson, 2024a, Anderson, 2024b]. The 2-Parameter Family of spending functions requires the specification of two shape parameters (a, b) and the desired parametric distribution, alongside the total error and information time, to generate boundaries.

Three distributions are supported in nQuery under this spending function option: the Logistic, Normal and Cauchy distributions. This approach is also extensible to other distributions.

The 2-Parameter Family spending function has the following form:

$$\varepsilon\left(t_k, \alpha, a, b\right) = \alpha F\left(a + bF^{-1}\left(t_k\right)\right)$$

where F is the cumulative distribution function (CDF) and F^{-1} is the inverse CDF (quantile) function for the selected distribution. Anderson shows that the Logistic distribution simplifies to:

$$\varepsilon\left(t_k, \alpha, a, b\right) = \alpha\left(1 - \left(1 + e^{a}\left(t_k / \left(1 - t_k\right)\right)^{b}\right)^{-1}\right)$$

These spending functions are very flexible so require careful consideration of parameter choice. However, Anderson outlines how the two parameters can be estimated for a given

distribution by specifying a pair of (t_k, α_k) co-ordinates. See the references above for details.

The a parameter can be any real value, the b parameter must be greater than zero.

Exponential The **Exponential spending function** was proposed by Keaven Anderson [Anderson and Clark, 2010] based on the Exponential distribution. It requires the specification of the exponential (ν) nu rate parameter, alongside the total error and information time, to generate boundaries.

The Exponential spending function has the following form:

$$\varepsilon\left(t_k, \alpha, \nu\right) = \alpha t_k^{-\nu}$$

Higher values of ν generate increasingly conservative boundaries. $\nu = 0.8$ generates boundaries similar to the **O'Brien-Fleming spending function** [Anderson, 2024a] - however Anderson notes that $\nu = 0.75$ generates a superior approximation of the **original O'Brien-Fleming design**'s boundaries than the O'Brien-Fleming spending function [Anderson, 2024b].

The Exponential (ρ) parameter must greater than zero. nQuery restricts this value to a maximum of 1.5, Anderson recommends values less than 1 [Anderson, 2024b].

Beta The **Beta spending function** was proposed by Keaven Anderson [Anderson and Clark, 2010] based on the Beta distribution. It requires the specification of the the two beta shape parameters (a, b), alongside the total error and information time, to generate boundaries.

The Beta spending function has the following form:

$$\varepsilon\left(t_k, \alpha, a, b\right) = \alpha I_{t_k}\left(a, b\right)$$

where I_{t_k} is the (regularized) incomplete beta function which is equivalent to cumulative distribution function of the beta distribution.

This is a highly flexible spending function that can be used to generate a wide range of spending function patterns and approximate other spending functions. For example, with parameters $(a = \rho, b = 1)$ the beta spending function will equal the **Power Family spending function** [Anderson, 2024b] and with parameters $(a = 1, b = 1)$ the beta spending function will equal the **Linear spending function** where $\alpha_k = t_k$.

Both Beta parameters (a, b) must be greater than zero.

t-distribution The **t-distribution spending function** was proposed by Keaven Anderson [Anderson and Clark, 2010] based on the Student's t-distribution. It requires the specification of two shape parameters (a, b) and the degrees of freedom for the t-distribution (df), alongside the total error and information time, to generate boundaries.

The t-distribution spending function has the following form:

$$\varepsilon\left(t_k, \alpha, a, b\right) = \alpha F_{df}\left(a + bF_{df}^{-1}\left(t_k\right)\right)$$

where F_{df} is the cumulative distribution function (CDF) and F_{df}^{-1} is the inverse CDF (quantile) function for the t-distribution with *df* degrees of freedom.

The t-distribution spending function is very flexible so requires careful consideration of parameter choice. However, Anderson outlines how the two shape parameters can be estimated for a given distribution by specifying a pair of (t_k, α_k) co-ordinates for a fixed degrees of freedom.

The *a* parameter can be any real value, the *b* parameter must be greater than zero. *df* must be an integer greater than two.

User Defined The **User Defined spending function** is a spending function where there is full flexibility to assign the cumulative error at each look as the user wants. This is also known as the piecewise linear or interpolated spending function. This spending function offers the maximum flexibility possible with the only restriction being that the cumulative errors are strictly increasing at each look and bounded between 0 and total Type I/II error (if specified).

This function requires the user to input the desired amount of alpha and/or beta error to spend at each interim analysis in the **GST Outputs** side-table directly - see subsection 7.3.2 for details. Note that when power is being solved for, the user will input the proportion of the total (unknown) Type I (β) spent rather than the amount of beta error spent directly.

Note that the **Custom Boundary** options for **Alpha Error** and **Beta Error** are equivalent to the user defined spending function for the efficacy and futility boundaries, see subsubsection 7.2.4.5 for details.

7.2.4.2 Haybittle-Peto (p-value) Boundaries

The **Haybittle-Peto** method is a simple method for boundary construction proposed by Haybittle [Haybittle, 1971] and expanded upon by Peto et al. [Peto et al., 1976]. In the Haybittle-Peto group sequential design, the efficacy boundaries are specified as p-values at each interim analysis - a p-value less than the boundary p-value from a standard unadjusted analysis (e.g. two sample Z-test for means) at an interim analysis would stop the trial early for efficacy. As the boundaries are specified on the p-value scale these are also sometimes known simply as p-value boundaries. Note that this method can be applied to both the 1 and 2 sided case.

There are two options in nQuery for Haybittle-Peto Boundaries: Total Alpha, Last P-value.

The **Total Alpha** method is where only the interim p-value boundaries are specified and the final analysis p-value is derived to ensure a specified overall Type I (α) error rate. The original Haybittle-Peto method proposed that the same p-value be used for each interim analysis before calculating the final analysis p-value. However, nQuery allows an arbitrary set of interim p-value boundaries be entered.

The **Last P-value** method allows for all p-value boundaries to be specified including for the final analysis. No Type I (α) error rate is specified, though this will be calculated by nQuery in the Group Sequential Report as the Exact Significance Level - see subsection 7.2.3 and subsection 7.3.4.

It is recommended that the interim p-values would typically be set to a small number (<0.005) so that the final analysis p-value would be reasonably close to the overall test significance level.

Note that the **Custom Boundary** option **p-value** is equivalent the Haybittle-Peto method for the efficacy boundary and this option can also be used to specify futility boundaries on the p-value scale, see subsubsection 7.2.4.5 for details.

7.2.4.3 Wang-Tsiatis/Pampallona-Tsiatis Boundaries

The **Wang-Tsiatis method** is a flexible method for boundary construction proposed by Wang & Tsiatis [Wang and Tsiatis, 1987] for efficacy boundaries and extended by Pampallona and Tsiatis [Pampallona and Tsiatis, 1994, Pampallona et al., 1995, Pampallona et al., 2001] for equivalent futility boundaries. These boundaries are also referred to as Power Family boundaries. Note that these methods can be applied to both the 1 and 2 sided case.

The Wang-Tsiatis method provides a flexible family of efficacy boundaries that are defined by a single shape parameter. The Pampallona-Tsiatis boundary method extended the Wang-Tsiatis method to include futility boundaries defined by their own separate shape parameter. For clarity, Δ_1 will refer to the Wang-Tsiatis efficacy shape parameter and Δ_2 will refer to the Pampallona-Tsiatis futility shape parameter.

Both papers discuss "near-optimal" designs which search over the shape parameter(s) to minimize the expected average sample size under a specific hypothesis such as the null (θ_0) or alternative hypothesis (θ_1) treatment effect.

The Wang-Tsiatis boundaries have the following form:

$$b_k = C\left(\Delta_1, \alpha, K\right) t_k^{\Delta_1 - 1/2}$$

where b_k is the standardized test statistic efficacy boundary at look k, $C\left(\Delta_1, \alpha, K\right)$ is a constant defined by the efficacy shape parameter (Δ_1), total type I error (α) and total number of looks (K), and t_k is the information time at look k.

As the boundaries are constructed as a function of this positive constant $C\left(\Delta_1, \alpha, K\right)$, a numerical search over this constant is performed until the generated boundaries have the specified total Type I error rate specified - see subsection 7.2.3 for detail on how the Type I error rate is calculated for a given set of boundaries.

The Pampallona-Tsiatis futility boundaries have the following form:

$$a_k = \theta\sqrt{I_k} - C\left(\Delta_2, \beta, K\right) t_k^{\Delta_2 - 1/2}$$

where a_k is the standardized test statistic futility boundary at look k, η is the drift parameter (see subsubsection 7.2.1.1), t_k is the information time and $C\left(\Delta_2, \beta, K\right)$ is a constant defined by the futility shape parameter (Δ_2), total type II error (β) and total number of looks (K), and t_k is the information time at look k.

For Pampallona-Tsiatis designs, a two-dimensional search is conducted across both constants. To simplify this search, the following relationships can be used:

$$C\left(\Delta_1, \alpha, K\right) = \theta_1\sqrt{I_K} - C\left(\Delta_2, \beta, K\right)$$

This constraint ensures that the efficacy and futility boundaries will meet at the final analysis and, via re-arrangement, calculates the maximum information for any given pair of constants.

The two-dimensional search will find the pair of constants which have boundaries with the specified Type I error rate under the null hypothesis (and power if calculating the maximum information) and specified total Type II error rate under the alternative based on the exit probability functions - see subsection 7.2.3.

For non-binding futility bounds, the Wang-Tsiatis boundaries will be specified first and then the Pampallona-Tsiatis boundaries will be calculated based on the fixed efficacy boundary. For binding futility bounds, both the Wang-Tsiatis and Pampallona-Tsiatis boundaries are evaluated simultaneously.

Note that the definition for the constants given here are for the standardized test statistic (Z_k) scale are as per Chapter 4 of Jennison and Turnbull [Jennison and Turnbull, 1999]. Note that the original derivations from Wang & Tsiatis/Pampallona & Tsiatis are based on the score statistic scale (S_k) - for example the Wang & Tsiatis paper gives the efficacy score boundaries as $b_k(WT) = C\left(\Delta_1, \alpha, K\right) t_k^{\Delta_1}$. As noted by Jennison and Turnbull, the constants on the score scale can be found by multiplying the standardized test statistic constants used above by $K^{0.5-\Delta}$.

A shape parameter (Δ) equal to 0 is equivalent to the original O'Brien-Fleming design boundaries [O'Brien and Fleming, 1979] and a value of 0.5 is equivalent to the original Pocock design boundaries [Pocock, 1977] - neither should be confused with the spending function approximations for these designs of the same name (see section 7.2.4.1, section 7.2.4.1).

7.2.4.4 Unified Family Boundaries

The **Unified Family method** is a highly flexible method for boundary construction proposed by Kittleson and Emerson [Kittelson and Emerson, 1999]. The Kittleson and Emerson proposal sought to unify a wide range of existing sequential designs [Pocock, 1977, O'Brien and Fleming, 1979, Whitehead and Stratton, 1983, Whitehead and Brunier, 1990, Wang and Tsiatis, 1987, Emerson and Fleming, 1989, Pampallona and Tsiatis, 1994] into a single group sequential family, while also extending to additional scenarios such as equivalence testing.

The Unified Family concept was based on the concept that the process for determining stopping boundaries could be split into 3 parts. The first is a boundary shape function that defines the relationship between the boundaries. The second is a "critical value" constant which is chosen to satisfy a given hypothesis (Type I/II error rates). The third is the reference hypothesis itself.

This section will discuss the two-sided efficacy and futility scenario that requires all four boundaries as this is the primary basis of the Unified Family work as described by Kittleson and Emerson. Simpler scenarios are easily accomodated by dropping the unused boundaries.

The Unified Family method provides a flexible family of efficacy and futility boundaries that are each defined by two shape parameters. The description of Kittleson and Emerson describes the Unified Family in terms of the four potential boundaries in a group sequential design: the upper efficacy boundaries ($b(u)_k$), the upper futility boundaries ($a(u)_k$), the lower futility boundaries ($a(l)_k$), the lower efficacy boundaries ($b(l)_k$). The Unified Family method requires $b(u)_k > a(u)_k > a(l)_k > b(l)_k$.

Note the terminology used here is for consistency with the prior sections, in Kittleson and Emerson these are referred to (in order) as a_k, b_k, c_k, d_k (note their paper uses j for the look index rather than k). There are also some other minor differences between the formulae below and those provided in Kittleson and Emerson, these will be summarized later.

The four boundaries have the following form on the standardized test statistic scale:

$$b(u)_k = f\left(t_k\right) C_{b(u)}$$

$$a(u)_k = \theta\sqrt{I_k} - f\left(t_k\right) C_{a(u)}$$

$$a(l)_k = \theta\sqrt{I_k} + f\left(t_k\right) C_{a(l)}$$

$$b(l)_k = -f\left(t_k\right) C_{b(l)}$$

where $f\left(t_k\right)$ is a shape function with the following form:

$$f\left(t_k\right) = \sqrt{t_k}\left(\tau + t_k^{(-\rho-1/2)}\right)$$

where (τ) is the first shape parameter and (ρ) is the second shape parameter.

In nQuery, ρ must be greater than zero and the range for τ is $0 \leq \tau \leq 2\rho$.

These shape parameters provide significant flexibility to define the shape of the boundaries. As referenced above, the Unified Family can be used to replicate several existing group sequential proposals using these shape parameters. A tabular summary of these is provided below:

Method	τ	ρ
Pocock (1977)	0	0
O'Brien-Fleming (1979)	0	0.5
Wang-Tsiatis (1987)	0	$0.5 - \rho$

Table 7.1: Unified Family Parameters for Other Sequential Designs

where $0.5-\rho$ becomes the shape parameter of the Wang-Tsiatis boundary Δ (subsubsection 7.2.4.3).

For Unified Family designs, to construct the boundaries a search is conducted over all the relevant constants $\left(C_{b(u)}, C_{a(u)}, C_{a(l)}, C_{b(l)}\right)$ until the required Type I and/or Type II error constraints are fulfilled. This evaluated using the appropriate exit probability function(s) as discussed previously (see subsection 7.2.3).

For non-binding futility bounds, the efficacy boundaries will be specified first and then the futility boundaries will be calculated based on the fixed efficacy boundary. For binding futility bounds, both the efficacy and futility boundaries are found simultaneously.

Similar to Wang-Tsiatis, constraints can be imposed to ensure that the appropriate efficacy and futility boundaries meet at the final analysis. For example, to ensure that the upper efficacy and upper futility boundaries (in a 2-sided example) meet at the final analysis the following constraint can be imposed:

$$f\left(1\right) C_{b(u)} = \theta\sqrt{I_K} - f\left(1\right) C_{a(u)}$$

There are number of differences between the implementation described here and that available in Kittleson and Emerson. A summary is provided below.

First, Emerson and Kittleson derive their boundaries on the score scale. For consistency with the prior sections, the standardized test statistic (Z_k) derivation was used here instead.

Second, ρ parameter used here is equal to $\rho^* - 1/2$ where ρ^* is the Kittleson and Emerson equivalent shape parameter definition.

Third, Kittleson and Emerson include a ϵ term in their boundaries definition to account for the equivalence testing extension. This has been excluded to focus on the inequality testing case.

Fourth, for the 2-sided case nQuery restricts the upper and lower boundaries to be symmetric for both the efficacy and futility boundaries: $b(u)_k = |b(l)_k|$, $a(u)_k = |a(l)_k|$

Fifth, Emerson and Kittleson provided an additional three parameter shape function. The 2-parameter version provided here is equivalent to this parameter (R_* in Kittleson and Emerson) being set to zero.

7.2.4.5 Custom Boundaries

nQuery provides support to enter custom efficacy and futility boundaries on a number of statistical scales. This provides the user full flexibility to input any series of boundary values on their preferred statistical scale.

In nQuery, the following boundary scales are available:

- Z-Scale
- p-value Scale
- Score Scale
- δ-scale
- Alpha Error (Efficacy Only)
- Beta Error (Futility Only)

- Conditional Power (Futility Only)

The **Z-scale** corresponds to setting the boundaries on the standardized test statistic scale. This is the default scale and is the most widely used in clinical trials due to the widespread usage of the standardized Z-statistic for hypothesis testing. The Z-statistic based on the (Fisher) information (I) will equal $\theta\sqrt{I}$.

The **p-value Scale** corresponds to setting the boundaries in terms of the p-value. The p-values to be compared to the boundaries are presumed to come from the appropriate unadjusted Z-test (e.g. Z-test for means, Chi-Squared Test for proportions, Log-Rank Test for survival). This is a common boundary scale requested by researchers. The p-value will equal $1-\Phi\left(Z_k\right)$ where Φ is the cumulative distribution function for the standard normal distribution.

The **Score Scale** corresponds to setting the boundaries in terms of the score statistic. Score statistisc (and other increment based statistics such as the B-value) are widely used in the derivation of group sequential designs, though less used in practice. The Score statistic based on the (Fisher) information (I) will equal θI.

The **δ-scale** corresponds to setting the boundaries in terms of the treatment effect. The definition will depend on the endpoint of interest. For example, this could be mean difference of the two-sample Z-test, the risk difference for the chi-squared test or the log hazard ratio for the log-rank test. This is a common boundary scale requested by researchers. δ corresponds to θ above.

The **Alpha Error** scale corresponds to setting the boundaries in terms of the cumulative exit probability for efficacy at a given look under the null hypothesis i.e. the α or Type I error. This is equivalent to using the User Defined spending function for the efficacy boundary - see section 7.2.4.1 for details.

The **Beta Error** scale corresponds to setting the boundaries in terms of the cumulative exit probability for futility at a given look under the alternative hypothesis i.e. the β or Type II error. This is equivalent to using the User Defined spending function for the futility boundary - see section 7.2.4.1 for details.

The **Conditional Power** scale corresponds to setting the futility boundaries in terms of the probability of significance conditional on the data accrued so far. Conditional power requires an assumption about the "true" treatment effect. nQuery provides two options for the assumed "true" treatment effect: **Estimated** θ and **Design** θ. **Estimated** θ assumes the treatment effect is equal to the futility boundary on the **δ-scale** at that interim analysis. **Design** θ assumes the treatment effect is equal to that set for the original group sequential calculation in the main design table (see subsection 7.3.1).

In nQuery, the underlying group sequential methods are based on the standardized test statistic **Z-scale**. The other scales are transformed to the Z-scale before being passed to the group sequential solver. A brief overview of this transformation is provided for each test statistic:

- p-value Scale: $\begin{cases} Z_k = -\varphi\left(p_k\right) & \theta > 0 \\ Z_k = \varphi\left(p_k\right) & \theta < 0 \end{cases}$, where φ is the standard normal inverse CDF (quantile) function
- Score Scale: $Z_k = S_k/\sqrt{I_k}$
- δ-Scale: $Z_k = \delta_k\sqrt{I_k}$

- Alpha Error: Found via sequential search over $\psi_k\left(a_1, b_1, \ldots, a_k, b_k; 0\right)$ as per other spending functions - see subsection 7.2.2 and subsubsection 7.2.4.1 for details.
- Beta Error: Found via sequential search over $\xi_k\left(a_1, b_1, \ldots, a_k, b_k; \theta\right)$ - see per other spending functions - see subsection 7.2.2 and subsubsection 7.2.4.1 for details.

Conditional Power: To calculate the exact conditional power, a search is required over the conditional power function to find standardized test statistic Z-scale futility boundaries that correspond to the target conditional power for the assumed "true" treatment effect (θ) chosen

To conduct an exact conditional power calculation for a given set of future efficacy and futility boundaries, the Type I error function (described in subsection 7.2.3) can be used under the selected θ if the future boundaries are transformed appropriately.

This transformation is shown below for the efficacy boundary at the next look $(k+1)$:

$$b_{k+1}^{*} = \frac{b_{k+1} - Z_k\sqrt{\frac{I_k}{I_{k+1}}}}{\sqrt{\frac{I_{k+1}-I_k}{I_{k+1}}}}$$

The same adjustment is made to all other subsequent efficacy boundaries $(b_{k+2,}..., b_K)$ and the futility boundaries $(a_{k+1,}..., a_K)$ as applicable:

These adjusted boundaries can be passed to the efficacy exit probability function ψ_k for the specified "true" θ as follows:

$$CP = \sum_{j=k+1}^{K} \psi_j\left(a_{k+1}^{*}, b_{k+1}^{*}, \ldots, a_j^{*}, b_j^{*}; \theta\right)$$

In nQuery, the choice of treatment effect is limited to the **Estimated ϑ** (where treatment effect equals the futility bound at the current look) or the **Design ϑ** (where treatment effect equals original value from power calculation). However, this could easily extended to an abritrary treatment effect. For the **Estimated ϑ**, the treatment effect for the conditional power function is equal to $Z_k/\sqrt{I_k}$ as implied by the δ-Scale transformation above.

To convert the specified per-look conditional power boundaries at each look to the equivalent standardized test statistic futility boundary, a search can be applied over the two functions above to boundaries in reverse order (i.e. starting with the final analysis, look K) to find the Z_K which has conditional power equal to the specified conditional power. The search is in reverse order as all future futility boundaries at given look must be known on the standardized test statistic scale to calculate the conditional power. The search at each look can be done via standard search algorithms such as the Brent algorithm [Brent, 1971].

7.2.5 Endpoint/Design Specific Sample Size Determination

The above sections has described group sequential design in terms of the maximum information (I_{max}) and treatment effect (θ). As discussed in subsubsection 7.2.1.1, these

concepts are easily extensible to any efficient estimator and consistent variance which covers a wide range of statistical tests and models.

The calculation for the power for a given maximum information and maximum information for a given power was given in subsection 7.2.3. Given a known relationship between the sample size and the maximum information, these calculations can be conducted to find the power or sample size given specified values for all other parameters required to calculate the maximum information.

In this section, the translation from (I_{max}, θ) to sample size (and events for survival analysis) is summarized for the current design scenarios covered in nQuery.

7.2.5.1 Two Means (GST1)

For an inequality two-sample Z-test for two means, the translations are as follows:

$$I_{max} = \left(\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}\right)^{-1}$$

$$\theta = \bar{X}_1 - \bar{X}_2$$

$$\eta = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\left(\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}\right)}}$$

where σ_1^2 and σ_2^2 are the group 1 and group 2 variances (standard deviation squared), n_1 and n_2 are the total planned (maximum) sample size per group and $\bar{X}_1 - \bar{X}_2$ is the mean difference.

To calculate the sample size, the maximum information can be calculated based on the target statistical power. The formula for I_{max} can be re-arranged for $n_1$and n_2 assuming a fixed sample size ratio ($R = n_2/n_1$) based on the per-group standard deviations.

To calculate the statistical power, the maximum information can be calculated using the specified per-group values for the standard deviation and sample size. The power can be calculated based on this maximum information.

7.2.5.2 Two Proportions (GST2)

For an inequality two-sample Z-test for two proportions (equivalent to the chi-squared test), the translations are as follows:

$$I_{max} = \begin{cases} \left(\frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}\right)^{-1} & V(Unpooled) \\ \left(\frac{\bar{\pi}(1-\bar{\pi})}{n_1} + \frac{\bar{\pi}(1-\bar{\pi})}{n_2}\right)^{-1} & V(Pooled) \end{cases}$$

$$\theta = \pi_1 - \pi_2$$

$$\eta = \begin{cases} \frac{\pi_1 - \pi_2}{\sqrt{\frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}}} & V(Unpooled) \\ \frac{\pi_1 - \pi_2}{\sqrt{\frac{\bar{\pi}(1-\bar{\pi})}{n_1} + \frac{\bar{\pi}(1-\bar{\pi})}{n_2}}} & V(Pooled) \end{cases}$$

$$\bar{\pi} = \frac{n_1\pi_1 + n_2\pi_2}{n_1 + n_2}$$

where π_1 and π_2 are the group 1 and group 2 proportions, $\bar{\pi}$ is the average proportion, $n_1$and n_2 are the total planned (maximum) sample size per group and $\pi_1 - \pi_2$ is the proportion (risk) difference e.g. the specified risk difference at the planning stage. $V(Unpooled)$ indicates the **Unpooled** variance was used and $V(Pooled)$ indicates the **Pooled** variance was used

To calculate the sample size, the maximum information can be calculated based on the target statistical power. The formula for I_{max} can be re-arranged for n_1 and n_2 assuming a fixed sample size ratio ($R = n_2/n_1$) based on the group 1 and group 2 proportions.

To calculate the statistical power, the maximum information can be calculated using the specified per-group values for the proportions and sample size. The power can be calculated based on this maximum information.

Note there is an alternative proposal for the pooled variance scenario where the drift parameter and boundaries are multiplied by a fixed factor (h) to improve the Type II error search performance.

7.2.5.3 Two Survival (Time-to-Event) Analysis (GST3) - Events Determination

For an inequality two sample log-rank test, the translations are as follows:

$$I_{max} = \begin{cases} \left(Ep_{n_1}\left(1 - p_{n_1}\right)\right)^{-1} & V(Null) \\ \left(Ep_{e_1}\left(1 - p_{e_1}\right)\right)^{-1} & V(Alternative) \end{cases}$$

$$\theta = \ln\left(HR\right)$$

$$\eta = \begin{cases} \frac{\ln(HR)}{\sqrt{Ep_{n_1}\left(1-p_{n_1}\right)}} & V(Null) \\ \frac{\ln(HR)}{\sqrt{Ep_{e_1}\left(1-p_{e_1}\right)}} & V(Alternative) \end{cases}$$

where E is the total number of events at the end of the study, p_{n_1} is the proportion of the total sample size from group 1 $\left(\frac{n_1}{N}\right)$, p_{e_1} is the proportion of the total events from group 1 $\left(\frac{e_1}{E}\right)$, E_k is the total events at look k (equal to E by t_k) and $\ln\left(HR\right)$ is the (natural) log hazard ratio, where HR is the hazard ratio.

$V(Null)$ indicates when the variance is calculated under the null hypothesis of a hazard ratio of 1 and therefore the sample size and event per-group allocations are the same. $V(Alternative)$ indicates when the variance is calculated under the alternative hypothesis when the hazard ratio is equal to its actual value e.g. alternative hypothesis HR at the

planning stage. The null hypothesis is the most common choice used for power calculations in clinical trials.

To calculate the total events, the maximum information can be calculated based on the target statistical power. The formula for I_{max} can be re-arranged for E. For $V(Null)$, calculate p_{n_1} using the specified sample size ratio ($R = n_2/n_1,$) using the following formula: $p_{n_1} = \left(\frac{1}{1+R}\right)$. For $V(Alternative)$, p_{e_1} is invariant to the total sample size so find the event allocation for an arbitrary sample size to determine p_{e_1} based on the provided inputs for the accrual process, hazard rates, dropout rates and censoring strategy for any value of the total sample size. See subsubsection 7.2.5.4 for details on calculating the number of events for a given sample size. It is recommended to calculate p_{e_1} with the unrounded events per-group.

To calculate the statistical power, the maximum information can be calculated using the specified events (E) and p_{n_1} under $V(Null)$. As above for the total events calculation, p_{e_1} for $V(Alternative)$ can be found for an arbitrary total sample size under the relevant design assumptions and can then calculate the maximum information based on this calculated value of p_{e_1} and the total events.

Note that while the assumption that the information time is proportional to Et_k is reasonable for the log-rank test (and Cox Model) under proportional hazards. For weighted rank tests, often used in the context of non-proportional hazards such as delayed effects, this proportionality assumption will not hold and the interim timing will be a function of additional information (e.g. hazard ratio pattern, event weighting) other than just the events.

As can be seen above, the maximum information and power is not related the sample size directly. Rather the sample size is estimated on the basis of calculating the required number of subjects needed to reach the target number of events based on assumptions regarding the accural process, hazard rates, dropout rates and censoring strategy. An overview of the relationship between the events and sample size based on these assumptions is provided below.

7.2.5.4 Survival (Time-to-Event) Analysis (GST3) - Sample Size Determination

The following describes how the sample size and power are calculated for a given number of events in a two sample log-rank test allowing for piecewise hazard rates, dropout rates and accrual. The methodology presented is based on the work of Kim & Tsiatis for survival sequential trials [Kim and Tsiatis, 1990].

Notation

The notation used to model the event and dropout processes are outlined here. Let $\lambda(t)$ be the hazard function for the event of interest and let $\delta(t)$ be the hazard function for the dropouts. Then:

- $\Lambda(t) = \int_0^t \lambda(t')dt'$ is the cumulative hazard function for the event.
- $D(t) = \int_0^t \delta(t')dt'$ is the cumulative hazard function for the dropouts.
- Probability that a subject has event before time t (and is not censored) $= \int_0^t K(t')dt'$, where $K(t) = \lambda(t)e^{-[\Lambda(t)+D(t)]}$

In nQuery, the event and dropout hazards are modelled as piecewise exponential functions (see subsection 7.3.3), while the accrual process is piecewise constant.

- $\boldsymbol{t}$ is a vector of P time periods. i.e. $\boldsymbol{t} = (0, ..., T)$,where $\boldsymbol{t}_P = T$ = total study duration.
- $\boldsymbol{\lambda}_i$ is a vector of event hazard rates in group i, where$\boldsymbol{\lambda}_{ij}$ is the hazard rate in group i between times $\boldsymbol{t}_{j-1}$ and $\boldsymbol{t}_j$ and $i \in \{1, 2\}$
- $\boldsymbol{\delta}_i$ is a vector of dropout rates in group i, where $\boldsymbol{\delta}_{ij}$ is the dropout rate in group i between times $\boldsymbol{t}_{j-1}$ and $\boldsymbol{t}_j$ and $i \in \{1, 2\}$
- $\boldsymbol{a}$ is a vector of P proportions used to describe the accrual process, where $\boldsymbol{a}_j$ is the proportion of the total subjects recruited between times $\boldsymbol{t}_{j-1}$ and $\boldsymbol{t}_j$
- $\boldsymbol{A}_j = \frac{\boldsymbol{a}_j}{\boldsymbol{t}_j - \boldsymbol{t}_{j-1}}$ is the proportion of the total subjects accrued per unit time between times $\boldsymbol{t}_{j-1}$ and $\boldsymbol{t}_j$ for $j \in \{2, ..., P\}$

Sample Size Calculations

The sample size in each group (n_i) is calculated from the number of events in that group (E_i), as well as the piecewise event rates ($\boldsymbol{\lambda}_i$), dropout rates, ($\boldsymbol{\delta}_i$) and accrual proportions ($\boldsymbol{A}$).

The formula used will depend on the type follow-up approach and length of the follow-up period. If the follow-up type is event driven, then each subject can be followed until the end of the study, regardless of when they were recruited.

If the follow-up type is fixed, then each subject is followed for a specified fixed period (f) after they were recruited, or until the end of the study (T), whichever comes first.

Note that if the fixed follow-up time equals the total study time then this is equivalent to event-driven follow-up.

Case 1: Follow-up type = Event-driven

Let q be the minimum integer such that $\sum_{j=1}^{q} \boldsymbol{a}_j = 1$, i.e. $\boldsymbol{t}_q$ is the accrual period.

Then:

$$n_i = E_i[\sum_{j=2}^{q} \boldsymbol{A}_j(\boldsymbol{t}_j - \boldsymbol{t}_{j-1})((\int_0^{T-\boldsymbol{t}_j} K_i(t)dt) + (T - \boldsymbol{t}_{j-1}) \int_{T-\boldsymbol{t}_j}^{T-\boldsymbol{t}_{j-1}} K_i(t)dt - \int_{T-\boldsymbol{t}_j}^{T-\boldsymbol{t}_{j-1}} tK_i(t)dt)]^{-1}$$

Total sample size, $N = n_1 + n_2$

Case 2: Total study time $\leq$ accrual period + follow-up period.

Let $\boldsymbol{\tau} = \boldsymbol{t}$ and let q_1 be the minimum integer such that $\boldsymbol{t}_{q_1} \geq T - f$. If $T - f \notin \boldsymbol{\tau}$,set $\boldsymbol{\tau}_{q_1} = T - f$

Let $\boldsymbol{s} = \boldsymbol{t}$ and let q_2 be the minimum integer such that $\boldsymbol{t}_{q_2} \leq T - f$. If $T - f \notin \boldsymbol{s}$,set $\boldsymbol{s}_{q_2} = T - f$

Let q_3 be the minimum integer such that $\sum_{j=1}^{q_3} \boldsymbol{a}_j = 1$, i.e. $\boldsymbol{t}_{q_3}$ is the accrual period.

Then

$$n_i = E_i[(\int_0^f K_i(t)dt)(\sum_{j=2}^{q_1} \boldsymbol{A}_j(\boldsymbol{\tau}_j - \boldsymbol{\tau}_{j-1}))+ (\sum_{j=q_2}^{q_3} \boldsymbol{A}_j(\boldsymbol{s}_j - \boldsymbol{s}_{j-1})((\int_0^{T-\boldsymbol{s}_j} K_i(t)dt)+(T-\boldsymbol{s}_{j-1})\int_{T-\boldsymbol{s}_j}^{T-\boldsymbol{s}_{j-1}} K_i(t)dt - \int_{T-\boldsymbol{s}_j}^{T-\boldsymbol{s}_{j-1}} tK_i(t)dt))]^{-1}$$

Total sample size, $N = n_1 + n_2$

Case 3: Total study time > accrual period + follow-up period.

Let q be the minimum integer such that $\sum_{j=1}^{q} \boldsymbol{a}_j = 1$, i.e. $\boldsymbol{t}_q$ is the accrual period.

Then:

$$n_i = E_i[(\int_0^f K_i(t)dt)(\sum_{j=2}^{q} \boldsymbol{A}_j(\boldsymbol{t}_j - \boldsymbol{t}_{j-1}))]^{-1}$$

Total sample size, $N = n_1 + n_2$

Power Calculation

The power is calculated from the number of events (E), significance level (α), hazard ratio (h) and sample size ratio ($R = \frac{n2}{n1}$)

$$Power = Z[\sqrt{E\ln(h)^2\frac{R}{1-R}} - Z^{-1}(1 - \frac{\alpha}{sided})]$$

Where $Z()$ is the cumulative distribution function of standard normal distribution.

7.3 Group Sequential Design Table User Interface

An overview of the user interface elements for the group sequential design tables is provided in this section. The group sequential design tables in nQuery have a large number of user interface elements in common with the other design tables in nQuery so the primary focus will be on the unique aspects for th suite of tables. See chapter 1, chapter 2, chapter 3 for further details on the nQuery UI and Assistant tools.

In this section, the following areas will be summarized:

- Main Design Table
- Group Sequential Side-table
- Group Sequential Report
- Boundary Plot
- Error Spending Plot
- Group Sequential Options Tab

7.3.1 Main Design Table

The main design table is the primary inputs for the design-specific parameters required for the sample size or power calculation - see section 1.7.

In the group sequential design tables, the main design table will consist of two primary types: Fixed Term Parameters, Group Sequential Design Parameters

Fixed Term Parameters are the parameters that would be required for the equivalent fixed term sample size determination. For example, for GST1 (Group Sequential for Two Means) this would be the mean difference (and optionally the per-group means), standard deviation (per-group), test significance level, power and sample size. For the equivalent Two Sample Z-test table (MTT10), the same parameters are required.

Note that the direction of the hypothesis will depend on the value for the row(s) which correspond to the treatment effect θ. If the treatment effect is positive then higher values for the treatment effect (and statistics such as the Z-statistic and Score statistic) are considered more "effective" and lower values more "futile". If the treatment effect is negative then lower values will be considered "better".

For GST1, positive treatment effect would correspond to a positive mean difference so the higher the mean difference (and Z-statistic etc) the "better". For GST2, a "positive" treatment effect would correspond to a positive proportion difference. For GST3, a "positive" treatment effect would correspond to a hazard ratio > 1.

Group Sequential Design Parameters are the parameters which will define the group sequential design. This includes the total number of looks (including the final analysis) and the Efficacy and/or Futility Boundary Calculation Methods.

This GST1 main design is shown in Figure 7.1:

GST1-1 / Group Sequential Designs for Two Means (Spending Function, Haybittle-Peto, Wang-Tsiatis, Unified Family, Custom Boundaries)

	1	2	3	4	5	6	7	8
Test Significance Level, α								
1 or 2 Sided Test?	1	1	1	1	1	1	1	1
Number of Looks, J								
Group 1 Mean, μ_1								
Group 2 Mean, μ_2								
Mean Difference, μ_1 - μ_2								
Group 1 Standard Deviation, σ_1								
Group 2 Standard Deviation, σ_2								
Efficacy Bound Calculation Method	Spending Function	Spending Func...	Spending Func...	Spending Func...	Spending Func...	Spending Func...	Spending Func...	Spending
Futility Bound Calculation Method	Custom Boundary	Don't Calculate	Don't Calculate	Don't Calculate	Don't Calculate	Don't Calculate	Don't Calculate	Don't Cal
Group 1 Sample Size, n_1								
Group 2 Sample Size, n_2								
Sample Size Ratio, n_2/n_1								
Power (%)								

Figure 7.1: GST1 Main Design Table

After the **Number of Looks, Efficacy Bound Calculation Method** and **Futility Calculation Method** fields are filled appropriately, the **Group Sequential Side-table** will appear below the main table and can then be filled - see subsection 7.3.2.

Note nQuery may provide defaults for a boundary calculation method which will allow a sample size or power calculation to occur before editing the Group Sequential Side-table e.g. O'Brien-Fleming for Spending Function. Therefore, it is highly recommended that

the side-table be assessed and edited appropriately before running a calculation. This is prevent solver activation occuring for every subsequent change made in the main design table or side-table.

A summary of the technical details for the group sequential boundary methods available in nQuery was provided in subsection 7.2.4. A brief overview of these methods is provided next.

7.3.1.1 Group Sequential Boundary Calculation Methods

The choice of group sequential boundary calculation method for efficacy and futility bounds selected in the main design table will affect the statistical and design properties of the group sequential design (subsection 7.2.4) and also affect the required additional inputs to run a group sequential design (subsection 7.3.2).

The user selects the desired method for the efficacy and futilty bounds separately using their respective dropdown fields in the main design table.

nQuery provides the following Efficacy Bound Calculation Methods:

- Spending Function
- Haybittle-Peto
- Wang-Tsiatis
- Unified Family
- Custom Boundary
- Don't Calculate

nQuery provides the following Futility Bound Calculation Methods:

- Spending Function
- Pampallona-Tsiatis
- Unified Family
- Custom Boundary
- Don't Calculate

Don't Calculate is used to indicate when an efficacy or futility only design is required by not including boundaries for the option set to Don't Calculate.

Note that not all group sequential methods efficacy and futility boundary calculation method options available in nQuery are mutually compatible with each other. A summary of the compatibility of the methods is provided below in Table 7.2.

Fut ↓, Eff →	SF	Haybittle-Peto	W-T	UF	Custom	DC
Spending Function (SF)	✓	✓*	X	X	✓	✓
Pampallona-Tsiatis (P-T)	X	X	✓	X	X	X
Unified Family (UF)	X	X	X	✓	X	X
Custom Boundary	✓	✓*	X	X	✓*	X
Don't Calculate (DC)	✓	✓	✓	✓	✓	X

Table 7.2: Group Sequential Method Compatibility (*1-sided Only)

7.3.2 Group Sequential Side-table

The Group Sequential side-table appears automatically below the main table after the **Number of Looks, Efficacy Bound Calculation Method** and **Futility Calculation Method** fields are filled appropriately. During the setup phase, the user can specify the additional parameters required to setup the desired group sequential design by setting the group sequential boundary method's specific additional parameters, the interim analysis timings, which efficacy or futility looks (if any) that are skipped and the statistical scale the boundaries will be displayed or inputted on.

The Group Sequential side-table is designed to dynamically update as the user makes changes in the main design table and within the side-table. After a solver calculation is activated, the group sequential side-table will also add tabs at the top of the side-table panel which provide additional results in the Group Sequential Report, Boundary Plot and Error Spending Plot. These will be described later as we focus on the GSTX-Y input side-table first.

The input Group Sequential side-table tab will be named **GSTX-Y** where X will be the table code number (e.g. GST1 for Two Means) and Y will be column number that the side-table is associated with.

The Group Sequential side-table will consist of three sub-tables: **GST Parameters** (top-left), **GST Outputs** (right), **Additional Parameter** (bottom-left, if required). An example side-table is shown in Figure 7.2.

GST1S-1

GST Simulation

GST Parameters	
Alpha Spending Function	Hwang-Shih-DeCani
Beta Spending Function	O'Brien-Fleming
Futility Bounds	Non-Binding
Boundary Scale	Z-scale

Additional Parameters	
Efficacy HSDC Parameter, γ(α)	

GST Outputs	1	2	3	4
Total Sample Size				
Information Time	0.250	0.500	0.750	1.000
Efficacy Bound				
Futility Bound				
Stop for Efficacy	Yes	Yes	Yes	Yes
Stop for Futility	Yes	Yes	Yes	Yes
Cumulative Alpha				
Cumulative Beta				

Figure 7.2: Group Sequential Side-table Example

The **GST Simulation** button (above the GST Parameters table in top-left if available for that design table) will open the **Group Sequential Design Simulation** tool. If no solver has been activated in the current column, the GST Simulation tool will open in a default "empty" state. If a solver is activated in the current column, the GST Simulation tool will inherit the relevant values from the main design table and the GST Output table. See chapter 8 for details on the Group Sequential Design Simulator tool and its integrations with the GSTX series of tables.

An overview of the each Group Sequential input sub-table is provided next.

7.3.2.1 GST Parameters

The **GST Parameters** tables specifies the primary Bound Calculation Method inputs, specifies the type of Futility Bound and the scale on which the bounds will be shown or inputted in the **GST Outputs** table. As the **GST Parameters** side-table will automatically update depending on **Efficacy Bound Calculation Method** and **Futility Bound Calculation Method** selected, the GST Parameters will be summarized in the following sections:

- Method Specific Inputs
  - Spending Function
  - Haybittle-Peto
  - Wang-Tsiatis/Pampallona-Tsiatis
  - Unified Family
- Futility Bounds (Non-Binding/Binding)
- Boundary Scale
  - Boundary Scale (Output)
  - Efficacy Boundary Scale (Input)
  - Futility Boundary Scale (Input)

Method Specific Inputs The fields shown in the GST Parameters table will depend on the **Efficacy Bound Calculation Method** and **Futility Bound Calculation Method** selected in the main design table with the efficacy and futility bounds defined separately. The three primary boundary calculation methods which affect the **GST Parameters** table are the **Spending Function, Haybittle-Peto, Wang-Tsiatis/Pampallona-Tsiatis** and **Unified Family** methods.

In terms of the other methods interaction with the GST Parameters table, **Custom Boundary** will be discussed in the **Boundary Scale** options section below and **Don't Calculate** has no additional inputs as it means there is no efficacy or futility boundary and therefore these methods can be skipped here. The relevant methods effect on the **GST Parameters** will be discussed in turn next:

Spending Function If **Spending Function** option is selected in the **Efficacy Bound Calculation Method** row in the main design table then a **Alpha Spending Function** row will be added to the **GST Parameters** table.

If **Spending Function** option is selected in the **Futility Bound Calculation Method** row in the main design table then a **Beta Spending Function** row will be added to the **GST Parameters** table.

If both efficacy and futility bounds are active, the spending functions are set separately for each boundary via the Alpha Spending Function and Beta Spending Function rows. The same set of spending functions are available for both efficacy and futility bounds. Technical detail on spending functions is provided in subsubsection 7.2.4.1These spending functions available are as follows :

- O'Brien-Fleming
- Pocock
- Hwang-Shih-DeCani (γ)
- Power Family (ρ)
- 2-Parameter Family ($Dist.$, a, b)
- Exponential (ν)
- Beta (a, b)
- t-Distribution (a, b, df)
- User Defined

For spending functions that require additional parameter inputs, the symbols in brackets indicate the inputs required in the **Additional Parameters** table (described in subsubsection 7.3.2.3) for that spending function. **User Defined** requires the input of the custom alpha/beta errors in the **GST Outputs** side-table (see subsubsection 7.3.2.2). For the **O'Brien-Fleming** and **Pocock** spending functions, solver activation can occur without any further input.

An example spending function **GST Outputs** table is provided in Figure 7.3.

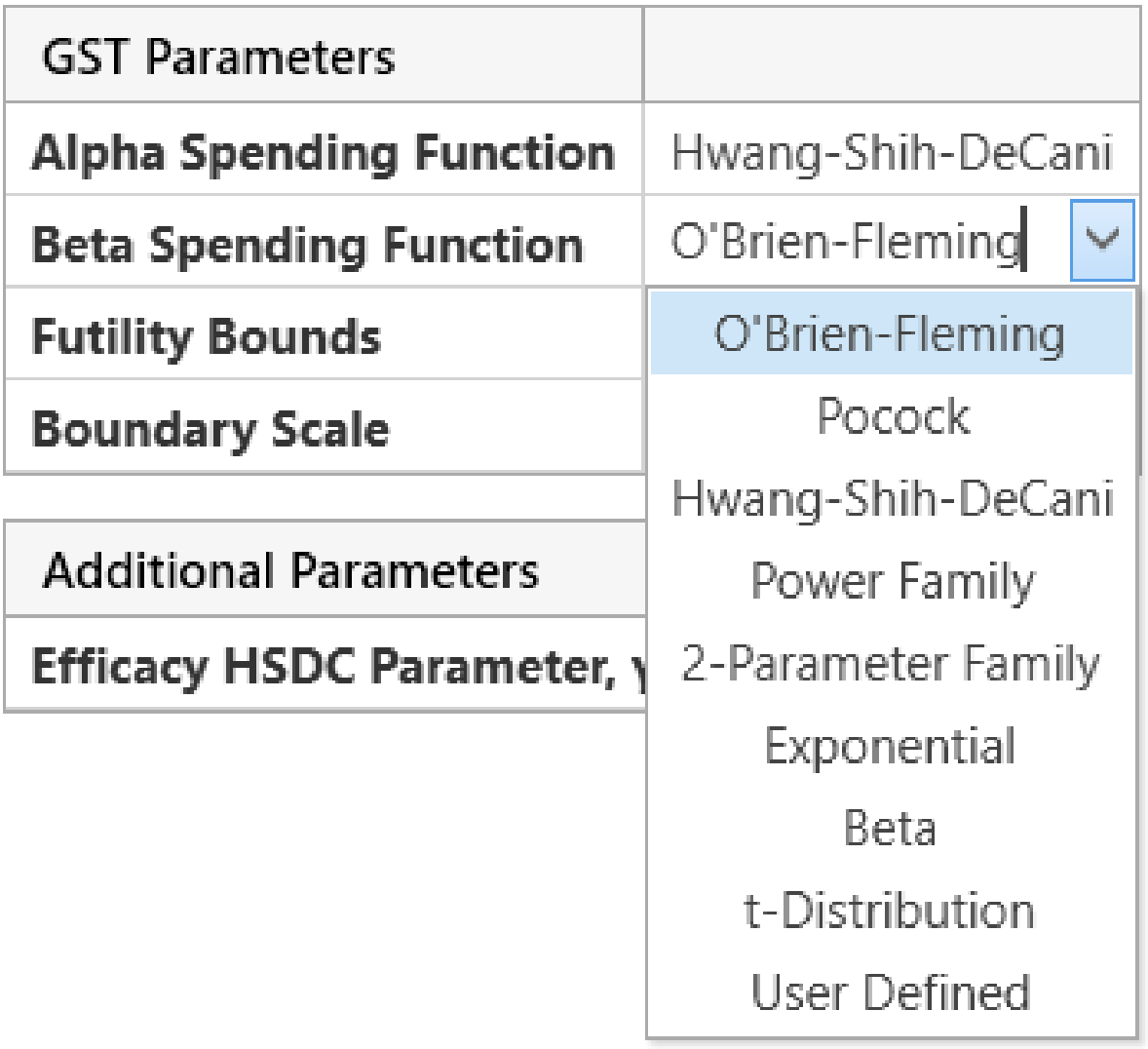


Figure 7.3: Spending Function GST Parameters Table Example

Haybittle-Peto If **Haybittle-Peto** is selected in the **Efficacy Bound Calculation Method** row in the main design table then a **Fixed Parameter** row will be added to the **GST Parameters** table. **Fixed Parameter** is a dropdown field that can be set to **Total Alpha** or **Final p-value.**

If **Fixed Parameter = Total Alpha**, the **p-value** row in the **GST Outputs** table will be editable except for the final column value. This method allows the user to set the interim p-values but calculate the final p-value to maintain the specified **Test Significance Level** from the main design table.

If **Fixed Parameter = Last p-value**, the **p-value** row in the **GST Outputs** table will be fully editable including the final column value. This method allows the user to set the interim p-values and the final p-value. This means the actual Type I error rate may diverge significantly from the **Test Significance Level** from the main design table. The **Exact Significance Level** field in the **Group Sequential Report** will provide the actual Type I error for the specified Haybittle-Peto boundaries.

In both cases, all editable **p-value** row values in **GST Outputs** will be set to 0.005. For further details on the p-value row in the **GST Outputs** table, see subsubsection 7.3.2.2. Technical details on the Haybittle-Peto method are provided in subsubsection 7.2.4.2.

Wang-Tsiatis/Pampallona-Tsiatis If **Wang-Tsiatis** is selected in the **Efficacy Bound Calculation Method** row in the main design table then a **Efficacy Shape,** Δ_1 row will be added to the **GST Parameters** table.

If **Pampallona-Tsiatis** is selected in the **Futility Bound Calculation Method** row in the main design table then a **Futility Shape,** Δ_2 row will be added to the **GST Parameters** table.

Note that while **Wang-Tsiatis** can be selected with **Pampallona-Tsiatis** or **Don't Calculate** for the **Futility Bound Calculation Method**, **Pampallona-Tsiatis** can only be selected with **Wang-Tsiatis**. Therefore, either the **Efficacy Shape,** Δ_1 will either be shown alone or alongside the **Futility Shape,** Δ_2 row. If both are active, the two parameters control the efficacy and futility bound respectively. By default, both parameters are set to zero which is equivalent to the O'Brien-Fleming design boundaries. [O'Brien and Fleming, 1979]

For technical detail on the **Wang-Tsiatis** and **Pampallona-Tsiatis** method see subsubsection 7.2.4.3 - this section also discusses common parameter choices and the allowable input range for each.

An example GST Parameters side-table with both **Wang-Tsiatis** and **Pampallona-Tsiatis** selected in the main table is provided in Figure 7.4.

GST Parameters	
Efficacy Shape, Δ_1	0.250
Futility Shape, Δ_2	-0.250
Futility Bounds	Non-Binding
Boundary Scale	Z-scale

Figure 7.4: Wang-Tsiatis/Pampallona-Tsiatis GST Parameters Table Example

Unified Family If **Unified Family** is selected in the **Efficacy Bound Calculation Method** row in the main design table then the **Efficacy Shape 1,** $\tau(\alpha)$ and **Efficacy Shape 2,** $\rho(\alpha)$ row will be added to the **GST Parameters** table.

If **Unified Family** is selected in the **Futility Bound Calculation Method** row in the main design table then the **Futility Shape 1,** $\tau(\beta)$ and **Efficacy Shape 2,** $\rho(\beta)$ row will be added to the **GST Parameters** table.

If **Efficacy Bound Calculation Method = Unified Family**, it can be selected with **Unified Family** or **Don't Calculate** for the **Futility Bound Calculation Method**. If **Futility Bound Calculation Method = Unified Family**, it can only be selected with **Unified Family** for the **Efficacy Bound Calculation Method**. Therefore, either the **Efficacy Shape** parameters will either be shown alone or alongside the **Futility Shape** parameter rows. If both are active, the two sets of parameters control the efficacy and futility bound respectively. No default values are set for the **Unified Family** parameters.

For technical detail on the **Unified Family** method see subsubsection 7.2.4.4- this section also discusses common parameter choices and the allowable input range for each.

An example GST Parameters side-table with both **Unified Family** options selected in the main table is provided in Figure 7.5.

GST Parameters	
Efficacy Shape 1, τ(α)	0.000
Efficacy Shape 2, ρ(α)	0.100
Futility Shape 1, τ(β)	0.200
Futility Shape 2, ρ(β)	0.200
Futility Bounds	Non-Binding
Boundary Scale	Z-scale

Figure 7.5: Unified Family GST Parameters Table Example

Futility Bounds The **Futility Bounds** row controls whether the futility bounds should be **Non-binding** or **Binding**. This row will be shown in the **Futility Bound Calculation Method** row in the main design table is set to **Spending Function, Pampallona-Tsiatis** or **Unified Family**. **Custom Boundary** futility bounds are always assumed to be **Non-binding** and **Don't Calculate** indicates there is no futility bound so this row is not shown for either of those options.

Non-binding calculates non-binding futility bounds where if the futility bound is crossed at a given look the trial can continue to future looks without inflating the Type I (α) error. This is the far more popular choice in clinical trials and is default in nQuery.

Binding calculates binding futility bounds where if the futility bound is crossed at a given look then continuing the trial to future looks will inflate the Type I (α) error.

For technical background on the difference between constructing non-binding or binding futility bounds, see subsection 7.2.3. In short, for non-binding futility bounds the efficacy bounds are calculated first as per an efficacy only design and then futility bounds are found with correct Type II (β) exit probabilities while for binding futility bounds the efficacy and futility bounds are constructed simultaneously for the correct Type I and Type II exit probabilities respectively.

Boundary Scale Boundary Scale type rows control the statistical scale under which the efficacy and/or futility bounds will be shown or inputted on in the **GST Outputs** table.

For **Bound Calculation Methods = Spending Function, Wang-Tsiatis/Pampallona-Tsiatis** or **Unified Family**, the **Boundary Scale** row will control the statistical scale on which the **Efficacy Bound** and/or **Futility Bound** rows will be shown in the **GST Outputs** table.

The **Boundary Scale** row has the following options:

- Z-scale
- p-value Scale
- Score Scale
- δ-scale

For **Efficacy Bound Calculation Method = Custom Boundary**, the **Efficacy Boundary Scale** will control the input scale of the **Efficacy Bound** (if 1-sided) or **Upper Efficacy Bound** (if 2-sided) row in the **GST Outputs** table.

The **Efficacy Boundary Scale** row has the following options:

- Z-scale
- p-value Scale
- Score Scale
- δ-scale
- Alpha Error

For **Futility Bound Calculation Method = Custom Boundary**, the **Futility Boundary Scale** will control the input scale of the **Futility Bound** (if 1-sided) or **Upper Futility Bound** (if 2-sided) row in the **GST Outputs** table.

The **Efficacy Boundary Scale** row has the following options:

- Z-scale
- p-value Scale
- Score Scale
- δ-scale
- Beta Error
- Conditional Power

Details on each of these statistical boundary scales is provided in subsubsection 7.2.4.5 including conversions to the Z-scale for all other scales.

These rows above are not shown for **Haybittle-Peto** method if **Futility Calculation Bound Method = Don't Calculate** as Haybittle-Peto has its own unique fixed **p-value** row in the **GST Outputs** table and **Don't Calculate** means there is no futility bound t control. All other **Don't Calculate** scenarios will have one of the boundary scale type rows as both boundary method rows cannot be set to **Don't Calculate.**

Examples are provided below for the following scenarios: **Boundary Scale** row only (top-left), **Efficacy Boundary Scale** only (top-right), **Futility Boundary Scale** and **Boundary Scale** (bottom-left), **Efficacy Boundary Scale** and **Futility Boundary Scale** (bottom-right).

GST Parameters	
Alpha Spending Function	O'Brien-Fleming
Beta Spending Function	O'Brien-Fleming
Futility Bounds	Non-Binding
Boundary Scale	Z-scale

GST Parameters	
Efficacy Boundary Scale	p-value scale

GST Parameters	
Alpha Spending Function	O'Brien-Fleming
Boundary Scale	Score scale
Futility Boundary Scale	δ-scale

GST Parameters	
Efficacy Boundary Scale	Alpha Error
Futility Boundary Scale	Conditional Power

Figure 7.6: Boundary Scale/Efficacy Boundary Scale/Futility Boundary GST Parameters Examples

7.3.2.2 GST Outputs

The **GST Outputs** table contains the key group sequential design boundary information where the rows indicate different types of key group sequential input (e.g. Information Time) or output (per-look sample sizes). It will contain the following types of row:

- Total Sample Size
- Information Time
- Efficacy Bounds/p-value
- Futility Bounds
- Stop for Efficacy/Stop for Futility
- Cumulative Alpha/Cumulative Beta

Depending on the **Efficacy Bound Calculation Method, Futility Bound Calculation Method, 1 or 2 Sided** values inputted into the main design table, the number and type of row in the **GST Outputs** table may change substantially. **GST Outputs** changes may also change the definition and behavior of some **GST Outputs** rows.

In the GST Outputs table, each column represents an analysis and therefore the number of columns will equal **Number of Looks** row value from the main design table. The final column will represent the final analysis planned for the trial. The **GST Outputs** table only provides the essential information required to understand the group sequential design, for a detailed review of a group sequential design (including information such as the average sample size and boundary exit probabilites) see the **Group Sequential Report** (subsection 7.3.4).

For context, an example of the GST Outputs table for **Efficacy Bound Calculation Method = Spending Function** and **Futility Bound Calculation Method = Spending Function** for the 1-sided case is shown before and after a solver calculation is shown in Figure 7.7.

GST Outputs	1	2	3	4	5
Total Sample Size					
Information Time	0.200	0.400	0.600	0.800	1.000
Efficacy Bound					
Futility Bound					
Stop for Efficacy	Yes	Yes	Yes	Yes	Yes
Stop for Futility	Yes	Yes	Yes	Yes	Yes
Cumulative Alpha					
Cumulative Beta					

GST Outputs	1	2	3	4	5
Total Sample Size	20.000	40.000	60.000	80.000	100.000
Information Time	0.200	0.400	0.600	0.800	1.000
Efficacy Bound	-4.877	-3.357	-2.680	-2.290	-2.031
Futility Bound	3.030	0.785	-0.452	-1.318	-2.031
Stop for Efficacy	Yes	Yes	Yes	Yes	Yes
Stop for Futility	Yes	Yes	Yes	Yes	Yes
Cumulative Alpha	0.000	0.000	0.004	0.012	0.025
Cumulative Beta	0.000	0.000	0.004	0.013	0.027

Figure 7.7: GST Outputs Examples

These the different type of GST Outputs row are summarized next.

Total Sample Size The **Total Sample Size** row represents the sample size at each look in the specified group sequential design.

The maximum sample size will be the value in the final column and will equal the sum of the sample size rows from the main design table. The sample size required at which each interim analysis will occur is displayed in the other prior columns of the **Total Sample Size** row. These will equal the maximum sample size times the **Information Time** in each column.

By default, interim sample sizes will be rounded to the nearest integer which will update the information fractions based on these rounded interim sample sizes during solver calculations. The unrounded sample sizes can be used instead by using the **Integer Interim N** option from the **Options** tab at the bottom of the **Help** window on the right - see subsection 7.3.7 for detail.

In certain tables, the **Total Sample Size** row will be replaced with an equivalent row on which the **Maximum Information** is based - subsection 7.2.5 for table specific technical details. The current replacements are currently in nQuery:

- GST0 (Information-Based): Cumulative Information
- GST3 (Survival): Total Events

Information Time The **Information Time** is the proportion of the information accrued at each look in the specified group sequential design.

The **Information Time** is formally equal to $(t_k = I_k/I_{max})$ as per subsubsection 7.2.1.1. In practice, this will equal the proportion of the total sample size (n_k/N) or events for survival analysis at which an interim analysis will occur. Assuming linear accrual and fixed follow-up, this would also be approximately the proportion of the total study length at which an interim analysis would occur.

The final information time is set to one and cannot be changed. This ensures Information Time is normalized to a $[0, 1]$ proportion support.

By default, the interim informations in all other columns are set to have equally spaced interim analyses (k/K). These interim information fractions can be edited to have unequally spaced interim analyses with the values restricted to between 0 and 1 and strictly increasing going right-wards within the **Information Time** row. An example where the Information Times from Figure 7.7 has been updated to information fractions of 0.3, 0.5, 0.7, 0.9 (representing interim analyses after 30%, 50%, 70% and 90% of subjects have had follow-up) is shown in Figure 7.8.

GST Outputs	1	2	3	4	5
Total Sample Size	30.000	50.000	70.000	90.000	100.000
Information Time	0.300	0.500	0.700	0.900	1.000
Efficacy Bound	-3.929	-2.966	-2.462	-2.149	-2.070
Futility Bound	1.622	0.046	-0.960	-1.717	-2.070
Stop for Efficacy	Yes	Yes	Yes	Yes	Yes
Stop for Futility	Yes	Yes	Yes	Yes	Yes
Cumulative Alpha	0.000	0.002	0.007	0.018	0.025
Cumulative Beta	0.000	0.002	0.009	0.022	0.029

Figure 7.8: Information Times Change Example

By default, interim sample sizes will be rounded to the nearest integer which will update the information fractions based on the rounded interim sample sizes during solver calculations. However, the **Information Time** values will not be changed within the **GST**

Outputs table, these updated **Information Times** rows are only shown in the **Group Sequential Report -** see subsection 7.3.4 for details. This is to prevent the information times iterating away from their original input values if multiple solver calculations are made in the same column.

The unrounded sample sizes can be used instead by using the **Integer Interim N** option from the **Options** tab at the bottom of the **Help** window on the right - see subsection 7.3.7 for detail. In this case, the **Information Times** in the **GST Outputs** table will always be the same as the true information times used by the solver.

Efficacy Bound/p-value The **Efficacy Bound** is the boundary beyond which the trial is planned to stop for efficacy. The efficacy bound row(s) will change substantially in terms of display and behavior based on the choice for the **1 or 2 Sided Test?** and **Efficacy Bound Calculation Method** rows in the main design table and with changes to the **Boundary Scale** or **Efficacy Boundary Scale** rows in the **GST Parameters** table. These changes will be summarized in turn next.

1 or 2 Sided Test? If **1 or 2 Sided Test? = 1** then there will be one **Efficacy Bound** row unless the **Efficacy Bound Calculation Method = Haybittle-Peto** then there will be a single **p-value** row shown instead which is equivalent to the efficacy bound row on the 1-sided test p-value scale

If **1 or 2 Sided Test? = 2** then there will be a **Upper Efficacy Bound** and a **Lower Efficacy Bound** row unless the **Efficacy Bound Calculation Method = Haybittle-Peto** then there will be a single **p-value** row shown instead which is equivalent to the efficacy bound row on the 2-sided test p-value scale

A 2-sided example (using **Spending Function**) for the efficacy bounds is provided in Figure 7.9.

GST Outputs	1	2	3	4	5
Total Sample Size	30.000	50.000	70.000	90.000	100.000
Information Time	0.300	0.500	0.700	0.900	1.000
Lower Efficacy Bound	4.412	3.346	2.782	2.429	2.333
Upper Efficacy Bound	-4.412	-3.346	-2.782	-2.429	-2.333
Cumulative Alpha	0.000	0.001	0.006	0.017	0.025

Figure 7.9: 2-Sided Efficacy Bounds GST Outputs Table Example

Efficacy Bound Calculation Method For **Efficacy Bound Calculation Method = Spending Function, Wang-Tsiatis, Unified Family, Custom Boundary** either an **Efficacy Bound** row (1-sided) or a **Lower Efficacy Bound** and **Upper Efficacy Bound** rows (2-sided) will be displayed.

For **Spending Function, Wang-Tsiatis** and **Unified Family**, all efficacy bound row (**Efficacy Bound, Lower Efficacy Bound, Upper Efficacy Bound** as applicable) values in the **GST Outputs** table will be a read-only and will only be populated with

the efficacy boundaries after a solver calculation is run in that column. The definition of the output rows will depend on the choice of **Boundary Scale** in the **GST Parameters** table. Examples of this are shown above in Figure 7.7 and Figure 7.9.

For **Custom Boundary**, the **Efficacy Bound** (1-sided) or **Upper Efficacy Bound** (2-sided) rows will editable - they will be empty by default and must be filled appropriately before solver calculations can occur. For 2-sided, the **Lower Efficacy Bound** will be read-only and will be set the symmetric lower bound - this will equal **-Upper Efficacy Bound** for the **Z-scale, Score Scale** and δ**-Scale** and set to equal to **Upper Efficacy Bound** for **p-value Scale** and **Alpha Error**. The definition and the range of the input rows will depend on the choice of **Efficacy Boundary Scale** in the **GST Parameters** table. A 2-sided **Efficacy Boundary Scale** example for **Custom Boundary** is shown for the δ-Scale in Figure 7.10.

GST Parameters	
Efficacy Boundary Scale	δ-scale

	GST Outputs	1	2	3	4	5
	Total Sample Size	30.000	50.000	70.000	90.000	100.000
	Information Time	0.300	0.500	0.700	0.900	1.000
	Lower Efficacy Bound	3.000	2.000	1.500	1.250	0.500
▸	**Upper Efficacy Bound**	-3.000	-2.000	-1.500	-1.250	-0.500

Figure 7.10: Custom Boundary Efficacy Example

For **Efficacy Bound Calculation Method = Haybittle-Peto** there will be a single **p-value** row shown instead of this efficacy bound rows.

If **Fixed Parameter = Total Alpha** in the **GST Parameters** table, the **p-value** row in the **GST Outputs** table will be editable except for the final column value. This method allows the user to set the interim p-values but calculate the final p-value to maintain the specified **Test Significance Level** from the main design table.

If **Fixed Parameter = Last p-value** in the **GST Parameters** table, the **p-value** row in the **GST Outputs** table will be fully editable including the final column value. This method allows the user to set the interim p-values and the final p-value. This means the actual Type I error rate may diverge significantly from the **Test Significance Level** from the main design table. The **Exact Significance Level** field in the **Group Sequential Report** will provide the actual Type I error for the specified Haybittle-Peto boundaries.

An example of the **GST Outputs** table for the **Haybittle-Peto** method is shown in Figure 7.11.

GST Parameters	
Fixed Parameter	Total Alpha

	GST Outputs	1	2	3	4	5
	Total Sample Size	30.000	50.000	70.000	90.000	100.000
	Information Time	0.300	0.500	0.700	0.900	1.000
	p-value	0.005	0.005	0.005	0.005	0.017

GST Parameters	
Fixed Parameter	Last P-Value

	GST Outputs	1	2	3	4	5
	Total Sample Size	30.000	50.000	70.000	90.000	100.000
	Information Time	0.300	0.500	0.700	0.900	1.000
	p-value	0.005	0.005	0.005	0.005	0.005

Figure 7.11: Haybittle-Peto Example

In both cases, all editable **p-value** row values in **GST Outputs** will be set to 0.005 by default. It is recommended that p-values be set to low values (<0.005) to ensure the final

p-value boundary is comparable to an equivalent fixed term trial. p-values can be set between 0 and 1 but for **Total Alpha** the following error will be displayed if the interim alpha makes it impossible to find a final p-value boundary which maintains the specified **Test Significance Level**: *Failed to calculate the efficacy bound. Please recheck input parameters.* Reduce one or more of the interim p-values to prevent this error.

Technical details on the Haybittle-Peto method are provided in subsubsection 7.2.4.2.

Boundary Scale The **Boundary Scale** row in the **GST Parameters** table will change the statistical scale on which the **Efficacy Bound** (1-sided) or **Upper Efficacy Bound** and **Lower Efficacy Bound** (2-sided) rows are displayed if these bounds are read-only output rows (i.e. **Spending Function, Wang-Tsiatis, Unified Family** as discussed above). These bounds can be shown on the **Z-scale, p-value Scale, Score Scale** and δ**-Scale.** Note that the **Boundary Scale** will also affect any read-only output **Futility Bounds** if present.

Note that the direction of the hypothesis will depend on the value for the row(s) which correspond to the treatment effect θ in the main design table. If the treatment effect is positive then higher values for the treatment effect (and statistics such as the Z-statistic and Score statistic) are considered more "effective" and lower values more "futile". If the treatment effect is negative in the main design table then lower values will be considered "better". This will change the sign and the relation to the **Futility Bounds** and between the **Upper and Lower Efficacy Bound** as applicable.

Note that for 2-sided efficacy boundaries, the **p-value Scale** will split the p-value at each look into $\alpha/2$ for Upper Efficacy Bound and $1-\alpha/2$ for the Lower Efficacy Bound as per the **GST Outputs** table. This is done for consistency with the other boundary scales but in practical terms if using a standard statistical test the efficacy boundary would be crossed if it provided a p-value of $< \alpha$ i.e. twice the Upper Efficacy p-value Bound at each look.

For GST1, positive treatment effect would correspond to a positive **mean difference** so the higher the mean difference (and Z-statistic etc) the "better". For GST2, a "positive" treatment effect would correspond to a positive proportion difference. For GST3, a "positive" treatment effect would correspond to a hazard ratio > 1.

To illustrate this compare the **GST Outputs** table in Figure 7.7 where the mean difference was negative (therefore **Efficacy Bounds < Futility Bounds**) to the same design except with the mean difference being of the opposite side in the first table in Figure 7.12.

GST Outputs	1	2	3	4	5
Total Sample Size	20.000	40.000	60.000	80.000	100.000
Information Time	0.200	0.400	0.600	0.800	1.000
Efficacy Bound	4.877	3.357	2.680	2.290	2.031
Futility Bound	-3.030	-0.785	0.452	1.318	2.031
Stop for Efficacy	Yes	Yes	Yes	Yes	Yes
Stop for Futility	Yes	Yes	Yes	Yes	Yes
Cumulative Alpha	0.000	0.000	0.004	0.012	0.025
Cumulative Beta	0.000	0.000	0.004	0.013	0.027

Figure 7.12: GST Outputs Bounds with Positive Effect Size

The effect of changing **Boundary Scale** in the **GST Parameters** table, on both the **Efficacy Bound** and **Futility Bound** rows, for the above example to the **p-value Scale**, **Score Scale** and δ**-Scale** (in that order) is shown in Figure 7.13.

Efficacy Bound	0.000	0.000	0.004	0.011	0.021
Futility Bound	0.999	0.784	0.325	0.094	0.021
Efficacy Bound	8.724	8.493	8.305	8.192	8.124
Futility Bound	-5.420	-1.986	1.402	4.714	8.124
Efficacy Bound	2.726	1.327	0.865	0.640	0.508
Futility Bound	-1.694	-0.310	0.146	0.368	0.508

Figure 7.13: Boundary Scale Change GST Outputs Example

Efficacy Boundary Scale The **Efficacy Boundary Scale** row changes the statistical scale definition of the values inputted into the **Efficacy Bound** (1-sided) or **Upper Efficacy Bound** (2-sided) when **Efficacy Bound Calculation Method = Custom Boundary**. The available statistical scales are **Z-scale, p-value Scale, Score Scale,** δ**-Scale** and **Alpha Error**.

At a general level, **Z-scale, Score Scale,** δ**-Scale** can take on any real values. The **p-value Scale** and **Alpha Error** options must be between 0 and 1.

Note that the direction of the hypothesis will depend on the value for the row(s) which correspond to the treatment effect θ in the main design table and this can have an effect on the input requirements. If the treatment effect is positive then higher values for the treatment effect (and statistics such as the Z-statistic and Score statistic) are considered more "effective" and lower values more "futile". If the treatment effect is negative in the main design table then lower values will be considered "better".

If both **Efficacy Boundary Method Calculation** and **Futility Boundary Calculation Method = Custom Boundary** then for a positive treatment effect, the Z-scale/Score Scale/δ-scale **Efficacy Bounds** must be higher than the **Futility Bounds**.

For a negative treatment effect, the Z-scale/Score Scale/δ-scale **Efficacy Bounds** must be lower than the **Futility Bounds**. For **p-value Scale**, the **Efficacy Bounds** must always be less than the **Futility Bounds**.

Note that for 2-sided efficacy boundaries, the **p-value Scale** will split the p-value at each look into $\alpha/2$ for Upper Efficacy Bound and $1-\alpha/2$ for the Lower Efficacy Bound as per the **GST Outputs** table. This is done for consistency with the other boundary scales but in practical terms if using a standard statistical test the efficacy boundary would be crossed if it provided a p-value of $< \alpha$ i.e. twice the Upper Efficacy p-value Bound at each look.

While these boundaries are not enforced for other **Futility Boundary Calculation Method** options (as the futility bound is unknown prior to solver calculation), efficacy bounds should ideally be selected to be consistent with the expected futility bounds for that method.

For GST1, positive treatment effect would correspond to a positive **mean difference** so the higher the mean difference (and Z-statistic etc) the "better". For GST2, a "positive" treatment effect would correspond to a positive **proportion difference**. For GST3, a "positive" treatment effect would correspond to a **hazard ratio** > 1 i.e. log hazard ratio > 0.

A **Custom Boundary** example was provided in Figure 7.10.

Futility Bound The **Futility Bound** is the boundary beyond which the trial is planned to stop for futility. The futility bound row(s) will change substantially in terms of display and behavior based on the choice for the **1 or 2 Sided Test?** and **Futility Bound Calculation Method** rows in the main design table and with changes to the **Boundary Scale** or **Futility Boundary Scale** rows in the **GST Parameters** table.

1 or 2 Sided Test? If **1 or 2 Sided Test? = 1** then there will be one **Futility Bound** row and if **1 or 2 Sided Test? = 2** then there will be a **Upper Futility Bound** and a **Lower Futility Bound** row

Futility Bound Calculation Method For **Futility Bound Calculation Method = Spending Function, Pampallona-Tsiatis, Unified Family, Custom Boundary** either an **Futility Bound** row (1-sided) or a **Lower Futility Bound** and **Upper Futility Bound** rows (2-sided) will be displayed.

For **Spending Function, Wang-Tsiatis** and **Unified Family**, all futility bound row (**Futility Bound, Lower Futility Bound, Upper Futility Bound** as applicable) values in the **GST Outputs** table will be a read-only and will only be populated with the futility boundaries after a solver calculation is run in that column. The definition of the output rows will depend on the choice of **Boundary Scale** in the **GST Parameters** table.

For **Custom Boundary**, the **Futility Bound** (1-sided) or **Upper Futility Bound** (2-sided) rows will editable - they will be empty by default and must be filled appropriately before solver calculations can occur. For 2-sided, the **Lower Futility Bound** will be read-only and will be set the symmetric lower bound - this will equal **-Upper Futility**

Bound for the **Z-scale, Score Scale** and δ**-Scale** and set to equal to **Upper Futility Bound** for **p-value Scale, Alpha Error** and **Conditional Power.** The definition and the range of the input rows will depend on the choice of **Futility Boundary Scale** in the **GST Parameters** table.

Boundary Scale The **Boundary Scale** row in the **GST Parameters** table will change the statistical scale on which the read-only output **Futility Bound** rows are displayed - this is relevant for the **Spending Function, Pampallona-Tsiatis** and **Unified Family** methods. These bounds can be shown on the **Z-scale, p-value Scale, Score Scale** and δ**-Scale.** This option also affects the applicable **Efficacy Bounds**. As referenced above, the direction will depend on the treatment effect direction. Examples of the **Boundary Scale** translations and effect of direction were shown for **Efficacy Bounds** and **Futility Bounds** was shown in Figure 7.13 and Figure 7.12 above.

Futility Boundary Scale The **Futility Boundary Scale** row changes the statistical scale definition of the values inputted into the **Futility Bound** (1-sided) or **Upper Futility Bound** (2-sided) when **Futility Bound Calculation Method = Custom Boundary**. The available statistical scales are **Z-scale, p-value Scale, Score Scale,** δ**-Scale**, **Beta Error** and **Conditional Power.**

At a general level, **Z-scale, Score Scale,** δ**-Scale** can take on any real values. The **p-value Scale, Beta Error** and **Conditional Power** options must be between 0 and 1.

Note that the direction of the hypothesis will depend on the value for the row(s) which correspond to the treatment effect θ in the main design table and this can have an effect on the input requirements. If the treatment effect is positive then higher values for the treatment effect (and statistics such as the Z-statistic and Score statistic) are considered more "effective" and lower values more "futile". If the treatment effect is negative in the main design table then lower values will be considered "better". For GST1, positive treatment effect would correspond to a positive **mean difference** so the higher the mean difference (and Z-statistic etc) the "better". For GST2, a "positive" treatment effect would correspond to a positive **proportion difference**. For GST3, a "positive" treatment effect would correspond to a **hazard ratio** > 1 i.e. log hazard ratio > 0.

If both **Efficacy Boundary Method Calculation** and **Futility Boundary Calculation Method = Custom Boundary** then for a positive treatment effect, the Z-scale/Score Scale/δ-scale **Efficacy Bounds** must be higher than the **Futility Bounds**. For a negative treatment effect, the Z-scale/Score Scale/δ-scale **Efficacy Bounds** must be lower than the **Futility Bounds**. For **p-value Scale**, the **Efficacy Bounds** must always be less than the **Futility Bounds**.

While these boundaries are not enforced for other **Fuility Boundary Calculation Method** options (as the efficacy bound is unknown prior to solver calculation), efficacy bounds should ideally be selected to be consistent with the expected efficacy bounds for that method.

Futility Method = Custom Boundary examples for the **Z-scale** (1-sided) and **p-value Scale** (2-sided) is provided in Figure 7.14.

GST Parameters	
Alpha Spending Function	O'Brien-Fleming
Boundary Scale	Z-scale
Futility Boundary Scale	Z-scale

GST Outputs	1	2	3	4	5
Total Sample Size	20.000	40.000	60.000	80.000	100.000
Information Time	0.200	0.400	0.600	0.800	1.000
Efficacy Bound	4.877	3.357	2.680	2.290	2.031
Futility Bound	-2.000	0.000	0.000	1.000	2.031
Cumulative Alpha	0.000	0.000	0.004	0.012	0.025

GST Parameters	
Alpha Spending Function	Pocock
Boundary Scale	p-value scale
Futility Boundary Scale	p-value scale

GST Outputs	1	2	3	4	5
Total Sample Size	20.000	40.000	60.000	80.000	100.000
Information Time	0.200	0.400	0.600	0.800	1.000
Lower Efficacy Bound	0.004	0.004	0.004	0.004	0.004
Upper Efficacy Bound	0.004	0.004	0.004	0.004	0.004
Lower Futility Bound	0.300	0.200	0.100	0.050	0.004
Upper Futility Bound	0.300	0.200	0.100	0.050	0.004
Cumulative Alpha	0.007	0.013	0.018	0.022	0.025

Figure 7.14: Custom Futility Boundary Examples

Stop for Efficacy/Stop for Futility The **Stop for Efficacy** and **Stop for Futility** rows in the **GST Outputs** table are used to skip either an efficacy or futility analysis at a specific look. This allows the user to have either an efficacy only or futility look while assessing both at other looks. To skip a look, select **No** instead of **Yes** at the desired look from the relevant **Stop for Efficacy** or **Stop for Futility** row.

The **Stop for Efficacy** and **Stop for Futility** rows will only be shown in the **GST Outputs** table if **Efficacy Bound Calculation Method = Spending Function, Wang-Tsiatis, Unified Family** and **Futility Bound Calculation Method = Spending Function, Pampallona-Tsiatis, Unified Family.** For these boundary calculation methods, "skipping" a look is equivalent to calculating the boundaries as if that look had not existed during the boundary calculation process. For example, if the information times were $(0.2, 0.4, 0.6, 0.8, 1)$ then skipping the third look would be equivalent to inputting information times of $(0.2, 0.4, 0.8, 1)$ into the boundary calculation method instead. See subsection 7.2.4 for technical details on boundary calculations.

For **Stop for Efficacy**, the user can select rhe first $K - 2$ look columns. For example, if **Number of Looks** $= 5$ then the user can skip the first three efficacy look columns. In nQuery, efficacy look skipping is restricted such that when an efficacy look is skipped all prior efficacy looks must also be skipped. For example, if **No** is selection in the **Stop for Efficacy** row in the second column then the **Stop for Efficacy** value in the first column will also be forced to equal **No.**

For **Stop for Futility**, the user can select rhe first $K - 1$ look columns. For example, if **Number of Looks** $= 5$ then the user can skip the first four look columns. Unlike **Stop for Efficacy**, there are no restrictions on the pattern for futility boundary skips outside of that **Stop for Efficacy** and **Stop for Futility** cannot both equal **No** in a given column.

When a look is skipped, the appropriate value in the **Efficacy Bound** or **Futility Bound** will be displayed as **NaN** in the **GST Outputs** table after solver calculation.

An example where the first two efficacy looks are skipped and the third futility look is skipped is provided in Figure 7.15.

GST Outputs	1	2	3	4	5
Total Sample Size	20.000	40.000	60.000	80.000	100.000
Information Time	0.200	0.400	0.600	0.800	1.000
Efficacy Bound	NaN	NaN	2.669	2.289	2.031
Futility Bound	-3.043	-0.794	NaN	1.347	2.031
Stop for Efficacy	No	No	Yes	Yes	Yes
Stop for Futility	Yes	Yes	No	Yes	Yes
Cumulative Alpha	0.000	0.000	0.004	0.012	0.025
Cumulative Beta	0.000	0.000	0.000	0.013	0.026

Figure 7.15: Skipping Looks GST Outputs Example

Cumulative Alpha/Cumulative Beta The **Cumulative Alpha** and **Cumulative Beta** rows in the **GST Outputs** table contain the cumulative Type I (α) and Type II (β) error spent at each look when using the **Spending Function** bound calculation method.

The **Cumulative Alpha** row will only be shown if **Efficacy Bound Calculation Method = Spending Function.** The **Cumulative Beta** row will only be shown if **Futility Bound Calculation Method = Spending Function.**

For all **Spending Functions** other than **User Defined**, these rows will be read-only outputs which will contain the outputs of the selected spending function from the **GST Parameters** table and the parameters, if any, provided in the **Additional Parameters** table - see subsubsection 7.3.2.1 and subsubsection 7.3.2.3 for spending function inputs and subsubsection 7.2.4.1 for technical background on spending functions. The **Cumulative Alpha** and **Cumulative Beta** rows were shown in several of the example figures provided in the prior sections.

If a **Alpha and/or Beta Spending Function** is set to **User Defined** in the **GST Parameters** table then the **Cumulative Alpha** and/or **Cumulative Beta** row will be editable except for the final column values. The desired cumulative Type I (α) and Type II (β) exit probabilities at each look are inputted for each look column except when calculating the power where the **Cumulative Beta** rows becomes the proportion of the total (unknown) **Beta Error** that will be spent rather than **Beta Error** spent directly. The actual **Beta Error** spent will replace these proportions after the power solver has ran.

These values should be strictly increasing from left to right and should not exceed the overall Type I error rate (i.e. Test Significance Level) or Type II error rate (i.e. 1-Power) respectively. For additional detail see section 7.2.4.1.

The user may be interested in viewing the error spending function visually after solver calculation. See subsection 7.3.6 for details on the **Error Spending Plot** tab for that purpose.

An example where both the **Alpha Spending Function** and **Beta Spending Function** were set to **User Defined** and user inputs were provided for their respective custom spending functions is provided in Figure 7.16.

GST Parameters	
Alpha Spending Function	User Defined
Beta Spending Function	User Defined
Futility Bounds	Non-Binding
Boundary Scale	Z-scale

GST Outputs	1	2	3	4	5
Total Sample Size	20.000	40.000	60.000	80.000	100.000
Information Time	0.200	0.400	0.600	0.800	1.000
Efficacy Bound	3.090	2.622	2.454	2.164	2.221
Futility Bound	-2.221	-0.919	-0.265	0.108	2.221
Stop for Efficacy	Yes	Yes	Yes	Yes	Yes
Stop for Futility	Yes	Yes	Yes	Yes	Yes
Cumulative Alpha	0.001	0.005	0.010	0.020	0.025
Cumulative Beta	0.000	0.000	0.001	0.001	0.030

Figure 7.16: User Defined Spending Function GST Outputs Example

7.3.2.3 Additional Parameters

The **Additional Parameters** table is an optional table which appears below the **GST Parameters** table when it is required for the selected group sequential method. There are two scenarios where the **Additional Parameters** table is required: spending functions, custom futility conditional power bounds

The **Additional Parameters** side-table is required for the following **Spending Functions:**

- Hwang-Shih-DeCani (γ)
- Power Family (ρ)
- 2-Parameter Family ($Dist.$, a, b)
- Exponential (ν)
- Beta (a, b)
- t-Distribution (a, b, df)

where the value in brackets indicate the parameter symbol. For technical detail on these spending functions and their additional parameters see subsubsection 7.2.4.1.

Note the **Additional Parameters** table will contain separate rows for the efficacy and futility bound spending functions if both require additional parameter input(s). Efficacy parameters are indicated by (α) and futility parameters by (β) after the symbol e.g. $\gamma\,(\alpha)$ for the Hwang-Shih-DeCani gamma parameter for the efficacy spending function and $\gamma\,(\beta)$ for the Hwang-Shih-DeCani gamma parameter for the futility spending function.

Example **Additional Parameters** tables are shown for a variety of scenarios in

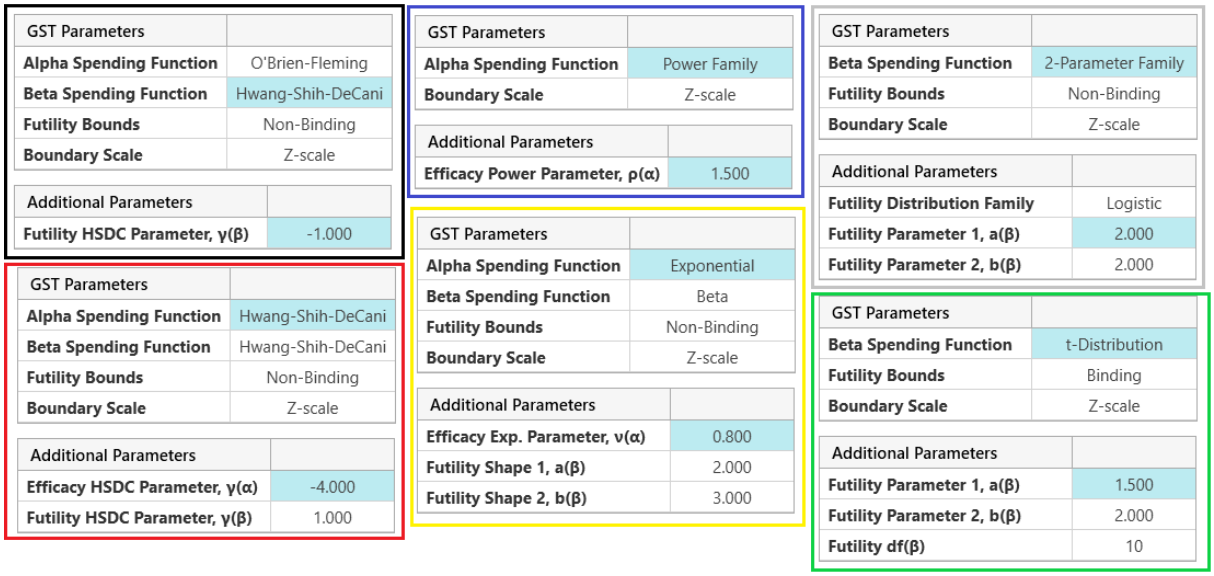


Figure 7.17: Additional Parameters Table Examples for Spending Functions

For **Futility Bound Calculation Method = Custom Boundary**, if **Futility Boundary Scale** is set to **Conditional Power** then the **Additional Parameters** table will contain the **Conditional Power Assumption** row. **Conditional Power Assumption** can be set to **Estimated** θ or **Design** θ**.**

Estimated θ assumes the "true" treatment effect (θ), such as the mean difference, will equal the treatment effect at the futility boundary itself for the purposes of calculating conditional power.

Design θ assumes the "true" treatment effect (θ), such as the mean difference, will equal the treatment effect specified for the original solver calculation (i.e. in the main design table) for the purposes of calculating conditional power.

Technical detail on **Conditional Power** boundaries can be found in subsubsection 7.2.4.5.

An custom boundary conditional power example including the additional parameters table is provided in Figure 7.18.

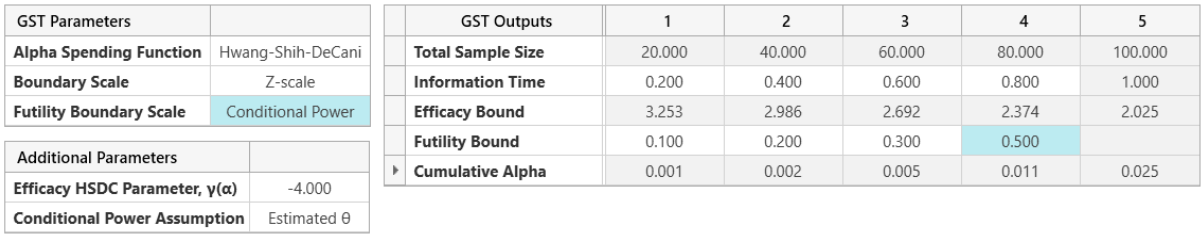


Figure 7.18: Custom Conditional Power Boundary Example

7.3.2.4 Summary

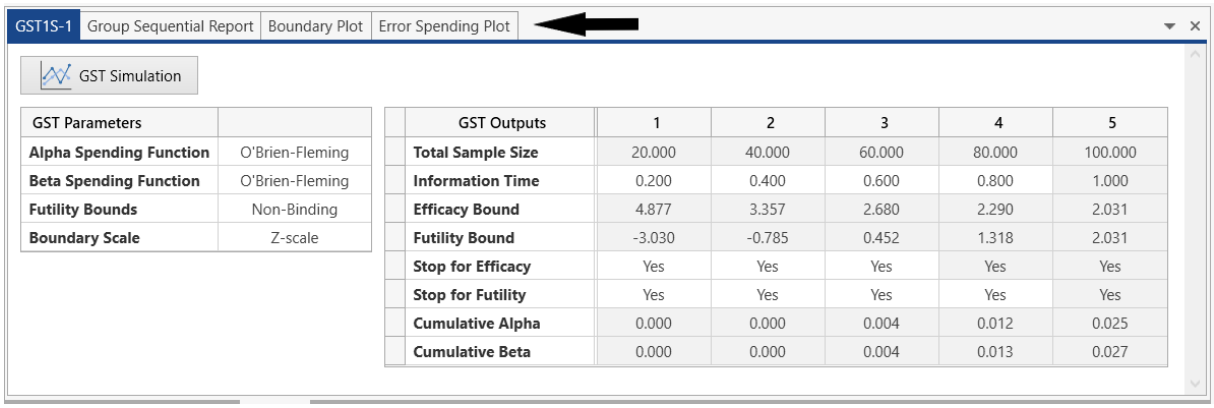
The above sections have covered the **Group Sequential Side-table** (GSTXS-Y) where the group sequential design inputs are provided, alongside some of the primary group

sequential design outputs, in the **GST Parameters, GST Outputs** and (if required) **Additional Parameters** tables.

For the majority of group sequential tables, before solver calculation the **Group Sequential Side-table** will only contain the input tab as per Figure 7.2. Solver calculation is dependent on the GSTXS-Y side-table being filled appropriately.

At present, the one exception to the above is GST3 (Two Survival Group Sequential Design) which will also have the **Piecewise Survival Information** table tab that must be filled prior to solver calculations. See subsection 7.3.3 for details.

After solver calculation, additional tabs are available at the top of the side-table panel which provide additional information about the calculated group sequential design. These are the **Group Sequential Report** (subsection 7.3.4), **Boundary Plot** (subsection 7.3.5) and **Error Spending Plot** (subsection 7.3.6) and these will be covered in the following sections. These tabs are present post-calculation in Figure 7.19.



GST Parameters	
Alpha Spending Function	O'Brien-Fleming
Beta Spending Function	O'Brien-Fleming
Futility Bounds	Non-Binding
Boundary Scale	Z-scale

GST Outputs	1	2	3	4	5
Total Sample Size	20.000	40.000	60.000	80.000	100.000
Information Time	0.200	0.400	0.600	0.800	1.000
Efficacy Bound	4.877	3.357	2.680	2.290	2.031
Futility Bound	-3.030	-0.785	0.452	1.318	2.031
Stop for Efficacy	Yes	Yes	Yes	Yes	Yes
Stop for Futility	Yes	Yes	Yes	Yes	Yes
Cumulative Alpha	0.000	0.000	0.004	0.012	0.025
Cumulative Beta	0.000	0.000	0.004	0.013	0.027

Figure 7.19: Group Sequential Side-Table including Group Sequential Report, Boundary Plot, Error Spending Plot

7.3.3 Piecewise Survival Information (GST3 only)

In nQuery, certain group sequential survival analysis tables will allow for piecewise information to be provided for the accrual process, hazard rates and dropout rates. These tables will require the user specify this piecewise survival information in the **Piecewise Survival Information** tab before solver calculation. This piecewise survival information table is similar to the mandatory side-table required for tables such as STT3 and STT24.

The **Piecewise Survival Information** tab will only be available after the user specified the **Number of Periods** and the **Hazard Ratio** in the main design table. The **Piecewise Survival Information** tab for GST3 (pre-calculation) is shown in Figure 7.20 for **Number of Period** $= 4$.

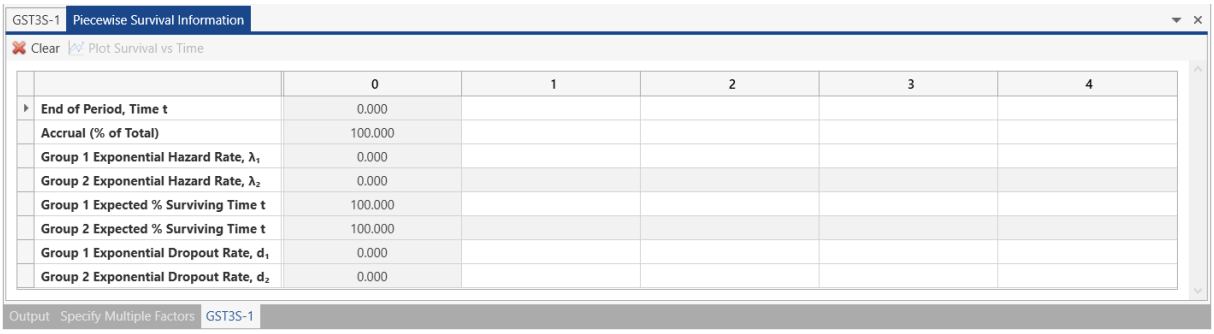


Figure 7.20: Piecewise Survival Information Example

Note that we have selected the **Piecewise Survival Information** at the top of the group sequential side-table window to open this tab. The previously discussed **Group Sequential Side-table** could be shown instead by selecting the **GST3S-1** tab shown here.

For GST3, the **Piecewise Survival Information** has the following rows: **End of Period, Time t, Accrual (% of Total), Group 1 Exponential Hazard Rate,** λ_1**, Group 2 Exponential Hazard Rate,** λ_2**, Group 1 Expected % Surviving Time t, Group 2 Expected % Surviving Time t, Group 1 Exponential Dropout Rate,** d_1**, Group 2 Exponential Dropout Rate,** d_2**.**

A brief overview of each is provided below:

End of Period, Time t: The time up to which the current column period will apply. The specified rates in a column will apply between the Time t specified in the previous column and the Time t specified in the current column. All values must be greater than zero and strictly increasing going from left to right. The Time t specified in the final column will correspond the planned study length, also known as the maximum follow-up.

Accrual (% of Total): The percentage of the total sample size accrual which will occur in the current time period. The Accrual % values must be between 0 to 100 (inclusive) and the writable columns values must sum to 100. The read-only **Column 0** will be equal to 100 - $\sum Accrual(\%)$ and therefore will equal 0 when this row is filled appropriately. For cases where the accrual period is shorter than the study length, enter the desired accrual pattern up the **Time t** corresponding the accrual period length and then set accrual % to 0 in all remaining post-accrual period rows.

Group 1 Exponential Hazard Rate, λ_1 is the piecewise exponential survival hazard rate in group 1 in the current time period. Theses values must all be zero or greater. When λ_1 is specified, the **Group 2 Exponential Hazard Rate,** λ_2 will be automatically calculated based on the **Hazard Ratio** specified in the main design table. If the **Time t** is specified for all columns up to and including the current column then the **Group 1 Expected % Surviving Time t** and **Group 1 Expected % Surviving Time t** will both be automatically calculated when λ_1 is specified. λ_1 can be automatically calculated for in a similar manner if the **Time t** row is fully specified up to the current column and the **Group 1 Expected % Surviving Time t** is inputted in the current column. The user may also be interested in the **Survival Parameter Converter** tool available from the **Assistants** file menu which can calculate the exponential hazard based on the median survival or proportion surviving (see section 3.5).

Group 2 Exponential Hazard Rate, λ_2 is the piecewise exponential survival hazard rate in group 2 in the current time period. This row is read-only and must be calculated on the basis of the **Group 1 Exponential Hazard Rate,** λ_1 in the current column and the **Hazard Ratio** specified in the main design table.

Group 1 Expected % Surviving Time t is the percentage of subjects expected to have not had the event of interest (e.g. death) in group 1 at **Time t** given the full piecewise survival pattern up to the end of the current time period **Time t**. These values must all be between 0 to 100 and strictly decreasing from left to right. If the **Time t** is specified for all columns up to and including the current column then when the **Group 1 Expected % Surviving Time t** is inputted then the **Group 2 Expected % Surviving Time t**, **Group 1 Exponential Hazard Rate,** λ_1 and **Group 2 Exponential Hazard Rate,** λ_2 will all be automatically calculated based on the **Hazard Ratio** specified in the main design table. Similarly, the **Group 1 Expected % Surviving Time t** can be calculated based on the **Group 1 Exponential Hazard Rate,** λ_1 in the current column and the **Time t** values specified up to and including the current column.

Group 2 Expected % Surviving Time t is the percentage of subjects expected to have not had the event of interest (e.g. death) in group 2 at **Time t** given the full piecewise survival pattern up to the end of the current time period **Time t**. This row is read-only and must be calculated on the basis of the **Time t** up to and including the current column, the **Group 1 Expected % Surviving Time t** in the current column and the **Hazard Ratio** specified in the main design table.

Group 1 Exponential Dropout Rate, d_1 is the piecewise exponential dropout hazard rate in group 1 in the current time period. Theses values must all be zero or greater. Note that these are the exponential dropout rates not the dropout rates per unit time. The user may wish to use the **Survival Parameter Converter** tool available from the **Assistants** file menu to calculate the exponential dropout rate based on the median survival or proportion surviving (see section 3.5) after a fixed period.

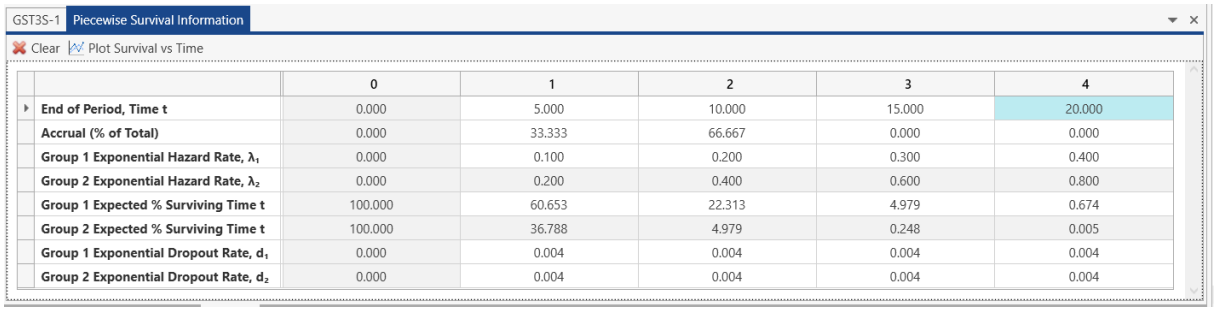
Group 2 Exponential Dropout Rate, d_2 is the piecewise exponential dropout hazard rate in group 2 in the current time period. Theses values must all be zero or greater. Note that these are the exponential dropout rates not the dropout rates per unit time. The user may wish to use the **Survival Parameter Converter** tool available from the **Assistants** file menu to calculate the exponential dropout rate based on the median survival or proportion surviving (see section 3.5) after a fixed period.

After the table is complete, the user can select **Plot Survival vs Time** to generate a plot showing the specified survival pattern for each group based on the % survival rows. The **Clear** button can be used to quickly remove all inputs in the **Piecewise Survival Information** table. The right-click context menu includes options for **Cut** (cut selected cells), **Copy** (copy selected cells), **Paste** (paste into current cell(s)), **Select All** (select all cells in table), **Fill Right** (fill all columns to right with same value/value pattern), **Clear** (clear selected cell(s)) and **Copy Table** (copy entire table).

Note that other versions of the piecewise survival table may remove some of these rows (e.g. % Surviving) and replace rows with similar variants (e.g. Accrual Rates per unit time rathet than Accrual %). These will be summarized as needed here.

As stated above, solver calculation requires the **Piecewise Survival Information** table to be filled appropriately. An example of piecewise survival trial are generated where

the accrual period was 10 months, the total study length was 20, one third of the accrual occured in the first five months and the rest in the remaining 5 months, the group exponential rate increased from 0.1 to 0.4 over time and dropout rate was set to an exponential rate of ~0.004 which is equivalent to 5% per year using the **Survival Parameter Converter** tool with Proportion Surviving = 0.95; Time = 12 months. This is shown in Figure 7.21.



	0	1	2	3	4
End of Period, Time t	0.000	5.000	10.000	15.000	20.000
Accrual (% of Total)	0.000	33.333	66.667	0.000	0.000
Group 1 Exponential Hazard Rate, λ_1	0.000	0.100	0.200	0.300	0.400
Group 2 Exponential Hazard Rate, λ_2	0.000	0.200	0.400	0.600	0.800
Group 1 Expected % Surviving Time t	100.000	60.653	22.313	4.979	0.674
Group 2 Expected % Surviving Time t	100.000	36.788	4.979	0.248	0.005
Group 1 Exponential Dropout Rate, d_1	0.000	0.004	0.004	0.004	0.004
Group 2 Exponential Dropout Rate, d_2	0.000	0.004	0.004	0.004	0.004

Figure 7.21: Piecewise Survival Information Example

7.3.4 Group Sequential Report

After a group sequential solver calculation occurs, the **Group Sequential Report** is generated which provides a full review of the inputs into the group sequential design and a detailed summary of the operating characteristics of the group sequential design.

As mentioned above, the **Group Sequential Report** tab will be shown at the top of the side-table window after a solver calculation has occured in the associated column. Select the **Group Sequential Report** tab to open the report within the side-table panel as per Figure 7.22.

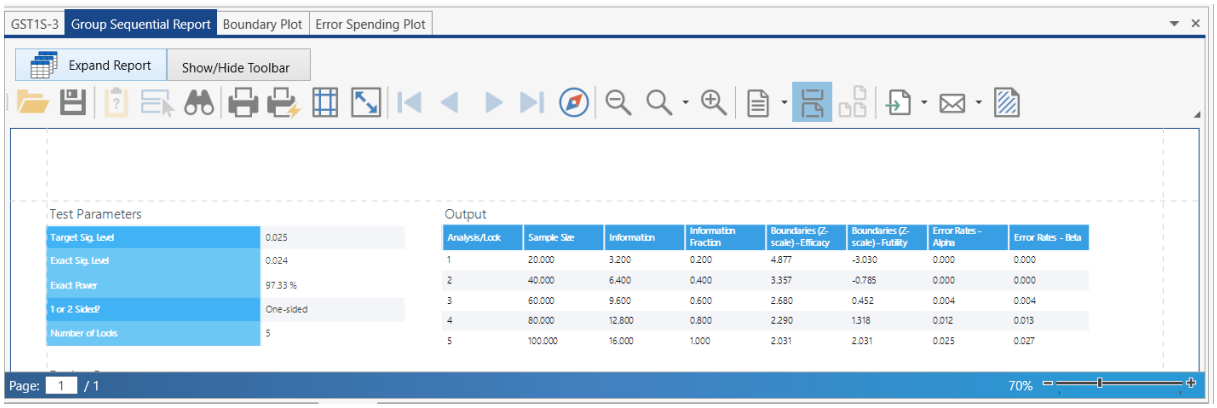


Figure 7.22: Group Sequential Report (Within Side-Table)

7.3.4.1 Group Sequential Report Buttons and Toolbar

At the top of the group sequential report, there is the **Expand Report** button, the **Show/Hide Toolbar** button and (just below those buttons) the **Toolbar**.

The **Expand Report** button will open a separate window which will contain the full report. Given the large amount of information within the **Group Sequential Report**, this window may be more convenient for exploring the report results.

The **Show/Hide Toolbar** button will collapse or uncollapse the **Toolbar** which is just below this button. By default, the toolbar is shown but the user may wish to hide the toolbar to provide additional viewing area for the report itself.

The **Toolbar** contains buttons which provide options for document search, printing, page setup, zoom, page view and export options. The toolbar options available for for the **Group Sequential Report** are shown in Figure 7.23.

Figure 7.23: Report Toolbar

These options are defined as follows (with the most important bolded):

1. Open: Open another nQuery Predict Report (.prnx) - not recommended as overwrites current report
2. Save: Save current nQuery Predict Report (.prnx) - not recommended, see Export (21) for better save options
3. Help: Unused here
4. URL: Unused here
5. **Search:** Search for text in current report. This will appear in Navigation Panel on right. Select "x" in top-right or Navigation Panel (14) button to hide.
6. **Print:** Open Print menu for current report
7. Quick Print: Print report using system defaults
8. **Page Setup:** Open Page Setup window to edit page size, orientation and margin sizes. Note that the report does **not** scale automatically to the new page setup.
9. **Scale:** Open Scale window to rescale size of report text by percentage or page size. Note the page size is **not** automatically updated to reflect changes to scale.
10. First Page: Return to first page (if report has multiple pages)
11. Page Up: Go up one page (if report has multiple pages)
12. Page Down: Go down one page (if report has multiple pages)
13. Last Page: Go to last page if report has multiple pages
14. Navigation Pane: Open and close Navigation Pane. Contains Pages list and Search Results window
15. **Zoom Out:** Zoom out report by one increment
16. **Zoom:** Change the current zoom level from list of options
17. **Zoom In:** Zoom in report by one increment

18. Page Layout: Set out how multiple pages are displayed (Single Page, Two Pages, Wrap Around)
19. Continuous Scolling: Enable or disable continuous scrolling in report
20. Show Cover Page: Show cover (first) page
21. **Export:** Export report as other file type. Select arrow to see list in-report or select icon to open Export window. The Export option can be used to save the report in the following file formats: PDF, HTML, MHT, RDF, DOCX, XLS, XLSX, CSV, Plain Text File (TXT), Image File (PNG, JPEG, BMP, GIF, EMF, WMF, TIFF).
22. Send: Send report as email in export file type using system default email client.
23. Watermark: Add watermark to report using Watermark menu

7.3.4.2 General Group Sequential Report Sections

The group sequential reports generated by the group sequential (GSTX) series of tables will have a significant number of sections in common regardless of the specific group sequential table selected. In this section, these in-common sections are described.

The **Group Sequential Report** can be split into two columns with the left-hand column containing fields summarizd by a single value while the right-hand column contains tabular information.

The following sections are included in the left-hand column in all group sequential reports:

- Test Parameters (Exact Error Rates, Number of Looks)
- Design Parameters (Fixed Term Parameters, Average Sample Size, Maximum Information, Drift)
- Boundary Parameters (Bound Calculation Method, GST Parameters)
- Calculation Specific Parameters (Group Sequential Options)

The following table sections are included in the right-hand column in all group sequential reports:

- Output (Boundary Information - Sample Size, Information Time, Boundaries)
- Incremental Exit (Boundary Crossing) Probabilities (Exit Probabilities under Null Hypothesis and Alternative Hypothesis)

Some group sequential tables will contain sections unique to that table (e.g. Piecewise Survival Parameter Table in GST3). These will be discussed in subsubsection 7.3.4.3.

A summary of each section is provided next which will cover the fields included in each section alongside providing an overview any changes due to the group sequential table selected and group sequential methods chosen:

Test Parameters The **Test Parameters** section provides the overall trial error rates and the high-level design parameters for the group sequential design.

The **Test Parameters** section will contain the following fields:

Target Sig. Level: The target significance level, equal to **Test Significance Level,** α from the main design table

Exact Sig. Level: The actual overall significance level (Type I error (α)) for the specified design. This will equal the sum of the exit probabilities for efficacy under the null hypothesis (e.g. Under H0 - Efficacy column in **Incremental Exit (Boundary Crossing) Probabilities** table). For most designs this should either equal or be quite closer to the **Target Sig. Level** - however certain designs (e.g. Haybittle-Peto using Last P-value) can cause the target and exact significance levels to diverge significantly.

Exact Power: The exact power achieved for the specified design. This will equal the **Power (%)** row in the main design table and also the sum of the exit probabilities for efficacy under the alternative hypothesis (e.g. Under H1 - Efficacy column in **Incremental Exit (Boundary Crossing) Probabilities** table).

1 or 2 Sided?: Whether the test was a one-sided or two-sided test. This will be hidden for tables without this option e.g. Non-inferiority designs are always 1-sided

Number of Looks: The total number of looks (including final analysis) specified for the group sequential design. Will equal **Number of Looks, J** from main design table.

An example **Test Parameters** section is provided in Figure 7.24.

Test Parameters

Target Sig. Level	0.025
Exact Sig. Level	0.024
Exact Power	97.33 %
1 or 2 Sided?	One-sided
Number of Looks	5

Figure 7.24: Group Sequential Report Test Parameters Section Example

Design Parameters The **Design Parameters** section provides an overview of the fixed term design parameters, sample size and important group sequential summary parameters.

The **Design Parameters** section will contain the following fields:

"Design-Specific" Fields: The set of fixed parameter inputs required for that specific design scenario. These will differ significantly depending on group sequential table and will typically be taken from the equivalent row in the main design table. For example, in GST1 (Two Means) the **Group 1 Mean, Group 2 Mean, Mean Difference, Group 1 Standard Deviation, Group 2 Standard Deviation** and **Effect Size** fields would be included in the **Design Parameters** section.

"Maximum Sample Size" Fields: The maximum sample size fields summarize the maximum sample size including the total sample size, the sample sizes per group and the sample size ratio as required. For example, in GST1 (Two Means) the **Group 1 Sample Size, Group 2 Sample Size, Sample Size Ratio** and **Total Sample Size** fields are included in the **Design Parameters** section.

Note that for survival analysis tables (e.g. GST3), the **Design Parameters** section will include similiar fields for the **Maximum Number of Events** and **Events per Group**, alongside the sample size fields above. For Information-Based designs (GST0), these fields will not be included as the **Maximum Information** field below is equivalent for Information–Based Designs.

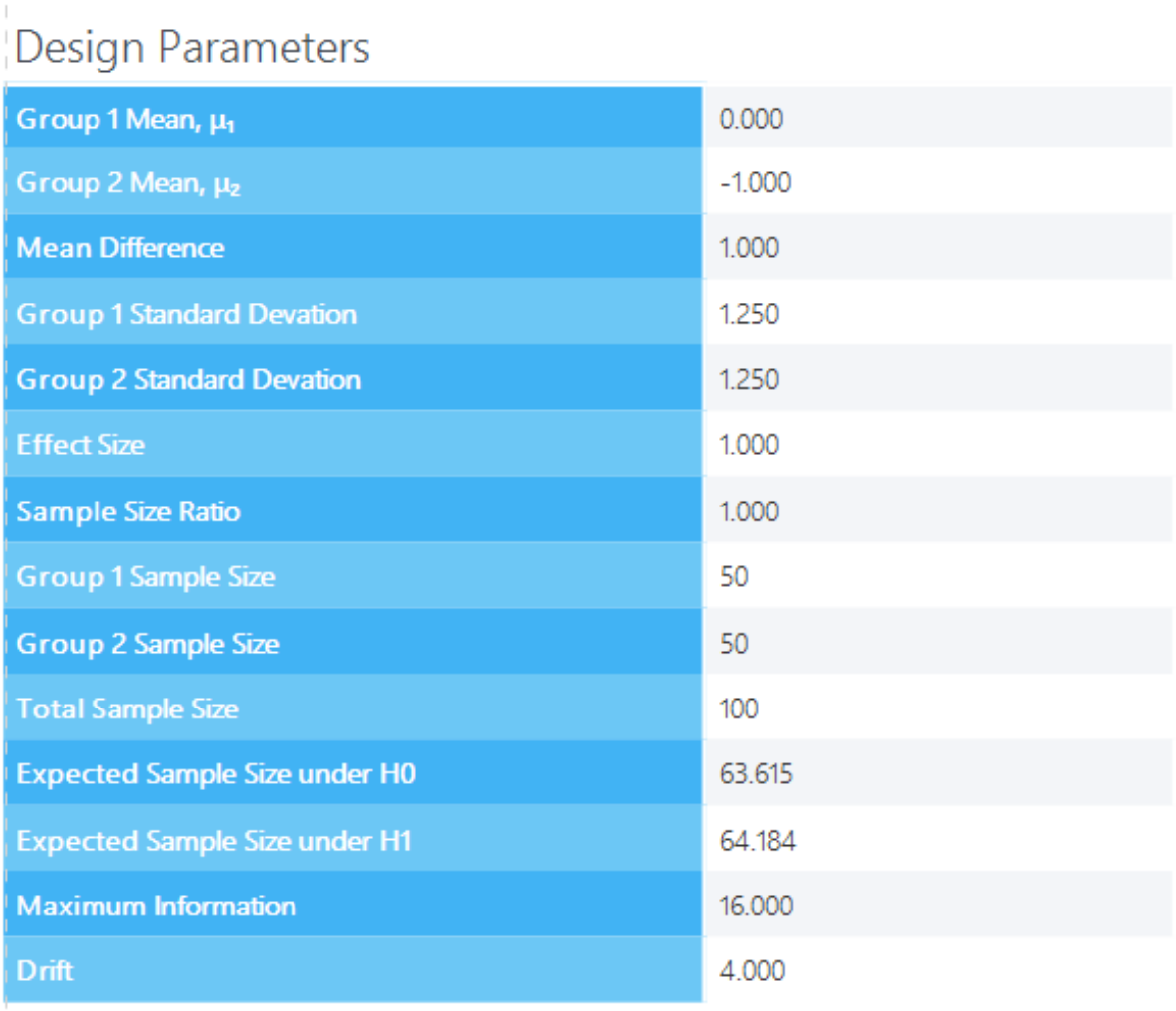
"Expected Sample Size" Fields: The expected sample size fields summarize the expected total sample size expected under the null hypothesis (H_0) and alternative hypothesis (H_1) given the probability of stopping early under the specified group sequential boundaries in the **Output Table**. For example in GST1, the **Expected Sample Size under** H_0 and **Expected Sample Size under** H_1 are included in the **Design Parameters** section. This can be calculated by taking the sum of all exit probabilities under a given hypothesis at a given look and multiplying this by the interim sample size at that look. Then sum these product values from each look to find the expected sample size.

Note that for survival analysis tables (e.g. GST3), the **Design Parameters** section will include similiar fields for the **Expected Events under** H_0 and **Expected Events under** H_1, alongside the sample size fields above. For Information-Based designs (GST0), these fields will be replaced with the **Expected Information under** H_0 and **Expected Information under** H_1.

Maximum Information: The maximum information (I_{max}) achieved at the final analysis. See subsubsection 7.2.1.1 and subsection 7.2.5 for details on what the maximum information is and how it is derived for specific design scenarios.

Drift: The drift parameter (η) for the group sequential design. See subsubsection 7.2.1.1 for details on the drift parameter.

An example **Design Parameters** section from GST1 is provided in Figure 7.25



Design Parameters

Group 1 Mean, μ_1	0.000
Group 2 Mean, μ_2	-1.000
Mean Difference	1.000
Group 1 Standard Devation	1.250
Group 2 Standard Devation	1.250
Effect Size	1.000
Sample Size Ratio	1.000
Group 1 Sample Size	50
Group 2 Sample Size	50
Total Sample Size	100
Expected Sample Size under H0	63.615
Expected Sample Size under H1	64.184
Maximum Information	16.000
Drift	4.000

Figure 7.25: Group Sequential Report Design Parameters Section Example

Boundary Parameters The **Boundary Parameters** section provides an overview of the methods used to construct the efficacy and/or futility boundaries for the group sequential design.

The **Boundary Parameters** section will contain the following fields:

Efficacy Bound Calc. Method: The group sequential method used to construct the efficacy boundaries. Will equal the **Efficacy Bound Calculation Method** value from the main design table. **Efficacy Bound Calc. Method** and the **"Efficacy Bound Method" Specific Fields** (see below) will be hidden if **Efficacy Calculation Method = Don't Calculate** as no efficacy boundaries were constructed.

Futility Bound Calc. Method: The group sequential method used to construct the futility boundaries. Will equal the **Futility Bound Calculation Method** value from the main design table. **Futility Bound Calc. Method** and the **"Futility Bound Method" Specific Fields** (see below) will be hidden if **Futility Calculation Method = Don't Calculate** as no futility boundaries were constructed.

"Efficacy Bound Method" Specific Fields: The specific additional fields specified for the **Efficacy Bound Calculation Method** in the **GST Parameters** and (if present) **Additional Parameters** tables within the **Group Sequential Side-Table.** A short summary of fields included in **Boundary Parameters** by calculation method is provided here:

- Spending Function: **Alpha Spending Function** provided in the **GST Parameters** table. If present, **Additional Parameters** specified for efficacy spending function are all included (see subsubsection 7.3.2.3) and will be indicated by $symbol(\alpha)$ e.g. $\gamma(\beta)$ for **Hwang-Shih-DeCani Alpha Spending Function**
- Haybittle-Peto: **Fixed Parameter** which will be **Total Alpha** or **Last P-value** as per **GST Parameters** table selection. The interim p-values are in the **Output** table.
- Wang-Tsiatis: **Efficacy Shape Parameter,** Δ_1 value provided in the **GST Parameters** table
- Unified Family: **Efficacy Shape 1,** $\tau\,(\alpha)$ and **Efficacy Shape 2,** $\rho\,(\alpha)$ values provided in the **GST Parameters** table.
- Custom Boundaries: N/A. Custom Boundaries are provided in the **Output Table** with chosen **Efficacy Boundary Scale** included in the column title of the custom efficacy boundaries.

"Futility Bound Method" Specific Fields: The specific additional fields specified for the **Futility Bound Calculation Method** in the **GST Parameters** and (if present) **Additional Parameters** tables within the **Group Sequential Side-Table.** A short summary of fields included in **Boundary Parameters** by calculation method is provided here:

- Spending Function: **Beta Spending Function** provided in the **GST Parameters** table. If present, **Additional Parameters** specified for futility spending function are all included (see subsubsection 7.3.2.3) and will be indicated by $symbol(\beta)$ e.g. $\gamma(\beta)$ for **Hwang-Shih-DeCani Beta Spending Function**
- Wang-Tsiatis: **Futility Shape Parameter,** Δ_2 value provided in the **GST Parameters** table
- Unified Family: **Futility Shape 1,** $\tau\,(\beta)$ and **Futility Shape 2,** $\rho\,(\beta)$ values provided in the **GST Parameters** table.
- Custom Boundaries: N/A. Custom Boundaries are provided in the **Output Table** with chosen **Futility Boundary Scale** included in the column title of the custom futility boundaries.

For further detail on the **"Efficacy Bound Method" Specific Fields** and **"Futility Bound Method" Specific Fields**, see subsubsection 7.3.2.1 and subsubsection 7.3.2.3.

Futility Bounds: Indicator for whether the futility boundaries are **Non-Binding** or **Binding**. This field will be hidden if **Futility Bound Calculation Method = Don't Calculate (No Futility Bounds), Custom Boundaries (alway Non-Binding)**

Examples of **Boundary Parameters** for a variety of scenarios is provided in Figure 7.26.

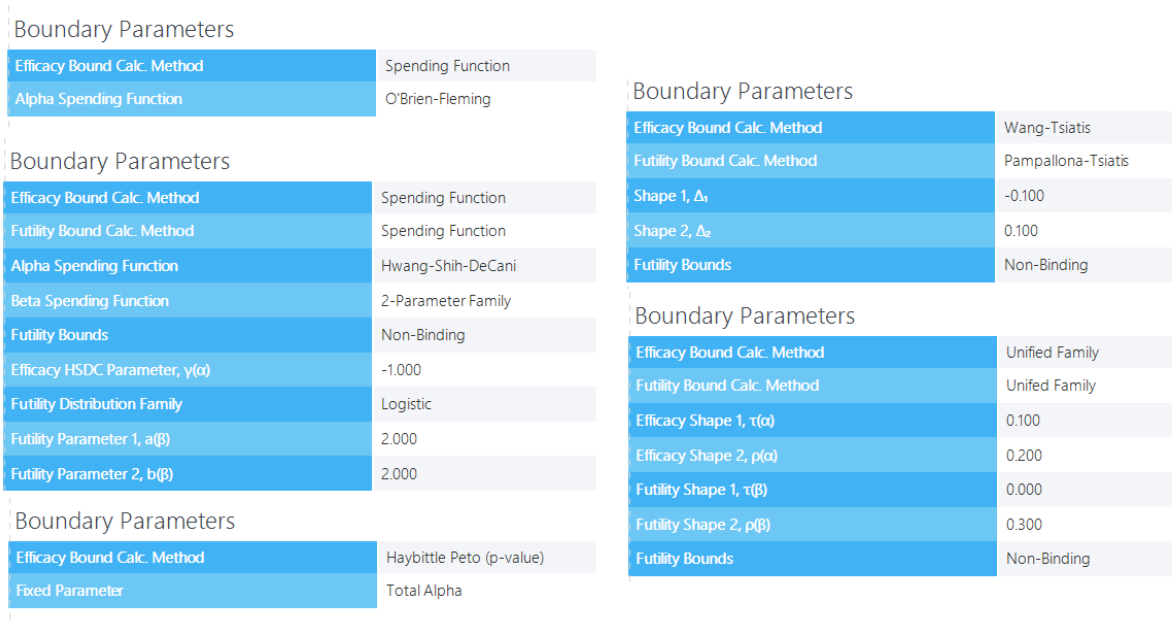


Figure 7.26: Group Sequential Report Boundary Parameters Examples

Calculation Specific Parameters The **Calculation Specific Parameters** provides an overview of the group sequential algorithm tuning parameters set in the **Group Sequential Options** tab (see subsection 7.3.7).

The **Calculation Specific Parameters** section will contain the following fields:

Extreme Z-value: The bound for the Z-statistic used by the search algorithm when searching for the group sequential boundaries. The search algorithm will search from $[-Z_{extreme}, Z_{extreme}]$. By default this will equal 8 which is adequate for any reasonable normally distributed statistic ($\Phi(8) = 6.220961e-16$)

R: The turning parameter used to determine the number of points that will be used to numerically evaluate the integral. See subsection 7.2.2 for details. By default this will be set to 20 which is reasonable for most group sequential design.

Integer Interim N: Set whether the interim sample sizes will be rounded to the nearest integer after finding the maximum sample size. This will re-run the solver using the updated maximum information to give the exact power. By default, this is set to Yes. For most cases, this will make minimal difference.

For survival tables (e.g. GST3) this is replaced with **Rounded N & E** which controls whether the sample size (N) and events (E) will be rounded to the nearest integer - note this is applied to both the interim values and the maximum values of the sample size and events.

Note this option is not included for Information-Based Designs (GST0) as the information is always unrounded.

Two-Sided Power: Set whether the lower tail efficacy exit probabilities under the alternative hypothesis should be included when calculating the exact power for a two-sided test.

The default is **Yes**, where the power will include the upper and lower efficacy exit probabilties under the alternative hypothesis - this is equivalent to the sum of all the **Under H1 - Lower Efficacy** and **Under H1 - Upper Efficacy** values from **Output** table. Selecting **No** will exclude the lower efficacy exit probabilities - this is equivalent to taking only the sum of the **Under H1 - Upper Efficacy** column from the **Output** table.

Output (Table) The **Output** table provides an overview of the per-look sample size, information, information times, boundaries and spending function error rates.

The **Output** table will have a number of rows equal to the **Number of Looks** specified in the main table and provided in the **Test Parameters** sections. The columns will change depending on the group sequential design specified with the following common column types:

Analysis/Look Number: The look number (k) associated with each row of the **Output** table. The final row corresponds to the final planned analysis.

Sample Size: The sample size required for each interim analysis. The final row will equal the **Maximum Sample Size** provided in the **Design Parameters** section. For survival tables (e.g. GST3), this will be replaced with **Events**. For Information-Based (GST0) designs, this column will be excluded.

Information: The (Fisher) information at each interim analysis. The final row value is equal to the **Maximum Information** provided in the **Design Parameters** section. The **Information** column is provided for all tables but effectively replaces **Sample Size** for Information-Based (GST0) designs. For detail on the Fisher Information see subsubsection 7.2.1.1 and subsection 7.2.5.

Information Fraction: The information fraction at each interim analysis. This is equivalent to the proportion of the total sample size/events/maximum information at a given look and will equal the **Information** at each look divided by the **Maximum Information.**

Boundaries: These column(s) provide the group sequential efficacy and/or futility boundaries on the desired statistical scale.

The columns will have a column title of the form "Boundaries (*Scale*) - (Upper/Lower) Efficacy/Futility" where *Scale* refers to the statistical scale the boundary is provided on, Upper/Lower are provided for a 2-sided design to differentiate between the upper and lower bounds and Efficacy/Futility refers to if the boundary is an efficacy or futility bound.

The six primary types are:

1. **Boundaries (*Scale*) - Efficacy:** The 1-sided efficacy boundary beyond which the trial would stop for efficacy. Only present if **1 or 2 Sided Test?** = 1 and **Efficacy Bound Calculation Method** ≠ **Don't Calculate** in main design table
2. **Boundaries (*Scale*) - Futility:** The 1-sided futility boundary beyond which the trial would stop for futility. Only present if **1 or 2 Sided Test?** = 1 and **Futility Bound Calculation Method** ≠ **Don't Calculate** in main design table
3. **Boundaries (*Scale*) - Upper Efficacy:** The 2-sided upper efficacy boundary above which the trial would stop for efficacy. Only present if **1 or 2 Sided Test?** = 2 and **Efficacy Bound Calculation Method** ≠ **Don't Calculate** in main design table. Note nQuery defines "upper" as the direction of the specified treatment effect from the main design table e.g. in GST1 if **Mean Difference** > 0 then upper boundaries will be higher than lower boundaries and vice-versa if **Mean Difference** < 0.
4. **Boundaries (*Scale*) - Lower Efficacy:** The 2-sided lower efficacy boundary below which the trial would stop for "efficacy" - *assuming both directions are truly considered "effective"!*. Only present if **1 or 2 Sided Test?** = 2 and **Efficacy Bound Calculation Method** ≠ **Don't Calculate** in main design table. Note nQuery defines "upper" as the direction of the specified treatment effect from the main design table e.g. in GST1 if **Mean Difference** > 0 then upper boundaries will be higher than lower boundaries and vice-versa if **Mean Difference** < 0.
5. **Boundaries (*Scale*) - Upper Futility:** The 2-sided upper futility boundary where the trial will stop early for futility if the test statistic falls between the upper and lower futility boundaries. Only present if **1 or 2 Sided Test?** = 2 and **Futility Bound Calculation Method** ≠ **Don't Calculate** in main design table. Note that 2-sided futility bounds may not be the most appropriate option for a clinical trial as they only consider values near the null hypothesis treatment effect to be futility, not treatment effects in the opposite direction of the specified treatment effect.
6. **Boundaries (*Scale*) - Lower Futility:** The 2-sided lower futility boundary where the trial will stop early for futility if the test statistic falls between the upper and lower futility boundaries. Only present if **1 or 2 Sided Test?** = 2 and **Futility Bound Calculation Method** ≠ **Don't Calculate** in main design table. Note that 2-sided futility bounds may not be the most appropriate option for a clinical trial as they only consider values near the null hypothesis treatment effect to be futility, not treatment effects in the opposite direction of the specified treatment effect.

The statistical scale that is provided in the **Group Sequential Report** for the **Boundaries** column(s) is determined by the choice of **Boundary Scale** (for **Spending Function, Wang-Tsiatis/Pampallona-Tsiatis, Unified Family)** or **Efficacy Boundary Scale/Futility Boundary Scale** (for **Custom Boundaries)** in the **GST Outputs.**

Boundary Scale can be set to **Z-scale, p-value Scale, Score Scale** and δ**-Scale** (i.e. treatment effect e.g. mean difference in GST1). The scale used for the **Boundaries** in the **Output** table will depend on the scale chosen at the time of solver calculation. If a different scale is desired in the **Group Sequential Report**, select the desired **Boundary Scale** in **GST Options** and then re-run the solver by selecting the **Run** button below the main design table.

Efficacy Boundary Scale can be set to **Z-scale, p-value Scale, Score Scale,** δ**-Scale** (i.e. treatment effect e.g. mean difference in GST1) and **Alpha Error**. The scale used for the **Boundaries** in the **Output** table will equal the **Efficacy Boundary Scale** option selected except for the **Alpha Scale** which will provide the **Z-scale** boundaries (and **Error Rates -Alpha** column) as per the equivalent **User Defined Spending Function** option.

Futility Boundary Scale can be set to **Z-scale, p-value Scale, Score Scale,** δ**-Scale** (i.e. treatment effect e.g. mean difference in GST1), **Beta Error** and **Conditional Power**. The scale used for the **Boundaries** in the **Output** table will equal the **Futility Boundary Scale** option selected except for the **Alpha Scale** which will provide the **Z-scale** boundaries (and **Error Rates -Alpha** column) as per the equivalent **User Defined Spending Function** option. Note the **Conditional Power** scale option leaves the final row value empty as conditional power is not defined for the end of a trial.

An exception to the above is when **Efficacy Bound Calculation Method = Haybittle-Peto.** In this case, the efficacy boundaries are shown on both the **Z-scale** and **p-value Scale** in separate columns.

Error Rates: These columns provide the alpha and/or beta error spent at each look by the spending function.

The **Error Rates - Alpha** column provides a summary of the alpha error "spent" at each look. Alpha (α) is the Type I error and is equivalent to the cumulative efficacy exit probability under the null hypothesis. The **Error Rates - Alpha** column will be only shown in the **Output** table if **Efficacy Bound Calculation Method = Spending Function** or **Spending Calculation Method = Custom Boundary + Efficacy Boundary Scale = Alpha Error.**

The **Error Rates - Beta** column provides a summary of the alpha error "spent" at each look. Alpha (α) is the Type I error and is equivalent to the cumulative efficacy exit probability under the null hypothesis. The **Error Rates - Alpha** column will be only shown in the **Output** table if **Efficacy Bound Calculation Method = Spending Function** or **Spending Calculation Method = Custom Boundary + Efficacy Boundary Scale = Alpha Error.**

Examples of **Output** tables for a variety of scenarios is provided in Figure 7.27.

Output

Analysis/Look	Sample Size	Information	Information Fraction	Boundaries (Z-scale) - Efficacy	Error Rates - Alpha
1	20.000	3.200	0.200	2.724	0.003
2	40.000	6.400	0.400	2.590	0.007
3	60.000	9.600	0.600	2.450	0.012
4	80.000	12.800	0.800	2.314	0.018
5	100.000	16.000	1.000	2.181	0.025

5 Look Design - 1-sided Efficacy Only - Spending Function Z-scale Bounds

Output

Analysis/Look	Sample Size	Information	Information Fraction	Boundaries (Score scale) - Lower Efficacy	Boundaries (Score scale) - Upper Efficacy	Boundaries (Score scale) - Lower Futility	Boundaries (Score scale) - Upper Futility	Error Rates - Alpha	Error Rates - Beta
1	33.000	5.280	0.330	6.354	-6.354	1.354	-1.354	0.006	0.042
2	67.000	10.720	0.670	8.459	-8.459	5.176	-5.176	0.014	0.071
3	100.000	16.000	1.000	9.624	-9.624	9.624	-9.624	0.025	0.093

3 Look Design - 2-sided Efficacy + Futility - Both Spending Function Score Scale Bounds

Output

Analysis/Look	Sample Size	Information	Information Fraction	Boundaries (Z-scale) - Efficacy	Boundaries (p-value scale) - Futility	Boundary p value - Efficacy
1	25.000	4.000	0.250	2.576	0.300	0.005
2	50.000	8.000	0.500	2.576	0.200	0.005
3	75.000	12.000	0.750	2.576	0.100	0.005
4	100.000	16.000	1.000	2.090	0.018	0.018

4 Look Design - 1-sided Efficacy = Haybittle-Peto Futility = Custom p-value

Output

Analysis/Look	Sample Size	Information	Information Fraction	Boundaries (Score scale) - Lower Efficacy	Boundaries (Score scale) - Upper Efficacy	Boundaries (Score scale) - Lower Futility	Boundaries (Score scale) - Upper Futility
1	100.000	16.000	0.500	-9.240	9.240	-0.000	0.000
2	200.000	32.000	1.000	-11.788	11.788	-11.788	11.788

2 Look Design - 2-sided Efficacy + Futility - Both Unified Family δ-Scale Bounds

Figure 7.27: Group Sequential Report Output Table Examples

Incremental Exit (Boundary Crossing) Probabilities (Table) The **Incremental Exit (Boundary Crossing) Probabilities** table provides an overview of the probability of crossing the specified boundaries under the null hypothesis and alternative hypothesis treatment effect.

The **Incremental Exit (Boundary Crossing) Probabilities** table will have a number of rows equal to the **Number of Looks** specified in the main table and provided in the **Test Parameters** sections.

As the title implies, this table provides the incremental exit probabilites which are the probabilities of exiting at a specific look. The cumulative exit probability, the probability of exiting at any look up to and including the present look, can be found by summing all the incremental probabilities up to and including the current look.

The columns will change depending on the group sequential design specified with the following common column types:

Analysis/Look Number: The look number (k) associated with each row of the **Output** table. The final row corresponds to the final planned analysis.

Under H0 The **Under H0** columns provide the exit probability for the specified boundaries under the null hypothesis treatment effect (e.g. mean difference = 0 in GST1).

These columns will have a column title of the following form: Under H0 - (*Bound Name*) where *Bound Name* will have the same name as the bounds included in the **Output** table (see section 7.3.4.2).

The six possible column names for **Under H0** are:

- Under H0 - Efficacy - Column present only if **1 or 2 Sided** = 1 and **Efficacy Bound Calculation Method** ≠ **Don't Calculate**
- Under H0 - Futility - Column present only if **Futility Bound Calculation Method** ≠ **Don't Calculate**
- Under H0 - Upper Efficacy - Column present only if **1 or 2 Sided** = 2 and **Efficacy Bound Calculation Method** ≠ **Don't Calculate**
- Under H0 - Lower Efficacy - Column present only if **1 or 2 Sided** = 2 and **Efficacy Bound Calculation Method** ≠ **Don't Calculate**

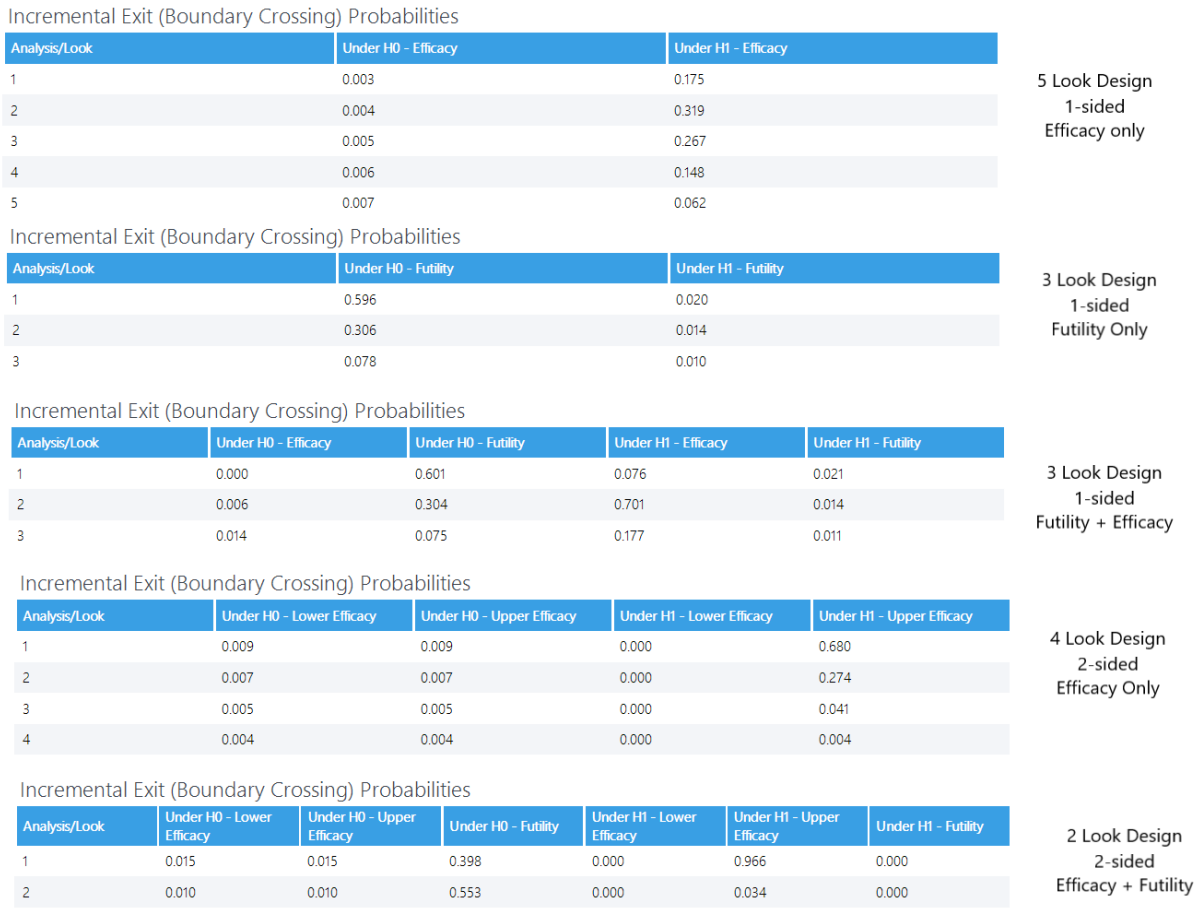
Under H1 The **Under H1** columns provide the exit probability for the specified boundaries under the alternative hypothesis treatment effect (e.g. mean difference equals value set in the main design table for GST1).

These columns will have a column title of the following form: Under H1 - (*Bound Name*) where *Bound Name* will have the same name as the bounds included in the **Output** table (see section 7.3.4.2).

The six possible column names for **Under H1** are:

- Under H1 - Efficacy - Column present only if **1 or 2 Sided** = 1 and **Efficacy Bound Calculation Method** ≠ **Don't Calculate**
- Under H1 - Futility - Column present only if **Futility Bound Calculation Method** ≠ **Don't Calculate**
- Under H1 - Upper Efficacy - Column present only if **1 or 2 Sided** = 2 and **Efficacy Bound Calculation Method** ≠ **Don't Calculate**
- Under H1 - Lower Efficacy - Column present only if **1 or 2 Sided** = 2 and **Efficacy Bound Calculation Method** ≠ **Don't Calculate**

Examples of **Output** tables for a variety of scenarios is provided in Figure 7.28.



Incremental Exit (Boundary Crossing) Probabilities

Analysis/Look	Under H0 - Efficacy	Under H1 - Efficacy
1	0.003	0.175
2	0.004	0.319
3	0.005	0.267
4	0.006	0.148
5	0.007	0.062

5 Look Design
1-sided
Efficacy only

Incremental Exit (Boundary Crossing) Probabilities

Analysis/Look	Under H0 - Futility	Under H1 - Futility
1	0.596	0.020
2	0.306	0.014
3	0.078	0.010

3 Look Design
1-sided
Futility Only

Incremental Exit (Boundary Crossing) Probabilities

Analysis/Look	Under H0 - Efficacy	Under H0 - Futility	Under H1 - Efficacy	Under H1 - Futility
1	0.000	0.601	0.076	0.021
2	0.006	0.304	0.701	0.014
3	0.014	0.075	0.177	0.011

3 Look Design
1-sided
Futility + Efficacy

Incremental Exit (Boundary Crossing) Probabilities

Analysis/Look	Under H0 - Lower Efficacy	Under H0 - Upper Efficacy	Under H1 - Lower Efficacy	Under H1 - Upper Efficacy
1	0.009	0.009	0.000	0.680
2	0.007	0.007	0.000	0.274
3	0.005	0.005	0.000	0.041
4	0.004	0.004	0.000	0.004

4 Look Design
2-sided
Efficacy Only

Incremental Exit (Boundary Crossing) Probabilities

Analysis/Look	Under H0 - Lower Efficacy	Under H0 - Upper Efficacy	Under H0 - Futility	Under H1 - Lower Efficacy	Under H1 - Upper Efficacy	Under H1 - Futility
1	0.015	0.015	0.398	0.000	0.966	0.000
2	0.010	0.010	0.553	0.000	0.034	0.000

2 Look Design
2-sided
Efficacy + Futility

Figure 7.28: Group Sequential Report Incremental Exit (Boundary Crossing) Probabilities Table Examples

7.3.4.3 Table Specific Group Sequential Report Sections

The **Group Sequential Report** has additional sections for certain specific tables. In this section, these unique sections will be outlined for the relevant tables.

GST3 - Group Sequential Design for Two Survival Curves using Log-Rank Test (Piecewise Accural %, Hazard Rates, Dropout Rates) In GST3, there are three additional sections added to the **Group Sequential Report.** These sections are:

- H_0 Trial Information Table
- H_1 Trial Information Table
- Piecewise Survival Parameter Table

A overview of each of these is provided below:

H_0 **Trial Information Table** The H_0 **Trial Information Table** provides practical information about the expected timing, sample size recruited, remaining accrual pipeline and dropouts at each analysis under the null hypothesis hazard ratio.

The timing of an interim analysis for a survival analysis group sequential trial is a function of the total events not the sample size. Given that the time-to-event is the random variable of interest this means that practical estimates of the likely length of study time are useful for study planning.

One scenario of particular interest would be the null hypothesis where the **Hazard Ratio = 1** i.e. hazard rates are both equal to the specified group 1 hazard rate. Based on this null hazard ratio, the provided piecewise accrual rates, hazard rates and dropout rates from the **Piecewise Survival Information** table and the relevant main design table parameters (**Group 1 Sample Size, Group 2 Sample Size, Follow-up Type - Event-Driven** or **Fixed Follow-up** - require **Fixed Follow-up Time** for latter**)** the practical outcomes at each interim analysis can be calculated via the same formulae used to calculate the sample size for survival analysis (see subsubsection 7.2.5.4 for details).

The columns that are provided in the H_0 **Trial Information Table** are:

Analysis/Look

The look number (k) associated with each row of the **Output** table. The final row corresponds to the final planned analysis.

Information Fraction

The information fraction at each interim analysis. This is equivalent to the proportion of the total sample size/events/maximum information at a given look and will equal the **Information** at each look divided by the **Maximum Information.**

Time

The expected calendar time at which the target number of **Events** will be achieved for each analysis under the null hypothesis. This assumes that the start of the study had **Time** = 0. It is possible for the target number of events not to be reached within the planned study time under the null hypothesis. In this case, the final **Time** values may be set to exceed the planned study length. In this case, a warning will be provided in the main table indicating this increase in the planned study length has occured.

Sample Size Recruited

The number of subjects expected to be recruited at the time of each analysis given the planned accural pattern. **Sample Size Recruited** is calculated based on the **Time** of each analysis from above and the accrual pattern specified in the **Piecewise Survival Information** table.

Events

The total number of events required to conduct analysis. As the timing of each analysis depends on reaching these target number of events, these values are fixed and taken directly from the **Output** table above where they equal the **Maximum Events** times the **Information Fraction** at each look.

Dropouts

The total number of dropouts expected to have occured by the time of each analysis. This can apply to any subject lost to follow-up who can no longer have the event of interest.

Dropouts is calculated based on the **Time** of each analysis from above and piecewise dropout exponential rates specified in the **Piecewise Survival Information** table.

In Pipeline

The expected number of subjects at each analysis who have already been recruited but who have not had the event of interest of dropped out. A common concern in survival analysis group sequential trials is the overhang of subjects who have been recruited but are still available at an interim analysis. **In Pipeline** provides a useful estimate of this expected overhang. **In Pipeline** will equal **Sample Size Recruited - Events - Dropout** in each row.

Remaining Recruitment

The maximum number of subjects expected to be left to be recruited by the time of each analysis. **Remaining Recruitment** provides insight into the remaining recruitment left to occur in the trial which can useful for resource allocation. **Remaining Recruitment** will equal **Maximum Sample Size - Sample Size Recruited.**

Maximum Available

The maximum number of subjects left who could have the event of interest who are already recruited or could be recruited in the future by the time of each analysis. **Maximum Available** provides insight into the total number of subjects left who could have the event of interest. Achieving the required number of events given the original planned sample size could become a concern if the dropout rate was higher than expected for example. **Maximum Available** will equal **In Pipeline + Remaining Recruitment.**

An example of the H_0 Trial Information Table is provided in Figure 7.29

H_0 Trial Information Table

Analysis/Look	Information Fraction	Time	Sample Size Recruited	Events	Dropout	In Pipeline	Remaining Recruitment	Maximum Available
1	0.250	8.077	256.000	72.000	2.000	182.000	88.000	270.000
2	0.500	11.068	344.000	145.000	4.000	195.000	0.000	195.000
3	0.753	14.069	344.000	218.000	6.000	120.000	0.000	120.000
4	1.000	18.340	344.000	290.000	8.000	46.000	0.000	46.000

Figure 7.29: Group Sequential Report H_0 Trial Information Table Example

H_1 Trial Information Table The **H_1 Trial Information Table** provides practical information about the expected timing, sample size recruited, remaining accrual pipeline and dropouts at each analysis under the alternative hypothesis hazard ratio.

The timing of an interim analysis for a survival analysis group sequential trial is a function of the total events not the sample size. Given that the time-to-event is the random variable of interest this means that practical estimates of the likely length of study time are useful for study planning.

One scenario of particular interest would be the alternative hypothesis under which the power was calculate. The alternative hypothesis **Hazard Ratio** will equal the **Hazard Ratio,** $h = \lambda_{2i}/\lambda_{1i}$ specified in the main design table. Based on this alternative hazard

ratio, the provided piecewise accrual rates, hazard rates and dropout rates from the **Piecewise Survival Information** table and the relevant main design table parameters (**Group 1 Sample Size, Group 2 Sample Size, Follow-up Type - Event-Driven** or **Fixed Follow-up** - require **Fixed Follow-up Time** for latter**)** the practical outcomes at each interim analysis can be calculated via the same formulae used to calculate the sample size for survival analysis (see subsubsection 7.2.5.4 for details).

The columns that are provided in the H_1 **Trial Information Table** are:

Analysis/Look

The look number (k) associated with each row of the **Output** table. The final row corresponds to the final planned analysis.

Information Fraction

The information fraction at each interim analysis. This is equivalent to the proportion of the total sample size/events/maximum information at a given look and will equal the **Information** at each look divided by the **Maximum Information.**

Time

The expected calendar time at which the target number of **Events** will be achieved for each analysis under the alternative hypothesis. This assumes that the start of the study had **Time** $= 0$.

Sample Size Recruited

The number of subjects expected to be recruited at the time of each analysis given the planned accural pattern. **Sample Size Recruited** is calculated based on the **Time** of each analysis from above and the accrual pattern specified in the **Piecewise Survival Information** table.

Events

The total number of events required to conduct analysis. As the timing of each analysis depends on reaching these target number of events, these values are fixed and taken directly from the **Output** table above where they equal the **Maximum Events** times the **Information Fraction** at each look.

Dropouts

The total number of dropouts expected to have occured by the time of each analysis. This can apply to any subject lost to follow-up who can no longer have the event of interest. **Dropouts** is calculated based on the **Time** of each analysis from above and piecewise dropout exponential rates specified in the **Piecewise Survival Information** table.

In Pipeline

The expected number of subjects at each analysis who have already been recruited but who have not had the event of interest of dropped out. A common concern in survival analysis group sequential trials is the overhang of subjects who have been recruited but are still available at an interim analysis. **In Pipeline** provides a useful estimate of this expected overhang. **In Pipeline** will equal **Sample Size Recruited - Events - Dropout** in each row.

Remaining Recruitment

The maximum number of subjects expected to be left to be recruited by the time of each analysis. **Remaining Recruitment** provides insight into the remaining recruitment left to occur in the trial which can useful for resource allocation. **Remaining Recruitment** will equal **Maximum Sample Size - Sample Size Recruited.**

Maximum Available

The maximum number of subjects left who could have the event of interest who are already recruited or could be recruited in the future by the time of each analysis. **Maximum Available** provides insight into the total number of subjects left who could have the event of interest. Achieving the required number of events given the original planned sample size could become a concern if the dropout rate was higher than expected for example. **Maximum Available** will equal **In Pipeline + Remaining Recruitment.**

An example of the H_1 Trial Information Table is provided in Figure 7.30. This is taken from the same example used for the H_0 Trial Information Table in Figure 7.29 so it may be valuable to compare these two tables for this case where the alternative hypothesis hazard ratio was 0.666.

H_1 Trial Information Table

Analysis/Look	Information Fraction	Time	Sample Size Recruited	Events	Dropout	In Pipeline	Remaining Recruitment	Maximum Available
1	0.250	8.618	281.000	72.000	2.000	207.000	63.000	270.000
2	0.500	11.821	344.000	145.000	6.000	193.000	0.000	193.000
3	0.753	15.183	344.000	218.000	7.000	119.000	0.000	119.000
4	1.000	20.000	344.000	290.000	9.000	45.000	0.000	45.000

Figure 7.30: Group Sequential Report H_0 Trial Information Table Example

Piecewise Survival Parameter Table The **Piecewise Survival Parameter** table provides information about the piecewise accrual process, hazard rates and dropout rates. It is based on the **Piecewise Survival Information** side-table.

While the **Piecewise Survival Parameter** table transposes the **Piecewise Survival Information** table (so each row now corresponds to each survival piece and each column corresponds to a parameter) and has some minor column name changes made for aesthetic fit, these two tables are effectively indentical and therefore refer to subsection 7.3.3 for further information on the definition of each column. An example **Piecewsie Survival Parameter** table is provided in Figure 7.31.

Piecewise Survival Parameter Table

End of Period, Time t	Accrual (% Total)	Group 1 Hazard Rate, λ_1	Group 2 Hazard Rate, λ_2	Group 1 % Surviving	Group 2 % Surviving	Group 1 Dropout Rate, d_1	Group 2 Dropout Rate, d_2
0.000	0.000	0.000	0.000	100.000	100.000	0.000	0.000
5.000	33.333	0.100	0.067	60.653	71.653	0.004	0.004
10.000	66.667	0.200	0.133	22.313	36.788	0.004	0.004
15.000	0.000	0.300	0.200	4.979	13.534	0.004	0.004
20.000	0.000	0.400	0.267	0.674	3.567	0.004	0.004

Figure 7.31: Group Sequential Report Piecewise Survival Parameter Table Example

7.3.5 Boundary Plot

The **Boundary Plot** provides a visual and tabular summary of the group sequential boundaries, which can be found in the **Group Sequential Side-Table** (see subsection 7.3.2) and **Group Sequential Report** (see subsection 7.3.4), and the associated exit and continuation regions at each look. It can be opened by selecting the **Boundary Plot** tab at the top of the **Group Sequential Side-table** panel after a solver calculation has occured in the associated main design table column.

The **Boundary Plot** allows the user to visually inspect the boundaries on multiple statistical scales (**Z-scale, p-value Scale, Score Scale, δ-Scale**) and also export these plots to assist in the exploration and communcation of a planned group sequential design.

An example **Boundary Plot** is shown in Figure 7.32.

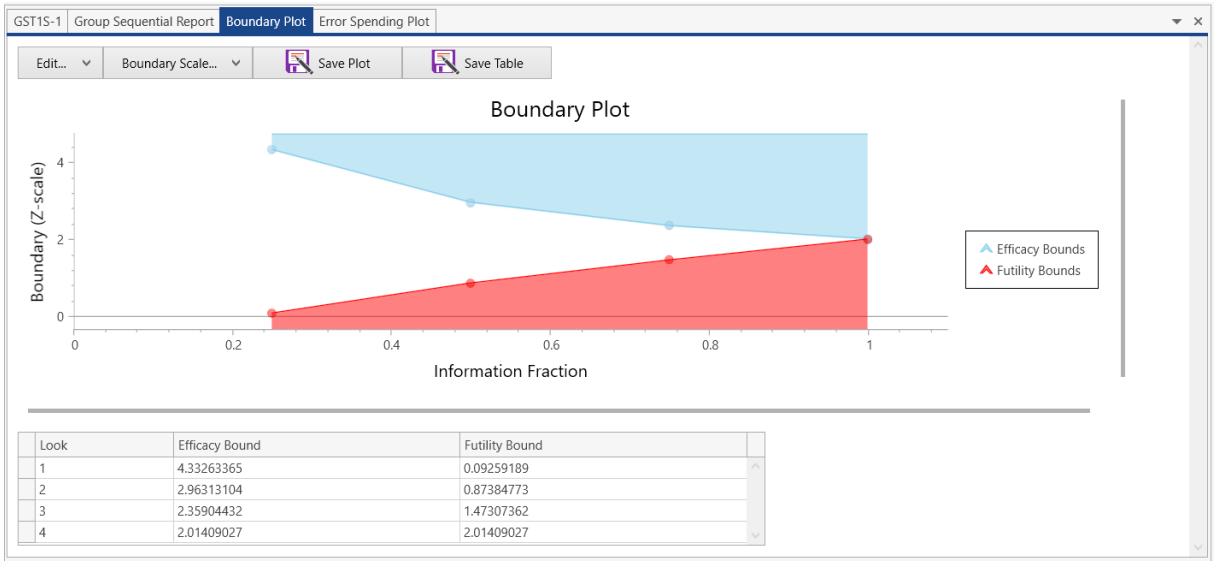


Figure 7.32: Group Sequential Boundary Plot Example - 1-sided Efficacy and Futility Design

The **Boundary Plot** tab consists of three primary elements: the **Boundary Plot** (middle), **Boundary Table** (bottom) and the **Toolbar** (top). Each of these will be summarized next.

7.3.5.1 Boundary Plot

The **Boundary Plot** provides a visual summary of the group sequential boundaries and the resulting continuation and exit regions on the specified statistical scale for the boundaries.

The **Boundary Plot** is a shaded line plot where each boundary, on the specified statistical scale, is plotted against a measure of trial progress on the X-axis.

X-axis The **X-axis** corresponds to how far into the trial each analysis occurs.

The X-axis will range from zero to the maximum value for the specified X-axis parameter scale (e.g. 1 for **Information Fraction**) but the series will only be plotted from the first analysis to the final analysis.

The **X-axis** can be plotted on the following scales: **Information Fraction, Cumulative Information, Total Sample Size**. The scale can be changed from the **Edit** menu in the **Toolbar** or right-click context menu under the **Series > X-axis Scale** option - see section 7.3.5.3.

By default, the **X-axis** will be shown on the **Information Fraction** scale which is equivalent to the proportion of the total sample size analyzed at each analysis. The name of the **X-axis** by default will be same as the statistical scale used for the **X-axis.** Use **Titles > X-axis Scale** option from the **Edit** menu to change the **X-axis Title** (show/hide, X-axis name, X-axis font) - see section 7.3.5.3.

Note that **Total Sample Size** scale is not available for Information-Based Design (GST0) and that **Total Sample Size** is replaced with **Total Events** for Survival Analysis (e.g. GST3).

Y-axis The **Y-axis** corresponds to the test statistical values achieved at a given time for the specified statistical scale and is used to plot the boundaries calculated and provided in the **GST Outputs** table and **Group Sequential Report.**

The Y-axis range will dynamically change to include the lowest and highest boundary value on the specified scale with an additional buffer to improve visual clarity. The one exception is that for the **Z-scale** (used here)**, Score Scale** and δ**-Scale** the Y-axis will be extended to include zero if it does not fall between the lowest and highest boundary value. Zero is always highlighted using a horizontal line for these scales.

The **Y-axis** can be plotted on the following statistical scales: **Z-scale, p-value Scale, Score Scale,** δ**-Scale.** Technical detail on the scales is provided in subsubsection 7.2.1.1 and subsubsection 7.2.4.5. The scale can be changed from **Boundary Scale...** option from the **Toolbar** or the **Edit** menu in the **Toolbar** or right-click context menu under the **Series > Y-axis Scale** option - see section 7.3.5.3 and section 7.3.5.3 .

The default statistical scale for the **Y-axis** will be set by the value selected in the **GST Options** table for the **Boundary Scale** or (if **Efficacy Boundary Calculation Method = Custom Boundary) Efficacy Boundary Scale** rows. Where neither field is available or **Efficacy Boundary Scale = Alpha Error**, the **Z-scale** is selected. The name of the **Y-axis** by default will equal Boundary (*Selected Scale*) e.g. Boundary (Z-scale) and will update automatially if the **Boundary Scale** is changed. Use **Titles > Y-axis Scale** option from the **Edit** menu to change the **Y-axis Title** (show/hide, X-axis name, X-axis font) - see section 7.3.5.3.

After an option is selected, the **Boundary Plot** and **Boundary Table** will automatically update to the boundaries to the selected statistical scale. See subsubsection 7.2.4.5 for technical detail on the statistical scale conversions.

Efficacy Bounds By default, the **Efficacy Bounds** are plotted as a blue line. The exit region for efficacy is the area highlighted in blue beyond the **Efficacy Bounds**, where the exit region specifies the range of values at which the trial would stop for efficacy at each look. For example, in Figure 7.32 the exit region for efficacy is shown as the blue area

above the **Efficacy Bounds** series. The continuation region where the trial will continue is the unhighlighted area between the bounds..

Note the **Z-scale** (used here)**, Score Scale** and δ**-Scale** can take on any real value therefore it is implied that the exit area extends beyond the upper edge of the Y-axi upwards to ∞.

For the **p-value scale,** the "maximum" p-value is 0 (lower p-values are better) so the efficacy bound is implied to extend to zero if that Y-axis does not include 0 in its range.

The visual aspects of the Efficacy Bounds such as the color, transparency of the exit area and marker style and size can be changed from the **Edit** menu in the **Toolbar** or right-click context menu under the **Series > Efficacy Bounds** option - see section 7.3.5.3.

Futility Bounds By default, the **Futility Bounds** are plotted as a red line. The exit region for futility is the area highlighted in red beyond the **Futility Bounds**, where the exit region specifies the range of values at which the trial would stop for futility at each look. For example, in Figure 7.32 the exit region for futility is shown as the red area below the **Futility Bounds** series. The continuation region where the trial will continue is the unhighlighted area between the bounds.

Note the **Z-scale** (used here)**, Score Scale** and δ**-Scale** can take on any real value therefore it is implied that the exit area extends beyond the lower edge of the Y-axi upwards to $-\infty$. For the **p-value scale**, the "minimum" p-value is 1 (higher p-values are worse) so the lower bound is implied extend to one if that Y-axisdoes not include 1 in its range.

The visual aspects of the Futility Bounds such as the color, transparency of the exit area and marker style and size can be changed from the **Edit** menu in the **Toolbar** or right-click context menu under the **Series > Futility Bounds** option - see section 7.3.5.3.

Legend The **Boundary Plot Legend** provides an indication of the color for the **Efficacy Bounds** and **Futility Bounds**.

By default, the **Legend** is shown to the right of the boundary plot. To toggle whether the **Legend** is shown, change the location of the **Legend** or change the **Legend Border** use the **Edit** menu in the **Toolbar** or right-click context menu under the **Legend** option - see section 7.3.5.3. The colors in the plot and legend are defined by the **Efficacy Bounds** and **Futility Bounds** series which are edited under the **Series** option in the **Edit** menu - see section 7.3.5.3.

Tooltip The **Boundary Plot Tooltip** provides the user information about the boundary values at a specific look based on which look is highlighted by the cursor within the area of the **Boundary Plot**. When the cursor is not within the **Boundary Plot** area the **Tooltip** will not be shown as in Figure 7.32. The values shown in the **Tooltip** will correspond to the values provided in the **Boundary Table** for the highlighted look.

A **Boundary Plot** with the **Tooltip** active for the third look is shown in Figure 7.33.

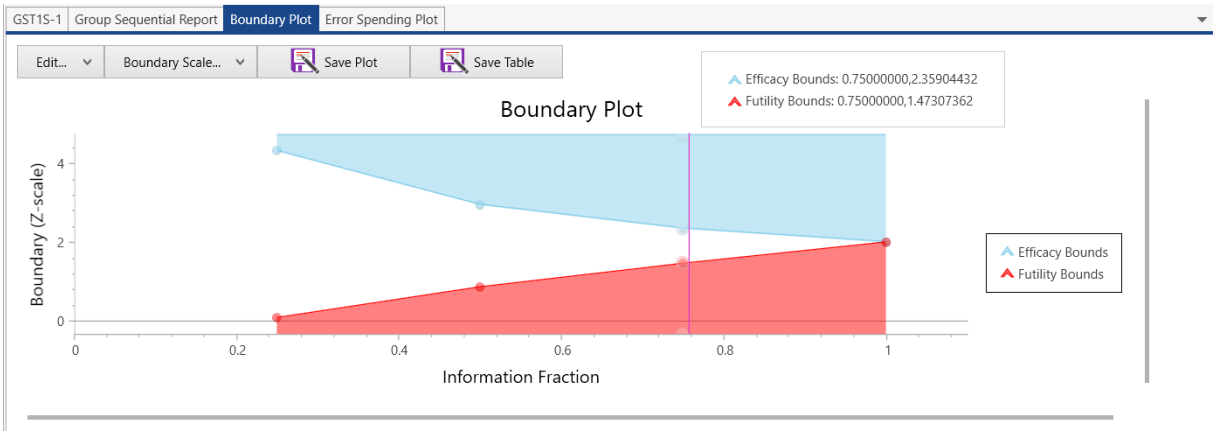


Figure 7.33: Boundary Plot Tooltip

Resize Boundary Plot The grey bars at the bottom and to the right of the can be used to re-size the **Boundary Plot**. Click and drag the grey bar to increase or decrease the vertical and horizontal size respectively. The **Boundary Plot** will also automatically scale if the side-table panel is resized.

The **Edit...** dropdown available from the **Toolbar** or right-click context menu provides options to edit the visual aspects of the plot such as the titles, legend and color alongside options to save or print the **Boundary Plot.** Some of the primary options where referenced above but see section 7.3.5.3 for details on the full set of options available to edit the **Boundary Plot**.

To provide additional clarity about the behavior of the **Boundary Plot** for different design scenarios examples of the changes due to changes to **1 or 2 Sided Test?**, certain combinations of the **Efficacy Bound Calculation Method** and **Futility Bound Calculation Method** rows and the **Boundary Scale...** option from the **Toolbar** are provided next for the following scenarios:

- **Efficacy Only 1-sided** (1 or 2 Sided Test? $= 1$, Futility Bound Calculation Method = Don't Calculate)
- **Futility Only 1-sided** (1 or 2 Sided Test? $= 1$, Efficacy Bound Calculation Method = Don't Calculate)
- **Efficacy and Futility 1-sided** (1 or 2 Sided Test? $= 1$, Efficacy Bound Calculation Method $\neq$ Don't Calculate & Futility Bound Calculation Method $\neq$ Don't Calculate)
- **Efficacy Only 1-sided** (1 or 2 Sided Test? $= 2$, Futility Bound Calculation Method = Don't Calculate)
- **Futility Only 1-sided** (1 or 2 Sided Test? $= 2$, Efficacy Bound Calculation Method = Don't Calculate)
- **Efficacy and Futility 1-sided** (1 or 2 Sided Test? $= 2$, Efficacy Bound Calculation Method $\neq$ Don't Calculate & Futility Bound Calculation Method $\neq$ Don't Calculate)

The exact boundaries for each of the example **Boundary Plots** below is provided in the next **Boundary Table** subsection (subsubsection 7.3.5.2).

Efficacy Only 1-sided Example **Boundary Plots** for the **Efficacy Only 1-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale, δ-Scale**) in **Figure 7.34.**

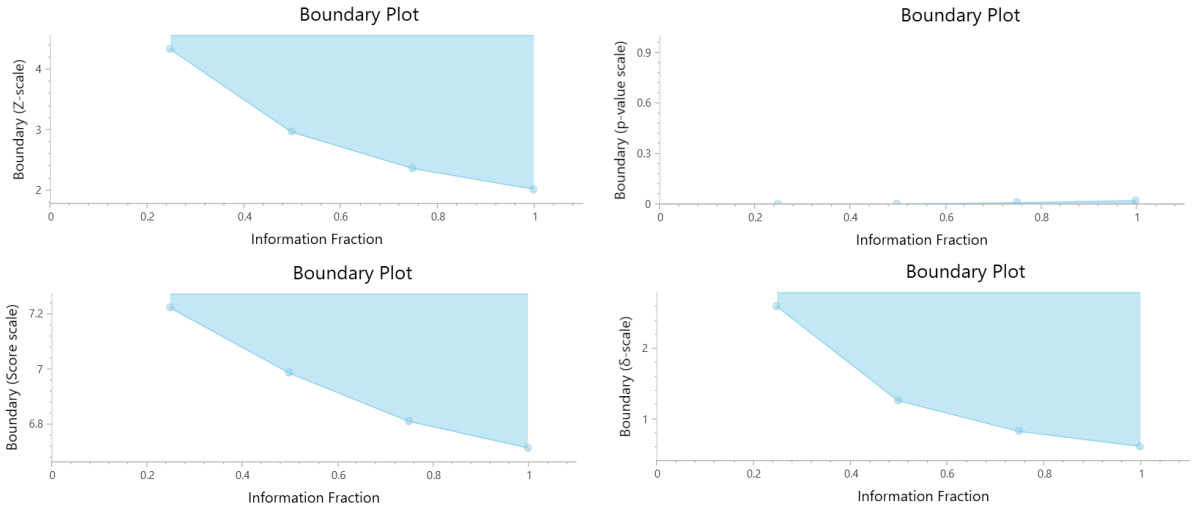


Figure 7.34: Boundary Plots for Efficacy Only 1-sided Scenario

For the **Efficacy Only 1-sided** scenario, the efficacy exit region (highlighted in blue) shows test statistic values higher than the **Efficacy Boundary** at each look will lead to early stopping for efficacy for the **Z-scale, Score Scale** and **δ-Scale**. Test statistics less than the **Efficacy Boundary** are in the continuation region where the trial will proceed to the next look.

In this example, a test statistic at the first interim analysis (**Information Time = 0.25**) greater than 4.333, 7.221, 2.600 would stop the trial early for efficacy on the **Z-scale, Score Scale** and **δ-Scale** (δ = mean difference in GST1 for Two Means) respectively. Otherwise, the trial would continue to the next look.

For the **p-value Scale**, an (unadjusted) test p-value less than the efficacy boundary will lead to early stopping for efficacy. In this example, a p-value (from two sample Z-test for GST1 Two Means) at the first interim analysis (**Information Time = 0.25**) less than 7.367E-06 would stop the trial early for efficacy. Otherwise, the trial would continue to the next look.

Futility Only 1-sided Example **Boundary Plots** for the **Futility Only 1-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale, δ-Scale**) in **Figure 7.35.**

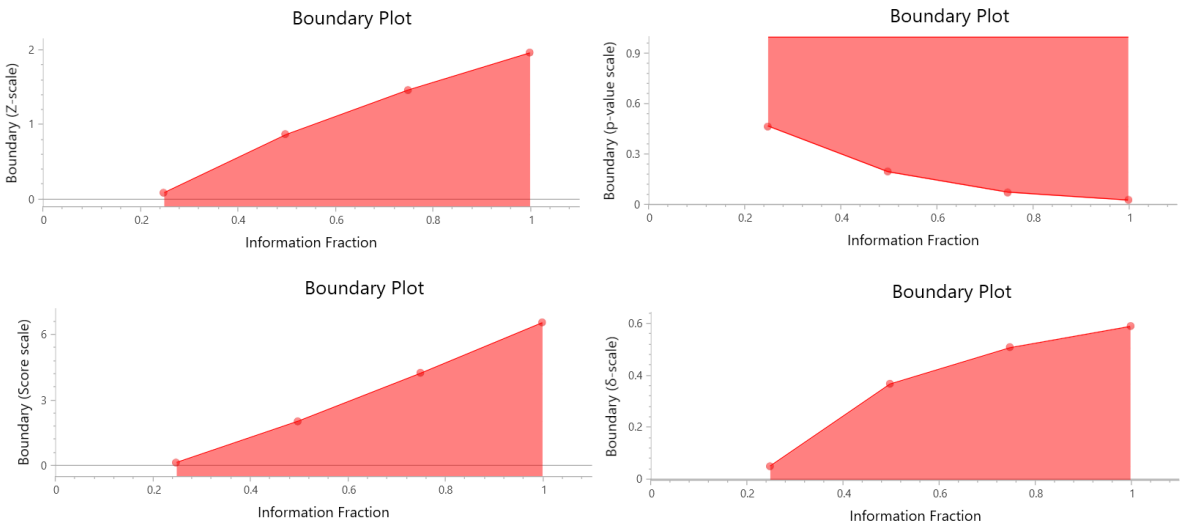


Figure 7.35: Boundary Plots for Futility Only 1-sided Scenario

For the **Futility Only 1-sided** scenario, the futility exit region (highlighted in red) shows test statistic values lower than the **Futility Boundary** at each look will lead to early stopping for futility for the **Z-scale, Score Scale** and δ**-Scale**. Test statistics greater than the **Futility Boundary** are in the continuation region where the trial will proceed to the next look.

In this example, a test statistic at the first interim analysis (**Information Time = 0.25**) less than than 0.083, 0.139, 0.050 would stop the trial early for futility on the **Z-scale, Score Scale** and δ**-Scale** (δ = mean difference in GST1 for Two Means) respectively. Otherwise, the trial would continue to the next look.

For the **p-value Scale**, an (unadjusted) test p-value greater than the efficacy boundary will lead to early stopping for efficacy. In this example, a p-value (from two sample Z-test for GST1 Two Means) at the first interim analysis (**Information Time = 0.25**) greater than 0.467 would stop the trial early for futility. Otherwise, the trial would continue to the next look.

Efficacy and Futility 1-sided Example **Boundary Plots** for the **Efficacy and Futility 1-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale,** δ**-Scale**) in **Figure 7.36.**

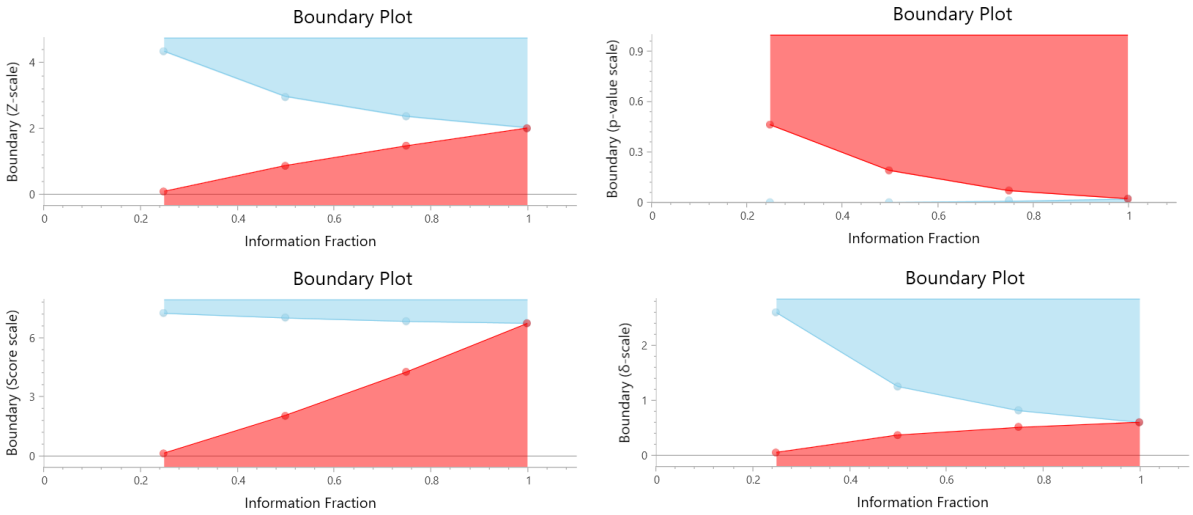


Figure 7.36: Boundary Plots for Efficacy and Futility 1-sided Scenario

For the **Efficacy and Futility 1-sided** scenario, the efficacy exit region (highlighted in blue) shows test statistic values greater than the **Efficacy Boundary** at each will look will lead to early stopping for efficacy and the futility exit region (highlighted in red) shows test statistic values lower than the **Futility Boundary** at each look will lead to early stopping for futility for the **Z-scale, Score Scale** and δ**-Scale**. Test statistics that fall between the **Efficacy Boundary** and **Futility Boundary** are in the continuation region where the trial will proceed to the next look.

In this example, a test statistic at the first interim analysis (**Information Time = 0.25**) greater than 4.333, 7.221, 2.600 would stop the trial early for efficacy on the **Z-scale, Score Scale** and δ**-Scale** (δ = mean difference in GST1 for Two Means) respectively, while a test statistic less than than 0.093, 0.154, 0.056 would stop the trial early for futility for the respective scales. If the test statistic falls between 4.333 and 0.093 (Z-scale), 7.221 and 0.154 (Score Scale) or 2.600 and 0.056 (δ-Scale) then the trial continues to the next look.

For the **p-value Scale**, an (unadjusted) test p-value less than the efficacy boundary will lead to early stopping for efficacy. In this example, a p-value (from two sample Z-test for GST1 Two Means) at the first interim analysis (**Information Time = 0.25**) less than 7.367E-06 would stop the trial early for efficacy, a p-value greater than 0.4631 would stop the trial early for futility and a p-value between 7.367E-06 and 0.4631 would mean the trial continues to the next look.

Efficacy Only 2-sided Example **Boundary Plots** for the **Efficacy Only 2-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale,** δ**-Scale**) in **Figure 7.37.**

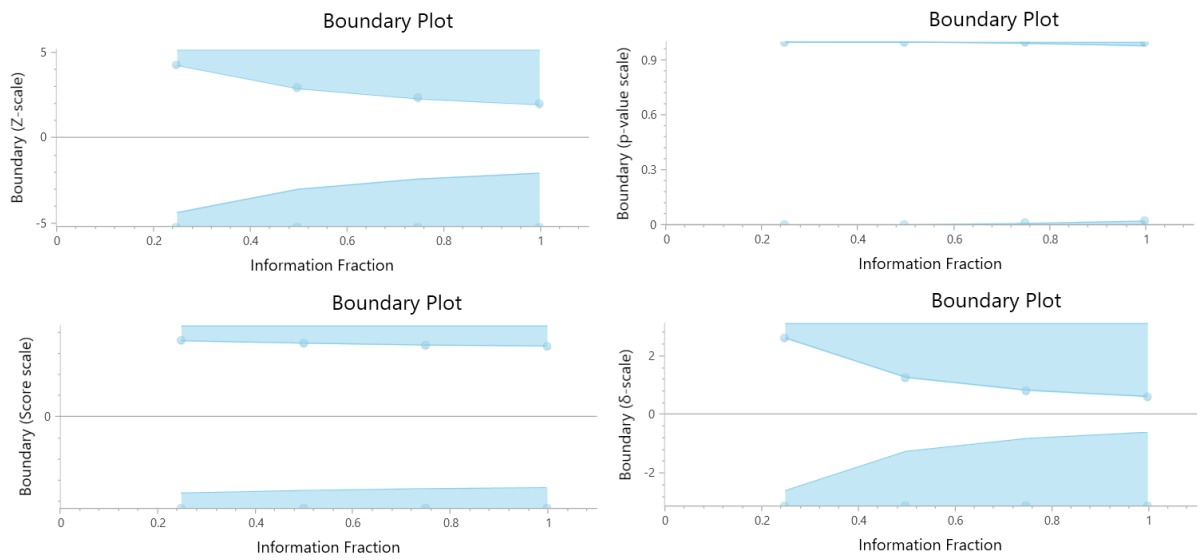


Figure 7.37: Boundary Plots for Efficacy Only 2-sided Scenario

For the **Efficacy Only 2-sided** scenario, the upper and lower efficacy exit regions (highlighted in blue) shows test statistics greater than the **Upper Efficacy Boundary** at each will look or less then the **Lower Efficacy Boundary** will lead to early stopping for efficacy for the **Z-scale, Score Scale** and δ**-Scale**. Test statistics that fall between the **Lower Efficacy Boundary** and **Upper Efficacy Boundary** are in the continuation region where the trial will proceed to the next look.

In this example, a test statistic at the first interim analysis (**Information Time = 0.25**) greater than 4.333, 7.221, 2.600 or less than -4.333, -7.221, -2.600 would stop the trial early for efficacy on the **Z-scale, Score Scale** and δ**-Scale** (δ = mean difference in GST1 for Two Means) respectively. If the test statistic falls between -4.333 and 4.333 (Z-scale), -7.221 and 7.221 (Score Scale) or -2.600 and 2.600 (δ-Scale) then the trial continues to the next look.

For the **p-value Scale**, the respective equivalent **"Upper"** (at bottom of **Boundary Plot**) and **"Lower"** (at top of **Boundary Plot**) 1-sided test p-values for a directional hypothesis are provided for comparability with the other boundary scales. However the **Lower Efficacy Boundaries** are unlikely to be used directly and in practice we compare the **Upper Efficacy Bound** directly to the p-value from a 1-sided test (e.g. two sample Z-test for GST1 Two Means) or double the **Upper Efficacy Bound** ($2UEL$) and compare this to 2-sided test p-value. In this example, at the first interim analysis (**Information Time = 0.25**), the **Upper Efficacy Bound** p-value is 7.367E-06 so for a 1-sided test the trial would stop early for a p-value less than 7.367E-06 and for a 2-sided test the trial would stop early for a p-value less than $2\,(7.367E-06)$ i.e. 1.473E-05.

As the **Upper Efficacy Bound** is effectively equivalent to the 1-sided **Efficacy Bound** for design with the **Test Significance Level** divided by two (e.g. 2-sided Test Signifiance Level of 0.05 is equivalent to 1-sided Test Significance Level of 0.025) then the choice of whether to design the group sequential design for a 1-sided or 2-sided test is relatively inconsequential for positive effect sizes. This is not true where **2-sided Futility Bounds** as will be shown next!

Futility Only 2-sided Example **Boundary Plots** for the **Futility Only 2-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale, δ-Scale**) in **Figure 7.38.**

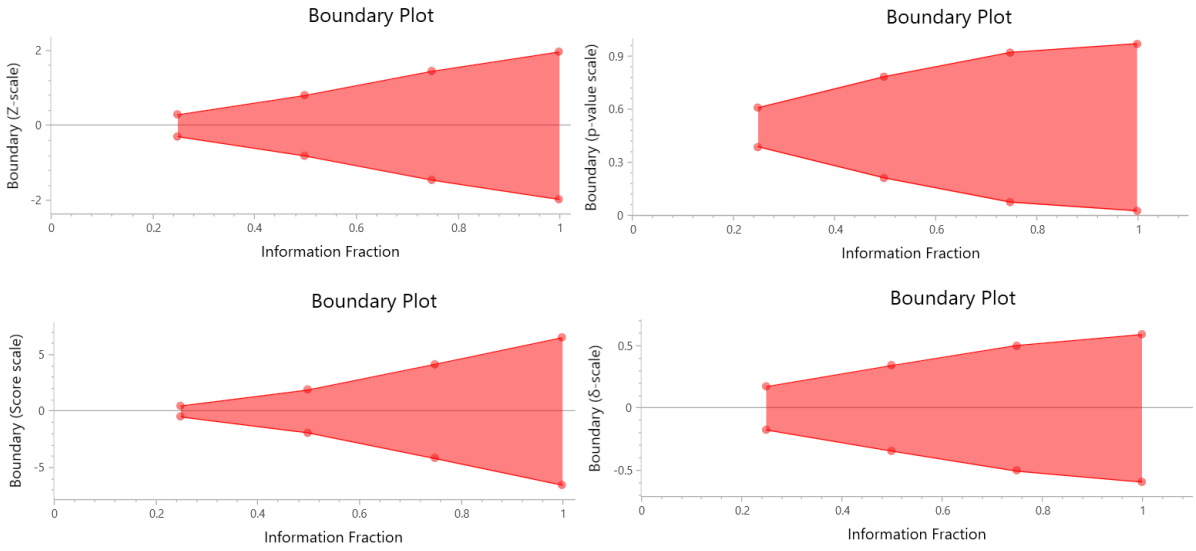


Figure 7.38: Boundary Plots for Futility Only 2-sided Scenario

For the **Futility Only 2-sided** scenario, the futility exit region (highlighted in red) shows test statistics between the **Lower Futility Boundary** and **Upper Futility Boundary** at each will look will lead to early stopping for futility for the **Z-scale, Score Scale** and **δ-Scale**. Test statistics that fall below the **Lower Futility Boundary** or above the **Upper Futility Boundary** are in the continuation region where the trial will proceed to the next look.

In this example, a test statistic at the first interim analysis (**Information Time = 0.25**) between -0.285 to 0.285 (**Z-scale**), -0.475 to 0.475 (**Score Scale**) or -0.171 to 0.171 (**δ-scale** e.g. mean difference in GST1 for Two Means) would stop the trial early for futility on the respective scales. If the test statistic falls below -0.285 or above 0.285 (**Z-scale**), below -0.475 or above 0.475 (**Score Scale**) or below -0.171 or above 0.171 (**δ-scale**) the trial continues to the next look

For the **p-value Scale**, the respective equivalent **"Upper"** and **"Lower"** 1-sided test p-values for a directional hypothesis are provided for comparability with the other boundary scales. However both boundaries are unlikely to be used directly and in practice we can compare two times the **Upper Futility Bound** directly to the p-value from a 2-sided test. In this example, at the first interim analysis (**Information Time = 0.25**), the **Upper Futility Bound** p-value is 0.387 so for a 2-sided test the trial would stop early for a p-value less than $2\,(0.387) = 0.774$.

2-sided **Futility Boundaries** are not comparable to 1-sided **Futility Boundaries** constructed at half the 2-sided **Test Significance Level** (e.g. 2-sided Test Significance Level of 0.05 equivalent to 1-sided Test Significance Level of 0.025). The enclosed area 2-sided **Futility Boundaries** around zero are correct for a true 2-sided hypothesis where a treatment is truly "effective" in both effect size directions but in practice most clinical

trials have an effect size direction of interest and therefore it is recommended that equivalent 1-sided **Futility Bounds** are used as per section 7.3.5.1 unless the consequences of 2-sided **Futility Bounds** are well understood.

Efficacy and Futility 2-sided Example **Boundary Plots** for the **Efficacy and Futility 2-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale, δ-Scale**) in **Figure 7.39.**

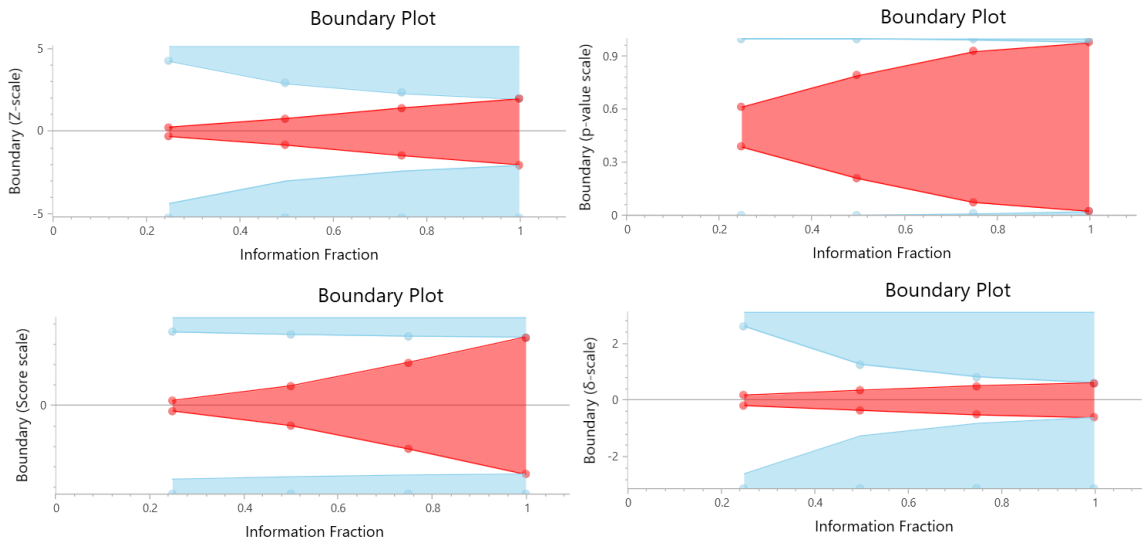


Figure 7.39: Boundary Plots for Efficacy and Futility 2-sided Scenario

For the **Efficacy and Futility 2-sided** scenario, the upper and lower efficacy exit regions (highlighted in blue) shows test statistics greater than the **Upper Efficacy Boundary** at each will look or less then the **Lower Efficacy Boundary** will lead to early stopping for efficacy for the **Z-scale, Score Scale** and **δ-Scale** while the futility exit region (highlighted in red) shows test statistics between the **Lower Futility Boundary** and **Upper Futility Boundary** at each will look will lead to early stopping for futility for the **Z-scale, Score Scale** and **δ-Scale**. Test statistics that fall between the **Lower Futility Boundary** and **Upper Futility Boundary** or between the **Upper Futility Boundary** and **Upper Efficacy Boundary** are in the continuation region where the trial will proceed to the next look.

In this example, a test statistic at the first interim analysis (**Information Time = 0.25**) greater than 4.333, 7.221, 2.600 or less than -4.333, -7.221, -2.600 would stop the trial early for efficacy on the **Z-scale, Score Scale** and **δ-Scale** (δ = mean difference in GST1 for Two Means) respectively while a test statistic at the first interim analysis (**Information Time = 0.25**) between -0.291 to 0.291 (**Z-scale**), -0.484 to 0.484 (**Score Scale**) or -0.174 to 0.174 (**δ-scale**) would stop the trial early for futility on the respective scales. If the test statistic falls between -4.333 and -0.291 or between 4.333 and 0.291 (**Z-scale**), between -7.221 and -0.484 or between 7.221 and 0.484 (**Score Scale**) or between -2.600 and -0.174 or between 2.600 and 0.174 (**δ-scale**) the trial continues to the next look

For the **p-value Scale**, the respective equivalent **"Upper"** and **"Lower"** 1-sided test p-values for a directional hypothesis are provided for comparability with the other boundary

scales. However these boundaries are unlikely to be used directly and in practice we can compare two times the **Upper Efficacy Bound** and two times the **Upper Futility Bound** directly to the p-value from a 2-sided test. In this example, at the first interim analysis (**Information Time = 0.25**), the **Upper Efficacy Bound** p-value is 7.367E-6 and the **Upper Futility Bound** is 0.386 so for a 2-sided test the trial would stop early for efficacy for a p-value less than $2\,(7.367E-6) = 1.473E-5$ or stop early for futility for a p-value greater than $2\,(0.386) = 0.772$.

2-sided **Futility Boundaries** are not comparable to 1-sided **Futility Boundaries** constructed at half the 2-sided **Test Significance Level** (e.g. 2-sided Test Significance Level of 0.05 equivalent to 1-sided Test Significance Level of 0.025). The enclosed area 2-sided **Futility Boundaries** around zero are correct for a true 2-sided hypothesis where a treatment is truly "effective" in both effect size directions but in practice most clinical trials have an effect size direction of interest and therefore it is recommended that equivalent 1-sided **Efficacy and Futility Bounds** are used as per section 7.3.5.1 unless the consequences of 2-sided **Futility Bounds** are well understood.

7.3.5.2 Boundary Table

The **Boundary Table** is a tabular summary of the group sequential boundaries as plotted in the **Boundary Plot**. The **Boundary Table** appears immediately below the **Boundary Plot**.

The **Boundary Scale** that the boundaries are shown in the **Boundary Table** will be the same for the current **Boundary Plot**. The **Boundary Scale** can be the following statistical scales: **Z-scale, p-value Scale, Score Scale, δ-Scale.** Technical detail on these statistical scales is provided in subsubsection 7.2.1.1 and subsubsection 7.2.4.5. The scale can be changed from **Boundary Scale...** option from the **Toolbar** or the **Edit** menu in the **Toolbar** or right-click context menu under the **Series > Y-axis Scale** option - see section 7.3.5.3 and section 7.3.5.3 .

The **Boundary Table** can be saved as a .CSV or .TXT file using the **Save Table...** button in the **Toolbar** or **Edit...** menu - see subsubsection 7.3.5.3.

The number of rows will equal the **Number of Looks** specificed in the main design table. The number of columns will depend on the scenario and will match the **Boundary Plot** scenarios outlined previously:

- **Efficacy Only 1-sided** (1 or 2 Sided Test? = 1, Futility Bound Calculation Method = Don't Calculate)
- **Futility Only 1-sided** (1 or 2 Sided Test? = 1, Efficacy Bound Calculation Method = Don't Calculate)
- **Efficacy and Futility 1-sided** (1 or 2 Sided Test? = 1, Efficacy Bound Calculation Method $\neq$ Don't Calculate & Futility Bound Calculation Method $\neq$ Don't Calculate)
- **Efficacy Only 1-sided** (1 or 2 Sided Test? = 2, Futility Bound Calculation Method = Don't Calculate)
- **Futility Only 1-sided** (1 or 2 Sided Test? = 2, Efficacy Bound Calculation Method = Don't Calculate)

- **Efficacy and Futility 1-sided** (1 or 2 Sided Test? = 2, Efficacy Bound Calculation Method ≠ Don't Calculate & Futility Bound Calculation Method ≠ Don't Calculate)

An example of the **Boundary Table** is provided for each scenario across the difference **Boundary Scale** options below. However, since the interpretation and decision rules for these boundaries was discussed in the subsubsection 7.3.5.1 above these will not be repeated here. The **Boundary Tables** here will be for the same plots shown in the subsubsection 7.3.5.1.

Efficacy Only 1-sided Boundary Table Example **Boundary Tables** for the **Efficacy Only 1-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale, δ-Scale**) in **Figure 7.40.**

Look	Efficacy Bound
1	3.74955184
2	2.53994224
3	2.01606987
4	1.72017715

Z-scale

Look	Efficacy Bound
1	0.00008858
2	0.00554354
3	0.02189633
4	0.04270012

p-value Scale

Look	Efficacy Bound
1	6.24925306
2	5.98670128
3	5.81989242
4	5.73392382

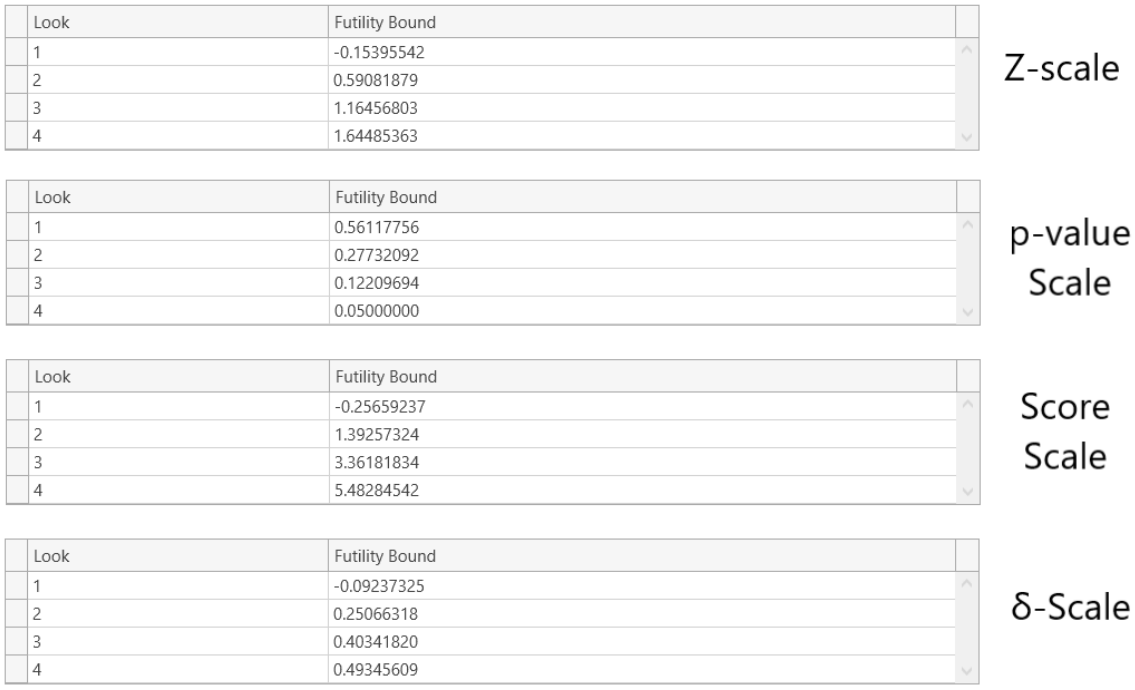
Score Scale

Look	Efficacy Bound
1	2.24973110
2	1.07760623
3	0.69838709
4	0.51605314

δ-Scale

Figure 7.40: Boundary Table for Efficacy Only 1-sided

Futility Only 1-sided Boundary Table Example **Boundary Tables** for the **Futility Only 1-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale, δ-Scale**) in **Figure 7.41.**



Look	Futility Bound
1	-0.15395542
2	0.59081879
3	1.16456803
4	1.64485363

Z-scale

Look	Futility Bound
1	0.56117756
2	0.27732092
3	0.12209694
4	0.05000000

p-value Scale

Look	Futility Bound
1	-0.25659237
2	1.39257324
3	3.36181834
4	5.48284542

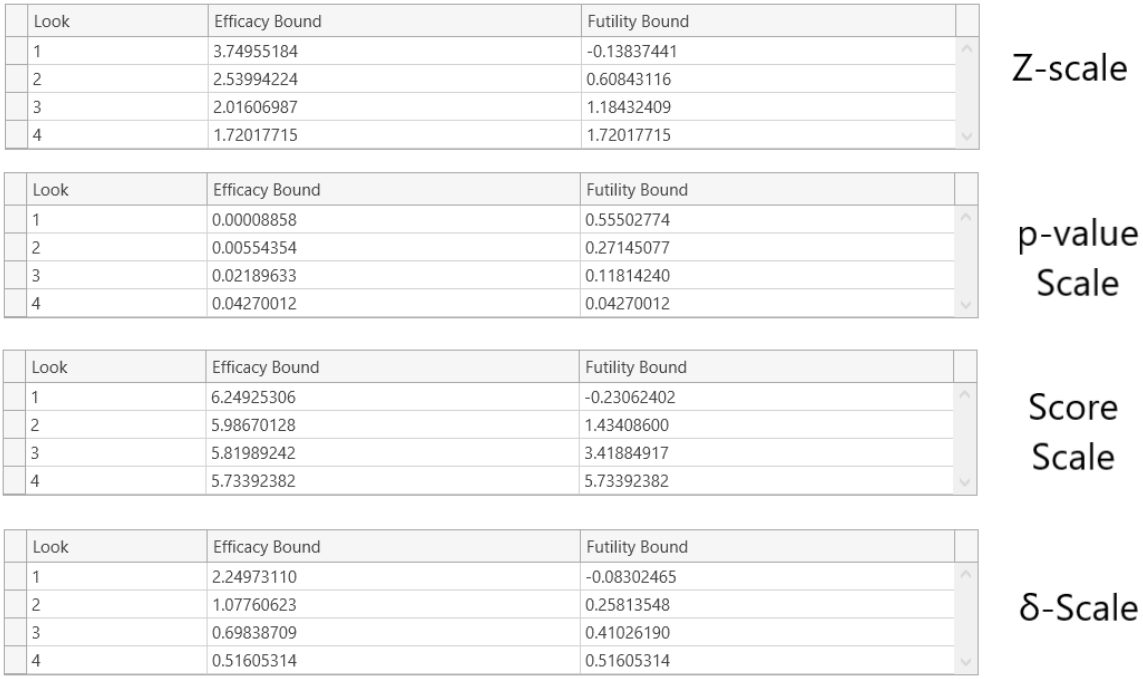
Score Scale

Look	Futility Bound
1	-0.09237325
2	0.25066318
3	0.40341820
4	0.49345609

δ-Scale

Figure 7.41: Boundary Table for Futility Only 1-sided

Efficacy and Futility 1-sided Boundary Table Example **Boundary Tables** for the **Efficacy and Futility 1-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale,** δ**-Scale**) in **Figure 7.42.**



Look	Efficacy Bound	Futility Bound
1	3.74955184	-0.13837441
2	2.53994224	0.60843116
3	2.01606987	1.18432409
4	1.72017715	1.72017715

Z-scale

Look	Efficacy Bound	Futility Bound
1	0.00008858	0.55502774
2	0.00554354	0.27145077
3	0.02189633	0.11814240
4	0.04270012	0.04270012

p-value Scale

Look	Efficacy Bound	Futility Bound
1	6.24925306	-0.23062402
2	5.98670128	1.43408600
3	5.81989242	3.41884917
4	5.73392382	5.73392382

Score Scale

Look	Efficacy Bound	Futility Bound
1	2.24973110	-0.08302465
2	1.07760623	0.25813548
3	0.69838709	0.41026190
4	0.51605314	0.51605314

δ-Scale

Figure 7.42: Boundary Table for Efficacy and Futility 1-sided

Efficacy Only 2-sided Boundary Table Example **Boundary Tables** for the **Efficacy Only 2-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale, δ-Scale**) in **Figure 7.43.**

Look	Efficacy Bound (Upper)	Efficacy Bound (Lower)
1	4.33263365	-4.33263365
2	2.96313104	-2.96313104
3	2.35904432	-2.35904432
4	2.01409027	-2.01409027

Z-scale

Look	Efficacy Bound (Upper)	Efficacy Bound (Lower)
1	0.00000737	0.99999263
2	0.00152263	0.99847737
3	0.00916103	0.99083897
4	0.02200003	0.97799997

p-value Scale

Look	Efficacy Bound (Upper)	Efficacy Bound (Lower)
1	7.22105608	-7.22105608
2	6.98416685	-6.98416685
3	6.80997437	-6.80997437
4	6.71363422	-6.71363422

Score Scale

Look	Efficacy Bound (Upper)	Efficacy Bound (Lower)
1	2.59958019	-2.59958019
2	1.25715003	-1.25715003
3	0.81719692	-0.81719692
4	0.60422708	-0.60422708

δ-Scale

Figure 7.43: Boundary Table for Efficacy Only 2-sided

Futility Only 2-sided Boundary Table Example **Boundary Tables** for the **Futility Only 2-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale, δ-Scale**) in **Figure 7.44.**

Look	Futility Bound (Upper)	Futility Bound (Lower)
1	0.28521646	-0.28521646
2	0.80112392	-0.80112392
3	1.44504156	-1.44504156
4	1.95996398	-1.95996398

Z-scale

Look	Futility Bound (Upper)	Futility Bound (Lower)
1	0.38773916	0.61226084
2	0.21152995	0.78847005
3	0.07422311	0.92577689
4	0.02500000	0.97500000

p-value Scale

Look	Futility Bound (Upper)	Futility Bound (Lower)
1	0.47536076	-0.47536076
2	1.88826719	-1.88826719
3	4.17147568	-4.17147568
4	6.53321328	-6.53321328

Score Scale

Look	Futility Bound (Upper)	Futility Bound (Lower)
1	0.17112987	-0.17112987
2	0.33988809	-0.33988809
3	0.50057708	-0.50057708
4	0.58798920	-0.58798920

δ-Scale

Figure 7.44: Boundary Table for Futility Only 2-sided

Efficacy and Futility 2-sided Boundary Table Example **Boundary Tables** for the **Efficacy and Futility 2-sided** scenario are shown for the four **Boundary Scale** options (**Z-scale, p-value Scale, Score Scale,** δ**-Scale**) in **Figure 7.45.**

Look	Efficacy Bound (Upper)	Efficacy Bound (Lower)	Futility Bound (Upper)	Futility Bound (Lower)
1	4.33263365	-4.33263365	0.29053278	-0.29053278
2	2.96313104	-2.96313104	0.81310958	-0.81310958
3	2.35904432	-2.35904432	1.45846773	-1.45846773
4	2.01409027	-2.01409027	2.01409027	-2.01409027

Z-scale

Look	Efficacy Bound (Upper)	Efficacy Bound (Lower)	Futility Bound (Upper)	Futility Bound (Lower)
1	0.00000737	0.99999263	0.38570434	0.61429566
2	0.00152263	0.99847737	0.20807762	0.79192238
3	0.00916103	0.99083897	0.07235583	0.92764417
4	0.02200003	0.97799997	0.02200003	0.97799997

p-value Scale

Look	Efficacy Bound (Upper)	Efficacy Bound (Lower)	Futility Bound (Upper)	Futility Bound (Lower)
1	7.22105608	-7.22105608	0.48422130	-0.48422130
2	6.98416685	-6.98416685	1.91651765	-1.91651765
3	6.80997437	-6.80997437	4.21023367	-4.21023367
4	6.71363422	-6.71363422	6.71363422	-6.71363422

Score Scale

Look	Efficacy Bound (Upper)	Efficacy Bound (Lower)	Futility Bound (Upper)	Futility Bound (Lower)
1	2.59958019	-2.59958019	0.17431967	-0.17431967
2	1.25715003	-1.25715003	0.34497318	-0.34497318
3	0.81719692	-0.81719692	0.50522804	-0.50522804
4	0.60422708	-0.60422708	0.60422708	-0.60422708

δ-Scale

Figure 7.45: Boundary Table for Efficacy and Futility 2-sided

7.3.5.3 Toolbar

The **Toolbar** for the group sequential **Boundary Plot** provides access to options to edit the **Boundary Plot**, change the statistical scale the **Boundary Plot** is displayed on and save the **Boundary Plot** or **Boundary Table**. The **Toolbar** is found at the top of the **Boundary Plot** window and consistes of the **Edit...** dropdown, **Boundary Scale** dropdown, **Save Plot** button and **Save Table** button. The **Toolbar** specifically is shown in Figure 7.46.

Figure 7.46: Boundary Plot Toolbar

Edit... The **Edit...** dropdown provides options to edit the visual aspects of the plot such as the titles, legend and color schemes while also providing options for printing and saving. The **Edit** menu for the **Boundary Plot** is similar to that described in section 1.9 for all plots so may be reviewed for additional context.

When selected the **Edit...** dropdown will display the options available for editing, printing and saving the **Boundary Plot**. Dropdown items with a ▶ at their right edge indicate a sub-menu which will open when that option is highlighted or selected. This **Edit...** menu can also be selected from the right-click context menu within the **Boundary Plot**. An example of the **Edit...** dropdown menu being open via the **Toolbar** is shown in Figure 7.47.

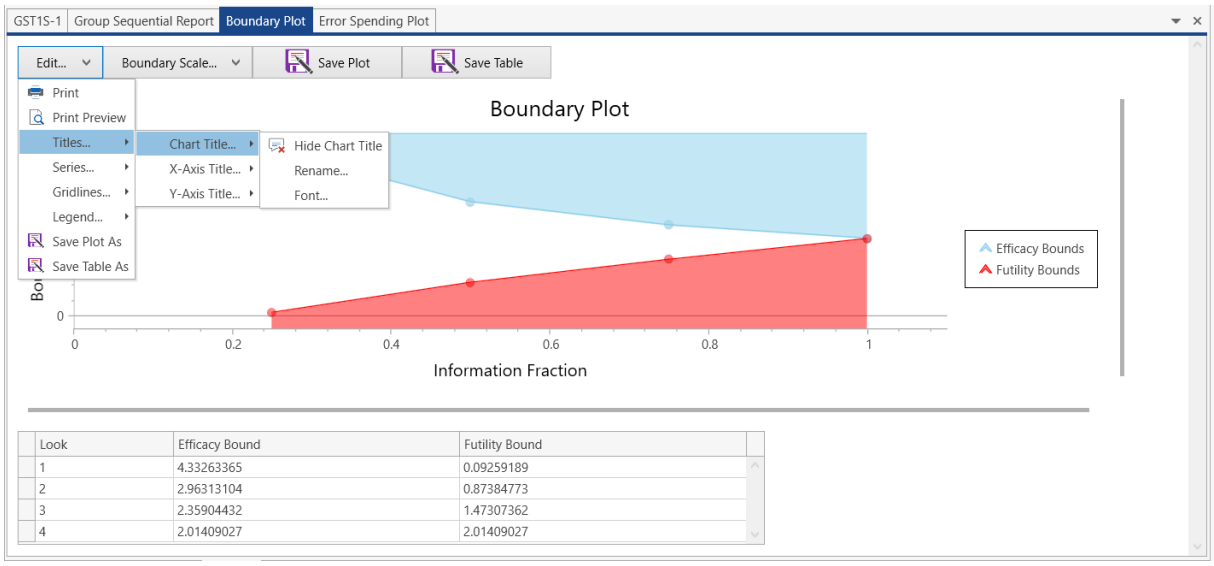


Figure 7.47: Boundary Plot Edit Menu

The full set of **Edit...** dropdown menu options is:

- Print: Open Print window for **Boundary Plot**
- Print Preview: Open Print Preview window for **Boundary Plot**

- Titles ▶: Edit Main Title, X-axis Title and Y-axis Title of **Boundary Plot**
- Series ▶: Edit Efficacy Bounds and Futility Bounds plot series of **Boundary Plot**
- Gridlines ▶: Add or remove gridlines from **Boundary Plot**
- Legend ▶: Edit **Boundary Plot** Legend
- Save Plot As: Save **Boundary Plot** as .pdf or .jpeg file
- Save Table As: Save **Boundary table** as .csv or .txt file

The **Print** and **Print Preview** options are available as per all other plots so will not be discussed further. The **Save Plot As** and **Save Table As** options are equivalent to the **Save Plot** and **Save Table** buttons in the **Toolbar** buttons so will be discussed separately.

A breakdown of the **Titles, Series, Gridlines** and **Legend** sub-menus is provided next.

Titles The **Titles** menu allows the user to edit the **Chart Title, X-axis Title** and **Y-axis Title** by choosing to show or hide that title, rename that title and change the font of that title. The tabular summary of the **Titles** menu , where ▶ indicate where an option will open an additional sub-menu and ⇒ indicates where an option will open a separate pop-out window, is as follows:

- Titles ▶
  - Chart Title ▶
    - Hide/Show Chart Title: Hide or show main **Chart Title**, name will depend on whether **Chart Title** is currently shown in **Boundary Plot** - *Default: Show*
    - Rename ⇒ : Opens **Rename Title** window where **Chart Title** can be edited. *Default: Boundary Plot*
    - Font ⇒ : Opens **Update Title Font** window for **Chart Title** where can edit the **Font** (select desired font from dropdown)**, Font Size**, **Font Type** (**Bold,** *Italics*), **Font Color** (select from **Color Panel** or create custom color in **Colors** window opened if select **More Colors**) *Default: Font: Segoe UI; Font Size: 21; Font Type: No Bold, No Italics; Font Color: Black (Automatic)*
  - X-axis Title ▶
    - Hide/Show Chart Title: Hide or show **X-axis Title**, name will depend on whether **X-axis Title** is currently shown in **Boundary Plot -** *Default: Show*
    - Rename ⇒ : Opens **Rename Title** window where **X-axis Title** can be edited - *Default: Selection from "Series > X-axis Scale" edit menu*
    - Font ⇒ : Opens **Update Title Font** window for **X-axis Title** where can edit the **Font** (select desired font from dropdown)**, Font Size**, **Font Type** (**Bold,** *Italics*), **Font Color** (select from **Color Panel** or create custom color in **Colors** window opened if select **More Colors**) - *Default: Font: Segoe UI; Font Size: 16; Font Type: No Bold, No Italics; Font Color: Black (Automatic)*

  - Y-axis Title ▶
    * Hide/Show Chart Title: Hide or show **Y-axis Title**, name will depend on whether **Y-axis Title** is currently shown in **Boundary Plot -** *Default: Show*
    * Rename ⇒ : Opens **Rename Title** window where **Y-axis Title** can be edited - *Default: Selection from "Series > Y-axis Scale" edit menu*
    * Font ⇒ : Opens **Update Title Font** window for **X-axis Title** where can edit the **Font** (select desired font from dropdown)**, Font Size**, **Font Type** (**Bold,** *Italics*), **Font Color** (select from **Color Panel** or create custom color in **Colors** window opened if select **More Colors**) - *Default: Font: Segoe UI; Font Size: 16; Font Type: No Bold, No Italics; Font Color: Black (Automatic)*

Series The **Series** menu allows the user to edit the **X-axis Scale**, the **Y-axis Scale**, the number of **Decimal Places** shown in the plot tooltip, edit the **Efficacy Bounds** aesthetic aspects and the edit the **Futility Bounds** aesthetic aspects. The tabular summary of the **Series** menu , where ▶ indicate where an option will open an additional sub-menu and ⇒ indicates where an option will open a separate pop-out window, is as follows:

- X-axis Scale ▶ : Choose the scale on which the **Boundary Plot** X-axis is defined. The sub-menu has the following options to select: Information Fraction, Cumulative Information, Total Sample Size - *Default: Information Fraction*
- Y-axis Scale ▶ Choose the scale on which the **Boundary Plot** Y-axis is defined. This sub-menu is equivalent to the **Boundary Scale** toolbar option and has the following options: Z-scale, p-value Scale, Score Scale, δ-Scale *Default: Same as Boundary Scale*
- Decimal Places ⇒ Opens **Choose Number of Decimal Places** window where user can set the number of decimals displayed in **Boundary Plot** tooltip - *Default: 8*
- Efficacy Bounds ▶
  - Marker Style ▶: Choose the marker style of the X-axis series plot points. This sub-menus has the following options to select: Hidden, Circle, Cross, Hexagon, Ring, Square, Star, Triangle - *Default: Circle*
  - Marker Size ⇒ : Opens **Update Marker Size** window where user can set size of X-axis series plot points - *Default: 8*
  - Rename ⇒ : Opens **Rename Series** window where user can edit name of X-axis series shown in the **Legend** - *Default: Efficacy Bounds*
  - Color ⇒ : Opens **Select Series Color** window where user can edit color of X-axis plot points and shaded areas. Select from **Color Panel** or create custom color using **More Colors** - *Default: Blue*
  - Transparency ▶: Choose transparency of the shaded area for efficacy bound exit and X-axis plot points. This sub-menu has the following options: 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100% - *Default: 50%*

- Futility Bounds ▶
  - Marker Style ▶: Choose the marker style of the Y-axis series plot points. This sub-menus has the following options to select: Hidden, Circle, Cross, Hexagon, Ring, Square, Star, Triangle - *Default: Circle*
  - Marker Size ⇒ : Opens **Update Marker Size** window where user can set size of Y-axis series plot points - *Default: 8*
  - Rename ⇒ : Opens **Rename Series** window where user can edit name of X-axis series shown in the **Legend** - *Default: Futility Bounds*
  - Color ⇒ : Opens **Select Series Color** window where user can edit color of X-axis plot points and shaded areas. Select from **Color Panel** or create custom color using **More Colors** - *Default: Red*
  - Transparency ▶: Choose transparency of the shaded area for futility bound exit and Y-axis plot points. This sub-menu has the following options: 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100% - *Default: 50%*

Gridlines The **Gridlines** menu consists of two options: **Show/Hide X-axis Gridlines** and **Show/Hide Y-axis Gridlines**. The options will change between **Show** and **Hide** depending on if that gridlines option is currently shown in the **Boundary Plot .**

By default both the X-axis and Y-axis gridlines are not shown. When shown the major gridlines will be shown at the numbered major ticks on the relevant axis and the minor gridlines at the 4 unnumbered ticks between each major tick.

Legend The **Legend** menu allows the user to edit the **Boundary Plot Legend** including whether to show the legend, legend border color and the vertical and horizontal position of the legend. The tabular summary of the **Legend** menu , where ▶ indicate where an option will open an additional sub-menu and ⇒ indicates where an option will open a separate pop-out window, is as follows:

- Show/Hide Legend: Hide or show **Legend**, name will depend on whether **Legend** is currently shown in **Boundary Plot** - *Default: Show*
- Border Color ⇒ Opens **Select Legend Border Color** window where user can edit color of border of the Legend. Select from **Color Panel** or create custom color using **More Colors** - *Default: Black*
- Horizontal Position ▶: Choose the horizontal position of the plot and whether the plot should be inside or outside the **Boundary Plot** area. This sub-menu has the following options: Left, Outside; Left, Inside; Center; Right, Outside; Right, Inside - *Default: Right, Outside*
- Vertical Position ▶: Choose the vertical position of the plot and whether the plot should be inside or outside the **Boundary Plot** area. This sub-menu has the following options: Top, Outside; Top, Inside; Center; Top, Outside; Top, Inside - *Default: Center*

Boundary Scale The **Boundary Scale** dropdown provides the option to quickly change the statistical scale on which the group sequential boundaries are shown on the Y-axis.

The **Boundary Scale** dropdown contains the following four options: **Z-scale, p-value Scale, Score Scale, δ-Scale**. These options are also available from the **Edit** menu under Edit > Series > Y-axis Scale.

The default scale the **Boundary Plot** will depend either on the option selected in the **GST Options** table for the **Boundary Scale** or (if **Efficacy Boundary Calculation Method = Custom Boundary) Efficacy Boundary Scale** rows. Where neither field is available or **Efficacy Boundary Scale = Alpha Error**, the **Z-scale** is selected. After an option is selected, the **Boundary Plot** and **Boundary Table** will automatically update to the boundaries to the selected statistical scale. See subsubsection 7.2.4.5 for technical detail on the statistical scale conversions.

Note that for 2-sided efficacy boundaries, the **p-value Scale** will split the p-value at each look into $\alpha/2$ for Upper Efficacy Bound and $1-\alpha/2$ for the Lower Efficacy Bound as per the **GST Outputs** table. This is done for consistency with the other boundary scales but in practical terms if using a standard statistical test the efficacy boundary would be crossed if it provided a p-value of $< \alpha$ i.e. twice the Upper Efficacy p-value Bound at each look.

Save Plot The **Save Plot** button will open the **Save As...** window as seen in Figure 1.17 except that the available **Save as type** filetypes will be .pdf and .jpeg. Use the Navigation bar on the left and main explorer window to find the desired save location, enter the desired file name in the **File Name** field and select **Save** to save the plot in the selected filetype above.

Save Table The **Save Table** button will open the **Save As...** window as seen in Figure 1.17 except that the available **Save as type** filetypes will be .csv and .txt. Use the Navigation bar on the left and main explorer window to find the desired save location, enter the desired file name in the **File Name** field and select **Save** to save the table in the selected filetype above.

7.3.6 Error Spending Plot

The **Error Spending Plot** provides a visual and tabular summary of **Error Spending Function** for the **Spending Function** method where a specified proportion of the Alpha (Type I (α)) and Beta (Type II (β)) errors are spent at each interim analysis.

The Alpha Error is the cumulative probability of exiting for efficacy under the null hypothesis (e.g. mean difference = 0 in GST1 Two Means) at any look up to and including the current look. The Beta Error is the cumulative probability of exiting for futility under the alternative hypothesis (e.g. mean difference = 0 in GST1 Two Means) at any look up to and including the current look. 1-Beta Error is also known as the statistical power. See subsection 7.2.3 and subsubsection 7.2.4.1 for the technical details on Type I and Type II errors, and the Lan-DeMets Spending Function method.

For **Spending Functions,** the error spent is provided in the **Cumulative Alpha** and/or **Cumulative Beta** rows of the **GST Outputs** table in the GSTXS-Y side-table - see subsubsection 7.3.2.2.

For methods other than the **Spending Function** such as **Wang-Tsiatis** and **Unified Family**, the **Error Spending Plot** provides the estimated **Type I** and **Type II** error at each look based on the **Incremental Exit (Boundary Crossing) Probabilities** table in the **Group Sequential Report**. Type I error can be calculated as the sum of the **Under H0 - Efficacy** rows up to the current look and Type II error as the sum of the **Under H1 - Futility** rows up the current look. Incremental exit probabilities are the probability of exiting at that specific look only.

The **Error Spending Plot** can be opened by selecting the **Error Spending Plot** tab at the top of the **Group Sequential Side-table** panel after a solver calculation has occured in the associated main design table column.

The **Error Spending Plot** allows the user to visually inspect the cumulative Type I and Type II error spent at each analysis and also export this plots to assist in the exploration and communcation of a planned group sequential design.

An example **Error Spending Plot** is shown in Figure 7.48.

Figure 7.48: Group Sequential Boundary Error Spending Plot

The **Error Spending Plot** tab consists of two primary elements: the **Error Spending Plot** (middle) and the **Toolbar** (top). Each of these will be summarized next.

7.3.6.1 Error Spending Plot

The **Error Spending Plot** provides a visual and tabular summary of **Error Spending Function** for the **Spending Function** method where a specified proportion of the Alpha (Type I (α)) and Beta (Type II (β)) errors are spent at each interim analysis or, for non-spending function methods, the estimated **Type I** and **Type II** error at each look based on the **Incremental Exit (Boundary Crossing) Probabilities** table in the **Group Sequential Report**.

The **Error Spending Plot** is a line plot where the **Alpha Error** and/or **Beta Error** probabilties are plotted against a measure of trial progress on the X-axis.

X-axis The **X-axis** corresponds to how far into the trial each analysis occurs.

The X-axis will range from zero to the maximum value for the specified X-axis parameter scale (e.g. 1 for **Information Fraction**). The first point will be plotted at a value of zero where the error spent will also be zero i.e. co-ordinate $(0, 0)$.

The **X-axis** is plotted on the **Information Fraction** scale. The scale can be changed from the **Edit** menu in the **Toolbar** or right-click context menu under the **Series > X-axis Scale** option. By default, the **X-axis** will be shown on the **Information Fraction** scale which is equivalent to the proportion of the total sample size analyzed at each analysis. The name of the **X-axis** by default will be "Information Fraction". Use **Titles > X-axis Scale** option from the **Edit** menu to change the **X-axis Title** (show/hide, X-axis name, X-axis font).

Note that **Total Sample Size** scale is not available for Information-Based Design (GST0) and that **Total Sample Size** is replaced with **Total Events** for Survival Analysis (e.g. GST3).

Y-axis The **Y-axes** corresponds to the amount of **Alpha Error** and/or **Beta Error** spent at each look. The **left Y-axis** will correspond to the amount of **Alpha Error** spent and the **right Y-axis** will correspond to the amount of **Beta Error** spent.

Both **Y-axis** will have a minimum value of zero for their range. The **left Y-axis** range will scale such that the Total Alpha (i.e. **Test Significance Level** from main design table) is the upper bound, with a small buffer for aesthetic clarity. The **right Y-axis** range will scale such that the Total Beta (i.e. **1-Power** from main design table) is the upper bound, with a small buffer for aesthetic clarity. **NB: The left and right axis are not on the same scale if both are present.**

The name of **left Y-axis** will be set to "Alpha Error" and the **right Y-axis** to "Beta Error" if **Alpha Error** and **Beta Error** are both active. If only one of **Alpha Error** or **Beta Error** are active then there will be only a left Y-axis named after the active error term. Use **Titles > Y-axis Scale (Left/Right)** option from the **Edit** menu to change the **Y-axis Title** (show/hide, Y-axis name, Y-axis font).

Alpha Error By default, the **Alpha Error** is plotted as a blue line with each point providing the cumulative amount of alpha spent at each look. The **Alpha Error** will equal 0 when the minimum X-axis value of zero and, for the **Spending Function** method, will equal the **Test Significance Level** for the maximum X-axis value (e.g. 1 for **Information Time**). For other methods than spending function, the **Alpha Error** will equal the **Exact Sig. Level** field in the **Test Parameters** section of the **Group Sequential Report** for the maximum X-axis value - seesubsection 7.3.4.

The **Alpha Error** color can changed from the **Edit** menu in the **Toolbar** or right-click context menu under the **Series** option.

Beta Error By default, the **Beta Error** is plotted as a red line with each point providing the cumulative amount of beta spent at each look. The **Beta Error** will equal 0 when the minimum X-axis value of zero and will equal **1 - Power** for the maximum X-axis value.

The **Beta Error** color can changed from the **Edit** menu in the **Toolbar** or right-click context menu under the **Series** option.

Legend The **Spending Function Plot Legend** provides an indication of the color for the **Alpha Error** and **Beta Error** series.

By default, the **Legend** is shown to the right of the boundary plot. To toggle whether the **Legend** is shown, change the location of the **Legend** or change the **Legend Border** use the **Edit** menu in the **Toolbar** or right-click context menu under the **Legend** option. The colors in the plot and legend are defined under the **Series** option in the **Edit** menu.

Tooltip The **Error Spending Plot Tooltip** provides the user information about the **Alpha Error** and/or **Beta Error** at a specific look based on which look is highlighted by the cursor within the area of the **Error Spending Plot**. When the cursor is not within the **Boundary Plot** area the **Tooltip** will not be shown as in Figure 7.48. The values shown in the **Tooltip** will correspond to the values provided in the **Boundary Table** for the highlighted look.

A **Error Spending Plot** with the **Tooltip** active for the second interim look (third point ignoring Information Time = 0 "look") is shown in Figure 7.49.

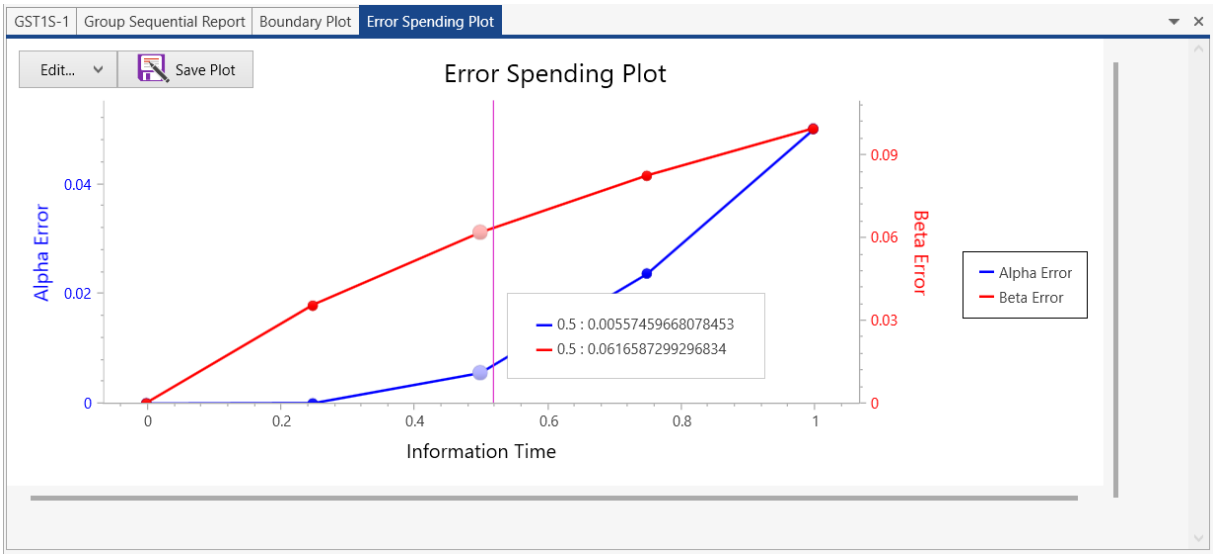


Figure 7.49: Error Spending Plot Tooltip

Resize Boundary Plot The grey bars at the bottom and to the right of the can be used to re-size the **Boundary Plot**. Click and drag the grey bar to increase or decrease the vertical and horizontal size respectively. The **Error Spending Plot** will also automatically scale if the side-table panel is resized.

Editing and Saving Options to edit, save or print the **Error Spending Plot** are available from the **Toolbar** in the top-right of the **Error Spending Plot** window or from the right-click context menu within the **Error Spending Plot**. These options are summarized in subsubsection 7.3.6.2.

To provide additional clarity about the behavior of the **Error Spending Plot** for different design scenarios examples of the changes due to changes to **Efficacy Bound Calculation Method** and **Futility Bound Calculation Method** rows and the **Boundary Scale...** option from the **Toolbar** are provided next for the following scenarios:

- **Alpha Error Only - Efficacy Only** (Futility Bound Calculation Method = Don't Calculate)
- **Beta Error Only - Futility Only** (Efficacy Bound Calculation Method = Don't Calculate)
- **Alpha Error and Beta Error - Efficacy and Futility** (Efficacy Bound Calculation Method ≠ Don't Calculate & Futility Bound Calculation Method ≠ Don't Calculate)

Alpha Error Only - Efficacy Only An example **Error Spending Plot** for the **Efficacy Only** scenario is shown for a **4-look equally spaced looks O'Brien-Fleming Spending Function** in **Figure 7.50.**

Figure 7.50: Error Spending Plot - Alpha Error Only

For the **Alpha Error Only** scenario there is only one Y-axis and it is for the **Alpha Error**.

Beta Error Only - Futility Only An example **Error Spending Plot** for the **Futility Only** scenario is shown for a **4-look equally spaced looks Pocock Spending Function** in **Figure 7.51.**

Figure 7.51: Error Spending Plot - Beta Error Only

For the **Beta Error Only** scenario there is only one Y-axis and it is for the **Beta Error**.

Alpha Error and Beta Error - Efficacy and Futility An example **Error Spending Plot** for the **Efficacy and Futility** scenario is shown for a **4-look equally spaced looks** with **Hwang-Shih-DeCani Alpha Spending Function** ($\gamma = -4$) and **Power Family Beta Spending Function** ($\rho = 1$) in **Figure 7.52.**

Figure 7.52: Error Spending Plot - Alpha Error Only

For the **Alpha Error and Beta Error** scenario there are two Y-axis. The **left Y-axis** is for the **Alpha Error** and the **right Y-axis** is for the **Beta Error**. Both Y-axis scales are **not** scaled to the same maximum error rate.

7.3.6.2 Toolbar

The **Toolbar** for the **Error Spending Plot** provides access to options to edit the **Error Spending Plot** and save **Error Spending Plot.** The **Toolbar** is found at the top of

the **Error Spending Plot** window and consistes of the **Edit...** and **Save Plot** button. The **Toolbar** specifically is shown in Figure 7.53 with the **Edit..** dropdown menu open.

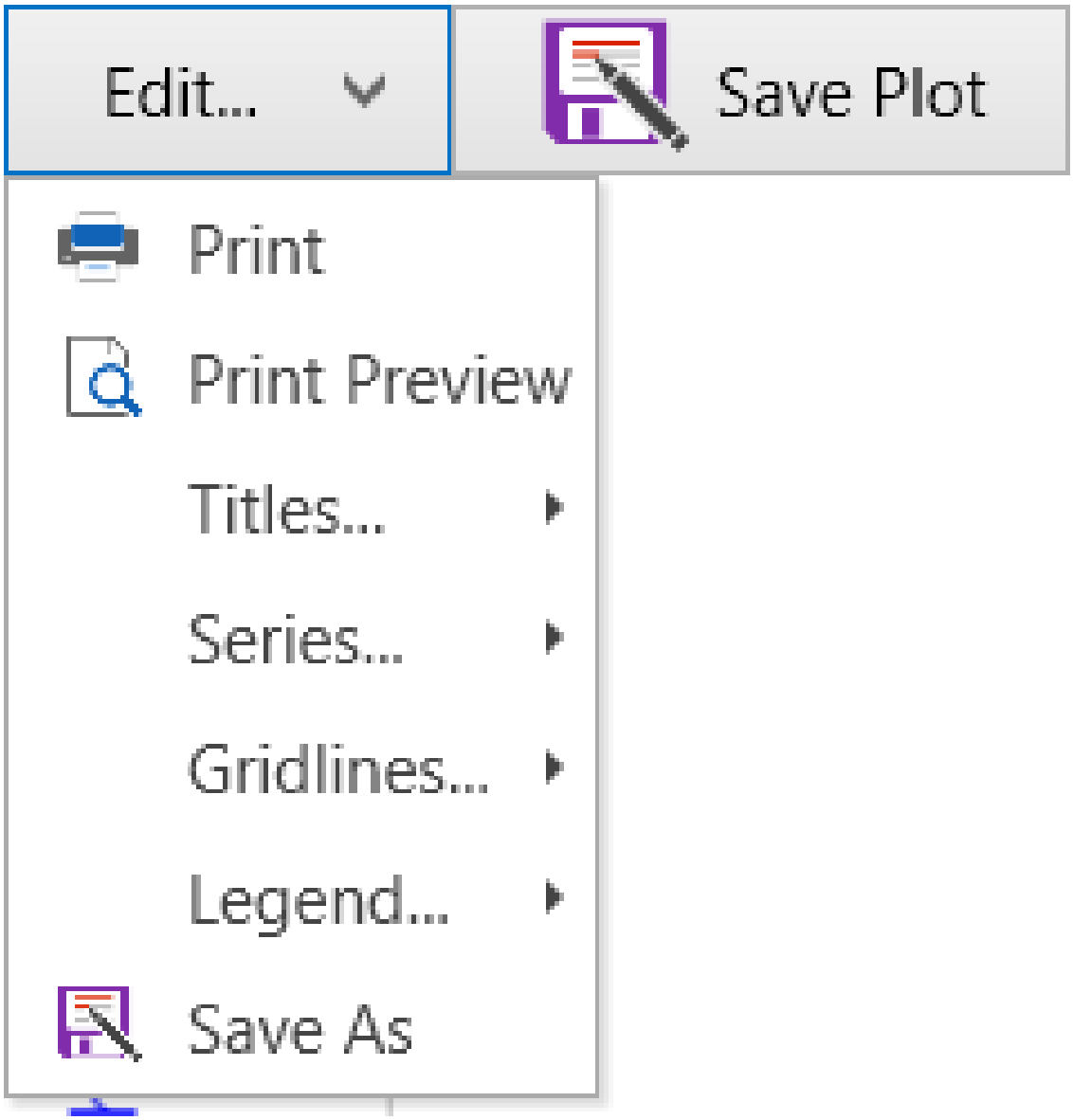


Figure 7.53: Boundary Plot Toolbar

Edit... The **Edit...** dropdown provides options to edit the visual aspects of the plot such as the titles, legend and color schemes while also providing options for printing and saving. The **Edit** menu for the **Error Spending Plot** is similar to that for the **Boundary Plot** and for plots generally.

When selected the **Edit...** dropdown will display the options available for editing, printing and saving the **Error Spending Plot**. Dropdown items with a ▶ at their right edge indicate a sub-menu which will open when that option is highlighted or selected. This **Edit...** menu can also be selected from the right-click context menu within the **Error Spending Plot**.

The full set of **Edit...** dropdown menu options is:

- Print: Open Print window for **Error Spending Plot**
- Print Preview: Open Print Preview window for **Error Spending Plot**
- Titles ▶: Edit Main Title, X-axis Title and Y-axis Title of **Error Spending Plot**
- Series ▶: Edit Color of **Alpha Error** and/or **Beta Error** series in **Error Spending Plot**
- Gridlines ▶: Add or remove gridlines from **Error Spending Plot**
- Legend ▶: Edit **Error Spending Plot** Legend
- Save As: Save **Error Spending** as .pdf or .jpeg file

The **Print** and **Print Preview** options are available as per all other plots so will not be discussed further. The **Save As** options is equivalent to the **Save Plot** buttons in the **Toolbar** buttons so will be discussed separately.

A breakdown of the **Titles, Series, Gridlines** and **Legend** sub-menus is provided next.

Titles The **Titles** menu allows the user to edit the **Chart Title, X-axis Title** and **Y-axis Title** by choosing to show or hide that title, rename that title and change the font of that title. The tabular summary of the **Titles** menu , where ▶ indicate where an option will open an additional sub-menu and ⇒ indicates where an option will open a separate pop-out window, is as follows:

- Titles ▶
  - Chart Title ▶
    - Hide/Show Chart Title: Hide or show main **Chart Title**, name will depend on whether **Chart Title** is currently shown in **Error Spending Plot** - *Default: Show*
    - Rename ⇒ : Opens **Rename Title** window where **Chart Title** can be edited. *Default: Error Spending Plot*
    - Font ⇒ : Opens **Update Title Font** window for **Chart Title** where can edit the **Font** (select desired font from dropdown)**, Font Size**, **Font Type** (**Bold,** *Italics*), **Font Color** (select from **Color Panel** or create custom color in **Colors** window opened if select **More Colors**) *Default: Font: Segoe UI; Font Size: 21; Font Type: No Bold, No Italics; Font Color: Black (Automatic)*
  - X-axis Title ▶
    - Hide/Show Chart Title: Hide or show **X-axis Title**, name will depend on whether **X-axis Title** is currently shown in **Error Spending Plot -** *Default: Show*
    - Rename ⇒ : Opens **Rename Title** window where **X-axis Title** can be edited - *Default: Information Time*
    - Font ⇒ : Opens **Update Title Font** window for **X-axis Title** where can edit the **Font** (select desired font from dropdown)**, Font Size**, **Font Type** (**Bold,** *Italics*), **Font Color** (select from **Color Panel** or create custom color in **Colors** window opened if select **More Colors**) - *Default: Font: Segoe UI; Font Size: 16; Font Type: No Bold, No Italics; Font Color: Black (Automatic)*

- Y-axis Title ▶ - ***Note if Alpha and Beta Error Active then Y-axis replaced with Y-axis Title (Left) and Y-axis Title (Left) which have same options and defaults as below except where indicated***
  - Hide/Show Chart Title: Hide or show **Y-axis Title**, name will depend on whether **Y-axis Title** is currently shown in **Error Spending Plot** - *Default: Show*
  - Rename ⇒ : Opens **Rename Title** window where **Y-axis Title** can be edited - *Default: Alpha Error for Left Y-axis and Beta Error for Right Y-axis (if present), unless Beta Error only then Left Y-axis is Beta Error*
  - Font ⇒ : Opens **Update Title Font** window for **X-axis Title** where can edit the **Font** (select desired font from dropdown)**, Font Size**, **Font Type** (**Bold,** *Italics*), **Font Color** (select from **Color Panel** or create custom color in **Colors** window opened if select **More Colors**) - *Default: Font: Segoe UI; Font Size: 16; Font Type: No Bold, No Italics; Font Color: Left Y-axis: Blue unless Beta Error only then Red, Right Y-axis: Red*

Series The **Series** menu contains two options: **Select color for alpha error** and **Select color for beta error**. If either the **Alpha Error** or **Beta Error** is not active in the plot then that color option will be not be selectable (*greyed out*).

Selecting either option will open the **Select Series Color** window where the user can edit color for the selected error series. Select from **Color Panel** or create custom color using **More Colors.**

By default, the **Alpha Error** series will be blue and the **Beta Error** series will be red.

Gridlines The **Gridlines** menu consists of two options: **Show/Hide X-axis Gridlines** and **Show/Hide Y-axis Gridlines**. The options will change between **Show** and **Hide** depending on if that gridlines option is currently shown in the **Error Spending Plot .** By default both the X-axis and Y-axis gridlines are not shown. When shown the major gridlines will be shown at the numbered major ticks on the relevant axis and the minor gridlines at the 4 unnumbered ticks between each major tick.

Legend The **Legend** menu allows the user to edit the **Error Spending Plot Legend** including whether to show the legend, legend border color and the vertical and horizontal position of the legend. The tabular summary of the **Legend** menu , where ▶ indicate where an option will open an additional sub-menu and ⇒ indicates where an option will open a separate pop-out window, is as follows:

- Show/Hide Legend: Hide or show **Legend**, name will depend on whether **Legend** is currently shown in **Error Spending Plot** - *Default: Show*
- Border Color ⇒ Opens **Select Legend Border Color** window where user can edit color of border of the Legend. Select from **Color Panel** or create custom color using **More Colors** - *Default: Black*
- Horizontal Position ▶: Choose the horizontal position of the plot and whether the plot should be inside or outside the **Error Spending Plot** area. This sub-menu has the following options: Left, Outside; Left, Inside; Center; Right, Outside; Right, Inside - *Default: Right, Outside*

- Vertical Position ▶: Choose the vertical position of the plot and whether the plot should be inside or outside the **Error Spending Plot** area. This sub-menu has the following options: Top, Outside; Top, Inside; Center; Top, Outside; Top, Inside - *Default: Center*

Save Plot The **Save Plot** button will open the **Save As...** window as seen in Figure 1.17 except that the available **Save as type** filetypes will be .pdf and .jpeg. Use the Navigation bar on the left and main explorer window to find the desired save location, enter the desired file name in the **File Name** field and select **Save** to save the plot in the selected filetype above.

7.3.7 Group Sequential Options Tab

The **Group Sequential Options Tab** provides access to additional tuning parameters for the group sequential algorithm (see subsection 7.2.2 for technical detail) and for choices regarding issues such as integer rounding for sample size or the events.

To open the **Group Sequential Options Tab** select the **Options** tab from the bottom of the **Help** window to the right of the main design table. An example where the **Options** tab is highlighted and has been selected is provided in for **GST1 - Group Sequential Design for Two Means.**

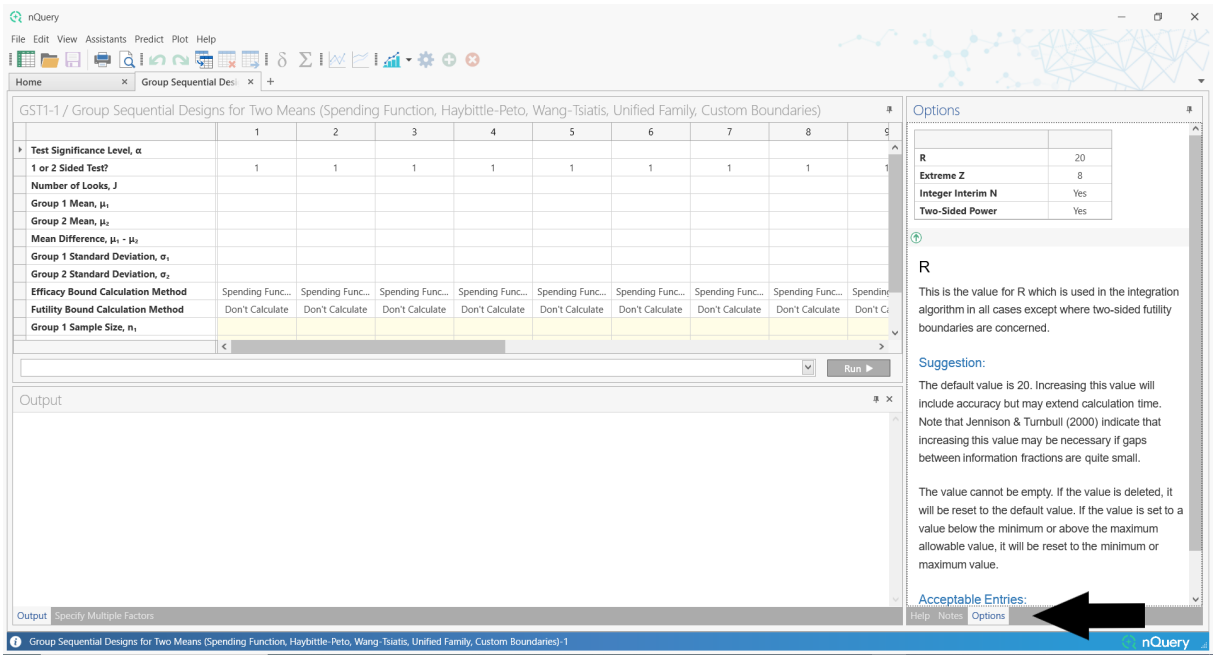


Figure 7.54: Group Sequential Menu Options Tab

The table of **Group Sequential Options** will be shown at the top of the window. Edit the desired fields in the **Group Sequential Options** table to update how the group sequential calculations are conducted for all columns in the currently open table.

A **Help** card is provided below the **Group Sequential Options** table which provides the definition, suggestions for setting the value and the acceptable entries range for that

field. The **Help** card will update automatically to reflect the currently selected field in the **Group Sequential Options** table. The **Help** card can be hidden by selecting the ↑ button between the **Group Sequential Options** and **Help** card. To re-open the **Help Card**, select the ↓ in the same spot.

The set of parameters shown in the **Group Sequential Options Tab** will depend on the specific GST table being used. For example, the **Integer Interim N** field is not included in GST0 (Information-Based Group Sequential Design) as this table uses the **Information** directly which is real value so never requires rounding to the nearest integer unlike the sample size (N).

The **Group Sequential Options Tab** will contain the following fields (applicable tables in brackets for each field) follows. A brief summary is provided with additional detail available, including the allowable range, in the **Help** card for each option within the **Options** tab.

7.3.7.1 Extreme Z-value (All GST Tables)

The bound for the Z-statistic used by the search algorithm when searching for the group sequential boundaries. The search algorithm will search from $[-Z_{extreme}, Z_{extreme}]$.

By default this will equal **8**. This is adequate for any reasonable normally distributed statistic e.g. under null hypothesis ($\Phi(-8) = 6.220961e-16$).

7.3.7.2 R (All GST Tables)

The turning parameter used to determine the number of points that will be used to numerically evaluate the integral. See subsection 7.2.2 for details.

By default this will be set to **20**. This is reasonable for most group sequential designs.

7.3.7.3 Two-Sided Power (GST0, GST1, GST2, GST3)

Set whether the lower tail efficacy exit probabilities under the alternative hypothesis should be included when calculating the exact power for a two-sided test.

The default is **Yes**, where the power will include the upper and lower efficacy exit probabilties under the alternative hypothesis - this is equivalent to the sum of all the **Under H1 - Lower Efficacy** and **Under H1 - Upper Efficacy** values from **Output** table from the **Group Sequential Report.** Selecting **No** will exclude the lower efficacy exit probabilities - this is equivalent to taking only the sum of the **Under H1 - Upper Efficacy** column from the **Output** table from the **Group Sequential Report.** See subsection 7.3.4 for additional detail on the **Group Sequential Report**.

7.3.7.4 Integer Interim N (GST1, GST2)

Integer Interim N sets whether the interim sample sizes will be rounded to the nearest integer after finding the maximum sample size. This will re-run the solver using the updated maximum information to give the exact power.

By default, this is set to **Yes**. For most cases, this will make minimal difference.

7.3.7.5 Rounded N & E (GST3)

Rounded N & E controls whether the sample size (N) and events (E) will be rounded to the nearest integer - this is applied to both the interim values and the maximum values of the sample size and events unlike **Integer Interim N** which only affects the interim sample sizes.

By default, this is set to **Yes**. There can be substantial differerences in the events and sample size depending on if rounding is used so the user may want to explore the effect of the option thoroughly.

8 Group Sequential Design Simulation Tool

The Group Sequential Design (chapter 7) and Group Sequential Design Simulation features will only be available to users if an nQuery Advanced Pro license is active. Active packages are displayed in the Packages section on the Home tab. To purchase additional packages, see `www.statsols.com`.

8.1 Group Sequential Design Simulation Overview

Understanding the operating characteristics of adaptive designs (where a decision or change is made to the trial based on interim data) such as group sequential designs is vital to generate trial designs which have strong performance for success criteria such as Type I error control, high statistical power and low average sample size. This information can help illustrate the value of a given adaptive design by allowing comparison to an equivalent fixed term trials, other types of adaptive design or the same type of adaptive design with different input parameters.

Monte Carlo simulation (referred to as simply simulation from hereon) is a powerful and flexible tool for assessing the operating characteristics of a given adaptive design over a wide variety of scenarios. For example, the FDA strongly supported simulation as a tool for assessing the performancen of an adaptive design in their **Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry** Guidance Document published in 2019. Simulation can find the operating characteristics not only for the standard null hypothesis or alternative hypothesis scenario but also easily for any arbitrary hypothesis and data generating process.

In nQuery, the **Group Sequential Design Simulation Tool** provides a powerful and accessible tool for performing simulations for the wide variety of group sequential designs scenarios available in nQuery. For detail on the group sequential design tables available in nQuery see chapter 7.

The following chapter provides an overview on how to use the **Group Sequential Design Simulation Tool** in the following sections:

- **Opening Group Sequential Design Simulation Tool**
  - From Assistants Menu
  - From Group Sequential Design (GST) Tables
- **Group Sequential Design Simulation Tool Layout**
- **Group Sequential Design Simulation Input Steps**
  - Step 0: Select GST Simulation Type

  - Step 1: Simulation Inputs
  - Step 2: Sequential Design Inputs
  - Step 3: Boundary Table
  - Step 4: Simulation Controls
- **Group Sequential Design Simulation Outputs**
  - Simulation Report
  - Rejection Plot
  - Boundary Plot
- **Saving/Loading Group Sequential Design Simulations**
- **Group Sequential Design Simulation Technical Background**
  - Data Generating Process
  - Test Statistic Calculation
  - Group Sequential Boundaries
  - Additional Input Options
  - Group Sequential Outputs

Opening Group Sequential Design Simulation Tool (section 8.2) will cover the steps required to open the **Group Sequential Design Simulation Tool** from either the **Assistants** File menu or from within a **Group Sequential Design** table based on the specified group sequential design.

Group Sequential Design Simulation Tool Layout (section 8.3) provides a high-level summary of the **Group Sequential Design Simulation Tool** user interface.

Group Sequential Design Simulation Input Steps (section 8.4) provides a detailed per-step breakdown of the input fields required to generate simulation results using the **Group Sequential Design Simulation Tool.**

Group Sequential Design Simulation Outputs () provides a breadown of the results and plots generated after running a simulation using the **Group Sequential Design Simulation Tool**

Saving/Loading Group Sequential Design Simulations provides an overview of how to save and open **Group Sequential Design Simulation Tool** files using the .nqgs file type.

Group Sequential Design Simulation Technical Background provides the technical details about statistical methods used by the **Group Sequential Design Simulation Tool** including the data generating process using to simulate data, the options for generating the test statistics and boundary adjustments, the group sequential boundary table for each available statistical scale and how summary results in the simulation report are generated.

8.2 Opening Group Sequential Design Simulation Tool

There are two methods available to open the **Group Sequential Design Simulator:**

- Select **Group Sequential Design Simulator** option from the **Assistants** file menu
- Open from within a **Group Sequential Design Table** using the **GST Simulation** button

The method selected to open the **Group Sequential Design Simulator** will affect at which **Input Step** the tool will open at and which default values (if any) are provided for the various fields at each **Input Step** so the route used to open the simulator tool should be carefully considered - see section 8.4 for details on the **Group Sequential Design Simulator Input Steps**.

An overview of each method to open the **Group Sequential Design Simulator** is provided next.

8.2.1 Open GSD Simulation Tool From Assistants Menu

The **Group Sequential Design Simulation** can be opened from the **Assistants** file menu. The **Assistants** file menu is found at the top of the nQuery application. The **Group Sequential Design Simulation** option is highlighted within the **Assistants** file menu in Figure 8.1.

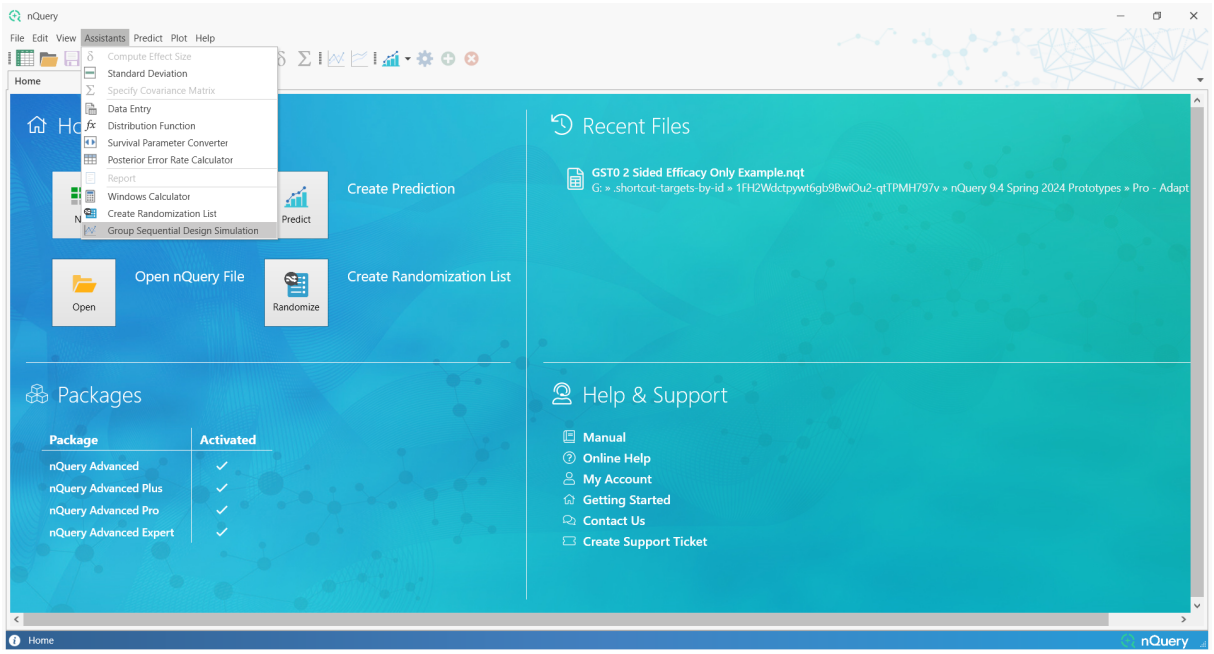


Figure 8.1: Group Sequential Design Simulation Tool in Assistant File Menu

If **Group Sequential Design Simulation** is opened from the **Assistants** file menu, it will open at **Step 0: Select GST Simulation Type** where the user will specify the **Endpoint of Interest** (Means, Proportions, Survival, Counts, Regression), the **Number of Groups** (1, 2, >2) and the **Analysis Method** (Inequality, Equivalence, Non-inferiority). Detail on **Step 0: Select GST Simulation Type** can be found in subsection 8.4.1.

No default values will be provided for the subsequent **Group Sequential Design Simulation Input Steps** if opening the **Group Sequential Design Simulation Tool** from the **Assistants** file menu.

8.2.2 Open GSD Simulation Tool From Group Sequential Design Table

The **Group Sequential Design Simulation Tool** can be opened from within **Group Sequential Design Tables** where that simulation scenario is supported by the tool. For detail on **Group Sequential Design Tables,** see chapter 7.

If the **Group Sequential Design Simulation Tool** is available for a selected **Group Sequential Design Tables**, the **GST Simulation** button will be available from the **Group Sequential Design Side-table** which appears in the bottom left panel after the **Number of Looks** field in filled in the main design table (top-left panel). An example for the design table **GST1 - Group Sequential Design for Two Means** with the **GST Simulation** button highlighted is provided in Figure 8.2.

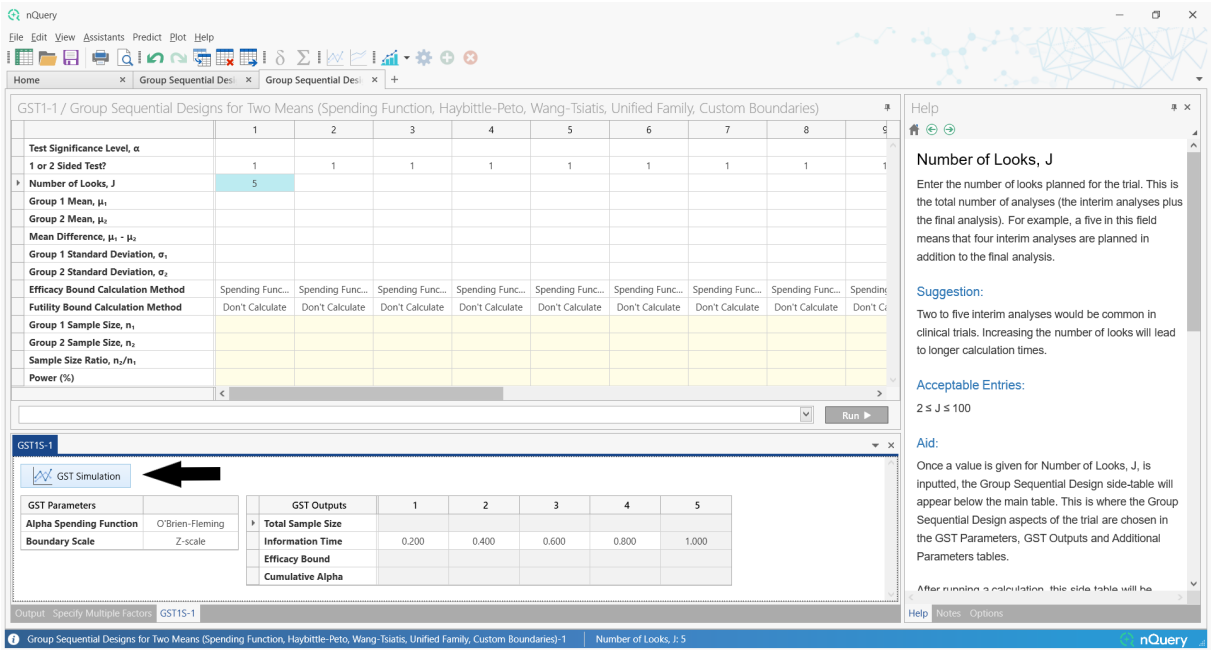


Figure 8.2: GST Simulation Button in GST1 Group Sequential Design for Two Means

When the **GST Simulation** button is selected, a **Group Sequential Design Simulation Tool** tab will be opened at **Step 1: Simulation Inputs** where the user specifies the **Design Parameters** and **Allocation Parameters.** The **Design Parameters** and **Allocation Parameters** available at **Step 1: Simulation Inputs** will be specific the scenario implied by the **Group Sequential Design Table** that the **Group Sequential Design Simulation Tool** was opened from.

In general, changing the **Endpoint of Interest** will change the **Design Parameters** (e.g. continuous data will requires means, binomial endpoints will require proportions, survival endpoints require hazard rates etc.) and changing the **Number of Groups** will change the **Allocation Parameters** (e.g. one group design would only have a Total Sample Size instead of Group 1 Sample Size and Group 2 Sample Size).

For example, the **Step 1: Simulation Inputs** opened from **GST1 - Group Sequential Design for Two Means** would have the following **Design Parameters:** Group 1 Mean, Group 2 Mean, Mean Difference, Group 1 Standard Deviation, Group 2 Standard

Deviation; and the following **Allocation Parameters:** Group 1 Sample Size, Group 2 Sample Size, Sample Size Ratio, Randomization Type.

A significant advantage of opening the **Group Sequential Design Simulation Tool** using the **GST Simulation** button is the potential to inherit defaults for the majority of inputs specified during the **Group Sequential Design Simulation Input Steps**. As the **Input Steps** are covered in detail in section 8.4, only a quick summary of this inherit behavior is provided here.

Defaults will only be passed for columns in a group sequential design table which have activated the **solver calculation**, such as for sample size or power. This requires the column in the main design table be fully specified and the **Group Sequential Design Side-table** be filled appropriately. An example where a sample size calculation has been run in column 1 is provided in Figure 8.3.

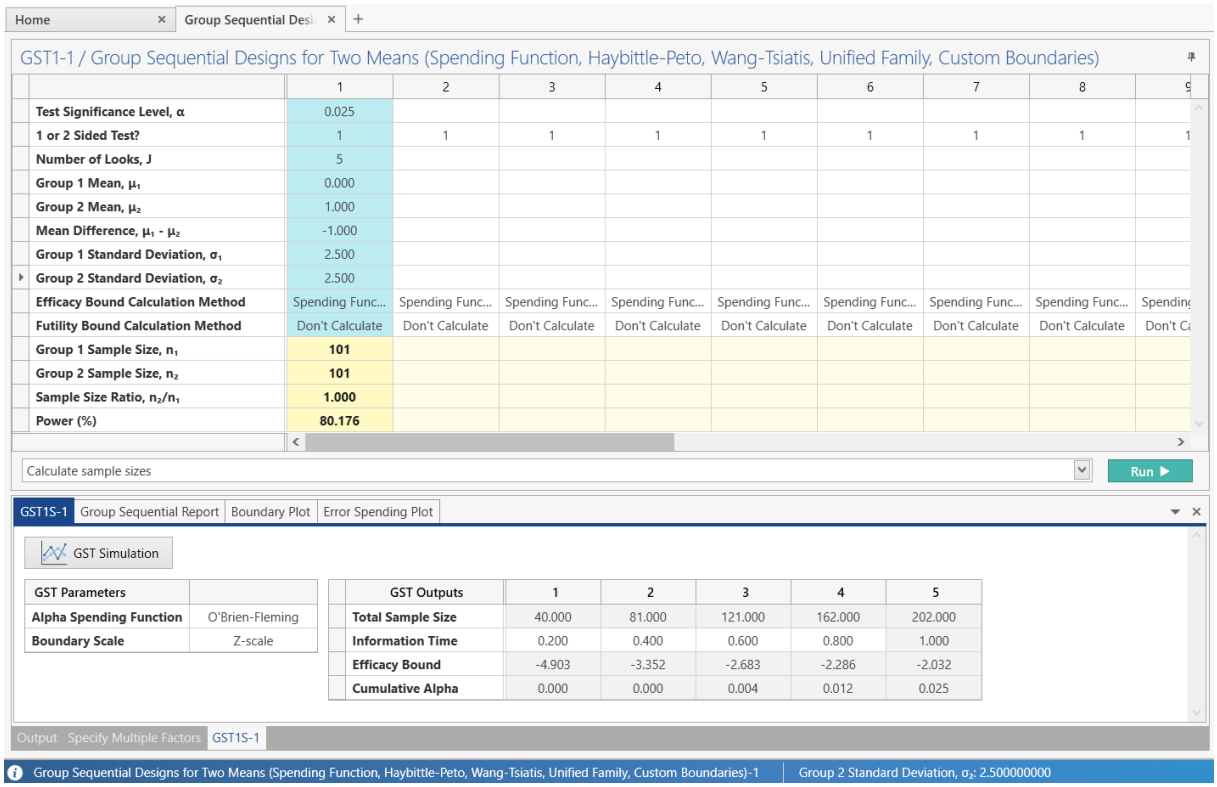


Figure 8.3: Group Sequential Design Table Example for Group Sequential Design Simulation Tool

When the **GST Simulation** button is selected in this **solver complete** column then the **Step 1: Simulation Inputs** fields will have been filled appropriately based on the main design table column values (under the alternative hypothesis) as in Figure 8.4.

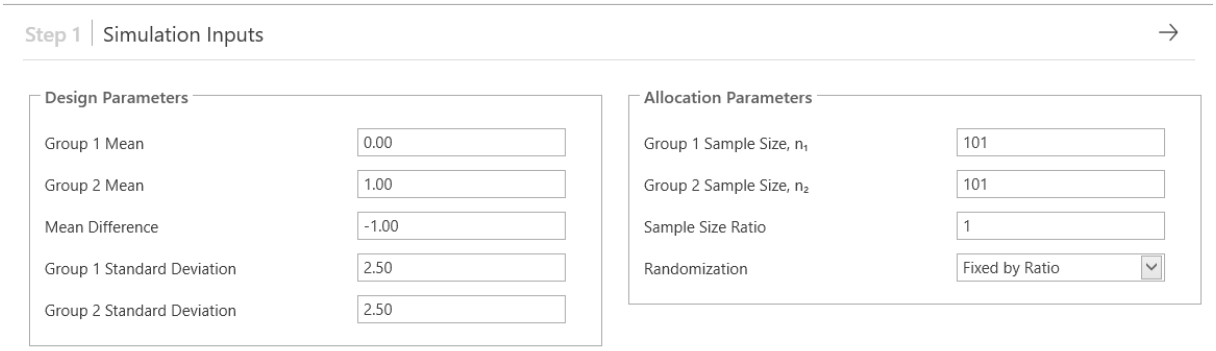
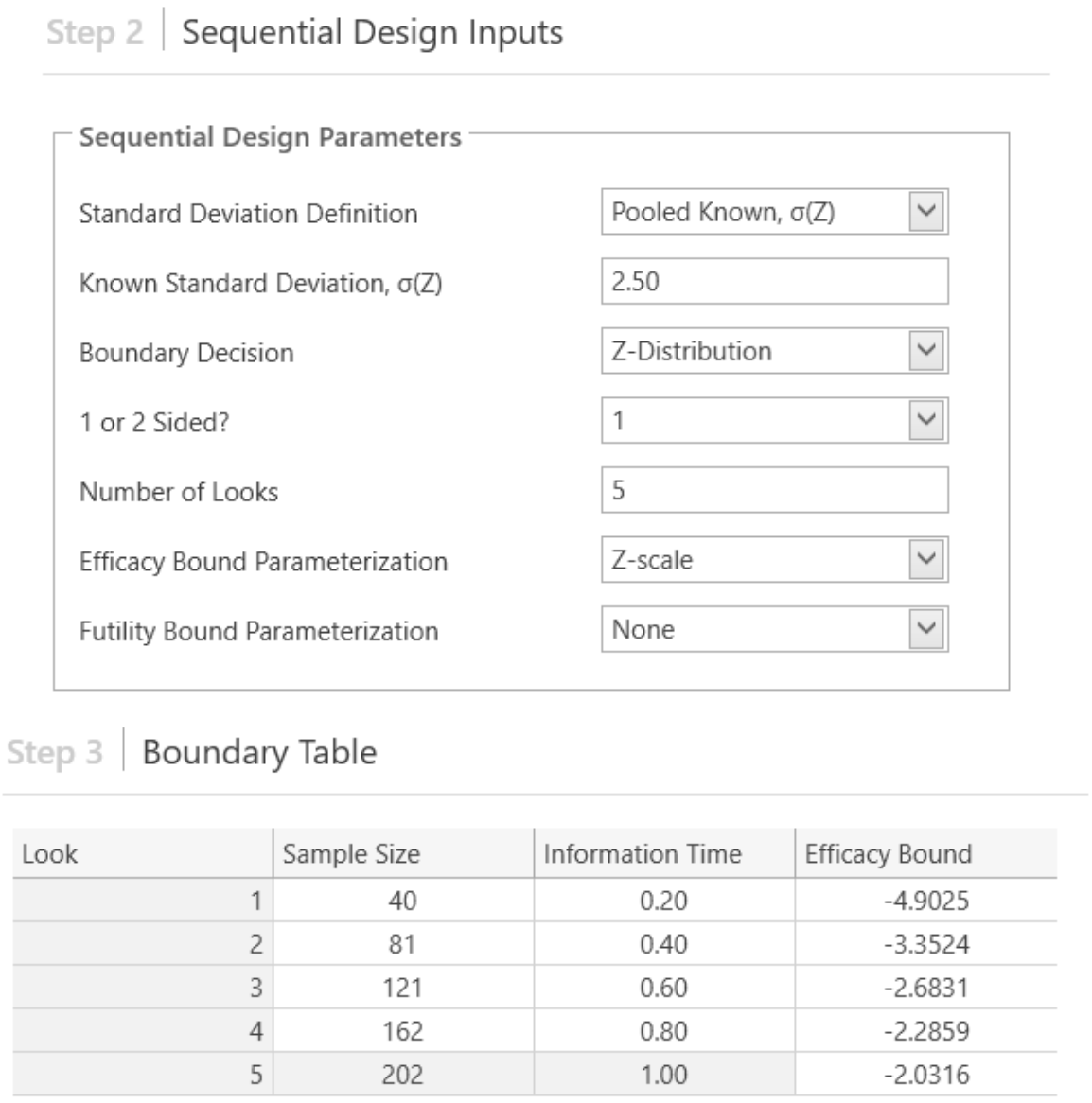


Figure 8.4: Inherited Values in Step 1 | Simulation Inputs from Group Sequential Design Example

Similarly, the **Input Steps** of **Step 2: Sequential Design Inputs** and **Step 3: Boundary Table** will inherit values from the relevant main design table and side-table rows from the original **solver complete** column.

Note the **Step 3: Boundary Table** fields will be cleared of the inherited defaults if **1 or 2 Sided?, Number of Looks, Efficacy Bound Parameterization or Futility Bound Parameterization** as these change the group sequential design sufficiently for the original boundaries to no longer be appropriate.

The **Step 2: Sequential Design Inputs** and **Step 3: Boundary Table** defaults inherited for this example are shown in Figure 8.5.



Look	Sample Size	Information Time	Efficacy Bound
1	40	0.20	-4.9025
2	81	0.40	-3.3524
3	121	0.60	-2.6831
4	162	0.80	-2.2859
5	202	1.00	-2.0316

Figure 8.5: Inherited Values for Step 2 and 3 from Group Sequential Design Example

Using these defaults, the user can quickly assess the operating characteristics of a group sequential design specified (for example in **GST1 - Group Sequential Design for Two Mean**) under the alternative hypothesis and by changing the **Step 1: Simulation Inputs** assess the operating characteristics for other important scenarios such as the null hypothesis (e.g. by setting **Mean Difference** to zero in the example above).

These defaults will only be inherited if a **solver calculation** has been activated in that column. Partially filled will not inherit any values and the majority of fields at each **Input Step** will be empty as per opening the **Group Sequential Simulation Tool** via the **Assistants** file menu (subsection 8.2.1)

If **GST Simulation** button is not shown in a specific **Group Sequential Design Table** that indicates that group sequential simulation is not currently supported for that design table scenario.

8.3 Group Sequential Design Simulation Tool Layout

This section provides a high level overview of the **Group Sequential Design Simulation Tool's** layout. While each **Input Step** has a series of unique input fields, these occur within a common user interface which has the following elements:

1. Main Window
2. Workspace Bar
3. Help Window
4. Next/Run Button (Input Stages Only)

These elements have been numbered as above for the **Step 1: Simulation Inputs Step** in Figure 8.6.

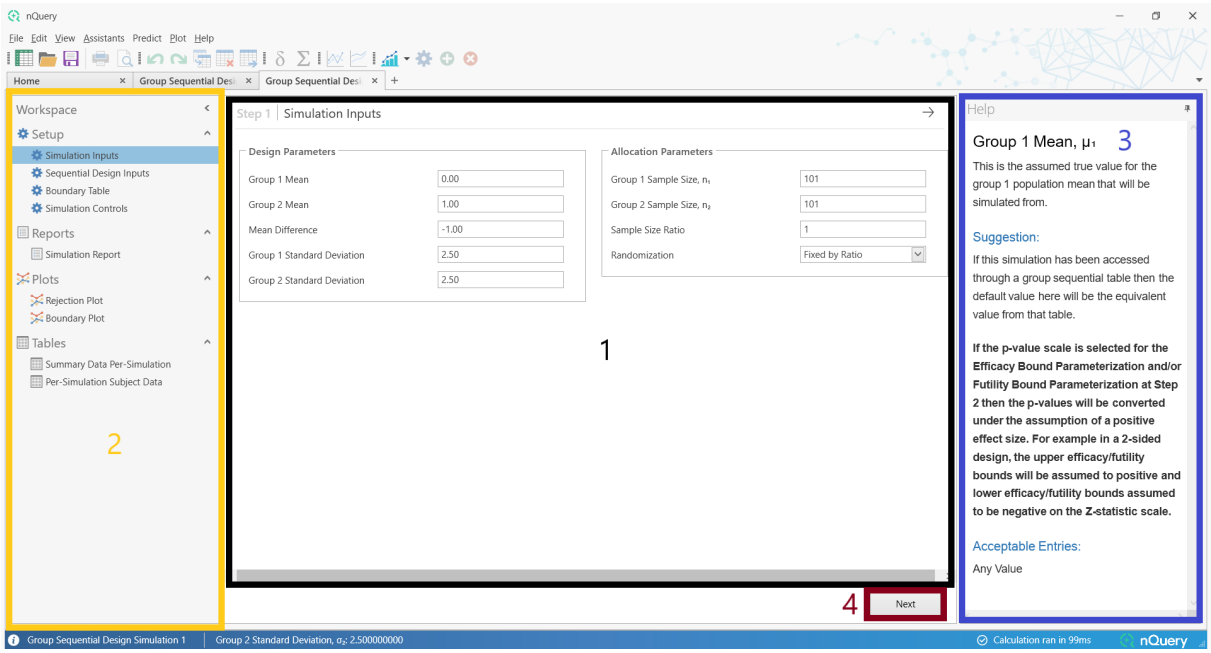


Figure 8.6: Group Sequential Simulation Tool Layout

A brief overview of each **Group Sequential Simulation Tool** layout element is provided next.

8.3.1 Main Window

The **Main Window** of the **Group Sequential Design Simulation Tool** is where inputs or outputs of the currently selected item in the **Workspace Bar** (subsection 8.3.2) are displayed.

For **Input Steps**, the **Main Window** will show the name of the input step at the top and provide the relevant input fields or input tables below that. Within most input fields there will be options to copy, paste and similar available from the right-click context menu.

For **Group Sequential Simulation Tool Outputs**, such as the **Reports, Plots** and **Tables** available from the **Workspace Bar** in Figure 8.6, the **Main Window** will show the currently selected report (e.g. **Simulation Report**), plot (e.g. **Rejection Plot**) or table (e.g. **Summary Data Per-Simulation**). For these fields there will often be additional options to edit, copy or save these outputs via a toolbar of the right-click context menu.

8.3.2 Workspace Bar

The **Workspace Bar** contains all the input and output objects associated with the current **Group Sequential Design Simulation** workspace. There are four primary headers under which the **Workspace Bar** organizes these objects. These are: **Setup, Reports, Plots** and **Tables**.

Setup contains a field for each **Group Sequential Design Simulation Input Step**. The **Input Steps** are described in section 8.4. Note that **Step 0: Select GST Simulation Type** will not be available if the **Group Sequential Design Simulation Tool** was opened using the **GST Simulation** button within a **Group Sequential Design Table** - see subsection 8.2.2 for details.

Reports will contain the reports generated in the **Group Sequential Design Outputs**. The only report available in the **Group Sequential Design Simulation Outputs** at present is the **Simulation Report** which summarizes the results of the simulation including the average sample size, power and proportion of simulations that stopped at each look - see subsection 8.5.1 for details.

Plots will contain the plots generated in the **Group Sequential Design Outputs**. Two plots are available in the **Group Sequential Design Simulation Outputs** at present. These are the **Rejection Plot** and the **Boundary Plot.** The **Rejection Plot** visually displays the proportion of simulations which had each outcome (stopped for efficacy, stopped for futility, continued to next look) at each look - see subsection 8.5.2 for details. The **Boundary Plot** visually displays the group sequential boundaries specified for the simulation at the **Step 3: Boundary Table Input Step** - see subsection 8.4.4 for details.

Tables will contain the tabular outputs (tables, spreadsheets) generated in the **Group Sequential Design Outputs**. Two optional tables are available in the **Group Sequential Design Simulation Outputs** at present. These are the **Summary Data Per-Simulation** spreadsheet and the **Per-Simulation Subject Data** spreadsheet**.** The **Summary Data Per-Simulation** spreadsheet provides a per-look overview of the summary statistics and decision for each simulation The **Per-Simulation Subject Data** spreadsheet provides the per-subject simulated values for the number of simulations specified at the **Step 4: Simulation Controls Input Step.** See subsection 8.5.4 for details on these table outputs. Both these tables can be added or removed from the outputs at the **Step 4: Simulation Controls Input Step** - see subsection 8.4.5.

If a primary header title (**Setup, Reports, Plots, Tables**) is selected within the **Workspace Bar**, this will either show the objects within that header (if they were hidden) or hide the objects with that head (if they were being shown). If an object (**Input Step, Report, Plot, Table**) is selected under a primary header this object will be displayed in the **Main Window**.

The **Workspace Bar** can be collapsed by the selecting the arrow in the top-right of the **Workspace Bar.** Select the arrow in top-left to uncollapse the **Workspace Bar**.

8.3.3 Help Card

The **Help Card** is provided to give the user information, context and suggestions for each **Input** (input fields, input tables) and **Output** (Reports, Plots and Tables) of the **Group Sequential Design Tool.** By default, it provided to the right of the **Main Window** and will update automatically to reflect the currently selected **Input/Output**. These **Help Cards** are mostly the same as those provided in standard design tables and are summarized further in subsection 1.7.2.

At **Group Sequential Design Simulation Inputs Steps**, the **Help Cards** provide information designed to help the user understand and fill the currently selected input field or table.

The most common structure is for a given **Help Card** to have an **Overview** section, a **Suggestions** section and an **Acceptable Entries** section.

The **Overview** section provides a summary of the selected input field, including that field's definition and high-value contextual information about that field.

The **Suggestions** section provides common values for the selected input field or provides methods for calculating the selected input field value from other commonly available sources.

The **Acceptable Entries** section provides the range of allowable values for the selected input field - if a value outside the **Acceptable Entries** is entered into the field an **Out-of-Range Error** will be shown in that field and user will not be able to continue to the next **Input Step -** see subsection 2.2.1 for details on **Out-of-Range Errors**.

For **Group Sequential Design Simulation Outputs**, the **Help Card** will provide information and context about he currently selected output.

For **Reports**, the **Help Card** provides a summary of the report overall and of each section in the selected report.

For **Plots**, the **Help Card** provides a summary of the plot, how to interpret the plot and guidance on the options available to edit and save the plot.

For **Tables**, the **Help Card** provides a summary of the overall table and a definition and overview of each column and row as necessary.

The **Help Card** can be hidden by selecting the pin icon in the top-right of the **Help Card** window. Select **Help** in the top-right to show the **Help Card** while it is highlighted, select the pin icon to permanently restore the **Help Card**.

8.3.4 Next/Run Button (Input Steps Only)

The **Next** button is selected to confirm that the current provided **Inputs** at the current step are correct and that these should be passed onto the next step and/or **Group Sequential Simulation algorithm**.

At the final **Input Step** of **Step 4: Simulation Controls**, the **Run** button is provided instead. When the **Run** button is selected this confirms that the user wants to run the **Group Sequential Simulation** and generate the **Group Sequential Simulation Outputs** based on the inputs from all prior **Input Steps**.

The user can manually navigate to any **Input Step** from the **Workspace Bar** on the left-hand side under the **Setup** header. Note that if changes are made at a given **Input Step** the **Next** button must be pressed for these changes to take effect and the **Run** button must be pressed for the **Group Sequential Simulation Outputs** to be updated based on all confirmed changes.

8.4 Group Sequential Design Simulation Input Steps

This section provides a summary of each **Input Step** required to use the **Group Sequential Design Simulation Tool** to generate simulation results for the desired group sequential design scenario.

As referenced in section 8.2, the default values provided at these **Input Steps** will depend on how the **Group Sequential Design Simulation Tool** was opened. For conveniece, the defaults used for the example where **Group Sequential Design Simulation Tool** was opened using the **GST Simulation** button within **GST1 - Group Sequential Design for Two Means** in subsection 8.2.2 will be used as starting point, with the exception of **Step 0: Select GST Simulation Type** as this **Input Step** is only available if using the **Assistants** menu option to open the **Group Sequential Simulation Tool** - see subsection 8.2.1. Additional changes and scenarios will the be explored as necessary.

8.4.1 Step 0: Select GST Simulation Type

The **Step 0: Select GST Simulation Type Input Step** provides the user the option to select the group sequential design simulation scenario of interest for their trial. This **Input Step** is only available if the user opened the **Group Sequential Design Simulation Tool** from the **Assistants** file menu at the top of the nQuery window as per subsection 8.2.1. As stated there, **Step 0: Select GST Simulation Type** will be the **Input Step** opened when **Group Sequential Design Simulation** is selected from the **Assistants** file menu. **Step 0: Select GST Simulation Type** is shown in

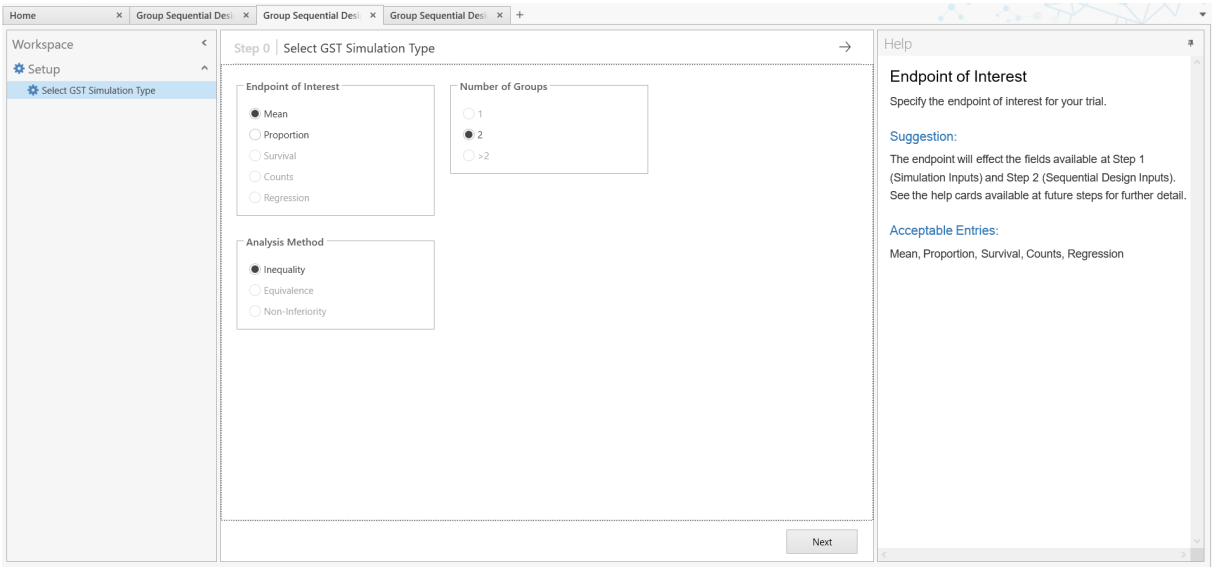


Figure 8.7: Step 0: Select GST Simulation Type

The **Step 0: Select GST Simulation Type** consists of the following radio button columns: **Endpoint of Interest, Number of Groups, Analysis Method**. At **Step 0: Select GST Simulation Type**, the user is required to select the desired option under each radio button column that corresponds the characteristics of the planned group sequential design.

Not all scenario combinations will be supported. For any given combination of column selections, the incompatible options in each other column will not be selectable and will be greyed out.

After the appropriate options are selected from each column, select the **Next** button in the bottom-right to continue to **Step 1: Simulation Inputs**.

A summary of the options available under the **Endpoint of Interest, Number of Groups, Analysis Method** columns is provided next.

8.4.1.1 Endpoint of Interest

Endpoint of Interest selects the endpoint type for the outcome of interest in the planned group sequential trial. It has the following options: **Mean, Proportion, Survival, Counts, Regression**.

Mean indicates the clinical trial endpoint is continuous and can be summarized by the mean(s) and standard deviation(s).

Proportion indicates the clinical trial endpoint is binary and can be summarized by the proportion(s).

Survival indicates the clinical trial endpoint is a time-to-event endpoint and can be summarized by the hazard rate(s) or equivalent parametric inputs.

Counts indicates the clinical trial endpoint is a count (or incidence rate) endpoint and can be summarized by the count/incidence rate(s).

Regression indicates the clinical trial endpoint is a coefficient from a regression model (e.g. linear regression) and can be summarized as the β_1 coefficient from the regression model and it's associated variance.

The effect of **Endpoint of Interest** choice on each subequent **Input Step** will be highlighted for the currently supported scenarios in the per input step summary sections provided later.

8.4.1.2 Number of Groups

Number of Groups selects the number of (independent) treatment groups there will be in the planned group sequential trial. It has the following options: **1, 2, >2**

1 indicates that there is a single treatment group in the study where the treatment effect will be compared to a standard value (e.g. based on database)

2 indicates that there are two (independent) treatment groups in the study where the treatment effect will be the average change between the two groups (e.g. mean difference, odds ratio, hazard ratio, rate ratio).

>2 indicates that there a greater than two (independent) treatment groups in the study. This is equivalent to specifying a **Multi-Arm Multi-Stage (MAMS) Design** where the treatment effect will (typically) be the difference between a control group and the multiple treatment groups.

8.4.1.3 Analysis Method

Analysis Method indicates the method or hypothesis type that will used for testing in the planned group sequential trial. It has the following options: **Inequality, Equivalence, Non-inferiority**

Inequality indicates the hypothesis of interest is for inequality where the objective is to test if the treatments are different. This corresponds to a null hypothesis where the treatment effect indicates the treatment groups are the same (e.g. null hypothesis mean difference = 0). This is also known as superiority testing and is the most common hypothesis type in clinical trials. Note that for **Number of Groups = 1**, **Inequality** and **Non-inferiority** are the same hypothesis test.

Non-inferiority indicates the hypothesis of interest is for non-inferiority where the objective is to show a treatment is no worse than another treatment by a specified amount. This corresponds to the null hypothesis where the treatment effect is below the **non-inferiority margin** ($H_0 : \theta < NIM$). This is a common objective in trials for medical devices. Note that for **Number of Groups = 1**, **Inequality** and **Non-inferiority** are the same hypothesis test.

Equivalence indicates the hypothesis of interest is for equivalence where the objective is to show a treatment is equivalent to another treatment in both treatment effect directions. This corresponds to the null hypothesis where the treatment effect is below the **lower equivalence margin** or above the **upper equivalence margin** ($H_0 : \theta < LEM$ or $\theta > UEM$) and is typically evaluated using the Two One-Sided Test (TOST) procedure [Schuirmann, 1987]. This is a common objective in bioequivalence trials for generic drug approval.

8.4.2 Step 1: Simulation Inputs

The **Step 1: Simulation Inputs** specifies the data generating model which will be used to generate simulations for the scenario of interest. **Step 1: Simulation Inputs** will include sections such as **Design Parameters** and **Allocation Parameters** where **Design Parameters** are the endpoint specific parameters passed to the statistical distribution(s) used to generate simulations and **Allocation Parameters** controls how the sample size is allocated across the treatment groups and the randomization process.

However, the input fields available in **Step 1: Simulation Inputs** will change significantly depending on the **Endpoint of Interest**, **Number of Groups** and **Analysis Method** selected at **Step 0: Select GST Simulation Type** either explicitly (if opened using **Group Sequential Design Simulation** option from the **Assistants** file menu - subsection 8.2.1) or implicitly (if opened using the **GST Simulation** button within a **Group Sequential Design Table -** see subsection 8.2.2).

Due to these significant differences, a summary is provided for all currently supported scenarios in the **Group Sequential Design Simulation Tool.** The supported scenarios at present are as follows:

- Endpoint of Interest = Mean; Number of Groups = 2; Analysis Method = Inequality (equivalent to GST Simulation from GST1 - Group Sequential for Two Means)
- Endpoint of Interest = Proportion; Number of Groups = 2; Analysis Method = Inequality (equivalent to GST Simulation from GST1 - Group Sequential for Two Means)

The **Step 1: Simulation Inputs** for each of these scenarios above is summarized next.

8.4.2.1 Two Means Inequality: Mean, 2 Groups, Inequality (GST1)

The **Step 1: Simulation Inputs** for the **Two Means Inequality** scenario is shown in Figure 8.8.

The **Two Means Inequality** scenario is equivalent to setting **Endpoint of Interest** to **Mean**, **Number of Groups** to **2** and **Analysis Method** to **Inequality** at **Step 0: Select GST Simulation Type** (see subsection 8.2.1 and subsection 8.4.1) or to opening the **Group Sequential Design Simulation Tool** using the **GST Simulation** button in the **GST1 - Group Sequential for Two Means** design table (see subsection 8.2.2).

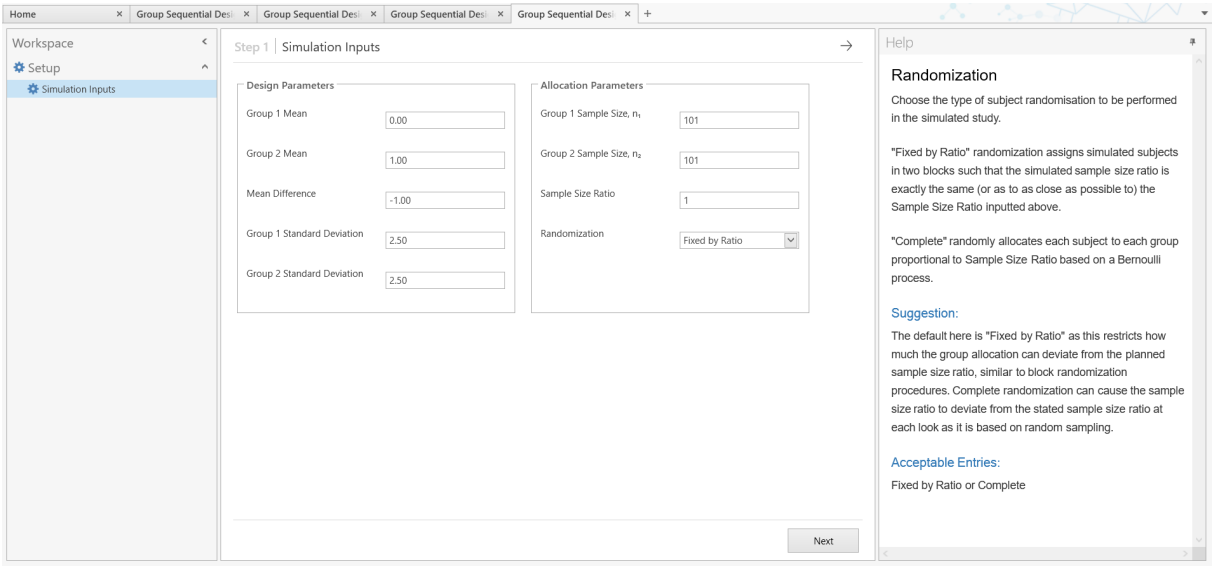


Figure 8.8: Step 1: Simulation Inputs for Two Means Inequality Scenario

For the **Two Means Inequality** scenario there are the following sections for the input fields: **Design Parameters** and **Allocation Parameters.** A summary of each is provided next.

Design Parameters The **Design Parameters** specifies the input parameters passed to the **Normal distributions** that will be used to generate simulations for the two independent groups in the **Two Means Inequality** scenario.

For each group, the algorithm will draw random simulations from a **Normal distribution** with a mean equal to the respective **Group Mean** and a variance equal to the respective **Group Standard Deviation** squared - see subsubsection 8.7.1.1 for the technical details.

For **Two Means Inequality** scenario the following fields will need to be filled in the **Design Parameters** section to proceed to the next **Input Step**:

- **Group 1 Mean:** The mean response expected in group 1
- **Group 2 Mean:** The mean response expected in group 2
- **Mean Difference:** The expected mean difference between group 1 and group 2
- **Group 1 Standard Deviation:** The expected standard deviation for responses in group 1
- **Group 2 Standard Deviation:** The expected standard deviation for responses in group 2

The **Group 1 Mean, Group 2 Mean** and **Mean Difference** have a fixed relationship where **Mean Difference** must equal **Group 1 Mean** minus **Group 2 Mean**. If two out of three of these input fields are specified, the third will be automatically calculated. If all three are specified and one of these parameters is changed then one of the other two parameters is updated accordingly - if **Group 1 Mean** or **Group 2 Mean** is updated then the **Mean Difference** will update and if the **Mean Difference** is changed the **Group 2 Mean** is updated - see subsection 1.7.4 for further informations on the **auto-calculation** feature.

If the **Group Sequential Design Simulation Tool** was opened from **GST1 - Group Sequential Design for Two Means** using the **GST Simulation** button for a **solver complete** column then each of the **Design Parameter** fields above will be filled with the values from the rows of the same name in the main design table - see subsection 8.2.2 for details. Otherwise, these fields will be empty and will need to be filled by the user.

Allocation Parameters The **Allocation Parameters** specifies the sample size of the two independent groups in the **Two Means Inequality** scenarios and also the randomization algorithm that will be used to assign simulation to each independent group.

For **Two Means Inequality** scenario the following fields will need to be filled in the **Allocation Parameters** section to proceed to the next **Input Step**:

- **Group 1 Sample Size,** n_1**:** The number of subjects planned to be recruited in group 1
- **Group 1 Sample Size,** n_2**:** The number of subjects planned to be recruited in group 2
- **Sample Size Ratio:** The planned ratio between the group 1 and group 2 sample sizes (n_2/n_1)
- **Randomization:** The randomization allocation algorithm to be used to assign simulations to the treatment groups. Select from **Fixed by Ratio** and **Complete Randomization**

The **Group 1 Sample Size, Group 2 Sample Size** and **Sample Size Ratio** have a fixed relationship where the **Sample Size Ratio** must equal the **Group 2 Sample Size** divided by the **Group 1 Sample Size** $(R = n_2/n_1)$**.** If two out of three of these input fields are specified, the third will be automatically calculated. If all three are specified and one of these parameters is changed then one of the other two parameters is updated accordingly - if **Group 1 Sample Size** or **Group 2 Sample Size** is updated then the **Sample Size Ratio** will update and if the **Sample Size Ratio** is changed the **Group 2 Sample Size** is updated - see subsection 1.7.4 for further informations on the **auto-calculation** feature. Note that since **Group 1 Sample Size** and **Group 2 Sample Size** must be integers that these values will be rounded to the nearest integer if the **Sample Size Ratio** would not lead to an auto-calculation providing an integer directly.

If the **Group Sequential Design Simulation Tool** was opened from **GST1 - Group Sequential Design for Two Means** using the **GST Simulation** button for a **solver complete** column then each of the **Design Parameter** sample size fields above will be filled with the values from the rows of the same name in the main design table - see subsection 8.2.2 for details. Otherwise, these fields will be empty and will need to be filled by the user.

If **Randomization = Fixed by Ratio**, the algorithm will generate simulations where the allocation of simulated subjects to each group is fixed to ensure the **Sample Size Ratio** specified here is retained at each look (excepting the small effect due to rounding of interim sample sizes).

If **Randomization = Complete Randomization**, the algorithm will treat treatment assignment as a random Binomial variable with probability of treatment group assignment to **Group 1** equal to $\left(\frac{n_1}{n_1+n_2}\right)$. **Complete Randomization** provides a treatment group

allocation similar that specified in the **Allocation Parameters** on average but is not guaranteed to be the same due to random variability. However, this randomness may better reflect the group allocation in a real clinical trial.

For technical detail on the **Randomization** algorithm for the **Two Means Inequality** scenario see subsubsection 8.7.1.1. For more information on randomization in clinical trials generally, see chapter 6 which covers the variety of allocation algorithms available in nQuery's **Randomization List** feature.

After all **Design Parameters** and **Allocations Parameters** are filled appropriately, select the **Next** button in the bottom right of the **Main Window** to proceed to **Step 2: Sequential Design Inputs**.

8.4.2.2 Two Proportion Inequality: Proportion, 2 Groups, Inequality (GST2)

The **Step 1: Simulation Inputs** for the **Two Proportions Inequality** scenario is shown in Figure 8.9.

The **Two Proportions Inequality** scenario is equivalent to setting **Endpoint of Interest** to **Proportion**, **Number of Groups** to **2** and **Analysis Method** to **Inequality** at **Step 0: Select GST Simulation Type** (see subsection 8.2.1 and subsection 8.4.1) or to opening the **Group Sequential Design Simulation Tool** using the **GST Simulation** button in the **GST2 - Group Sequential for Two Proportions** design table (see subsection 8.2.2).

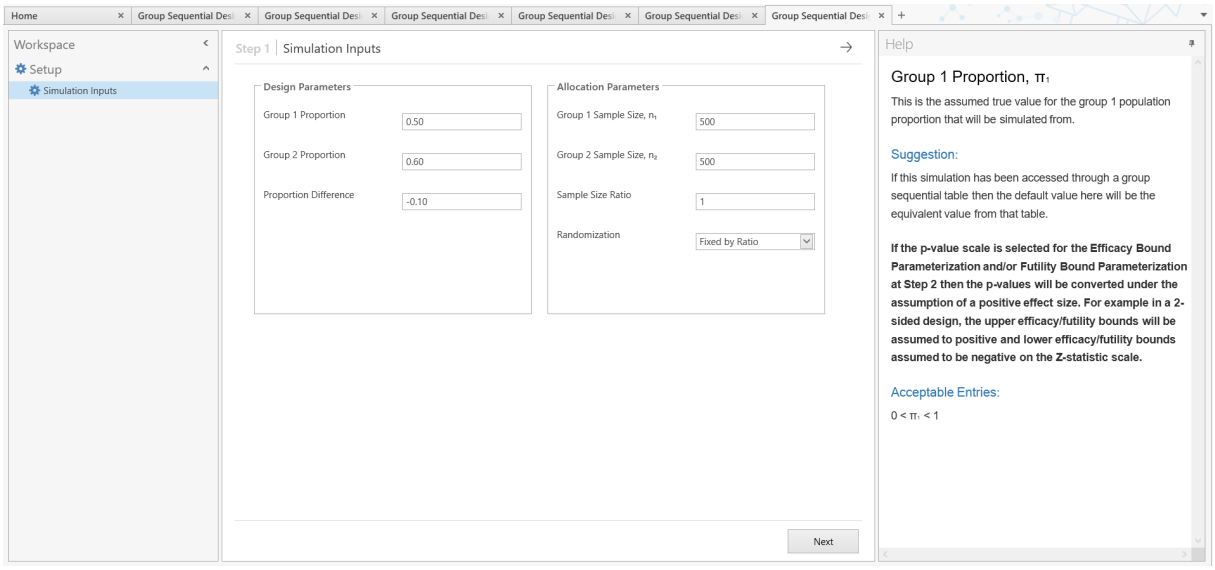


Figure 8.9: Step 1: Simulation Inputs for Two Proportions Inequality Scenario

For the **Two Proportions Inequality** scenario there are the following sections for the input fields: **Design Parameters** and **Allocation Parameters.** A summary of each is provided next.

Design Parameters The **Design Parameters** specifies the input parameters passed to the **Binomial distributions** that will be used to generate simulations for the two independent groups in the **Two Proportions Inequality** scenario.

For each group, the algorithm will draw random simulations from a **Binomial Distribution** with the probability of each trial success (p) equal to the respective **Group Proportion** - see subsubsection 8.7.1.2 for the technical details.

For **Two Proportions Inequality** scenario the following fields will need to be filled in the **Design Parameters** section to proceed to the next **Input Step**:

- **Group 1 Proportion:** The proportion of successes expected in group 1
- **Group 2 Proportion:** The proportion of successes expected in group 2
- **Proportion Difference:** The proportion difference between group 1 and group 2

The **Group 1 Proportion, Group 2 Proportion** and **Proportion Difference** have a fixed relationship where **Proportion Difference** must equal **Group 1 Proportion** minus **Group 2 Proportion**. If two out of three of these input fields are specified, the third will be automatically calculated. If all three are specified and one of these parameters is changed then one of the other two parameters is updated accordingly - if **Group 1 Proportion** or **Group 2 Proportion** is updated then the **Proportion Difference** will update and if the **Proportion Difference** is changed the **Group 2 Proportion** is updated - see subsection 1.7.4 for further informations on the **auto-calculation** feature.

Note that while the allowable range for **Proportion Difference** is $(-1, 1)$, the **auto-calculation** can still generate a **Group 1 Proportion** or **Group 2 Proportion** that is not within their allowable range of $[0, 1]$ when the other proportion is specified. In these cases, an **Out-of-Range** error will be shown in the auto-calculated cell.

If the **Group Sequential Design Simulation Tool** was opened from **GST2 - Group Sequential Design for Two Proportions** using the **GST Simulation** button for a **solver complete** column then each of the **Design Parameter** fields above will be filled with the values from the rows of the same name in the main design table - see subsection 8.2.2 for details. Otherwise, these fields will be empty and will need to be filled by the user.

Allocation Parameters The **Allocation Parameters** specifies the sample size of the two independent groups in the **Two Proportions Inequality** scenarios and also the randomization algorithm that will be used to assign simulation to each independent group.

For **Two Proportions Inequality** scenario the following fields will need to be filled in the **Allocation Parameters** section to proceed to the next **Input Step**:

- **Group 1 Sample Size, n_1:** The number of subjects planned to recruited in group 1
- **Group 1 Sample Size, n_2:** The number of subjects planned to recruited in group 2
- **Sample Size Ratio:** The planned ratio between the group 1 and group 2 sample sizes (n_2/n_1)
- **Randomization:** The randomization allocation algorithm to be used to assign simulations to the treatment groups. Select from **Fixed by Ratio** and **Complete Randomization**

The **Group 1 Sample Size, Group 2 Sample Size** and **Sample Size Ratio** have a fixed relationship where the **Sample Size Ratio** must equal the **Group 2 Sample Size**

divided by the **Group 1 Sample Size** ($R = n_2/n_1$)**.** If two out of three of these input fields are specified, the third will be automatically calculated. If all three are specified and one of these parameters is changed then one of the other two parameters is updated accordingly - if **Group 1 Sample Size** or **Group 2 Sample Size** is updated then the **Sample Size Ratio** will update and if the **Sample Size Ratio** is changed the **Group 2 Sample Size** is updated - see subsection 1.7.4 for further informations on the **auto-calculation** feature. Note that since **Group 1 Sample Size** and **Group 2 Sample Size** must be integers that these values will be rounded to the nearest integer if the **Sample Size Ratio** would not lead to an auto-calculation providing an integer directly.

If the **Group Sequential Design Simulation Tool** was opened from **GST2 - Group Sequential Design for Two Proportions** using the **GST Simulation** button for a **solver complete** column then each of the **Design Parameter** sample size fields above will be filled with the values from the rows of the same name in the main design table - see subsection 8.2.2 for details. Otherwise, these fields will be empty and will need to be filled by the user.

If **Randomization = Fixed by Ratio** (the default), the algorithm will generate simulations where the allocation of simulated subjects to each groups is fixed to ensure the **Sample Size Ratio** specified here is retained at each look (excepting the small effect due to rounding of interim sample sizes).

If **Randomization = Complete Randomization**, the algorithm will treat treatment assignment as a random Binomial variable with probability of treatment group assignment to **Group 1** equal to $\left(\frac{n_1}{n_1+n_2}\right)$. **Complete Randomization** provides a treatment group allocation similar that specified in the **Allocation Parameters** on average but is not guaranteed to be the same due to random variability. However, this randomness may better reflect the group allocation in a real clinical trial.

For technical detail on the **Randomization** algorithm for the **Two Proportions Inequality** scenario see subsubsection 8.7.1.2. For more information on randomization in clinical trials generally, see chapter 6 which covers the variety of allocation algorithms available in nQuery's **Randomization List** feature.

After all **Design Parameters** and **Allocations Parameters** are filled appropriately, select the **Next** button in the bottom right of the **Main Window** to proceed to **Step 2: Sequential Design Inputs**.

8.4.3 Step 2: Sequential Design Inputs

The **Step 2: Sequential Design Inputs** step allows the user to specify the **Sequential Design Parameters** which specify the number of looks, whether to conduct a one or two sided tests, the scale on which the group sequential boundaries will be inputted and additional scenario specific options such as using t-test adjusted boundaries for the **Two Means Inequality** scenario.

A number of input fields for **Step 2: Sequential Design Inputs** will be shared across different scenarios but there will also be unique input fields depending on the **Endpoint of Interest**, **Number of Groups** and **Analysis Method** selected at **Step 0: Select GST Simulation Type** either explicitly (if opened using **Group Sequential Design Simulation** option from the **Assistants** file menu - subsection 8.2.1) or implicitly (if

opened using the **GST Simulation** button within a **Group Sequential Design Table -** see subsection 8.2.2).

A summary is provided for all currently supported scenarios in the **Group Sequential Design Simulation Tool.** The supported scenarios at present are as follows:

- Endpoint of Interest = Mean; Number of Groups = 2; Analysis Method = Inequality (equivalent to GST Simulation from GST1 - Group Sequential for Two Means)
- Endpoint of Interest = Proportion; Number of Groups = 2; Analysis Method = Inequality (equivalent to GST Simulation from GST1 - Group Sequential for Two Means)

The **Step 2: Sequential Design Inputs** for each of these scenarios is summarized next.

8.4.3.1 Two Means Inequality: Mean, 2 Groups, Inequality (GST1)

The **Step 2: Sequential Design Inputs** for the **Two Means Inequality** scenario is shown in Figure 8.10.

The **Two Means Inequality** scenario is equivalent to setting **Endpoint of Interest** to **Mean**, **Number of Groups** to **2** and **Analysis Method** to **Inequality** at **Step 0: Select GST Simulation Type** (see subsection 8.2.1 and subsection 8.4.1) or to opening the **Group Sequential Design Simulation Tool** using the **GST Simulation** button in the **GST1 - Group Sequential for Two Means** design table (see subsection 8.2.2).

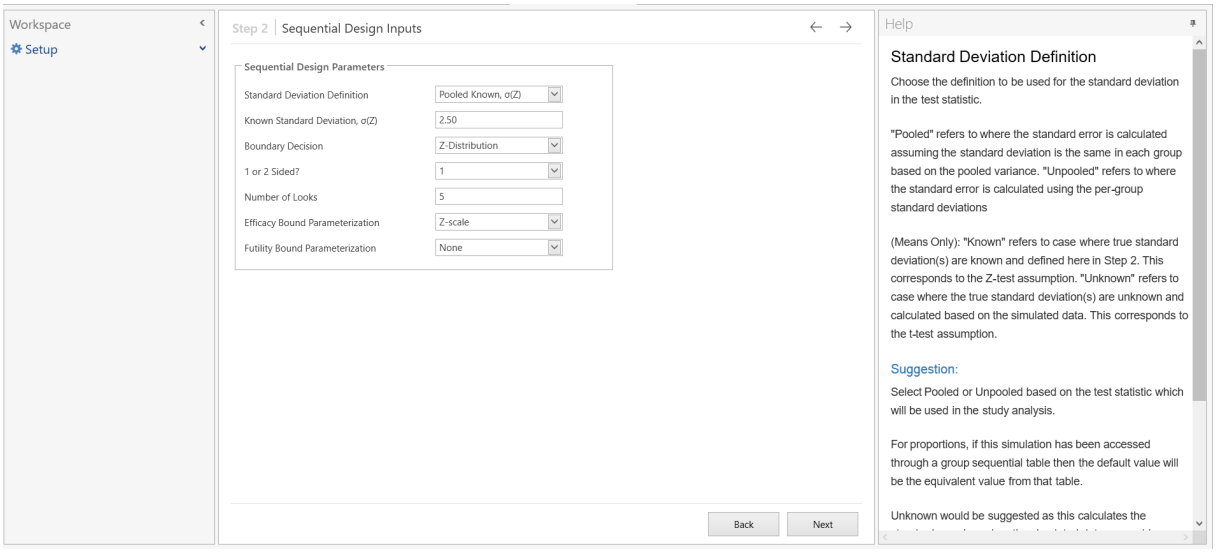


Figure 8.10: Step 2: Sequential Design Inputs for Two Means Inequality Scenario

For the **Two Means Inequality** scenario there is the following section for the input fields: **Sequential Design Parameters.**

Sequential Design Parameters The **Sequential Design Parameters** specifies the standard deviation used to calculate the standard error used for test statistic calculations, whether to use the t-test adjusted boundaries, whether the test is one-sided or two-sided,

the number of looks and the efficacy and futility boundary scale parameterizations in the **Two Means Inequality** scenario.

For **Two Means Inequality** scenario the following fields will need to be filled in the **Sequential Design Parameters.** section to proceed to the next **Input Step**:

- **Standard Deviation Definition:** Select the standard deviation used in the standard error for test statistic calculation, choose from: **Pooled Known** $\sigma(Z)$**, Unpooled Known** $\sigma(Z)$**, Pooled Unknown** $s(t)$**, Unpooled Unknown** $s(t)$
  - **Known Standard Deviation,** $\sigma(Z)$ (*Standard Deviation Definition = Pooled Known* $\sigma(Z)$ *only*): Assumed known true pooled standard deviation used to calculate standard error
  - **Group 1 Known Standard Deviation,** $\sigma(Z)$ (*Standard Deviation Definition = Unpooled Known* $\sigma(Z)$ *only*): Assumed known true group 1 standard deviation used to calculate standard error
  - **Group 2 Known Standard Deviation,** $\sigma(Z)$ (*Standard Deviation Definition = Unpooled Known* $\sigma(Z)$ *only*): Assumed known true group 2 standard deviation used to calculate standard error
- **Boundary Decision:** Select whether to use original Z-test boundaries or adjusted approximate t-test boundaries, choose from **Z-distribution, t-Distribution**
- **1 or 2 Sided?:** Select if the test will be a 1-sided or 2-sided, choose from **1** or **2**
- **Number of Looks:** Specify the total number of looks (including the final analysis) the group sequential design will have
- **Efficacy Bound Parameterization:** Select the statistical scale on which the efficacy boundaries will be specified at **Step 3: Boundary Table**, choose from **Z-scale, p-value Scale, Score Scale,** δ**-Scale**
- **Futility Bound Parameterization:** Select the statistical scale on which the futility boundaries will be specified at **Step 3: Boundary Table**, choose from **Z-scale, p-value Scale, Score Scale,** δ**-Scale**

A summary of each of these fields is provided next.

Standard Deviation Definition allows the user to specify how the standard error will be calculated.

The **Z-test** requires the standard deviation to be known therefore for simulation results to match the equivalent group sequential design (e.g. from **GST1 - Group Sequential Design for Two Means**) the standard deviation should be fixed to its **Known** value from the design stage when calculating the standard error. However, in practice most clinical trials will calculate the standard error based on the interim estimate of the standard deviation(s), which is **Unknown** a priori, even if the group sequential Z-test analysis.

In addition, different trials may used the **Pooled** or **Unpooled** estimate of the variance to calculate the standard error - for example, if using the two sample t-test which assumes a common within-group standard deviation.

To accomodate all these scenarios, **Standard Deviation Definition** field contains the following options: **Pooled Known** $\sigma(Z)$**, Unpooled Known** $\sigma(Z)$**, Pooled Unknown** $s(t)$**, Unpooled Unknown** $s(t)$

For **Pooled Known** $\sigma(Z)$ the standard error is calculated using the "known" estimate for the pooled standard deviation in the **Known Standard Deviation,** $\sigma(Z)$ field which will appear below the **Pooled Known** $\sigma(Z)$ when that option is selected. **Known Standard Deviation,** $\sigma(Z)$ will not be shown for the other **Standard Deviation Definition** options.

For **Unpooled Known** $\sigma(Z)$ the standard error is calculated using the "known" estimates for the per-group standard deviations in the **Group 1 Known Standard Deviation,** $\sigma(Z)$ and **Group 2 Known Standard Deviation,** $\sigma(Z)$ fields which will appear below the **Pooled Known** $\sigma(Z)$ when that option is selected. **Group 1 Known Standard Deviation,** $\sigma(Z)$ and **Group 2 Known Standard Deviation,** $\sigma(Z)$ will not be shown for the other **Standard Deviation Definition** options.

For **Pooled Known** $s(t)$**,** the standard error is calculated using the interim estimate for the pooled standard deviation based on the simulated data. **Pooled Unknown** $s(t)$**,** does not require any addiitonal field inputs.

For **Unpooled Known** $s(t)$**,** the standard error is calculated using the interim estimates for the group 1 standard deviation and group 2 standard deviation based on the simulated data. **Unpooled Unknown** $s(t)$**,** does not require any addiitonal field inputs.

By default, **Pooled Known** $\sigma(Z)$ is selected for **Standard Deviation Definition** with the **Known Standard Deviation,** $\sigma(Z)$ calculating the pooled standard deviation based on the **Group 1 Standard Deviation, Group 2 Deviation, Group 1 Sample Size** and **Group 2 Sample Size** specified at **Step 1: Simulation Inputs**.

For **Unpooled Known** $\sigma(Z)$, the **Group 1 Known Standard Deviation,** $\sigma(Z)$ and **Group 2 Known Standard Deviation,** $\sigma(Z)$ will by default be filled with **Group 1 Standard Deviation** and **Group 2 Standard Deviation** specified at **Step 1: Simulation Inputs**

Technical details on how the test statistic is constructed using the above assumptions regarding the standard deviation is provided in subsubsection 8.7.2.1.

Boundary Decision allows the user to specify whether to use the Z-test boundaries or the (approximate) t-test boundaries. Select from **Z-Distribution** (default) and **t-Distribution.**

In clinical trials, the **t-test** is the most popular test for comparing means. However, the group sequential boundaries are calculated under the assumption of a (multvariate) Z-distribution process (subsubsection 7.2.1.1 for details) which corresponds to using the **Z-test.** While it is possible to construct exact boundaries for the **t-test**, this adds significant complication compared to constructing under a Z-distribution assumptions.

However, Jennison and Turnbull [Jennison and Turnbull, 1999] showed that approximate **t-test** boundaries can be constructed based on the more commonly available Z-test boundaries by applying the standard normal cumulative distribution function (Φ) to the Z-test boundaries (e.g. $\Phi(-1.96) \simeq 0.025$) to generate the p-value boundaries and then applying the (central) t-distribution inverse cumulative distribution (quantile) function $\left(T_{df}^{-1}\right)$ to the p-value boundaries where the degrees of freedom, $df = N_k - 2$ where N_k is the total sample size at look k. A formal technical treatment is provided in subsection 8.7.3.

1 or 2 Sided? determines if the test will a one-sided (**1**) or two-sided (**2**) test. Note that if this value is changed any existing values in the **Boundary Table** at **Step 3:**

Boundary Table will be deleted as this option will significantly alter the **Boundary Table.** Note this deletion will apply to boundaries inherited from **GST1 - Group Sequential Design for Two Means** see subsection 8.2.2.

If the **Group Sequential Design Simulation Tool** was opened from **GST1 - Group Sequential Design for Two Means** using the **GST Simulation** button for a **solver complete** column then each of the **1 or 2 Sided?** will be filled with the **1 or 2 Sided Test?** value from the main design table - see subsection 8.2.2 for details. Otherwise, a default of **1** (1-sided) will be used.

Number of Looks determines the total number of looks (including final analysis) in the group sequential design. This will determine the number of rows in the **Boundary Table** at **Step 3: Boundary Table**. Due to this if this value is changed any existing values in the **Boundary Table** at **Step 3: Boundary Table** will be deleted as this option will significantly alter the **Boundary Table.** Note this deletion will apply to boundaries inherited from **GST1 - Group Sequential Design for Two Means** see subsection 8.2.2.

If the **Group Sequential Design Simulation Tool** was opened from **GST1 - Group Sequential Design for Two Means** using the **GST Simulation** button for a **solver complete** column then the **Number of Looks** field above will be filled with the **Number of Looks** value from the main design table - see subsection 8.2.2 for details. Otherwise, the **Number of Looks** field will be empty and will need to be filled by the user.

Efficacy Bound Parameterization defines the statistical scale on which the group sequential efficacy boundaries will be specified in the **Boundary Table** at **Step 3: Boundary Table**. The available statistical scales are: **Z-scale, p-value Scale, Score Scale, δ-Scale** (i.e. treatment effect scale - **Mean Difference** for **Two Means Inequality** scenario) and **Don't Calculate** (i.e. no efficacy boundary). Detail on these statistical scales and the conversions between them are provided in subsubsection 7.2.1.1, subsubsection 7.2.4.5 and subsection 8.7.3 - note that the conversions which require the **Information** will derive that value based on the the fields in **Step 1: Simulation Inputs**.

Here the focus will be on the practical aspects of filling the **Bounds** columns. Note that for the **Z-scale, Score Scale** and **δ-Scale** the direction of the hypothesis if **1 or 2 Sided? = 1** will depend on the final boundary value specified in the **Boundary Table** but that for the **p-value Scale** it is always assumed that higher values for the treatment effect (mean difference for the **Two Means Inequality** scenario) are considered better. Note that if this value is changed any existing values in the **Boundary Table** at **Step 3: Boundary Table** will be deleted as this option will significantly alter the **Boundary Table.** Note this deletion will apply to boundaries inherited from **GST1 - Group Sequential Design for Two Means** see subsection 8.2.2.

Futility Bound Parameterization defines the statistical scale on which the group sequential efficacy boundaries will be specified in the **Boundary Table** at **Step 3: Boundary Table**. The available statistical scales are: **Z-scale, p-value Scale, Score Scale, δ-Scale** (i.e. treatment effect scale - **Mean Difference** for **Two Means Inequality** scenario) and **Don't Calculate** (i.e. no futility boundary). Detail on these statistical scales and the conversions between them are provided in subsubsection 7.2.1.1, subsubsection 7.2.4.5 and subsection 8.7.3 - note that the conversions which require the **Information** will derive that value based on the fields in **Step 1: Simulation Inputs**.

Here the focus will be on the practical aspects of filling the **Bounds** columns.Note that for the **Z-scale, Score Scale** and δ**-Scale** the direction of the hypothesis if **1 or 2 Sided? = 1** will depend on the final boundary value specified in the **Boundary Table** but that for the **p-value Scale** it is always assumed that higher values for the treatment effect (mean difference for the **Two Means Inequality** scenario) are considered better. Note that if this value is changed any existing values in the **Boundary Table** at **Step 3: Boundary Table** will be deleted as this option will significantly alter the **Boundary Table.** Note this deletion will apply to boundaries inherited from **GST1 - Group Sequential Design for Two Means** see subsection 8.2.2.

If the **Group Sequential Design Simulation Tool** was opened from **GST1 - Group Sequential Design for Two Means** using the **GST Simulation** button for a **solver complete** column then the **Efficacy Bound Parameterization** and **Futility Bound Parameterization** fields above will be based on the **Boundary Scale** used in the **GST Outputs** side-table - see subsubsection 7.3.2.2 and subsection 8.2.2 for details. Otherwise, the **Efficacy Bound Parameterization = Z-scale** and **Futility Bound Parameterization = Don't Calculate.**

8.4.3.2 Two Proportion Inequality: Proportion, 2 Groups, Inequality (GST2)

The **Step 2: Sequential Design Inputs** for the **Two Proportions Inequality** scenario is shown in Figure 8.11.

The **Two Proportions Inequality** scenario is equivalent to setting **Endpoint of Interest** to **Proportion**, **Number of Groups** to **2** and **Analysis Method** to **Inequality** at **Step 0: Select GST Simulation Type** (see subsection 8.2.1 and subsection 8.4.1) or to opening the **Group Sequential Design Simulation Tool** using the **GST Simulation** button in the **GST2 - Group Sequential for Two Proportions** design table (see subsection 8.2.2).

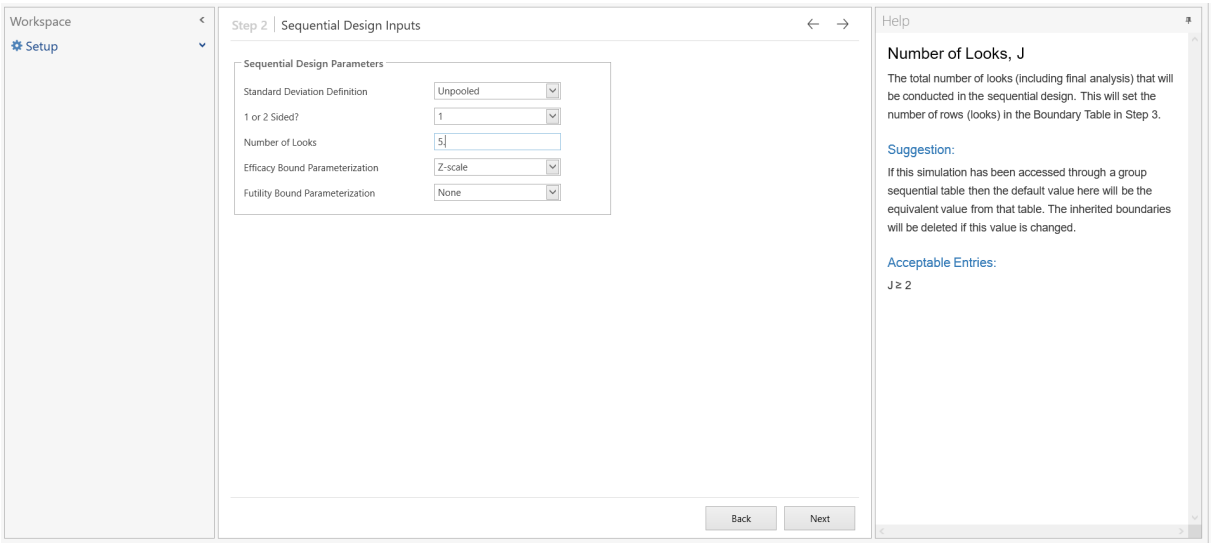


Figure 8.11: Step 2: Sequential Design Inputs for Two Proportions Inequality Scenario

For the **Two Proportions Inequality** scenario there is the following section for the input fields: **Sequential Design Parameters.**

Sequential Design Parameters The **Sequential Design Parameters** specifies the standard deviation used to calculate the standard error used for test statistic calculations, whether to use the t-test adjusted boundaries, whether the test is one-sided or two-sided, the number of looks and the efficacy and futility boundary scale parameterizations in the **Two Means Inequality** scenario.

For **Two Means Inequality** scenario the following fields will need to be filled in the **Sequential Design Parameters.** section to proceed to the next **Input Step**:

- **Standard Deviation Definition:** Select the standard deviation used in the standard error for test statistic calculation, choose from: **Pooled, Unpooled**
- **1 or 2 Sided?:** Select if the test will be a 1-sided or 2-sided, choose from **1** or **2**
- **Number of Looks:** Specify the total number of looks (including the final analysis) the group sequential design will have
- **Efficacy Bound Parameterization:** Select the statistical scale on which the efficacy boundaries will be specified at **Step 3: Boundary Table**, choose from **Z-scale, p-value Scale, Score Scale, δ-Scale**
- **Futility Bound Parameterization:** Select the statistical scale on which the futility boundaries will be specified at **Step 3: Boundary Table**, choose from **Z-scale, p-value Scale, Score Scale, δ-Scale**

A summary of each of these fields is provided next.

Standard Deviation Definition allows the user to specify how the standard error will be calculated. For the two sample Z-test for two proportions (equivalent to the chi-squared test), two common choices for the standard error is the **Pooled** standard error and **Unpooled** standard error. The **Unpooled** standard error uses the **Group 1 Proportion** and **Group 2 Proportion** to calculate the per-group variances ($p_i\left(1-p_i\right)$) while the **Pooled** standard error calculates the variance in each group using the average proportion ($\hat{p}\left(1-\hat{p}\right)$). The choice of standard deviation should reflect that which will be used in the clinical trial of interest.

Technical details on how the test statistic is constructed using the above assumptions regarding the standard deviation is provided in subsubsection 8.7.2.2.

1 or 2 Sided? determines if the test will a one-sided (**1**) or two-sided (**2**) test. Note that if this value is changed any existing values in the **Boundary Table** at **Step 3: Boundary Table** will be deleted as this option will significantly alter the **Boundary Table.** Note this deletion will apply to boundaries inherited from **GST2 - Group Sequential Design for Two Proportions** see subsection 8.2.2.

If the **Group Sequential Design Simulation Tool** was opened from **GST2 - Group Sequential Design for Two Proportions** using the **GST Simulation** button for a **solver complete** column then each of the **1 or 2 Sided?** will be filled with the **1 or 2 Sided Test?** value from the main design table - see subsection 8.2.2 for details. Otherwise, a default of **1** (1-sided) will be used.

Number of Looks determines the total number of looks (including final analysis) in the group sequential design. This will determine the number of rows in the **Boundary Table** at **Step 3: Boundary Table**. Due to this if this value is changed any existing values in the **Boundary Table** at **Step 3: Boundary Table** will be deleted as this option will significantly alter the **Boundary Table.** Note this deletion will apply to

boundaries inherited from **GST2 - Group Sequential Design for Two Proportions** see subsection 8.2.2.

If the **Group Sequential Design Simulation Tool** was opened from **GST2 - Group Sequential Design for Two Proportions** using the **GST Simulation** button for a **solver complete** column then the **Number of Looks** field above will be filled with the **Number of Looks** value from the main design table - see subsection 8.2.2 for details. Otherwise, the **Number of Looks** field will be empty and will need to be filled by the user.

Efficacy Bound Parameterization defines the statistical scale on which the group sequential efficacy boundaries will be specified in the **Boundary Table** at **Step 3: Boundary Table**. The available statistical scales are: **Z-scale, p-value Scale, Score Scale, δ-Scale** (i.e. treatment effect scale - **Proportion Difference** for **Two Proportions Inequality** scenario) and **Don't Calculate** (i.e. no efficacy boundary). Detail on these statistical scales and the conversions between them are provided in subsubsection 7.2.1.1, subsubsection 7.2.4.5 and subsection 8.7.3 - note that the conversions which require the **Information** will derive that value based on the the fields in **Step 1: Simulation Inputs**.

Here the focus will be on the practical aspects of filling the **Bounds** columns.Note that for the **Z-scale, Score Scale** and **δ-Scale** the direction of the hypothesis if **1 or 2 Sided? = 1** will depend on the final boundary value specified in the **Boundary Table** but that for the **p-value Scale** it is always assumed that higher values for the treatment effect (proportion difference for the **Two Proportions Inequality** scenario) are considered better. Note that if this value is changed any existing values in the **Boundary Table** at **Step 3: Boundary Table** will be deleted as this option will significantly alter the **Boundary Table.** Note this deletion will apply to boundaries inherited from **GST2 - Group Sequential Design for Two Proportionss** see subsection 8.2.2.

Futility Bound Parameterization defines the statistical scale on which the group sequential efficacy boundaries will be specified in the **Boundary Table** at **Step 3: Boundary Table**. The available statistical scales are: **Z-scale, p-value Scale, Score Scale, δ-Scale** (i.e. treatment effect scale - **Proportion Difference** for **Two Proportions Inequality** scenario) and **Don't Calculate** (i.e. no futility boundary). Detail on these statistical scales and the conversions between them are provided in subsubsection 7.2.1.1, subsubsection 7.2.4.5 and subsection 8.7.3 - note that the conversions which require the **Information** will derive that value based on the fields in **Step 1: Simulation Inputs**.

Here the focus will be on the practical aspects of filling the **Bounds** columns. Note that for the **Z-scale, Score Scale** and **δ-Scale** the direction of the hypothesis if **1 or 2 Sided? = 1** will depend on the final boundary value specified in the **Boundary Table** but that for the **p-value Scale** it is always assumed that higher values for the treatment effect (proportion difference for the **Two Proportions Inequality** scenario) are considered better. Note that if this value is changed any existing values in the **Boundary Table** at **Step 3: Boundary Table** will be deleted as this option will significantly alter the **Boundary Table.** Note this deletion will apply to boundaries inherited from **GST2 - Group Sequential Design for Two Proportions**see subsection 8.2.2.

If the **Group Sequential Design Simulation Tool** was opened from **GST2 - Group Sequential Design for Two Proportions** using the **GST Simulation** button for a **solver complete** column then the **Efficacy Bound Parameterization** and **Futility**

Bound Parameterization fields above will be based on the **Boundary Scale** used in the **GST Outputs** side-table - see subsubsection 7.3.2.2 and subsection 8.2.2 for details. Otherwise, the **Efficacy Bound Parameterization = Z-scale** and **Futility Bound Parameterization = Don't Calculate.**

After all **Design Parameters** and **Allocations Parameters** are filled appropriately, select the **Next** button in the bottom right of the **Main Window** to proceed to **Step 3: Boundary Table**.

8.4.4 Step 3: Boundary Table

Step 3: Boundary Table is the **Input Step** where the group sequential boundaries are specified in the **Boundary Table**. The simulated test statistics calculated for each look, based on the **Inputs** from **Step 1: Simulation Inputs** and relevant **Step 2: Sequential Design Inputs** fields, will be compared to the specified boundaries to evaluate what outcome (stop for efficacy, stop for futility, continue) occured at that look. Given a sufficient number of simulations this will provide an estimate of the exit probability at each look for the specified simulation data generating process and design scenario.

An example **Boundary Table** from **Step 3: Boundary Table** is shown in subsection 8.4.4.

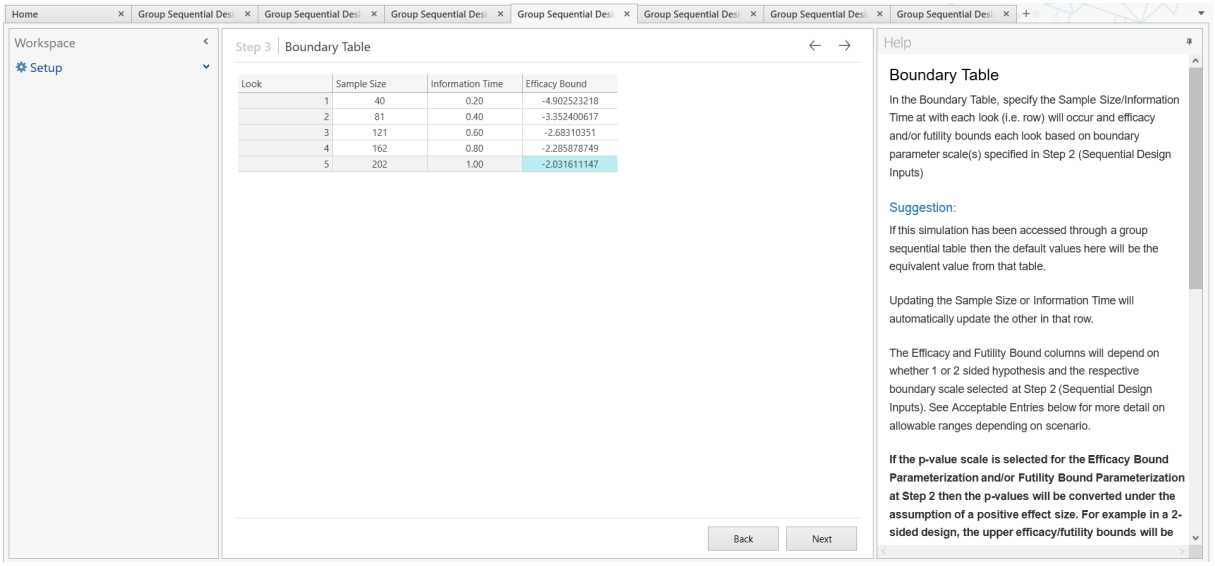


Figure 8.12: Step 3: Boundary Table

The **Boundary Table** allows the user to edit the **Sample Size/Information Time** at each **Look** where each row of the **Boundary Table** corresponds to a planned interim analysis with the final row (Look 5 in subsection 8.4.4) being the final planned analysis. The number of rows is set by the **Number of Looks** field at **Step 2: Sequential Design Inputs**. Note that if the **Number of Looks** is changed any existing values in the **Boundary Table** will be deleted**.**

The **Boundary Table** columns will consist of the **Look, Sample Size, Information Time** and at least one **Bound** row from the following options: **Efficacy Bound, Futility Bound, Upper Efficacy Bound, Lower Efficacy Bound, Upper Futility Bound, Lower Futility Bound**. The boundaries shown will depend on the selection made

for the **1 or 2 Sided?, Efficacy Bound Parameterization** and **Futility Bound Parameterization** fields at **Step 2: Sequential Design Inputs**. These boundary scenarios will be discussed later but the **Look, Sample Size** and **Information** columns will be discussed first.

The **Look** column is a read-only column which allows the user quickly see which **Look** number each row in the **Boundary Table** corresponds to. The **Look** column value in the final row will equal **Number of Looks** from **Step 2: Sequential Design Inputs.**

The **Sample Size** column in the **Boundary Table** is the total sample size planned for the specified **Look's** interim analysis to occur. This **Sample Size** value in the final row for the final analysis will equal the **Maximum Sample Size** and is based on the sample sizes specified at **Step 1: Simulation Inputs**. This final row **Maximum Sample Size** value is read-only and can only be changed by editing relevant sample size related fields in **Step 1: Simulation Inputs** and selecting the **Next** button. For example, for the **Two Means Inequality Scenario** referenced above this final row **Sample Size** value would equal the sum of the **Group 1 Sample Size** and **Group 2 Sample Size** fields. Note that **Sample Size** will be replaced with **Events** for survival analysis (**Endpoint of Interest = Survival** in **Step 0: Select GST Simulation Type** or table such as **GST3 - Group Sequential Design for Two Survival**)

The **Information Time** column in the **Boundary Table** specifies the proportion of the **Maximum Sample Size** (sample size is proportional to the (Fisher) **Information** - see subsection 7.2.5) required for a specified **Look's** interim analysis to occur. The value for the **Information Time** is set to 1 and cannot be edited as this is maximum value by definition for the **Information Time** (subsubsection 7.2.1.1).

In rows other than the final row, the **Sample Size** row values will equal the **Maximum Sample Size** multiplied by the **Information Time** in that row. Alternatively, the **Information Time** will equal the **Sample Size** in that row divided by the **Maximum Sample Size.** Given this relationship if either the **Sample Size** or **Information Time** are edited in a given row then the other value will be automatically updated to ensure consistency. Note that since **Sample Size** is an integer, the calculated sample size may be rounded for a given **Information Time** input.

If the **Group Sequential Design Simulation Tool** was opened using the **GST Simulation** button for a **solver complete** column in **Group Sequential Design Table** (e.g. **GST1 - Group Sequential Design for Two Means**) then the **Sample Size** and **Information Time** column values will be based on the **Total Sample Size** and **Information Time** rows in the **GST Outputs** side-table - see subsubsection 7.3.2.2 and subsection 8.2.2 for details. Note that all defaults for the **Boundary Table** will be deleted if following fields are changed at **Step 2: Sequential Design Inputs: 1 or 2 Sided?, Number of Looks, Efficacy Bound Parameterization, Futility Bound Parameterization**.

Otherwise, an equally spaced design is assumed where the **Information Time** equals the value for **Look** column in each row divided by the value for **Look** in the final row (k/K).

We will now discuss the **Boundary** column(s) available in the **Boundary Table**. As stated earlier, the **Boundary Table** must include at least one **Bound** column from the following options: **Efficacy Bound, Futility Bound, Upper Efficacy Bound, Lower Efficacy Bound, Upper Futility Bound, Lower Futility Bound**.

The **Boundary** columns displayed will depend on the options chosen for the **1 or 2 Sided?, Efficacy Bound Parameterization** and **Futility Bound Parameterization** fields at **Step 2: Sequential Design Inputs.**

Both the **Bound Parameterization** fields have the same options **(Z-scale, p-value Scale, Score Scale,** δ**-Scale** and **Don't Calculate**). For the purposes of the deciding which which **Bound** columns appear the **Z-scale, p-value Scale, Score Scale,** δ**-Scale** are inter-changeable with the **Don't Calculate** providing different outcomes. The full list of combinations possible for the **Bound** columns with their associated **Step 2: Sequential Design Inputs** is as follows:

- **Efficacy Bound - 1 or 2 Sided? = 1** & **Efficacy Bound Parameterization** $\neq$ **Don't Calculate** & **Futility Bound Parameterization = Don't Calculate**
- **Futility Bound - 1 or 2 Sided? = 1** & **Efficacy Bound Parameterization = Don't Calculate** & **Futility Bound Parameterization** $\neq$ **Don't Calculate**
- **Efficacy Bound, Futility Bound - 1 or 2 Sided? = 1** & **Efficacy Bound Parameterization** $\neq$ **Don't Calculate** & **Futility Bound Parameterization** $\neq$ **Don't Calculate**
- **Upper Efficacy Bound , Lower Efficacy Bound - 1 or 2 Sided? = 2** & **Efficacy Bound Parameterization** $\neq$ **Don't Calculate** & **Futility Bound Parameterization = Don't Calculate**
- **Upper Futility Bound, Lower Futility Bound - 1 or 2 Sided? = 2** & **Efficacy Bound Parameterization = Don't Calculate** & **Futility Bound Parameterization** $\neq$ **Don't Calculate**
- **Upper Efficacy Bound, Lower Efficacy Bound, Upper Futility Bound, Lower Futility Bound - 1 or 2 Sided? = 2** & **Efficacy Bound Parameterization** $\neq$ **Don't Calculate** & **Futility Bound Parameterization** $\neq$ **Don't Calculate**

All six scenario **Boundary Table** are shown in (unfilled) in Figure 8.12.

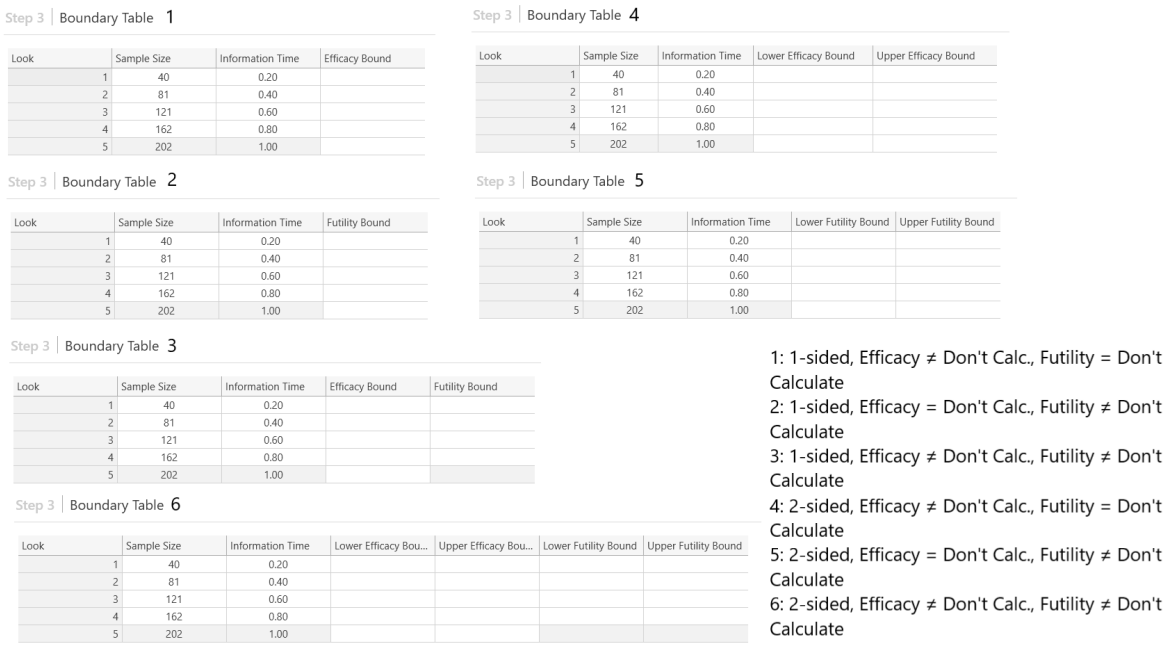


Figure 8.13: Boundary Table Scenarios

To simplify future discussions, these will be referred to as the **1-sided Efficacy Only, 1-sided Futility Only, 1-sided Efficacy and Futility, 2-sided Efficacy Only, 2-sided Futility Only** and **2-sided Efficacy and Futility** respectively.

The interpretation of the **Bounds** in terms of user input will depend on the choice of **Efficacy Bound Parameterization** and/or **Futility Bound Parameterization** fields at **Step 2: Sequential Design Inputs.** Assuming a **Bound column** is available it was specified on one of the following scales: **Z-scale, p-value Scale, Score Scale, δ-Scale**

Technical detail on each of these scales and conversions between them can be found in subsubsection 7.2.1.1, subsubsection 7.2.4.5 and subsection 8.7.3. Note that the conversions which require the **Information** will derive that value based on the the fields in **Step 1: Simulation Inputs**.

Here the focus will be on the practical aspects of filling the **Bounds** columns.

If the **Bound Parameterization = Z-scale, Score Scale, δ-Scale** then the **Bounds** row values can take on any real value - restrictions on these scales will only exist to ensure the **Bounds** are consistent. The **p-value Scale Bounds** must be between 0 and 1 and also consistent. Consistent means the boundaries are not contradictory e.g. **Efficacy Bounds** crossing over with **Futility Bounds** mid-trial.

In addition, the directionality of the hypothesis is determined by the **Bound** values in the final row of the **Boundary Table**. The directionality refers to which direction of the treatment effect (e.g. mean difference for **Two Means Inequality** scenario) is considered "better". This will determine the exit regions for the specified **(Upper/Lower) Efficacy Bounds** and/or **(Upper/Lower) Futility Bounds**.

For example, for the **1-sided Efficacy Only** scenario if the final **Efficacy Bound** value is greater than zero (i.e. positive) when **Efficacy Bound Parameterization = Z-scale, Score Scale, δ-Scale** then this implies that higher treatment effects (e.g. more

positive mean differences) are "better" and lower treatment effects are "worse". Therefore, **Stopping for Efficacy** will only occur at each interim look if the simulated test statistic is greater than the specified **Efficacy Bound** value on the selected boundary scale. Conversely, if the final **Efficacy Bound** was negative (<0) then **Stopping for Efficacy** would only occur if the simulated test statistic is less than the specified **Efficacy Bound** value at each look.

Note that for the **p-value Scale**, the hypothesis is always assumed to positive but for p-values this equates to lower p-values being considered "better" than higher p-values. This is expected given the normal usage of p-values within the context of null hypothesis testing where the test is rejected for sufficiently low p-value regardless of hypothesis direction. Therefore, for p-value scale can invert the rules discussed for other scales below for "higher treatment effect better" e.g. **Efficacy p-value** must always be lower than **Futility p-value, Stopping for Efficacy** always happens if below **Efficacy p-value Bound**.

If the **Group Sequential Design Simulation Tool** was opened using the **GST Simulation** button for a **solver complete** column in **Group Sequential Design Table** (e.g. **GST1 - Group Sequential Design for Two Means**) then the relevant **Bounds** column values will be based on the corresponds **Bounds** rows of the same name in the **GST Outputs** side-table - see subsubsection 7.3.2.2 and subsection 8.2.2 for details. Note that all defaults for the **Boundary Table** will be deleted if following fields are changed at **Step 2: Sequential Design Inputs: 1 or 2 Sided?, Number of Looks, Efficacy Bound Parameterization, Futility Bound Parameterization**.

To assist users, a summary of the **consistency** and **directionality** criteria are collated for the six scenarios referenced above for the **Z-scale, Score Scale, δ-Scale** (p-value Scale always same direction - see above).. Note we will assume that where **Efficacy Bounds** and **Futility Bounds** are both present that both have been selected on the same **Parameterization**. Note this is not required in the nQuery interface, which will automatically convert all bounds to the Z-scale and check for consistency, but is done for clarity.

8.4.4.1 1-Sided Efficacy Only

Consistency No consistency constraints

Directionality Defined by final row value in **Efficacy Bound** column

- If **Final Efficacy Bound > 0** then higher treatment effects better ⇒ **Stop Early for Efficacy** if **Test Statistic > Efficacy Bound, otherwise continue to next look**
- If **Final Efficacy Bound > 0** then lower treatment effects better ⇒ **Stop Early for Efficacy** if **Test Statistic < Efficacy Bound, otherwise continue to next look**

8.4.4.2 1-Sided Futility Only

Consistency No consistency constraints

Directionality Defined by final row value in **Futility Bound** column

- If **Final Futility Bound > 0** then higher treatment effects better ⇒ **Stop Early for Futility** if **Test Statistic < Futility Bound, otherwise continue to next look**
- If **Final Futility Bound > 0** then lower treatment effects better ⇒ **Stop Early for Futility** if **Test Statistic > Futility Bound, otherwise continue to next look**

8.4.4.3 1-Sided Efficacy and Futility

Consistency All **Efficacy Bound > Futility Bound** or All **Efficacy Bound < Futility Bound**

Directionality Defined by order of interim bounds

- If **Interim Efficacy Bounds > Interim Efficacy Bounds** then higher treatment effects better ⇒ **Stop Early for Efficacy** if **Test Statistic > Efficacy Bound** or **Stop Early for Futility** if **Test Statistic < Futility Bound, otherwise continue to next look**
- If **Interim Efficacy Bounds < Interim Efficacy Bound** then lower treatment effects better ⇒ **Stop Early for Efficacy** if **Test Statistic < Efficacy Bound** or **Stop Early for Futility** if **Test Statistic > Futility Bound, otherwise continue to next look**

8.4.4.4 2-Sided Efficacy Only

Consistency All **Upper Efficacy Bound > Lower Efficacy Bound** or All **Upper Efficacy Bound < Lower Efficacy Bound**

Directionality Defined by order of all bounds

- If **All Upper Efficacy Bound > All Lower Efficacy Bound** then higher treatment effects better ⇒ **Stop Early for Efficacy** if **Test Statistic > Upper Efficacy Bound** or **Test Statistic < Lower Efficacy Bound, otherwise continue to next look**
- If **All Upper Efficacy Bound < All Lower Efficacy Bound** then lower treatment effects better ⇒ **Stop Early for Efficacy** if **Test Statistic < Upper Efficacy Bound** or **Test Statistic > Lower Efficacy Bound, otherwise continue to next look**

8.4.4.5 2-Sided Futility Only

Consistency All **Upper Futility Bound > Lower Futility Bound** or All **Upper Futility Bound < Lower Futility Bound**

Directionality Defined by order of all bounds

- If **All Upper Futility Bound > All Futility Efficacy Bound** then higher treatment effects better ⇒ **Stop Early for Futility** if **Lower Futility Bound < Test Statistic < Upper Futility Bound** i.e. between futility bounds, **otherwise continue to next look**
- If **All Upper Futility Bound > All Lower Futility Bound** then lower treatment effects better ⇒ **Stop Early for Futility** if **Lower Futility Bound > Test Statistic > Upper Futility Bound** i.e. between futility bounds, **otherwise continue to next look**

8.4.4.6 2-Sided Efficacy and Futility

Consistency **Upper Efficacy Bound > Upper Futility Bound > Lower Futility Bound > Lower Efficacy Bound** or **Upper Efficacy Bound < Upper Futility Bound < Lower Futility Bound < Lower Efficacy Bound**

Directionality Defined by order of all bounds

- If **All Upper Efficacy Bound > Upper Futility Bound > Lower Futility Bound > Lower Efficacy Bound** then higher treatment effects better ⇒ **Stop Early for Efficacy** if **Test Statistic > Upper Efficacy Bound** or **Test Statistic < Lower Efficacy Bound** or **Stop Early for Futility** if **Lower Futility Bound < Test Statistic < Upper Futility Bound** i.e. between futility bounds, **otherwise continue to next look** i.e. continue if between **Upper Futility Bound** and **Upper Efficacy Bound** or between **Lower Efficacy Bound** and **Lower Futility Bound**
- If **All Upper Efficacy Bound < Upper Futility Bound < Lower Futility Bound < Lower Efficacy Bound** then lower treatment effects better ⇒ **Stop Early for Efficacy** if **Test Statistic < Upper Efficacy Bound** or **Test Statistic > Lower Efficacy Bound** or **Stop Early for Futility** if **Lower Futility Bound > Test Statistic > Upper Futility Bound** i.e. between futility bounds, **otherwise continue to next look** i.e. continue if between **Upper Futility Bound** and **Upper Efficacy Bound** or between **Lower Efficacy Bound** and **Lower Futility Bound**

Practical examples of the rules for stopping were provided in subsubsection 7.3.5.2 so may be worth reviewing. A technical treatment of the above is provided in subsection 8.7.3.

After the **Boundary Table** has been filled appropriately, select the **Next** button in the bottom right of the **Main Window** to proceed to **Step 4: Simulation Controls**.

8.4.5 Step 4: Simulation Controls

Step 4: Simulation Controls provides control over the number of simulation, refresh frequency during the simulation process, the random seed used by the simulation quasi-random process and which options **Tables** should be provided in the **Group Sequential Design Simulation Outputs**. **Step 4: Simulation Controls** is shown in Figure 8.14.

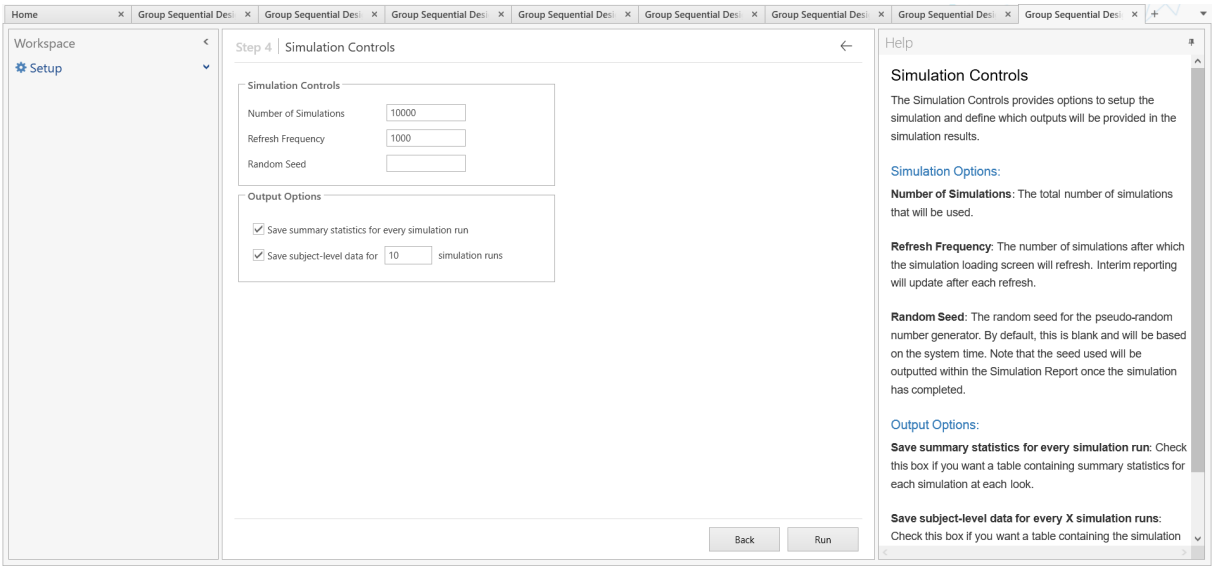


Figure 8.14: Step 4: Simulation Controls

The **Step 4: Simulation Controls** is unaffected by any of the prior **Input Steps** and therefore the same for all scenarios. **Step 4: Simulation Controls** has two sections: **Simulation Controls**, **Output Options**

8.4.5.1 Simulation Controls

The **Simulation Controls** fields controls the simulation overall and has the following input fields:

- **Number of Simulations:** The total number of simulated trials that will be generated. The higher this value the more reliable the estimates will be but it will take longer to generate simulation results - *Default: 10000*
- **Refresh Frequency:** Controls how often the **Calculation in Progress** window will be updated while simulations are being generated. The **Calculation in Progress** window will show the **Average Sample Size, Efficacy %** and **Futility %** based for the displayed proportion of the total simulations complete at that point in time. The total number of updates equals Number of Simulations divided by Refresh Frequency. Higher values will update the **Calculation in Progress** values more often at a small performance cost - *Default: 1000*
- **Random Seed:** Random seed for quasi-random method used to generate random simulations. This can be set to an explicit value so that a simulation can be exactly replicated later. If left blank, a random seed is generated based on the system clock - this seed is provided in the **Simulation Summary** section of the **Simulation Report** (subsection 8.5.1). - *Default: (Blank)*

Note that to prevent slow performance nQuery sets a limit on the maximum **Number of Simulations.** By default this limit is 100000. This limit can be changed by editing the **Maximum Number of Simulations** field under the **Predict** heading in the **Options** menu available under the **File** menu. See section 2.3 for details on the **Options** menu.

Output Options

The **Output Options** fields control which additional spreadsheet outputs are generated under the **Tables** header in the **Group Sequential Design Simulation Outputs**. It has the following fields:

- **Save summary statistics for every simulation run:** Select if a spreadsheet containing a summary of every simulation run (on per-look basis) should be provided in the **Summary Data Per-Simulation** table in the **Group Sequential Design Simulation Outputs.** Check or uncheck the box to the left of this option to include or exclude the **Summary Data Per-Simulation** table - *Default: On*
- **Save subject-level data for every X simulation runs:** Select if a spreadsheet containing "X" number of runs of the simulated data should be provided in the **Per-Simulation Subject Data** table in the **Group Sequential Design Simulation Outputs.** Specify the desired number of simulation runs to include in the "X" field and check or uncheck the box to the left of this option to include or exclude the **Per-Simulation Subject Data** table. - *Default: On, X = 10*

Note that to prevent slow performance nQuery sets a limit on the maximum number of rows that can be displayed in **Table** outputs**.** By default this limit is 20000. This limit can be changed by editing the **Maximum Number of Rows in Generated Reports** field under the **Predict** heading in the **Options** menu available under the **File** menu. See section 2.3 for details on the **Options** menu.

Save summary statistics for every simulation run number of rows will equal **Number of Simulations**

Save subject-level data for every X simulation runs number of rows will depend on when a given simulation stopped (data after stopping early is excluded) but will have maximum equal to "X" multipled by **Maximum Sample**

After the **Simulation Controls** has been filled appropriately, select the **Run** button in the bottom right of the **Main Window.** This will open the **Calculation in Progress** dialog which will provide updated estimates for the **Average Sample Size, Efficacy %** and **Futility %** until the simulation is complete and the **Group Sequential Design Simulation Outputs** are generated. The **Main Window** will then display the **Simulation Report** containing the simulation results.

8.5 Group Sequential Design Simulation Outputs

After all **Group Sequential Design Simulation Input** steps have filled appropriately in turn, **Run** is selected at **Step 4: Simulation Controls** step to run the simulation algorithm. After the **Calculation in Progress** dialog is complete, simulation is finished and the **Group Sequential Design Simulation Outputs** are generated.

Group Sequential Design Simulation Outputs provide multiple outputs which allow the user to understand, explore and visualize the results of the simulation that was ran. These outputs can also be saved and exported for further collaboration.

The are four primary **Group Sequential Design Simulation Outputs:**

- **Simulation Report**
- **Rejection Plot**

- **Boundary Plot**
- **Output Tables (optional)**
  - **Summary Data Per-Simulation**
  - **Per-Simulation Subject Data**

A detailed summary of each of these **Group Sequential Design Simulation Outputs** is provided next.

8.5.1 Simulation Report

The **Simulation Report** provides a detailed summary of the inputs and simulation results for the current simulation. The **Simulation Report** is shown by default after a simulation is run but can also be opened from the **Reports** header in the **Workspace Bar** on the left side (section 8.3). An example **Simulation Report** is shown in Figure 8.15.

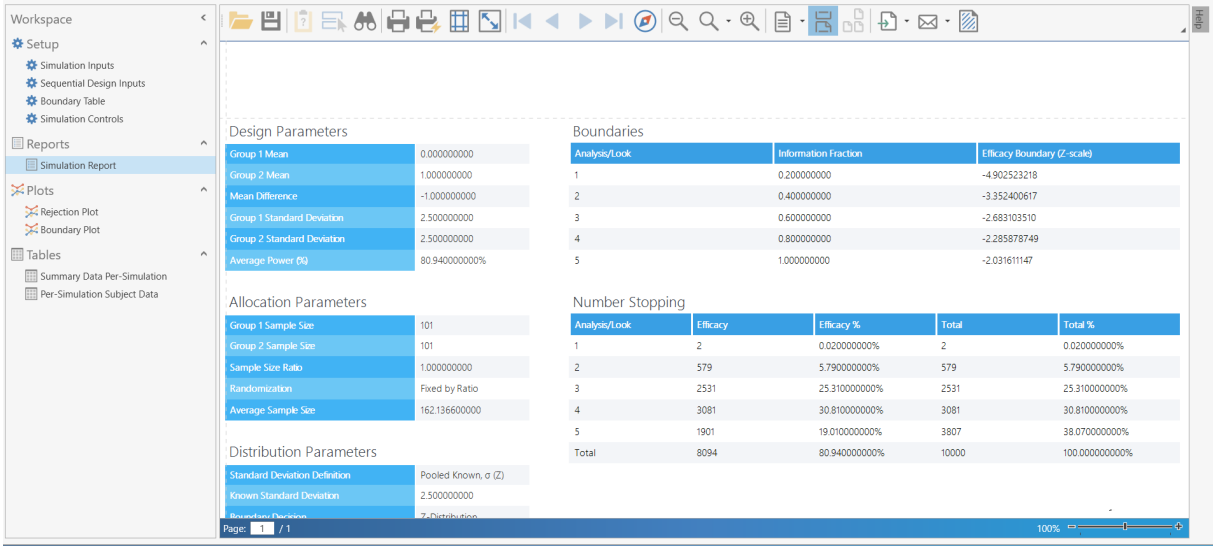


Figure 8.15: Group Sequential Simulation Report

8.5.1.1 Simulation Report Toolbar

At the top of the group sequential report, there is the **Toolbar**. The **Toolbar** contains buttons which provide options for document search, printing, page setup, zoom, page view and export options. The toolbar options available for for the **Simulation Report** are shown in Figure 8.16.

Figure 8.16: Report Toolbar

These options are defined as follows (with the most important bolded):

1. Open: Open another nQuery Predict Report (.prnx) - not recommended as overwrites current report
2. Save: Save current nQuery Predict Report (.prnx) - not recommended, see Export (21) for better save options
3. Help: Unused here
4. URL: Unused here
5. **Search:** Search for text in current report. This will appear in Navigation Panel on right. Select "x" in top-right or Navigation Panel (14) button to hide.
6. **Print:** Open Print menu for current report
7. Quick Print: Print report using system defaults
8. **Page Setup:** Open Page Setup window to edit page size, orientation and margin sizes. Note that the report does **not** scale automatically to the new page setup.
9. **Scale:** Open Scale window to rescale size of report text by percentage or page size. Note the page size is **not** automatically updated to reflect changes to scale.
10. First Page: Return to first page (if report has multiple pages)
11. Page Up: Go up one page (if report has multiple pages)
12. Page Down: Go down one page (if report has multiple pages)
13. Last Page: Go to last page if report has multiple pages
14. Navigation Pane: Open and close Navigation Pane. Contains Pages list and Search Results window
15. **Zoom Out:** Zoom out report by one increment
16. **Zoom:** Change the current zoom level from list of options
17. **Zoom In:** Zoom in report by one increment
18. Page Layout: Set out how multiple pages are displayed (Single Page, Two Pages, Wrap Around)
19. Continuous Scolling: Enable or disable continuous scrolling in report
20. Show Cover Page: Show cover (first) page
21. **Export:** Export report as other file type. Select arrow to see list in-report or select icon to open Export window. The Export option can be used to save the report in the following file formats: PDF, HTML, MHT, RDF, DOCX, XLS, XLSX, CSV, Plain Text File (TXT), Image File (PNG, JPEG, BMP, GIF, EMF, WMF, TIFF).
22. Send: Send report as email in export file type using system default email client.
23. Watermark: Add watermark to report using Watermark menu

8.5.1.2 Simulation Report Sections

The **Simulation Report** can be split into two columns with the left-hand column containing fields summarizd by a single value while the right-hand column contains tabular information.

The following sections are included in the left-hand column:

- Design Parameters (Step 1 Design Parameters, Average Power)
- Allocation Parameters (Step 1 Allocation Parameters, Average Sample Size)
- Distribution Parameters (Endpoint Specific Step 2 Parameters)
- Simulation Summary (Step 4 Parameters)

The following table sections are included in the right-hand column:

- Boundaries (Step 3 Boundary Table)
- Number Stopping (Number of Simulation and % Simulations stopped at each look for each boundary)

Some group sequential simulation scenarios require sections unique to that scenario (e.g. Piecewise Survival table for survival endpoint). These will be discussed later.

A summary of each section is provided next.

Design Parameters The **Design Parameters** section provides an overview of the fixed term design parameters and average power.

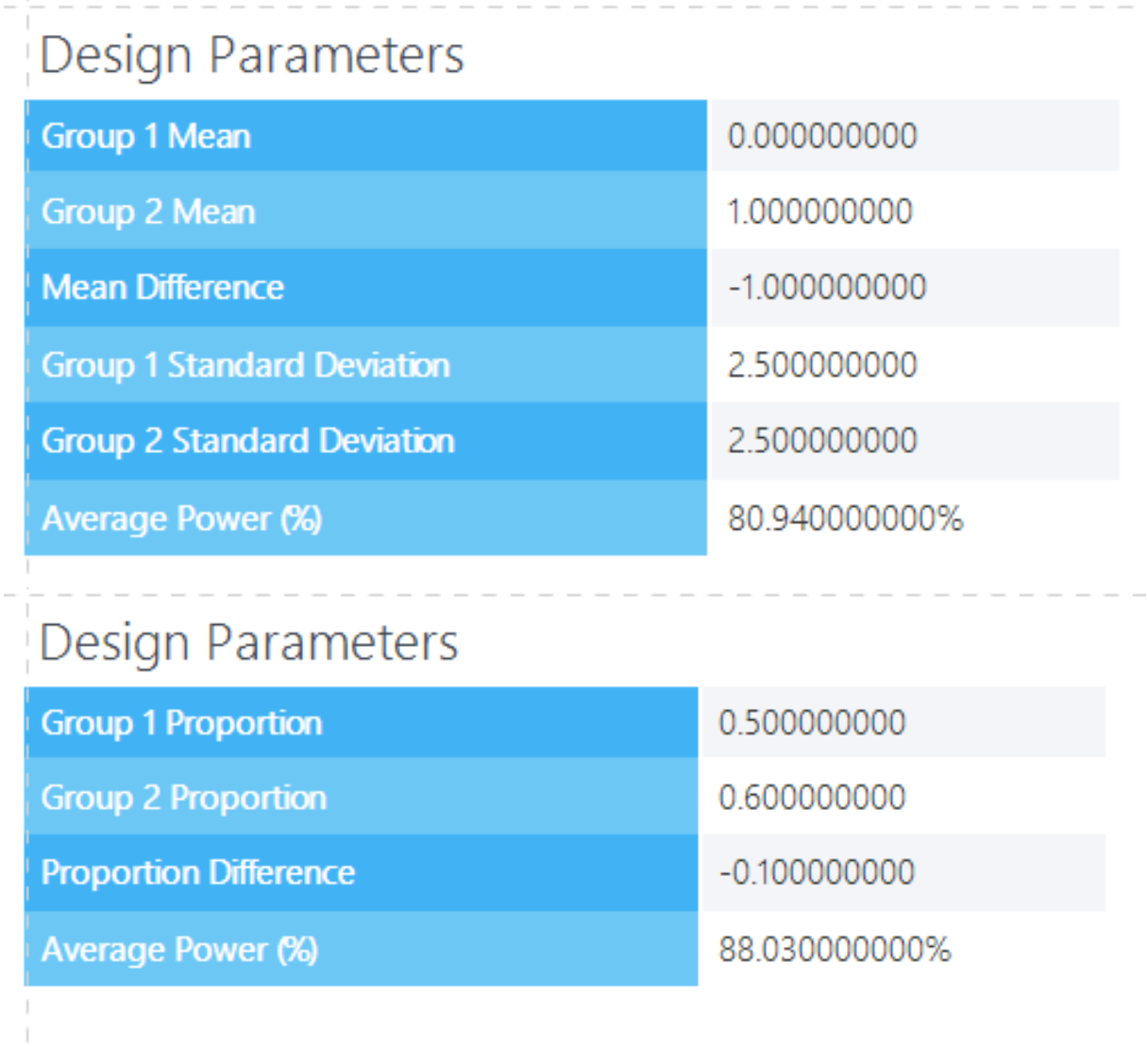
The **Design Parameters** section will contain the following fields:

"Design-Specific" Fields: The set of fixed parameter inputs required for that specific design scenario. These will differ significantly depending on group sequential scenario and will be taken from the **Design Parameters** section in **Step 1: Simulation Inputs**. For example for the **Two Means Inequality** scenario (**Endpoint of Interest = Mean, Number of Groups = 2, Analysis Method = Inequality),** the **Group 1 Mean, Group 2 Mean, Mean Difference, Group 1 Standard Deviation** and **Group 2 Standard Deviation** fields would be included in the **Design Parameters** section. See subsection 8.4.2 for **Design Parameters** required at **Step 1: Simulation Inputs** for all currently supported **Group Sequential Design Simulation** scenarios.

Average Power The **Average Power** is the percentage of simulations where the trial **Stopped for Efficacy**. This will equal the sum of all the **(Upper/Lower) Efficacy %** rows in the **Number Stopping** table in the **Simulation Report** (or 100 - $\sum$**(Upper/Lower) Efficacy %** if only **Futility %** available)

In statistical testing, statistical power is the probability of rejecting the null hypothesis given a specified alternative hypothesis. It also equals 1 - Type II error, which the probability of finding for **Futility** given a specified alternative hypothesis. Simulation provides a very flexible mechanism to find statistical power for a given group sequential design for a wide variety of scenarios. See subsection 7.2.3 for technical discussion on Type II error and statistical power in the context of group sequential designs.

Example **Design Parameters** sections for the **Two Mean Inequality** and **Two Proportion Inequality** scenarios are provided in Figure 8.17



Design Parameters

Group 1 Mean	0.000000000
Group 2 Mean	1.000000000
Mean Difference	-1.000000000
Group 1 Standard Deviation	2.500000000
Group 2 Standard Deviation	2.500000000
Average Power (%)	80.940000000%

Design Parameters

Group 1 Proportion	0.500000000
Group 2 Proportion	0.600000000
Proportion Difference	-0.100000000
Average Power (%)	88.030000000%

Figure 8.17: Simulation Report Design Parameters Section Examples

Allocation Parameters The **Allocation Parameters** section provides an overview of the allocation parameters such as the sample size and randomization method.

The **Allocation Parameters** section will contain the following fields:

Allocation Parameters "Sample Size" Fields: The sample size fields summarize the sample size parameters from the **Allocation Parameters** section from **Step 1: Simulation Inputs**. For example, for the **Two Means Inequality** and **Two Proportions Inequality** scenarios the **Allocation Parameters** section will contain **Group 1 Sample Size, Group 2 Sample Size** and **Sample Size Ratio** as per their respective **Step 1: Simulation Inputs**.

Note that for **Endpoint of Interest = Survival**, the **Allocation Parameters** section will include similiar fields for the **Number of Events** and **Events per Group**, alongside the sample size fields above.

Randomization The randomization algorithm selected from the **Allocation Parameters** section in **Step 1: Simulation Inputs**. Will equal either **Fixed Allocation** (data simulated to have exact per-group sample sizes specified in **Step 1: Simulation Inputs**) or **Complete Randomization** (allocation controlled by random binomial variable). These allocation methods are discussed in detail in subsection 8.4.2 and section 8.7. Note this option will not be shown if **Number of Groups = 1** since there is no allocation in single arm trials.

Average Sample Size The expected sample size the expected total sample size expected given the **Group Sequential Design Simulation Inputs** provided. This will equal taking sum of the multiplication of each row of **Total %/100** (from **Number Stopping** table) by the **Sample Size** (from **Boundary Table**).

For example, if values were inherited from a **Group Sequential Design Table** using the **GST Simulation** button (see subsection 8.2.2) then if the defaults were used for each step this would be the average sample size under the alternative hypothesis (H_1) and should approximately equal the **Expected Sample Size under** H_1 in the **Group Sequential Report** (subsection 7.3.4) from the original design table. Similarly if the only change made was set the treatment effect to the null hypothesis (e.g. Mean Difference = 0 for **Two Means Inequality** scenario) then this should approximate **Expected Sample Size under** H_0.

An example **Allocation Parameters** section for the **Two Mean Inequality** scenario is provided in Figure 8.18

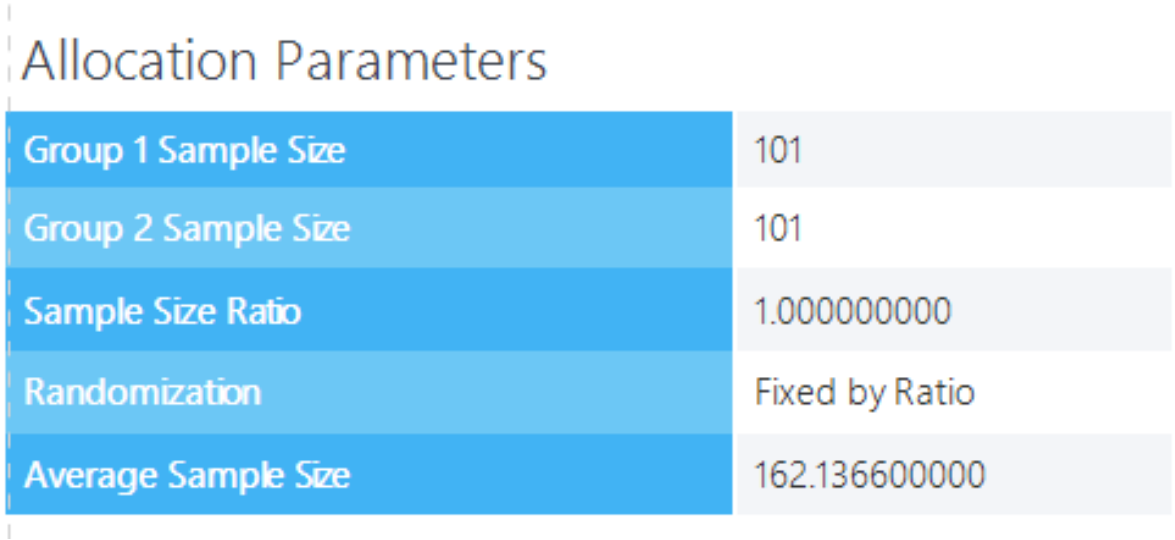


Figure 8.18: Simulation Report Allocation Parameters Section

Distribution Parameters The **Distribution Parameters** section provides an overview of scenario specific fields specified at **Step 2: Sequential Design Inputs**.

For example for the **Two Means Inequality** scenario where **Standard Deviation Definition** = Known Pooled Z(σ), the following fields are included in the **Distribution Parameters** section: **Standard Deviation Definition, Known Standard Deviation, Boundary Decision**

Given that the **Distribution Parameters** required will change depending on the design scenario, the reader is referred to subsection 8.4.3 for details for a summary of the scenario specific **Distribution Parameters.**

Example **Distribution Parameters** sections (first two **Two Mean Inequality**, third for **Two Proportion Inequality**) are provided in Figure 8.19

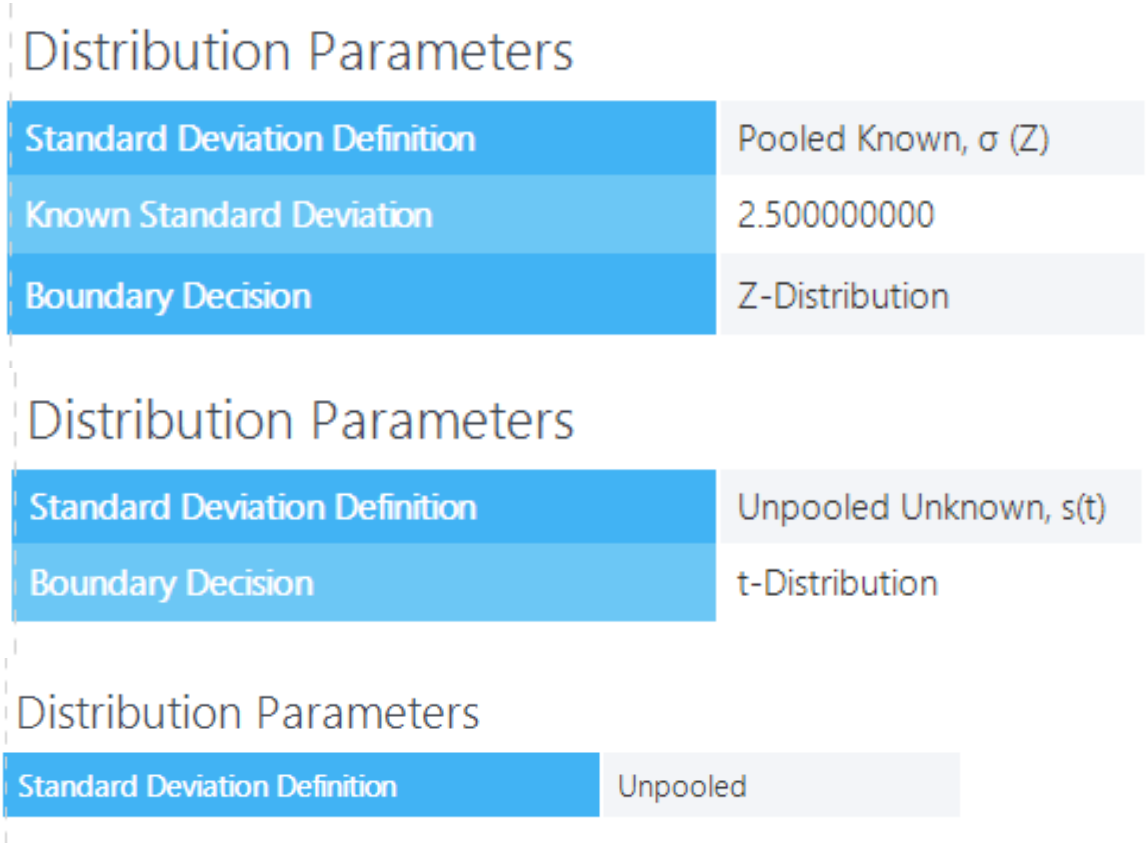


Figure 8.19: Simulation Report Distribution Parameters Section

Simulation Summary The **Simulation Summary** section provides an overview of simulation tuning parameters specified at **Step 4: Simulation Controls.** It contains the following fields for all scenarios:

Random Seed Random seed for quasi-random method used to generate random simulations. If this was left blank at **Step 4: Simulation Controls.** a random seed was generated based on the system clock which is being provided in this field.

Number of Simulations The total number of simulated trials generated. The higher this value the more reliable the estimates will be.

Simulation Time (s) The length of time, in seconds, it took for the simulation to complete.

An example **Simulation Summary** section is provided in Figure 8.20

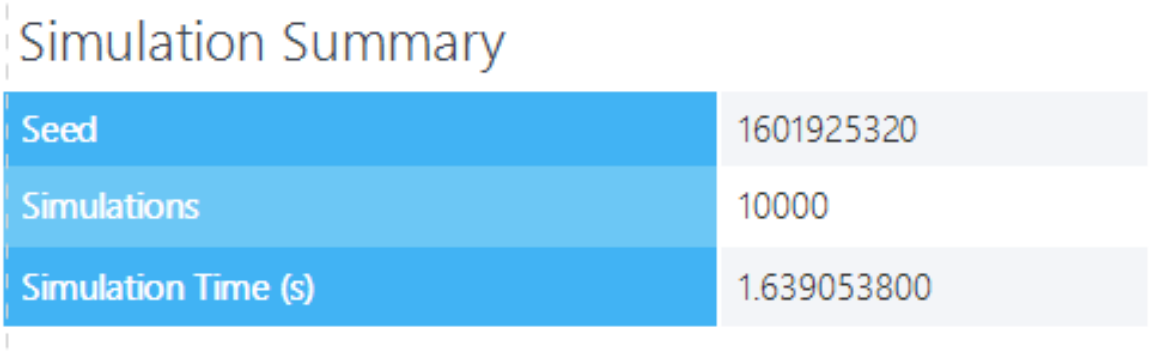


Figure 8.20: Simulation Report Allocation Parameters Section

Boundaries The **Boundaries** table provides a summary of the group sequential efficacy and/or futility boundaries on the desired statistical scale. Each row will correspond to a **Look**. The table will contain the following columns: **Analysis/Look Number, Information Fraction** and **Boundaries** columns.

Analysis/Look Number: The look number (k) associated with each row of the **Boundary Table** from **Step 3: Boundary Table**. The final row corresponds to the final planned analysis.

Information Fraction The information fraction at each interim analysis. This is equivalent to the proportion of the total sample sizeat a given look and will equal the **Information Fraction** column from **Step 3: Boundary Table**.

Boundaries The **Boundaries** columns provide the efficacy and/or futility boundaries used for decision making about early stopping during the simulation. There can be anywhere between 1-4 **Boundaries** columns depending on the inputs from **Step 2: Sequential Design Inputs**.

Each **Boundaries** column will have a column title of the form "Boundaries (*Scale*) - (Upper/Lower) Efficacy/Futility" where *Scale* refers to the statistical scale the boundary is provided on, Upper/Lower are provided for a 2-sided designs to differentiate between the upper and lower bounds and Efficacy/Futility refers to if the boundary is an efficacy or futility bound.

The six primary types are:

1. **Boundaries (*Scale*) - Efficacy:** The 1-sided efficacy boundary beyond which the trial would stop for efficacy. Only present if **1 or 2 Sided?** $= 1$ and **Efficacy Bound Parameterization** $\neq$ **Don't Calculate** at **Step 2: Sequential Design Inputs**
2. **Boundaries (*Scale*) - Futility:** The 1-sided futility boundary beyond which the trial would stop for futility. Only present if **1 or 2 Sided?** $= 1$ and **Futility Bound Parameterization** $\neq$ **Don't Calculate** at **Step 2: Sequential Design Inputs**

3. **Boundaries (*Scale*) - Upper Efficacy:** The 2-sided upper efficacy boundary above which the trial would stop for efficacy. Only present if **1 or 2 Sided?** = 2 and **Efficacy Bound Parameterization** $\neq$ **Don't Calculate** at **Step 2: Sequential Design Inputs**
4. **Boundaries (*Scale*) - Lower Efficacy:** The 2-sided lower efficacy boundary below which the trial would stop for "efficacy" - *assuming both directions are truly considered "effective"!*. Only present if **1 or 2 Sided?** = 2 and **Efficacy Bound Parameterization** $\neq$ **Don't Calculate** at **Step 2: Sequential Design Inputs**
5. **Boundaries (*Scale*) - Upper Futility:** The 2-sided upper futility boundary where the trial will stop early for futility if the test statistic falls between the upper and lower futility boundaries. Only present if **1 or 2 Sided?** = 2 and **Futility Bound Parameterization** $\neq$ **Don't Calculate** at **Step 2: Sequential Design Inputs**
6. **Boundaries (*Scale*) - Lower Futility:** The 2-sided lower futility boundary where the trial will stop early for futility if the test statistic falls between the upper and lower futility boundaries. Only present if **1 or 2 Sided?** = 2 and **Futility Bound Parameterization** $\neq$ **Don't Calculate** at **Step 2: Sequential Design Inputs**

The statistical scale shown in (***Scale***) above depends on the choices in **Efficacy Bound Parameterization** and **Futility Bound Parameterization** at **Step 2: Sequential Design Inputs** for the **Efficacy** and **Futility** bounds respectively. The available scales are **Z-scale, p-value Scale, Score Scale** and δ**-Scale** (i.e. treatment effect e.g. mean difference for **Two Means Inequality** scenario).

Note that the direction "beyond" which the test will stop for efficacy and/or futility will depend on value in the final row for **Boundaries (*Scale*) - Efficacy/Boundaries (*Scale*) - Upper Efficacy** or if **Efficacy Bound Parameterization = Don't Calculate** then **Boundaries (*Scale*) - Futility/Boundaries (*Scale*) - Upper Futility.** See subsection 8.4.4 for a detailed breakdown for every scenario above.

Examples of the **Boundaries** table for a variety of scenarios is shown in Figure 8.21.

Boundaries

Analysis/Look	Information Fraction	Efficacy Boundary (Z-scale)
1	0.200000000	-4.876884949
2	0.400000000	-3.357011194
3	0.600000000	-2.680279717
4	0.800000000	-2.289816770
5	1.000000000	-2.031032169

Boundaries

Analysis/Look	Information Fraction	Efficacy Boundary (p-value scale)	Futility Boundary (p-value scale)
1	0.500000000	0.015502863	0.152590667
2	1.000000000	0.017405036	0.017405036

Boundaries

Analysis/Look	Sample Size	Lower Futility Boundary (score scale)	Upper Futility Boundary (score scale)
1	93	0.884805068	-0.884805068
2	187	3.850034629	-3.850034629
3	280	7.501168262	-7.501168262

Boundaries

Analysis/Look	Sample Size	Lower Efficacy Boundary (δ-scale)	Upper Efficacy Boundary (δ-scale)	Lower Futility Boundary (δ-scale)	Upper Futility Boundary (δ-scale)
1	76	2.797019116	-2.797019116	0.214732221	-0.214732221
2	153	1.352037033	-1.352037033	0.420023635	-0.420023635
3	230	0.879220874	-0.879220874	0.566146695	-0.566146695
4	306	0.652151611	-0.652151611	0.652151611	-0.652151611

Figure 8.21: Simulation Report Boundaries Table Examples

Number Stopping The **Numbers Stopping** table provides the number and percentage of the simulations stopped at each look where each table row will correspond to a **Look**. The table will contain the following columns: **Analysis/Look Number, (Upper/Lower) Efficacy, (Upper/Lower) Efficacy %, Futility, Futility %, Total, Total %**

Analysis/Look Number: The look number (k) associated with each row of the **Boundary Table** from **Step 3: Boundary Table**. The final **Total** row refers to the sum of all cells in that column.

(Upper/Lower) Efficacy and (Upper/Lower) Efficacy % The **Efficacy** column(s) provide the count of how many simulations **Stopped for Efficacy** at each analysis based on the **Efficacy Boundaries** provided in the **Boundaries** table above. The **Efficacy** value in the final **Total** row provides the total number of subjects who **Stopped for Efficacy** in the simulation. If there are no **Futility Boundaries** then 1 - **Total** row provides the number of simulations which **Stopped for Futility** at the final analysis.

The **Efficacy %** column(s) provide the percentage of how many simulations **Stopped for Efficacy** at each analysis based on the **Efficacy Boundaries** provided in the **Boundaries** table above. The **Efficacy** value in the final **Total** row provides the total percentage of subjects who **Stopped for Efficacy** in the simulation. This will equal the **Average Power** in the **Design Parameters** table. If there are no **Futility Boundaries** then 1 - **Total** row the percentage of simulations which **Stopped for Futility** at the final analysis.

If **1 or 2 Sided?** = 1 at **Step 2: Sequential Design Inputs** then there will be one column named **Efficacy** containing the efficacy counts per look and one column named **Efficacy %** containing the efficacy percentages per look.

If **1 or 2 Sided?** = 2 at **Step 2: Sequential Design Inputs** then there will be a **Upper Efficacy** column containing the efficacy counts and a **Lower Efficacy** column containing the efficacy counts for the **Lower Efficacy Boundary**. Similarly there will be a **Upper Efficacy %** column and a **Lower Efficacy %** column containing the efficacy percentages per look for the **Upper Efficacy** and **Lower Efficacy** boundaries respsectively.

If **Efficacy Bound Parameterization = Don't Calculate** at **Step 2: Sequential Design Inputs** then the **Efficacy** and **Efficacy %** columns will not be shown.

Note that the direction "beyond" which the test will stop for efficacy and/or futility will depend on value in the final row for **(Upper) Efficacy Boundaries** (or if **Efficacy Bound Parameterization = Don't Calculate** then **(Upper) Efficacy Boundaries).** See subsection 8.4.4 for a detailed breakdown for every scenario.

Futility and Futility % The **Futility** column provides the count of how many simulations **Stopped for Futility** at each analysis based on the **Futility Boundaries** provided in the **Boundaries** table above. The **Futility** value in the final **Total** row provides the total number of subjects who **Stopped for Futility** in the simulation. If there are no **Efficacy Boundaries** then 1 - **Total** row provides the number of simulations which **Stopped for Efficacy** at the final analysis.

The **Futility** % column provides the percentage of how many simulations **Stopped for Futility** at each analysis based on the **Futility Boundaries** provided in the **Boundaries** table above. The **Futility** value in the final **Total** row provides the total percentage of subjects who **Stopped for Futility** in the simulation. If there are no **Efficacy Boundaries** then 1 - **Total** row the percentage of simulations which **Stopped for Efficacy** at the final analysis.

If **Futility Bound Parameterization = Don't Calculate** at **Step 2: Sequential Design Inputs** then the **Futility** and **Futility %** columns will not be shown.

Note that the direction "beyond" which the test will stop for efficacy and/or futility will depend on value in the final row for **(Upper) Efficacy Boundaries** (or if **Efficacy Bound Parameterization = Don't Calculate** then **(Upper) Efficacy Boundaries).** See subsection 8.4.4 for a detailed breakdown for every scenario.

Total and Total % The **Total** column provides the count of how many simulations **Stopped for Efficacy** or **Stopped for Futility** at each analysis based on the **Boundaries** provided in the **Boundaries** table above. The **Total** value in the final **Total** row

provides the total number of subjects who **Stopped Overall** in the simulation. The final **Total** row will equal the **Number of Simulations**.

The **Total** column provides the percentage of how many simulations **Stopped for Efficacy** or **Stopped for Futility** at each analysis based on the **Boundaries** provided in the **Boundaries** table above. The **Total** value in the final **Total** row provides the total percentage of subjects who **Stopped Overall** in the simulation. The final **Total** row will equal 100%.

Examples of the **Number Stopped** table for a variety of scenarios is provided in Figure 8.22

Number Stopping

Analysis/Look	Efficacy	Efficacy %	Total	Total %
1	4	0.040000000%	4	0.040000000%
2	968	9.680000000%	968	9.680000000%
3	3104	31.040000000%	3104	31.040000000%
4	3113	31.130000000%	3113	31.130000000%
5	1649	16.490000000%	2811	28.110000000%
Total	8838	88.380000000%	10000	100.000000000%

Number Stopping

Analysis/Look	Futility	Futility %	Total	Total %
1	1712	17.120000000%	1712	17.120000000%
2	6519	65.190000000%	6519	65.190000000%
3	1578	15.780000000%	1769	17.690000000%
Total	9809	98.090000000%	10000	100.000000000%

Number Stopping

Analysis/Look	Efficacy	Futility	Efficacy %	Futility %	Total	Total %
1	4202	538	42.020000000%	5.380000000%	4740	47.400000000%
2	3487	428	34.870000000%	4.280000000%	3915	39.150000000%
3	1042	303	10.420000000%	3.030000000%	1345	13.450000000%
Total	8731	1269	87.310000000%	12.690000000%	10000	100.000000000%

Number Stopping

Analysis/Look	Lower Efficacy	Upper Efficacy	Efficacy	Efficacy %	Total	Total %
1	1	17	18	0.180000000%	18	0.180000000%
2	3	69	72	0.720000000%	72	0.720000000%
3	1	167	168	1.680000000%	168	1.680000000%
4	1	245	246	2.460000000%	246	2.460000000%
5	2	315	317	3.170000000%	9496	94.960000000%
Total	8	813	821	8.210000000%	10000	100.000000000%

Figure 8.22: Simulation Report Number Stopping Examples

8.5.2 Rejection Plot

The **Rejection Plot** provides a visual summary of the decisions made at each analysis about **Stopping for Efficacy**, **Stopping for Futility** or **Continuing to the Next Look**.

The **Rejection Plot** can be found under the **Plots** header in the **Workspace Bar** on the left side (section 8.3). An example **Rejection Plot** is shown in .

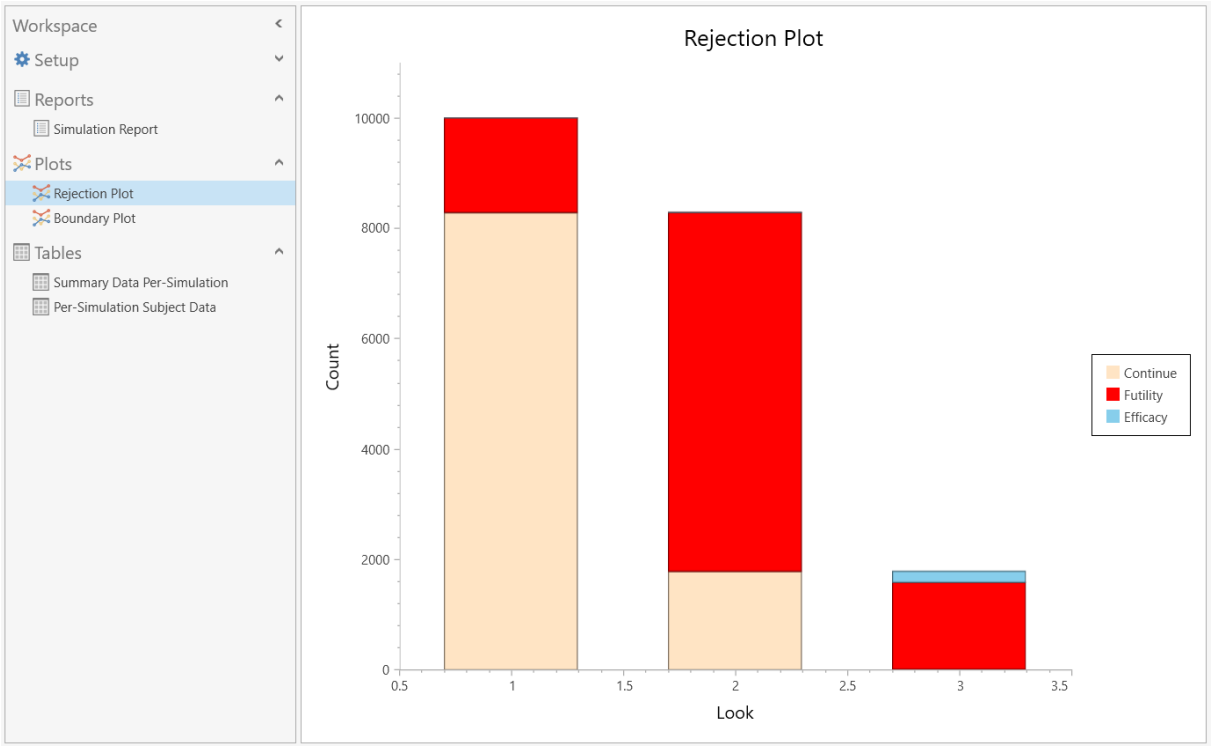


Figure 8.23: Group Sequential Simulation Rejection Plot

The **Rejection Plot** provides a visual summary the count of how many simulations stopped for either efficacy and futility and, for interim analyses, the number of simulations which continued until the next look.

The **Rejection Plot** is a **Bar Chart** where the count of the number of simulations which **Stopped for Efficacy, Stopped for Futility** or **Continued** (to next look) is plotted on the Y-axis for each **Look** on the X-axis.

8.5.2.1 Look (X-axis)

The X-axis corresponds to the **Look Number** where the X-axis will range from 1 to **Number of Looks** specified at **Step 2: Sequential Design Inputs**. Note that the **Looks** will be equally spaced from each other in the **Rejection Plot** even if the looks are not equally spaced in terms of sample size/information time.

Use **Titles > X-axis Scale** option from the **Edit** menu to change the **X-axis Title** (show/hide, X-axis name, X-axis font). See subsubsection 8.5.2.5 for details.

8.5.2.2 Count (Y-axis)

The **Y-axis** corresponds to the **Count** of how many subjects has the status **Continue, Efficacy** or **Futility** at each **Look.**

Subjects who have the **Efficacy** or **Futility** status stop at that **Look**. Therefore the height of **Count** at the next **Look** will equal the height of the current **Look** minus the sum of the heights of the **Efficacy** and **Futility** sections. Therefore, in most **Rejection Plots** the **Count** will reduce as **Look** increases representing the subjects who have stopped already. The **Count** at **Look 1** will equal the **Number of Simulations** set in **Step 4: Simulation Controls.**

By default **Continue** is indicated by a cream color, **Efficacy** by blue and **Futility** by red. Use **Series** from the **Edit** menu to change the color or name of any of the **Continue, Efficacy** or **Look** series. See subsubsection 8.5.2.5 for details.

Use **Titles > Y-axis Scale** option from the **Edit** menu to change the **Y-axis Title** (show/hide, Y-axis name, Y-axis font). See subsubsection 8.5.2.5 for details.

8.5.2.3 Legend

The **Rejection Plot Legend** provides an indication of the color for the **Continue, Efficacy** and **Futility series.**

By default, the **Legend** is shown to the right of the boundary plot. To toggle whether the **Legend** is shown, change the location of the **Legend** or change the **Legend Border** use the the **Legend** option in the **Edit** menu . The colors in the plot and legend are defined under the **Series** option in the **Edit** menu. See subsubsection 8.5.2.5 for details.

8.5.2.4 Tooltip

The **Rejection Plot Tooltip** provides the user information about the **Count** for either the **Continue**, **Efficacy** or **Futility** at a given **Look** by placing the cursor over the **Count** area of interest.

A **Rejection Plot** with the **Tooltip** active for the **Futility Count** at **Look = 2** is shown in Figure 8.24.

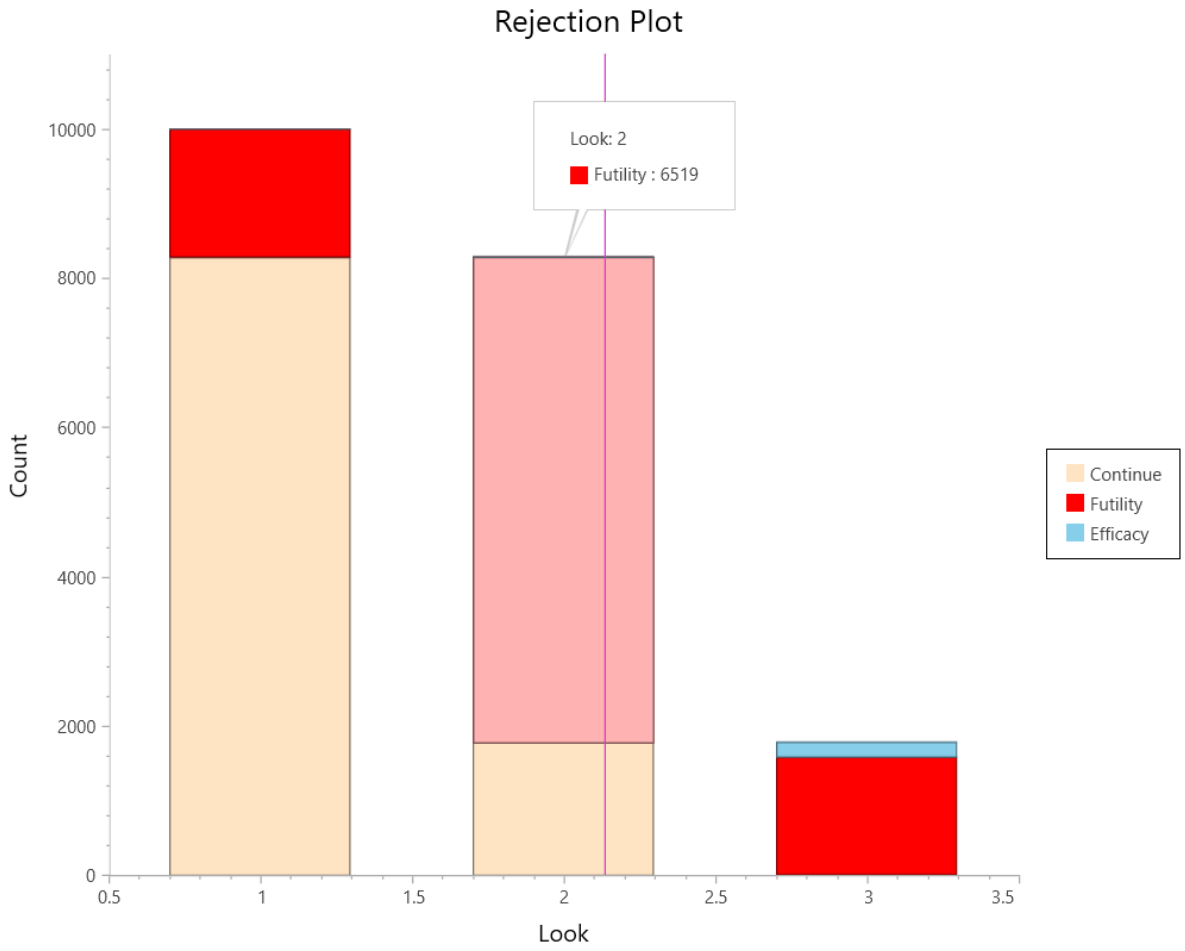


Figure 8.24: Rejection Plot Tooltip

8.5.2.5 Editing and Saving

Options to edit, save or print the **Rejection Plot** are available from the right-click context menu within the **Rejection Plot**. This menu is shown in Figure 8.25.

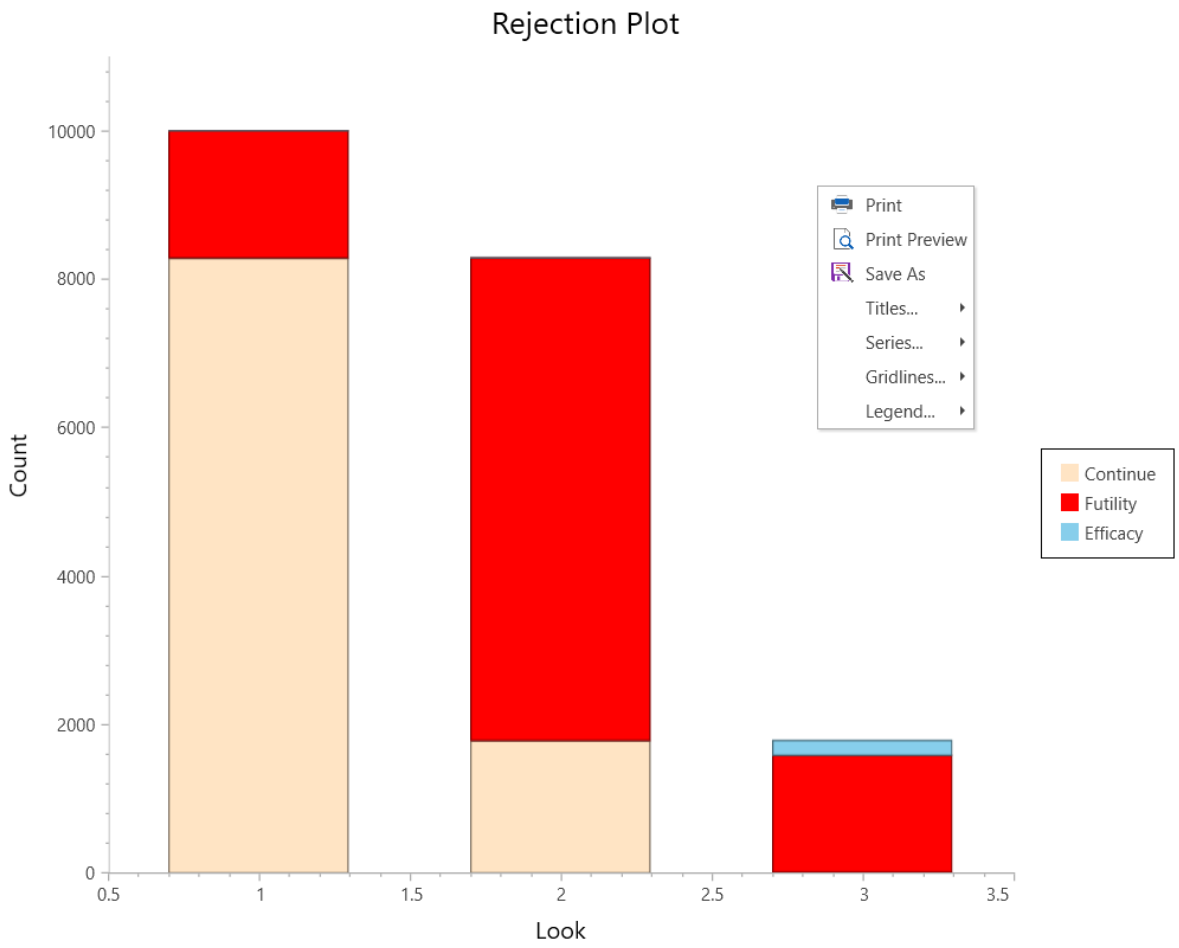


Figure 8.25: Boundary Plot Toolbar

This menu provides options to edit the visual aspects of the plot such as the titles, legend and color schemes while also providing options for printing and saving. This menu is similar to **Edit** options available for other plots - section 1.9 for an overview.

The full set of dropdown menu options is as follows, where dropdown items with a ▶ at their right edge indicate a sub-menu which will open when that option is highlighted or selected:

- Print: Open Print window for **Rejection Plot**
- Print Preview: Open Print Preview window for **Rejection Plot**
- Save As: Save **Rejection Plot** as .pdf or .jpeg file
- Titles ▶: Edit Main Title, X-axis Title and Y-axis Title of **Rejection Plot**
- Series ▶: Edit Color of **Alpha Error** and/or **Beta Error** series in **Rejection Plot**
- Gridlines ▶: Add or remove gridlines from **Rejection Plot**
- Legend ▶: Edit **Rejection Plot** Legend

The **Print**, **Print Preview** and **Save As** options are available as per all other plots so will not be discussed further.

A breakdown of the **Titles, Series, Gridlines** and **Legend** sub-menus is provided next.

Titles The **Titles** menu allows the user to edit the **Chart Title, X-axis Title** and **Y-axis Title** by choosing to show or hide that title, rename that title and change the font of that title. The tabular summary of the **Titles** menu , where ▶ indicate where an option will open an additional sub-menu and ⇒ indicates where an option will open a separate pop-out window, is as follows:

- Titles ▶
  - Chart Title ▶
    - Hide/Show Chart Title: Hide or show main **Chart Title**, name will depend on whether **Chart Title** is currently shown in **Error Spending Plot** - *Default: Show*
    - Rename ⇒ : Opens **Rename Title** window where **Chart Title** can be edited. *Default: Rejection Plot*
    - Font ⇒ : Opens **Update Title Font** window for **Chart Title** where can edit the **Font** (select desired font from dropdown)**, Font Size**, **Font Type** (**Bold,** *Italics*), **Font Color** (select from **Color Panel** or create custom color in **Colors** window opened if select **More Colors**) *Default: Font: Segoe UI; Font Size: 21; Font Type: No Bold, No Italics; Font Color: Black (Automatic)*
  - X-axis Title ▶
    - Hide/Show Chart Title: Hide or show **X-axis Title**, name will depend on whether **X-axis Title** is currently shown in **Error Spending Plot** - *Default: Show*
    - Rename ⇒ : Opens **Rename Title** window where **X-axis Title** can be edited - *Default: Look*
    - Font ⇒ : Opens **Update Title Font** window for **X-axis Title** where can edit the **Font** (select desired font from dropdown)**, Font Size**, **Font Type** (**Bold,** *Italics*), **Font Color** (select from **Color Panel** or create custom color in **Colors** window opened if select **More Colors**) - *Default: Font: Segoe UI; Font Size: 16; Font Type: No Bold, No Italics; Font Color: Black (Automatic)*
  - Y-axis Title ▶
    - Hide/Show Chart Title: Hide or show **Y-axis Title**, name will depend on whether **Y-axis Title** is currently shown in **Error Spending Plot** - *Default: Show*
    - Rename ⇒ : Opens **Rename Title** window where **Y-axis Title** can be edited - *Default: Count*
    - Font ⇒ : Opens **Update Title Font** window for **X-axis Title** where can edit the **Font** (select desired font from dropdown)**, Font Size**, **Font Type** (**Bold,** *Italics*), **Font Color** (select from **Color Panel** or create custom color in **Colors** window opened if select **More Colors**) - *Default: Font: Segoe UI; Font Size: 16; Font Type: No Bold, No Italics; Font Color: Left Y-axis: Blue unless Beta Error only then Red, Right Y-axis: Red*

Series The **Series** menu allows the user to edit the color and name of the series. It will contain three sub-menus corresponding the three series: **Continue, Efficacy, Futility**. Each sub-menu will contain the same two options: **Rename, Color**

Selecting **Rename** will open the **Rename Series** window where the user can the name of the series which appears in the **Legend**. Select from **Color Panel** or create custom color using **More Colors.**

Selecting **Color** will open the **Select Series Color** window where the user can edit color for the selected error series. Select from **Color Panel** or create custom color using **More Colors.** By default **Continue** will be cream, **Efficacy** will be blue and **Futility** will be red.

Gridlines The **Gridlines** menu consists of two options: **Show/Hide X-axis Gridlines** and **Show/Hide Y-axis Gridlines**. The options will change between **Show** and **Hide** depending on if that gridlines option is currently shown in the **Error Spending Plot .** By default both the X-axis and Y-axis gridlines are not shown. When shown the major gridlines will be shown at the numbered major ticks on the relevant axis and the minor gridlines at the 4 unnumbered ticks between each major tick.

Legend The **Legend** menu allows the user to edit the **Error Spending Plot Legend** including whether to show the legend, legend border color and the vertical and horizontal position of the legend. The tabular summary of the **Legend** menu , where ▶ indicate where an option will open an additional sub-menu and ⇒ indicates where an option will open a separate pop-out window, is as follows:

- Show/Hide Legend: Hide or show **Legend**, name will depend on whether **Legend** is currently shown in **Error Spending Plot** - *Default: Show*
- Border Color ⇒ Opens **Select Legend Border Color** window where user can edit color of border of the Legend. Select from **Color Panel** or create custom color using **More Colors** - *Default: Black*
- Horizontal Position ▶: Choose the horizontal position of the plot and whether the plot should be inside or outside the **Error Spending Plot** area. This sub-menu has the following options: Left, Outside; Left, Inside; Center; Right, Outside; Right, Inside - *Default: Right, Outside*
- Vertical Position ▶: Choose the vertical position of the plot and whether the plot should be inside or outside the **Error Spending Plot** area. This sub-menu has the following options: Top, Outside; Top, Inside; Center; Top, Outside; Top, Inside - *Default: Center*

8.5.3 Boundary Plot

The **Boundary Plot** provides a visual and tabular summary of the group sequential boundaries, which can be found in the **Boundaries** table in the **Simulation Report**, and the associated exit and continuation regions at each look. It can be opened by selecting the **Boundary Plot** option under the **Plots** header in the **Navigation Bar** on the left (see section 8.3)

The **Boundary Plot** allows the user to visually inspect the boundaries on multiple statistical scales (**Z-scale, p-value Scale, Score Scale,** δ**-Scale**) and also export these plots to assist in the exploration and communcation of the simulated group sequential design.

An example **Boundary Plot** is shown in Figure 8.26.

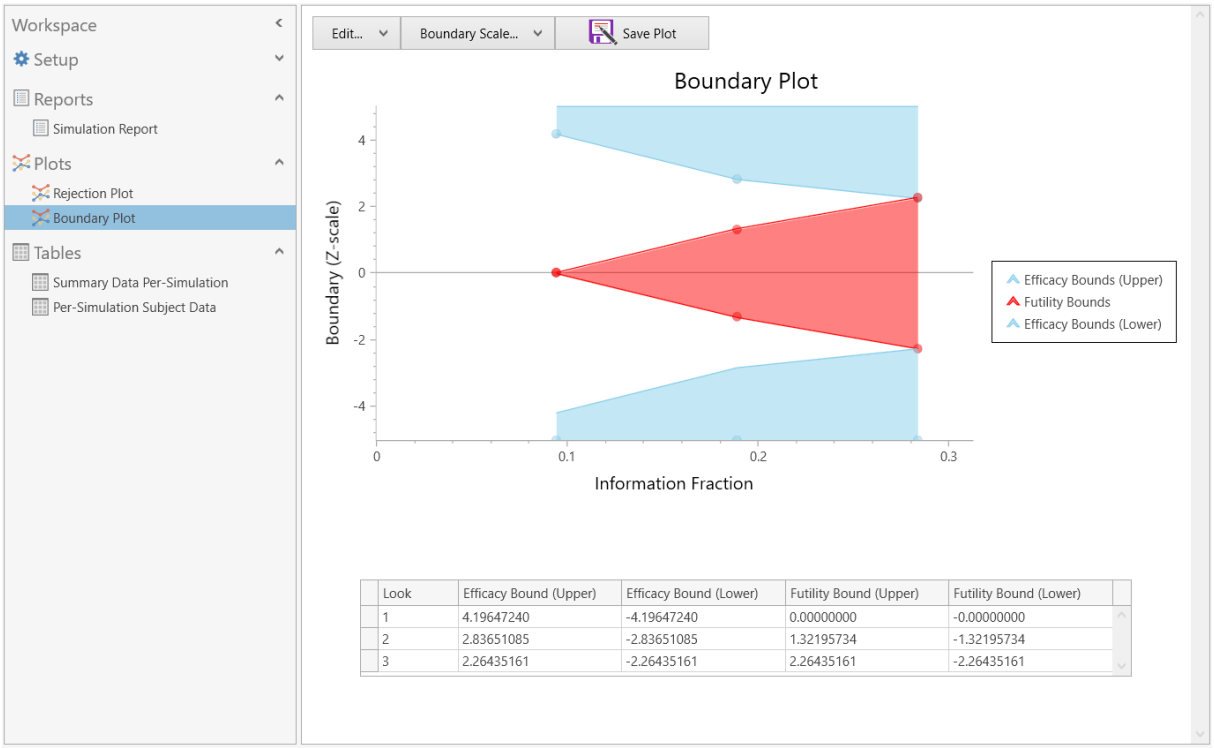


Figure 8.26: Boundary Plot in Group Sequential Design Simulation Outputs

The **Boundary Plot** tab consists of three primary elements: the **Boundary Plot** (middle), **Boundary Table** (bottom) and the **Toolbar** (top).

The **Boundary Plot** visually displayed the **Efficacy Boundaries** and/or **Futility Boundaries.**

The **Boundary Table** provides a tabular summary of the **Efficacy Boundaries** and/or **Futility Boundaries.**

The **Toolbar** allows the user to edit the plot, change the boundary parameterization scale or save the **Boundary Plot** or **Boundary Table.**

However, the **Boundary Plot** in the **Group Sequential Design Simulation Tool** is identical to the **Boundary Plot** within the GSTX series of **Group Sequential Design** tables discussed in chapter 7. For a detailed breakdown of the **Boundary Plot** therefore refer to subsubsection 7.3.5.1.

8.5.4 Output Tables

The **Output Tables** are optional tables which provide access the underlying simulation data on a summary and per-simulation basis. The **Tables** available are as follows:

- Summary Data Per-Simulation
- Per-Simulation Subject Data

The options to include to these tables is provided in **Step 4: Simulation Controls**. Refer to subsection 8.4.5 for details.

A summary of these **Table** options is provided next.

8.5.4.1 Summary Data Per-Simulation

The **Summary Data Per-Simulation** table provides the important summary statistic outputs for each individual simulation.

In the **Summary Data Per-Simulation** table, each row corresponds to an individual **Look** within an individual simulation.

When a simulation **Stops for Efficacy** or **Stops for Futility** (indicated by the **Status** column) then no further **Looks** are assessed for that simulation since it is assumed that simulated trial stopped early. If **Status = Continue** then further **Looks** are assessed. As the **Look** at which a trial will stop is unknown a-priori, the number of **Looks** shown per-simulation will range between 1 and the **Number of Looks** specified at **Step 2: Sequential Design Inputs**.

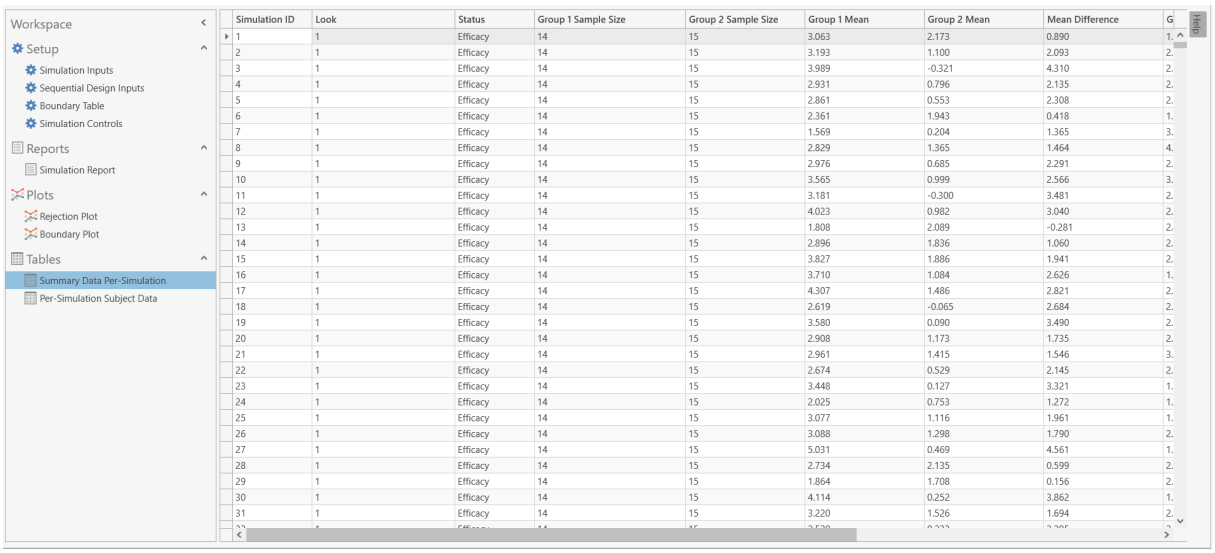
The columns represent outcomes of interest at each look. There are some differences in the columns provided depending on the simulation scenario. However, there are number of columns which are in every **Summary Data Per-Simulation** table and these will be summarized first. These columns and their definitions are as follows:

- **Simulation ID:** The unique indentifier for each simulation. Equals the order simulation was in simulation queue. Rows with the same **Simulation ID** indicates all **Looks** that were conducted for that simulation
- **Look:** The **Look** number of the simulation associated with the **Simulation ID** in the current row. This will vary between 1 and the **Number of Simulations**
- **Status**: The outcome status of the **Look** in the current row. Can equal **Efficacy, Futility** or **Continue** where **Efficacy = Stopped for Efficacy, Futility = Stopped for Futility, Continue = Continued to next Look**. For **Look Number = Number of Looks**, **Continue** status cannot occur. Refer to subsection 8.4.4 for details on how stopping rules are implemented
- **Information:** The (Fisher) Information achieve for the **Look** in the current row. See subsubsection 7.2.1.1 for a technical overview of **Information** in the context of **Group Sequential Designs**.
- **Test Statistic:** The standardised (Z) test statistic calculated based on the simulated data at the current **Look**. Note this column is always the Z-statistic even if the boundaries were specified on a different statistical scale in **Step 2: Sequential Design Inputs**. For details on how the **Test Statistic** is calculated for different simulation scenarios (including the effect of scenario specific **Step 2: Sequential Design Inputs** fields) and how the test statistic is compared to the group sequential boundaries see section 8.7. For conversions from the Z-scale to other statistical scales see subsubsection 7.2.1.1 and subsubsection 7.2.4.5.

The remaining columns in the **Summary Data Per-Simulation** table will be design specific inputs taken from the **Design Parameters** and **Allocation Parameters** in **Step 1: Simulation Inputs**. See subsection 8.4.2 for details on the scenario specific **Design Parameters** and **Allocation Parameters** inputs for all currently supported scenarios.

For example for the **Two Means Inequality** scenario, the following fields will be provided: Group 1 Sample Size, Group 2 Sample Size, Group 1 Mean, Group 2 Mean, Mean Difference, Group 1 Standard Deviation, Group 2 Standard Deviation

An example of the **Summary Data Per-Simulation** table is provided in Figure 8.27.



Simulation ID	Look	Status	Group 1 Sample Size	Group 2 Sample Size	Group 1 Mean	Group 2 Mean	Mean Difference	G
1	1	Efficacy	14	15	3.063	2.173	0.890	1.
2	1	Efficacy	14	15	3.193	1.100	2.093	2.
3	1	Efficacy	14	15	3.989	-0.321	4.310	2.
4	1	Efficacy	14	15	2.931	0.796	2.135	2.
5	1	Efficacy	14	15	2.861	0.553	2.308	2.
6	1	Efficacy	14	15	2.361	1.943	0.418	1.
7	1	Efficacy	14	15	1.569	0.204	1.365	3.
8	1	Efficacy	14	15	2.829	1.365	1.464	4.
9	1	Efficacy	14	15	2.976	0.685	2.291	2.
10	1	Efficacy	14	15	3.565	0.999	2.566	3.
11	1	Efficacy	14	15	3.181	-0.300	3.481	2.
12	1	Efficacy	14	15	4.023	0.982	3.040	2.
13	1	Efficacy	14	15	1.808	2.089	-0.281	2.
14	1	Efficacy	14	15	2.896	1.836	1.060	2.
15	1	Efficacy	14	15	3.827	1.886	1.941	2.
16	1	Efficacy	14	15	3.710	1.084	2.626	1.
17	1	Efficacy	14	15	4.307	1.486	2.821	2.
18	1	Efficacy	14	15	2.619	-0.065	2.684	2.
19	1	Efficacy	14	15	3.580	0.090	3.490	2.
20	1	Efficacy	14	15	2.908	1.173	1.735	2.
21	1	Efficacy	14	15	2.961	1.415	1.546	3.
22	1	Efficacy	14	15	2.674	0.529	2.145	2.
23	1	Efficacy	14	15	3.448	0.127	3.321	1.
24	1	Efficacy	14	15	2.025	0.753	1.272	1.
25	1	Efficacy	14	15	3.077	1.116	1.961	1.
26	1	Efficacy	14	15	3.088	1.298	1.790	2.
27	1	Efficacy	14	15	5.031	0.469	4.561	1.
28	1	Efficacy	14	15	2.734	2.135	0.599	2.
29	1	Efficacy	14	15	1.864	1.708	0.156	2.
30	1	Efficacy	14	15	4.114	0.252	3.862	1.
31	1	Efficacy	14	15	3.220	1.526	1.694	2.

Figure 8.27: Summary Data Per-Simulation Table

8.5.4.2 Per-Simulation Subject Data

The **Per-Simulation Subject Data** table provides the simulated outcomes for each subject from a pre-specified number of simulations. The number of simulations is specified by editing the (X) value in the **Save subject-level data for (X) simulation runs** field in **Step 4: Simulation Controls.**

Each row correponds to a single simulated subject in the trial and each column is characteristic about that simulated subject regarding which simulation they were generated from, their simulated characteristics (e.g. group allocation) and outcome of interest.

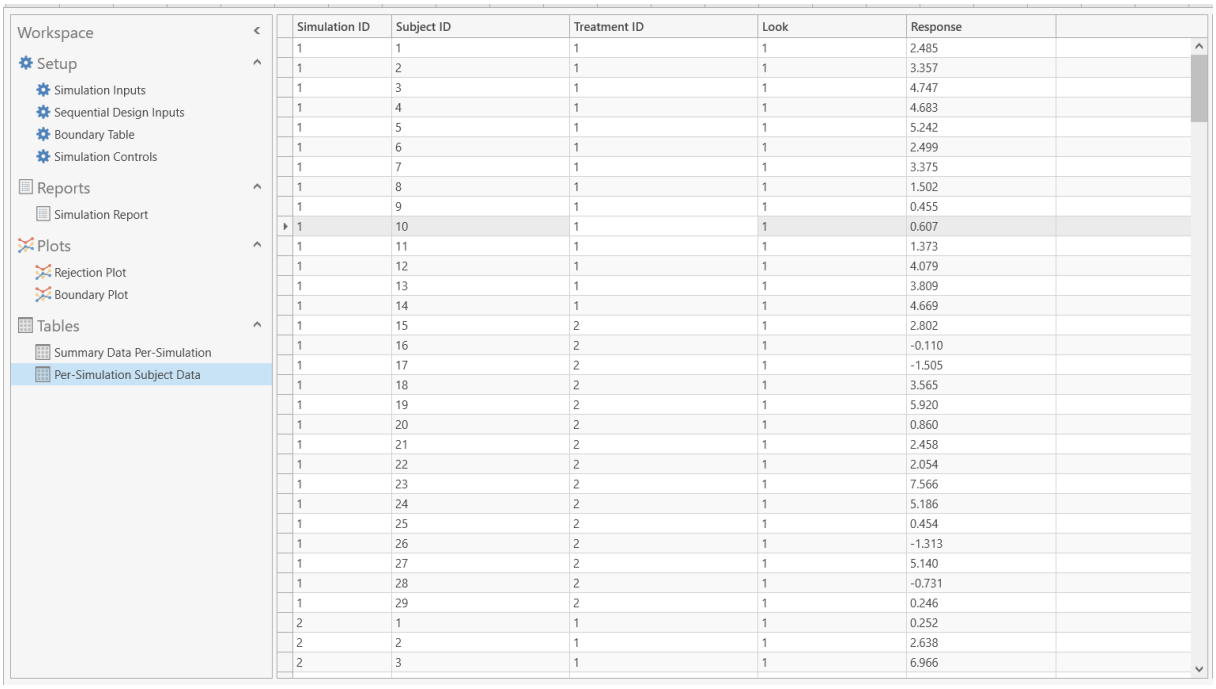
The **Per-Simulation Subject Data** table will have the following fields:

- **Simulation ID:** The unique indentifier for each simulation. Equals the order simulation was in simulation queue.
- **Subject ID:** The unique indentifier for the simulated subject within the simulation with **Simulation ID** in the current row. Equals the order simulation was in subject simulation queue.
- **Treatment ID**: The treatment group the subject was assigned to. For **Number of Groups = 1** all subjects will have value of 1. For **Number of Groups = 2**, subjects will have value of 1 or 2 based on randomization algorithm selected

in **Step 1: Simulations Inputs** under the **Allocation Parameters section.** For **Number of Groups > 2**, subjects will have value up the number of groups specified.

- **Look:** The **Look** before which the simulated subject was recruited. For example, **Look = 1** means the subject was recruited before the first look, **Look = 2** means subject was recruited after the first look but before second look etc. This will vary between 1 and the **Number of Simulations**
- **Response:** The simulated response for the subject. This will depend on the design scenario e.g. a normal variate for **Means**, a 0/1 binary variable for **Proportion.** See subsection 8.7.1 for detail on the **Data Generating Process** for currently supported scenarios.

An example of the **Per-Simulation Subject Data** table is provided in Figure 8.28.



Simulation ID	Subject ID	Treatment ID	Look	Response
1	1	1	1	2.485
1	2	1	1	3.357
1	3	1	1	4.747
1	4	1	1	4.683
1	5	1	1	5.242
1	6	1	1	2.499
1	7	1	1	3.375
1	8	1	1	1.502
1	9	1	1	0.455
1	10	1	1	0.607
1	11	1	1	1.373
1	12	1	1	4.079
1	13	1	1	3.809
1	14	1	1	4.669
1	15	2	1	2.802
1	16	2	1	-0.110
1	17	2	1	-1.505
1	18	2	1	3.565
1	19	2	1	5.920
1	20	2	1	0.860
1	21	2	1	2.458
1	22	2	1	2.054
1	23	2	1	7.566
1	24	2	1	5.186
1	25	2	1	0.454
1	26	2	1	-1.313
1	27	2	1	5.140
1	28	2	1	-0.731
1	29	2	1	0.246
2	1	1	1	0.252
2	2	1	1	2.638
2	3	1	1	6.966

Figure 8.28: Per-Simulation Subject Data Table

8.6 Saving/Loading Group Sequential Design Simulation Files

nQuery provides the file format of **.nqgs** to save an **nQuery Group Sequential Design Simulation Workspace**. To save an **nQuery Group Sequential Design Simulation Workspace**, select **Save** from the File Menu or select the **Save** icon from the toolbar or use the **CTRL+S** keyboard shortcut. This will open the **Save Workspace** window which is shown in Figure 8.29.

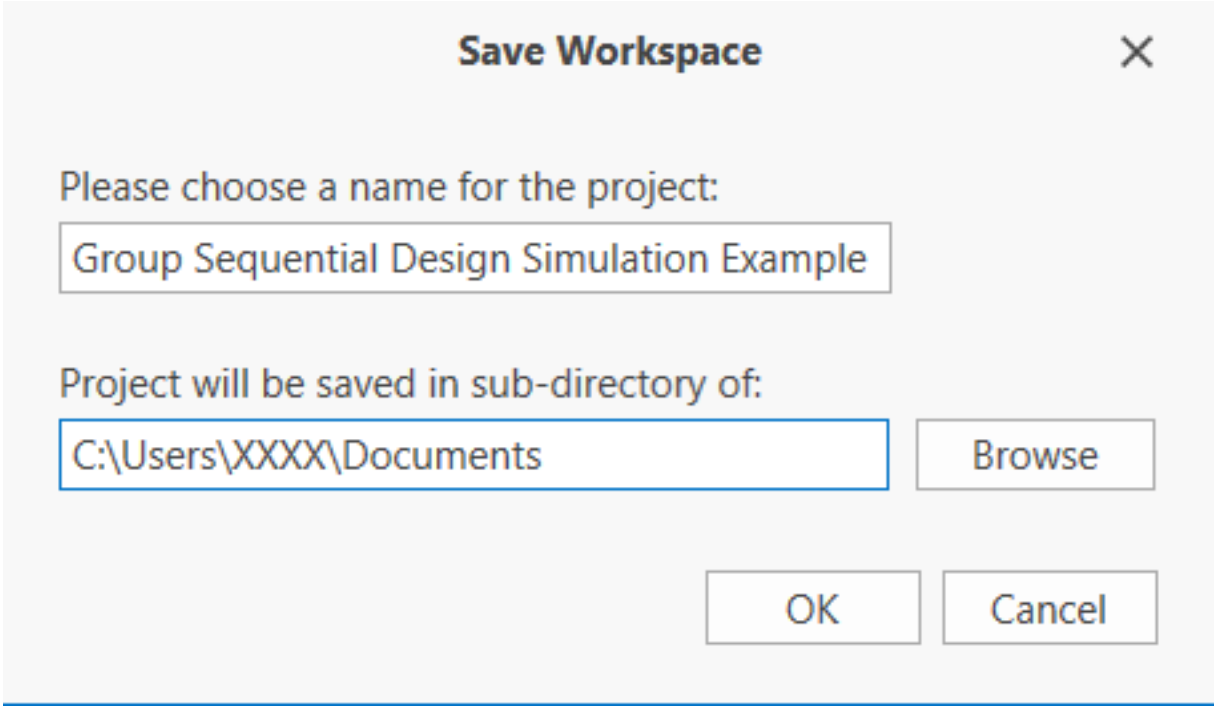


Figure 8.29: Save Workspace Window

The **Save Workspace** window allows the user to specify the name of the .nqgs file in the **Please choose a name for the project:** field and the location to save the .nqgs file in the **Project will be saved in sub-directory of:** field. The user can also edit the **Project will be saved in sub-directory of:** using the Browse button, which will open the **Browse for Folder** window. To save the project, select the OK button.

When a project is saved, a folder with the **Please choose a name for the project:** name will be present in the folder specified in the **Project will be saved in sub-directory of:** field. This project folder will contain the .nqgs file alongside all tables under the **Tables** header generated in the current simulation (all as .csv files).

After an nQuery Workspace is saved if a change is made to the workspace the user can save over the prior save using the Save options (see above) or save a separate version using Save As from the File menu.

To open a saved .nqgs file, select the file in Window Explorer or find the file from the Open Menu which can be selected from the File Menu, the toolbar icon or **CTRL+O** keyboard shortcut. Opening a .nqgs file works as for other nQuery file types (see subsection 1.7.5).

8.7 Group Sequential Design Simulation Technical Background

This section provides technical information about the processes used to generate simulation, calculate test statistics, make decisions based on the simulated test statistics compared to specified boundaries and the derivation for some outputs provided in the simulation results. This section is focussed on the implementation of simulation for group

sequential designs. If interested in knowing the statistical theory and technical background for group sequential design, see chapter 7.

This section is broken up into the following domains:

- **Data Generating Process:** Statistical model for generating responses for all supported group sequential design simulation scenarios
- **Test Statistic Calculation:** Formulae for calculating standardized test statistics for all supported group sequential design scenarios
- **Group Sequential Boundaries:** Technical overview of group sequential boundary decision process and details on converting between statistical scales
- **Group Sequential Outputs**: Calculations used for certain highlighted group sequential simulation results e.g. Power, Average Sample Size

8.7.1 Data Generating Process

The **Data Generating Process** specifies the statistical model that will generate simulations, the number of subjects to simulate per-simulations, the allocation process to treatment groups and the total number of simulations overall.

As the **Data Generating Process** is dependent on the design scenario so an overview is provided for all currently supported scenarios. The current scenarios available are:

- Two Means - seesubsubsection 8.7.1.1
- Two Proportions - subsubsection 8.7.1.2

The **Data Generating Process** for each scenario is provided next.

8.7.1.1 Two Means

The **Two Means** scenario refers to a trial design where there are **two independent groups** where the response for each subject is simulated from the **Normal Distribution**.

Before describing the **Data Generating Process**, we will set out some definitions:

- Maximum Group 1 Sample Size: n_1
- Maximum Group 2 Sample Size: n_2
- Group 1 Mean: μ_1
- Group 2 Mean: μ_2
- Group 1 Standard Deviation: σ_1
- Group 2 Standard Deviation: σ_2
- Total Number of Looks: K
- Look Index: k
- Group 1 Sample Size at Look k: n_{1k}
- Group 1 Sample Size at Look k: n_{2k}
- Information Time at Look k: $t_k = \left(\frac{n_{1k}+n_{2k}}{n_1+n_2}\right)$

The **Data Generating Process** is as follows:

Assume that the subjects in **Group 1** have a continuous response which can be drawn from a **Normal Distribution** with a mean equal to μ_1 and variance equal to σ_1^2 and that subjects in **Group 2** responses can be drawn from a **Normal Distribution** with a mean equal to μ_2 and variance equal to σ_2^2 . This is equivalent to:

$$X_1 \sim N(\mu_1, \sigma_1^2)$$

$$X_2 \sim N(\mu_2, \sigma_2^2)$$

For simplicity[1], nQuery will generate n_1 Normal variates from the $N(\mu_1, \sigma_1^2)$ for Group 1 and n_2 Normal variates from the $N(\mu_1, \sigma_1^2)$ from Group 2 in each simulation run.

We can simulate normal variates using a variety of methods. nQuery uses the Box-Muller algorithm [Box and Muller, 1958] with random number generation via the quasi-random Mersenne-Twister algorithm [Matsumoto and Nishimura, 1998].

This process is repeated until the specified number of simulations is reached. We will define the simulated Normal data for Group 1 as $x_1^{(j)}$ and for Group 2 as $x_2^{(j)}$ where (j) indicates the simulation index and where each $x_1^{(j)}$ is of length n_1 and each $x_2^{(j)}$ is of length n_2

We can then define the simulated data up to look k in simulation j as $x_{1_k}^{(j)}$ and $x_{2_k}^{(j)}$ with each defined as the first n_{1k} variates in Group 1 and the first n_{2k} variates in Group 2 respectively [2].

The per-look data cohorts $\left(x_{1_k}^{(j)}, x_{2_k}^{(j)}\right)$ can then be passed to the test statistic calculation formulae described in subsubsection 8.7.2.1.

Randomization The above section assumed that n_1 and n_2 are known a-priori. This is equivalent to the **Fixed Allocation** option in **Step 1: Simulation Inputs** where the size of group 1 and group 2 is defined by the **Group 1 Sample Size** and **Group 2 Sample Size** fields.

The other option is **Complete Randomization** which is where allocation is based on random allocation[3]. This is described below.

The random allocation for a given subject is simulated from the following **Bernoulli Distribution:**

[1] Alternatively, the samples can be simulated up to each Look k sequentially and then conditionally stop the simulation if a boundary is crossed. While this reduces the number of simulations required, it provides minimal performance improvement for plausible trial conditions and number of simulations. It should be noted that the post-stopping data can be valuable for communicating the estimate bias in the treatment effect estimate after early stopping.

[2] This is equivalent to taking the first n_1 times t_k variates and first n_2 times t_k variates respectively.

[3] Fixed Allocation and Complete Randomization represent extremes for the randomization process where on one end the allocation is fixed at every pair to ensure the correct allocation and the other end allocation is a random process which gives the specified allocation on average. In practice most trials use a compromise option such as Block Randomization, where the allocation balance is achieved within blocks of a specified size. For detail on different randomization schemes, see the Randomization List chapter (chapter 6).

$$A \sim Bernoulli(\pi_R)$$

where π_R is the proportion of subjects assigned to group 1 based on the **Sample Size Ratio** (R) specified at **Step 1: Simulation Inputs**. The formula for π_R is as follows:

$$\pi_R = \left(\frac{1}{1+R}\right)$$

As above for **Fixed Allocation**, nQuery will generate n_1 Normal variates from the $N(\mu_1, \sigma_1^2)$ for Group 1 and n_2 Normal variates from the $N(\mu_2, \sigma_2^2)$ from Group 2 in each simulation run

For **Complete Randomization**, nQuery will generate n_1+n_2 Bernoulli variates from $Bernoulli(\pi_R)$ which are assigned to each subject, where the proportion of "successes" should equal $\left(\frac{1}{1+R}\right)$ on average.

The "successes" are assigned to **Group 1** and the "failures" are assigned to **Group 2**. The sum of the number of "successes" becomes the updated value for the **Group 1 Sample Size,** we will designate this as the group 1 sample size in simulation with index j as $n_1^{(j)}$. Similarly, the sum of the "failures" becomes the **Group 2 Sample Size**, with the group 2 sample size in simulation j being $n_2^{(j)}$. On average, $n_1^{(j)} = n_1$ and $n_2^{(j)} = n_2$ but due to random variation the sample size allocation can diverge from the originally planned allocation.

For the interim analyses, it is assumed that the $Bernoulli(\pi_R)$ allocation process defined the entry order to the simulated trial. Therefore, the interim timings are based on first $t_k\,(n_1 + n_2)$ as per the **Information Time** (t_k) values in the **Boundary Table** at **Step 3**.

The interim group 1 and group 2 sample sizes for simulation j are designated as $n_{1_k}^{(j)}$ and $n_{2_k}^{(j)}$. Note that based on the random allocation sequence that the **Sample Size Ratio** can vary over each of the looks.

Interm sample size values per-simulation are passed to the **Test Statistic Calculation** (subsubsection 8.7.2.1) as above where $n_{1k}^{(j)}$ and $n_{2k}^{(j)}$ replace $n_{1_k}$and n_{2_k} respectively if using the **Complete Randomization** algorithm.

8.7.1.2 Two Proportions

The **Two Proportions** scenario refers to a trial design where there are **two independent groups** where the response for each subject is simulated from the **Bernoulli Distribution**.

Before describing the **Data Generating Process**, we will set out some definitions:

- Maximum Group 1 Sample Size: n_1
- Maximum Group 2 Sample Size: n_2
- Group 1 Proportion: π_1
- Group 2 Proportion: π_2
- Total Number of Looks: K

- Look Index: k
- Group 1 Sample Size at Look k: n_{1k}
- Group 1 Sample Size at Look k: n_{2k}
- Information Time at Look k: $t_k = \left(\frac{n_{1k}+n_{2k}}{n_1+n_2}\right)$

The **Data Generating Process** is as follows:

Assume that the subjects in **Group 1** have a Bernoulli response (also known as a binary response e.g. 0 or 1) which can be drawn from a **Bernoulli Distribution** with a success proportion equal to π_1 and that subjects in **Group 2** can be drawn from a **Bernoulli Distribution** with a success proportion equal to π_2. This is equivalent to:

$$X_1 \sim Bernoulli(\pi_1)$$

$$X_2 \sim Bernoulli(\pi_2)$$

For simplicity, nQuery will generate n_1 Bernoulli variates from the $Bernoulli(\pi_1)$ distribution for Group 1 and n_2 Bernoulli outcomes from the $Bernoulli(\pi_2)$ dstribution for Group 2 in each simulation run.

We can simulate Bernoulli variates using a variety of methods. nQuery uses the algorithm from Kachitvichyanukul and Schmeiserwith [Kachitvichyanukul and Schmeiser, 1988] for the Binomial distribution with Size set to 1, random number generation is via the quasi-random Mersenne-Twister algorithm [Matsumoto and Nishimura, 1998].

This process is repeated until the specified number of simulations is reached. We will define the simulated Bernoulli responses for Group 1 as $x_1^{(j)}$ and for Group 2 as $x_2^{(j)}$ where (j) indicates the simulation index and where each $x_1^{(j)}$ is of length n_1 and each $x_2^{(j)}$ is of length n_2

We can then define the simulated data up to look k in simulation j as $x_{1_k}^{(j)}$ and $x_{2_k}^{(j)}$ with each defined as the first n_{1k} variates in Group 1 and the first n_{2k} variates in Group 2 respectively

The per-look data cohorts $\left(x_{1_k}^{(j)}, x_{2_k}^{(j)}\right)$can then be passed to the test statistic calculation formulae described in subsubsection 8.7.2.2.

Randomization The above section assumed that n_1 and n_2 are known a-priori. This is equivalent to the **Fixed Allocation** option in **Step 1: Simulation Inputs** where the size of group 1 and group 2 is defined by the **Group 1 Sample Size** and **Group 2 Sample Size** fields.

The other option is **Complete Randomization** which is where allocation is based on random allocation. This is described below.

The random allocation for a given subject is simulated from the following **Bernoulli Distribution:**

$$A \sim Bernoulli(\pi_R)$$

where π_R is the proportion of subjects assigned to group 1 based on the **Sample Size Ratio** (R) specified at **Step 1: Simulation Inputs**. The formula for π_R is as follows:

$$\pi_R = \left(\frac{1}{1+R}\right)$$

As above for **Fixed Allocation**, nQuery will generate n_1 Bernoulli variates from the $Bernoulli(\pi_1)$ distribution for Group 1 and n_2 Bernoulli outcomes from the $Bernoulli(\pi_2)$ dstribution for Group 2 in each simulation run.

For **Complete Randomization**, nQuery will generate n_1+n_2 Bernoulli variates from $Bernoulli(\pi_R)$ which are assigned to each subject, where the proportion of "successes" should equal $\left(\frac{1}{1+R}\right)$ on average.

The "successes" are assigned to **Group 1** and the "failures" are assigned to **Group 2**. The sum of the number of "successes" becomes the updated value for the **Group 1 Sample Size,** we will designate this as the group 1 sample size in simulation with index j as $n_1^{(j)}$. Similarly, the sum of the "failures" becomes the **Group 2 Sample Size**, with the group 2 sample size in simulation j being $n_2^{(j)}$. On average, $n_1^{(j)} = n_1$ and $n_2^{(j)} = n_2$ but due to random variation the sample size allocation can diverge from the originally planned allocation.

For the interim analyses, it is assumed that the $Bernoulli(\pi_R)$ allocation process defined the entry order to the simulated trial. Therefore, the interim timings are based on $t_k\,(n_1 + n_2)$ as per the **Information Time** (t_k) values in the **Boundary Table** at **Step 3**.

The interim group 1 and group 2 sample sizes for simulation j are designated as $n_{1_k}^{(j)}$ and $n_{2_k}^{(j)}$. Note that based on the random allocation sequence that the **Sample Size Ratio** can vary over each of the looks.

Interm sample size values per-simulation are passed to the **Test Statistic Calculation** (subsubsection 8.7.2.1) as above where $n_{1k}^{(j)}$ and $n_{2k}^{(j)}$ replace $n_{1_k}$and n_{2_k} respectively if using the **Complete Randomization** algorithm.

8.7.2 Test Statistic Calculation

The **Test Statistic Calculation** specifies the formula used to calculate the standardized test statistic (i.e. Z-statistic) for each design scenario.

The **Test Statistic Calculation** is dependent on the scenario (including the scenario specific options) so an overview is provided for all currently supported scenarios. The current scenarios available are:

- Two Means - seesubsubsection 8.7.2.1
- Two Proportions - subsubsection 8.7.2.2

The **Test Statistic Calculation** for each scenario is provided next.

8.7.2.1 Two Means

The standardized test statistic for the mean difference is equal to the following:

$$Z = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}}}$$

$$\bar{X} = \frac{\sum x}{n}$$

where $\bar{X}_1 - \bar{X}_2$ is the mean difference and $SE = \sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}}$ is the standard error[4], based on the per-group variances and sample sizes.

Recall that the n_{1_k} Normal data variates simulated for Group 1 up to look k for simulation index j was defined as $x_{1_k}^{(j)}$ and the n_{2_k} Normal data variates simulated for Group 2 up to look k for simulation index j was defined as $x_{2_k}^{(j)}$.

Then the standardized test statistic at look k in simulation j can be defined as:

$$Z_k^{(j)} = \frac{\bar{X}_{1_k}^{(j)} - \bar{X}_{2_k}^{(j)}}{SE_k^{(j)}}$$

where

$$\bar{X}_{1_k}^{(j)} = \frac{\sum_1^{n_{1_k}} x_{1_k}^{(j)}}{n_{1_k}}$$

$$\bar{X}_{2_k}^{(j)} = \frac{\sum_1^{n_{2_k}} x_{2_k}^{(j)}}{n_{2_k}}$$

The calculation of the standard error will depend on the **Standard Deviation Definition** (chosen at **Step 2: Sequential Design Inputs**) where there are two primary choices:

1. Between **Known** (assume variance is based on standard deviation values provided for the **Data Generating Process**) or **Unknown** (variance is calculated based on the interim simulated data) variance
2. Between **Pooled** (per-group variances replaced with pooled variance in SE formula) and **Unpooled** (per-group variances used direclty in SE formula) variance

We will define the interim estimate for the variance as s^2 and this will be calculated for the data up to look k in simulation j as:

$$s_{1_k}^{2(j)} = \frac{\sum_1^{n_{1_k}} \left(\bar{X}_{1_k}^{(j)} - x_{1_k}^{(j)}\right)^2}{n_{1_k} - 1}$$

$$s_{2_k}^{2(j)} = \frac{\sum_1^{n_{1_k}} \left(\bar{X}_{2_k}^{(j)} - x_{2_k}^{(j)}\right)^2}{n_{2_k} - 1}$$

[4]Note that $\left(\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}\right)^{-1}$ is the (Fisher) Information

Based on either σ_1^2 and σ_2^2 or $s_{1_k}^{2(j)}$ and $s_{2_k}^{2(j)}$ the **Pooled** variance under the **Known** and **Unknown** scenarios can be calculated using the following formulae:

$$\sigma^2 = \frac{n_{1_k}\sigma_1^2 + n_{2_k}\sigma_2^2}{n_{1_k} + n_{2_k}}$$

$$s_k^{2(j)} = \frac{(n_{1_k} - 1)s_{1_k}^{2(j)} + (n_{2_k} - 1)s_{2_k}^{2(j)}}{n_{1_k} + n_{2_k} - 2}$$

For the four scenarios (**Known + Pooled, Known + Unpooled, Unknown + Pooled, Unknown + Unpooled**) the standard error (SE) at look k in simulation j is defined as follows:

$$\begin{cases} SE_k^{(j)} = \sqrt{\frac{\sigma^2}{n_{1_k}} + \frac{\sigma^2}{n_{2_k}}} & Known + Pooled \\ SE_k^{(j)} = \sqrt{\frac{\sigma_1^2}{n_{1_k}} + \frac{\sigma_2^2}{n_{2_k}}} & Known + Unpooled \\ SE_k^{(j)} = \sqrt{\frac{s_k^{2(j)}}{n_{1_k}} + \frac{s_k^{2(j)}}{n_{2_k}}} & Unknown + Pooled \\ SE_k^{(j)} = \sqrt{\frac{s_{1_k}^{2(j)}}{n_{1_k}} + \frac{s_{2_k}^{2(j)}}{n_{2_k}}} & Unknown + Unpooled \end{cases}$$

The standardized (**Z-scale**) test statistic $\left(Z_k^{(j)}\right)$ at look k in simulation j is then compared to the boundaries at look k to determine the outcome at that analysis. For each simulation, the $\left(Z_k^{(j)}\right)$ will be compared sequentially $(1, 2...K-1, K)$ until an early stop occurs or the trial ends.

The counts for the outcome in each simulation are then used to calculate the simulated exit probability and resulting summary statistics. This is covered in subsection 8.7.3.

8.7.2.2 Two Proportions

The standardized test statistic for the proportion difference is equal to the following:

$$Z = \frac{\pi_1 - \pi_2}{\sqrt{\frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}}}$$

$$\pi = \frac{\sum x}{n}$$

where $\bar{\pi}_1 - \bar{\pi}_2$ is the proportion difference and $SE = \sqrt{\frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}}$ is the (unpooled) standard error[5], based on the per-group success proportions (π_1, π_2) and sample sizes.

Recall that the n_{1_k} Bernoulli data variates simulated for Group 1 up to look k for simulation index j was defined as $x_{1_k}^{(j)}$ and the n_{2_k} Bernoulli data variates simulated for Group 2 up to look k for simulation index j was defined as $x_{2_k}^{(j)}$.

Then the standardized test statistic at look k in simulation j can be defined as:

[5]Note that $\left(\frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}\right)^{-1}$ is the (Fisher) Information

$$Z_k^{(j)} = \frac{\pi_{1_k}^{(j)} - \pi_{2_k}^{(j)}}{SE_k^{(j)}}$$

where

$$\pi_{1_k}^{(j)} = \frac{\sum_{1}^{n_{1_k}} x_{1_k}^{(j)}}{n_{1_k}}$$

$$\pi_{2_k}^{(j)} = \frac{\sum_{1}^{n_{2_k}} x_{2_k}^{(j)}}{n_{2_k}}$$

The calculation of the standard error will depend on the **Standard Deviation Definition** (chosen at **Step 2: Sequential Design Inputs**) where the choice is between **Pooled** (per-group success proportions replaced with the pooled success proportion in SE formula) and **Unpooled** (per-group success proportions used direclty in SE formula).

The pooled success proportion at look k in simulation j can be defined as:

$$\bar{\pi}_k^{(j)} = \frac{n_{1_k}\pi_{1_k}^{(j)} + n_{2_k}\pi_{2_k}^{(j)}}{n_{1_k} + n_{2_k}}$$

For the two scenarios of **Pooled** and **Unpooled**, the standard error (SE) at look k in simulation j is defined as follows:

$$\begin{cases} SE_k^{(j)} = \sqrt{\frac{\bar{\pi}_k^{(j)}\left(1-\bar{\pi}_k^{(j)}\right)}{n_{1_k}} + \frac{\bar{\pi}_k^{(j)}\left(1-\bar{\pi}_k^{(j)}\right)}{n_{2_k}}} & Pooled \\ SE_k^{(j)} = \sqrt{\frac{\pi_{1_k}^{(j)}\left(1-\pi_{1_k}^{(j)}\right)}{n_{1_k}} + \frac{\pi_{2_k}^{(j)}\left(1-\pi_{2_k}^{(j)}\right)}{n_{2_k}}} & Unpooled \end{cases}$$

The standardized (**Z-scale**) test statistic $\left(Z_k^{(j)}\right)$ at look k in simulation j is then compared to the boundaries at look k to determine the outcome at that analysis. For each simulation, the $\left(Z_k^{(j)}\right)$ will be compared sequentially $(1, 2...K-1, K)$ until an early stop occurs or the trial ends.

The counts for the outcome in each simulation are then used to calculate the simulated exit probability and resulting summary statistics. This is covered in subsection 8.7.3.

8.7.3 Group Sequential Boundaries

In subsection 8.7.2 the calculation for the stamdardized test statistic (Z-statistic) was described for each supported scenario for group sequential design simulation.

Recall that the standardized test statistic at look k in simulation run i is defined as $Z_k^{(i)}$. For each group sequential design simulation the test statistics will be compared to the available boundaries sequentially until either early stopping occurs or the final analysis.

For the simulation results, we are interested in the count of how many simulations stopped at each look k for efficacy and futility. We will define the count of how many simulations stopped at look k for efficacy as E_k and the count of how many simulations stopped at look k for futility as F_k. The count of the number of subjects who continue to the next look $k+1$ will be designated as C_k.

At the the final look k a decision for efficacy (E_K) or futility (F_K) is required, therefore $C_K = 0$.

The decision rules for all supported group sequential scenarios, depending on the presence of efficacy and/or futility boundaries and whether a one-sided or two-sided test was used, is covered next.

8.7.3.1 Boundary Decision Rules

The **Boundary Decision Rules** will depend on the following criteria:

1. Which boundaries are present
2. The direction of the test

For **1. Which boundaries are present**, the following scenarios are possible based on which of the efficacy or futility boundaries are present and whether the test is one-sided or two-sided. The combination of these two factors provides the following six scenarios with associated boundaries (with notation definition in brackets):

- **Efficacy Only 1-sided:** Efficacy Bound (e_k)
- **Futility Only 1-sided:** Futility Bound (f_k)
- **Efficacy and Futility 1-sided:** Efficacy Bound (e_k), Futility Bound (f_k)
- **Efficacy Only 2-sided:** Upper Efficacy Bound ($e(U)_k$), Lower Efficacy Bound ($e(L)_k$)
- **Futility Only 1-sided:** Upper Futility Bound ($f(U)_k$), Lower Futility Bound ($f(L)_k$)
- **Efficacy and Futility 2-sided:** Upper Efficacy Bound ($e(U)_k$), Lower Efficacy Bound ($e(L)_k$), Upper Futility Bound ($f(U)_k$), Lower Futility Bound ($f(L)_k$)

For **2. The direction of the test**, this will control the direction of the test and therefore whether the exit or continuation area is above or below a given boundary. **Direction** is based either on the sign of the bound at the final look K for designs with only one boundary or on the relative positions of the bounds if there are multiple bounds. Where multiple bounds are present, the direction condition will also indicate the **consistency** condition where boundaries must be consistent across all looks e.g. **Upper** boundaries cannot start above **Lower** boundaries and then switch to **Upper < Lower** at later looks.

A **higher** direction is equivalent to assuming that higher values for the treatment effect θ (e.g. mean difference $\bar{X}_1 - \bar{X}_2$ from subsubsection 8.7.2.1) are "better" or "worse" respectively and vice-versa for the **lower** direction.

A summary of the decision rules for the six boundary scenarios under the **higher** or **lower** direction assumption is provided next.

Efficacy Only 1-sided The boundaries present are the following:

- Efficacy Bounds (e)

$$e = e_1, e_2 \dots e_{K-1}, e_K$$

The **direction** is defined as:

$$\begin{cases} higher & e_K > 0 \\ lower & e_K < 0 \end{cases}$$

If **direction = higher**, the stopping rules for the interim analyses $(1, 2 \dots, K-1)$ are

$$\begin{cases} Z_k^{(j)} > e_k & Stop(Efficacy) \\ Z_k^{(j)} < e_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} Z_K^{(j)} > e_K & Stop(Efficacy) \\ Z_K^{(j)} < e_K & Stop(Futility) \end{cases}$$

If **direction = lower**, the stopping rules for the interim analysis $(1, 2 \dots, K-1)$ are

$$\begin{cases} Z_k^{(j)} < e_k & Stop(Efficacy) \\ Z_k^{(j)} > e_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} Z_K^{(j)} < e_K & Stop(Efficacy) \\ Z_K^{(j)} > e_K & Stop(Futility) \end{cases}$$

Based on the above:

$$E_k = \sum_{j=1}^{J} Stop(Efficacy)_k^{(j)}$$

$$F_k = \begin{cases} 0 & k < K \\ \sum_{j=1}^{J} Stop(Futility)_K^{(j)} & k = K \end{cases}$$

Futility Only 1-sided The boundaries present are the following:

- Futility Bounds (f)

$$f = f_1, f_2 \dots f_{K-1}, f_K$$

The **direction** is defined as:

$$\begin{cases} higher & f_K > 0 \\ lower & f_K < 0 \end{cases}$$

If **direction = higher**, the stopping rules for the interim analyses $(1, 2 \ldots, K-1)$ are

$$\begin{cases} Z_k^{(j)} < f_k & Stop(Futility) \\ Z_k^{(j)} > f_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} Z_K^{(j)} < f_K & Stop(Futility) \\ Z_K^{(j)} > f_K & Stop(Efficacy) \end{cases}$$

If **direction = lower**, the stopping rules for the interim analysis $(1, 2 \ldots, K-1)$ are

$$\begin{cases} Z_k^{(j)} > f_k & Stop(Futility) \\ Z_k^{(j)} < f_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} Z_K^{(j)} > f_K & Stop(Futility) \\ Z_K^{(j)} < f_K & Stop(Efficacy) \end{cases}$$

Based on the above:

$$F_k = \sum_{j=1}^{J} Stop(Futility)_k^{(j)}$$

$$E_k = \begin{cases} 0 & k < K \\ \sum\limits_{j=1}^{J} Stop(Efficacy)_K^{(j)} & k = K \end{cases}$$

Efficacy and Futility 1-sided The boundaries present are the following:

- Efficacy Bounds (e)

$$e = e_1, e_2 \ldots e_{K-1}, e_K$$

- Futility Bounds (f)

$$f = f_1, f_2 \ldots f_{K-1}, f_K$$

The **direction** is defined as:

$$\begin{cases} higher & e_k > f_k \\ lower & e_k < f_k \end{cases}$$

with exception of look K where $e_K = f_K$

If **direction = higher**, the stopping rules for the interim analyses $(1, 2 \ldots, K-1)$ are

$$\begin{cases} Z_k^{(j)} > e_k & Stop(Efficacy) \\ Z_k^{(j)} < f_k & Stop(Futility) \\ f_k < Z_k^{(j)} < e_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} Z_K^{(j)} > e_K & Stop(Efficacy) \\ Z_K^{(j)} < e_K & Stop(Futility) \end{cases}$$

If **direction = lower**, the stopping rules for the interim analysis $(1, 2 \ldots, K-1)$ are

$$\begin{cases} Z_k^{(j)} < e_k & Stop(Efficacy) \\ Z_k^{(j)} > f_k & Stop(Futility) \\ e_k < Z_k^{(j)} < f_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} Z_K^{(j)} < e_K & Stop(Efficacy) \\ Z_K^{(j)} > e_K & Stop(Futility) \end{cases}$$

Based on the above:

$$E_k = \sum_{j=1}^{J} Stop(Efficacy)_k^{(j)}$$

$$F_k = \sum_{j=1}^{J} Stop(Futility)_k^{(j)}$$

Efficacy Only 2-sided The boundaries present are the following:

- Upper Efficacy Bounds $(e(U))$

$$e(U) = e(U)_1, e(U)_2 \ldots e(U)_{K-1}, e(U)_K$$

- Lower Efficacy Bounds $(e(L))$

$$e(L) = e(L)_1, e(L)_2 \ldots e(L)_{K-1}, e(L)_K$$

The **direction** is defined as:

$$\begin{cases} higher & e(U)_k > e(L)_K \\ lower & e(U)_k < e(L)_K \end{cases}$$

If **direction = higher**, the stopping rules for the interim analyses $(1, 2 \ldots, K-1)$ are

$$\begin{cases} Z_k^{(j)} > e\left(U\right)_k & Stop(Efficacy) \\ Z_k^{(j)} < e\left(L\right)_k & Stop(Efficacy) \\ e\left(L\right)_k < Z_k^{(j)} < e\left(U\right)_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} Z_K^{(j)} > e\left(U\right)_K & Stop(Efficacy) \\ Z_K^{(j)} < e\left(L\right)_K & Stop(Efficacy) \\ e\left(L\right)_K < Z_K^{(j)} < e\left(U\right)_K & Stop(Futility) \end{cases}$$

If **direction = lower**, the stopping rules for the interim analysis $(1, 2 \ldots, K-1)$ are

$$\begin{cases} Z_k^{(j)} < e\left(U\right)_k & Stop(Efficacy) \\ Z_k^{(j)} > e\left(L\right)_k & Stop(Efficacy) \\ e\left(U\right)_k < Z_k^{(j)} < e\left(L\right)_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} Z_K^{(j)} < e\left(U\right)_K & Stop(Efficacy) \\ Z_K^{(j)} > e\left(L\right)_K & Stop(Efficacy) \\ e\left(U\right)_K < Z_K^{(j)} < e\left(L\right)_K & Stop(Futility) \end{cases}$$

It may be of interest to find the **Upper Efficacy** and **Lower Efficacy** exit counts separately. This is equivalent to designating the first condition in all the above $Stop(Efficacy_U)$ and the second condition as $Stop(Efficacy_L)$ but otherwise is unchanged.

Based on the above:

$$E_k = \sum_{j=1}^{J} Stop(Efficacy)_k^{(j)}$$

$$F_k = \begin{cases} 0 & k < K \\ \sum\limits_{j=1}^{J} Stop(Futility)_K^{(j)} & k = K \end{cases}$$

Futility Only 2-sided The boundaries present are the following:

- Upper Futility Bounds $(f\left(U\right))$

$$f\left(U\right) = f\left(U\right)_1, f\left(U\right)_2 \ldots f\left(U\right)_{K-1}, f\left(U\right)_K$$

- Lower Futility Bounds $(f\left(L\right))$

$$f\left(L\right) = f\left(L\right)_1, f\left(L\right)_2 \ldots f\left(L\right)_{K-1}, f\left(L\right)_K$$

The **direction** is defined as:

$$\begin{cases} higher & f(U)_k > f(L)_K \\ lower & f(U)_k < f(L)_K \end{cases}$$

If **direction = higher**, the stopping rules for the interim analyses $(1, 2 \ldots, K-1)$ are

$$\begin{cases} f(L)_k < Z_k^{(j)} < f(U)_k & Stop(Futility) \\ Z_k^{(j)} > f(U)_k & Continue \\ Z_k^{(j)} < f(L)_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} f(L)_K < Z_K^{(j)} < f(U)_K & Stop(Futility) \\ Z_K^{(j)} > f(U)_K & Stop(Efficacy) \\ Z_K^{(j)} < f(L)_K & Stop(Efficacy) \end{cases}$$

If **direction = lower**, the stopping rules for the interim analysis $(1, 2 \ldots, K-1)$ are

$$\begin{cases} f(U)_k < Z_k^{(j)} < f(L)_k & Stop(Futility) \\ Z_k^{(j)} < f(U)_k & Continue \\ Z_k^{(j)} > f(L)_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} f(U)_K < Z_K^{(j)} < f(L)_K & Stop(Futility) \\ Z_K^{(j)} < f(U)_K & Stop(Efficacy) \\ Z_K^{(j)} > f(L)_K & Stop(Efficacy) \end{cases}$$

Based on the above:

$$F_k = \sum_{j=1}^{J} Stop(Futility)_k^{(j)}$$

$$E_k = \begin{cases} 0 & k < K \\ \sum_{j=1}^{J} Stop(Efficacy)_K^{(j)} & k = K \end{cases}$$

Efficacy and Futility 2-sided The boundaries present are the following:

- Upper Efficacy Bounds $(e(U))$

$$e(U) = e(U)_1, e(U)_2 \ldots e(U)_{K-1}, e(U)_K$$

- Lower Efficacy Bounds $(e(L))$

$$e(L) = e(L)_1, e(L)_2 \ldots e(L)_{K-1}, e(L)_K$$

- Upper Futility Bounds $(f(U))$

$$f(U) = f(U)_1, f(U)_2 \ldots f(U)_{K-1}, f(U)_K$$

- Lower Futility Bounds ($f(L)$)

$$f(L) = f(L)_1, f(L)_2 \ldots f(L)_{K-1}, f(L)_K$$

The **direction** is defined as:

$$\begin{cases} higher & e(U)_k > f(U)_k > f(L)_k > e(L)_k \\ lower & e(U)_k < f(U)_k < f(L)_k < e(L)_k \end{cases}$$

with exception of look K where $e(U)_K = f(U)_K$ and $e(L)_K = f(L)_K$

If **direction = higher**, the stopping rules for the interim analyses $(1, 2 \ldots, K-1)$ are

$$\begin{cases} Z_k^{(j)} > e(U)_k & Stop(Efficacy) \\ Z_k^{(j)} < e(L)_k & Stop(Efficacy) \\ f(L)_k < Z_k^{(j)} < f(U)_k & Stop(Futility) \\ f(U)_k < Z_k^{(j)} < e(U)_k & Continue \\ e(L)_k < Z_k^{(j)} < f(L)_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} Z_K^{(j)} > e(U)_K & Stop(Efficacy) \\ Z_K^{(j)} < e(L)_K & Stop(Efficacy) \\ f(L)_K < Z_K^{(j)} < f(U)_K & Stop(Futility) \end{cases}$$

If **direction = lower**, the stopping rules for the interim analysis $(1, 2 \ldots, K-1)$ are

$$\begin{cases} Z_k^{(j)} < e(U)_k & Stop(Efficacy) \\ Z_k^{(j)} > e(L)_k & Stop(Efficacy) \\ f(U)_k < Z_k^{(j)} < f(L)_k & Stop(Futility) \\ e(U)_k < Z_k^{(j)} < f(U)_k & Continue \\ f(L)_k < Z_k^{(j)} < e(L)_k & Continue \end{cases}$$

and at the final analysis (K) the stopping rules are

$$\begin{cases} Z_K^{(j)} < e(U)_K & Stop(Efficacy) \\ Z_K^{(j)} > e(L)_K & Stop(Efficacy) \\ f(U)_K < Z_K^{(j)} < f(L)_K & Stop(Futility) \end{cases}$$

It may be of interest to find the **Upper Efficacy** and **Lower Efficacy** exit counts separately. This is equivalent to designating the first condition in all the above $Stop(Efficacy_U)$ and the second condition as $Stop(Efficacy_L)$ but otherwise is unchanged.

Based on the above:

$$F_k = \sum_{j=1}^{J} Stop(Futility)_k^{(j)}$$

$$E_k = \sum_{j=1}^{J} Stop(Efficacy)_K^{(j)}$$

Summary Based on the above, the algorithm should generate the a series of counts for the number of simulations which stopped at each look for the specified boundaries. We will indicate these objects as the following for the efficacy (E) and futility (F) stopping counts respectively:

$$E = E_1, E_2, \ldots E_{K-1}, E_K$$

$$F = F_1, F_2, \ldots F_{K-1}, F_K$$

8.7.3.2 Statistical Scale Conversions

nQuery provides four statistical scales that the boundaries can be parameterized on. These are the **Z-scale, p-value Scale, Score Scale** and δ**-Scale**.

As referenced above, the test statistic (subsection 8.7.2) and group sequential boundary decisions (subsubsection 8.7.3.1) in nQuery are made the standardized test statistic scale - this corresponds to the **Z-scale**. Within nQuery, when other scales are used they are converted to the **Z-scale** and the algorithm is implemented as above. Further detail on these scales is provided in subsubsection 7.2.1.1 and subsubsection 7.2.4.5

These conversions are provided next.

p-value Scale The **p-value Scale** (p_k) corresponds to setting the boundaries in terms of the p-value. The p-values to be compared to the boundaries are presumed to come from the appropriate unadjusted Z-test (e.g. Z-test for means, Chi-Squared Test for proportions, Log-Rank Test for survival). This is a common boundary scale requested by researchers.

The conversion to the **Z-scale** is as follows:

$$\begin{cases} Z_k = -\varphi(p_k) & 1 - sided|Upper \\ Z_k = \varphi(p_k) & Lower \end{cases},$$

where the first condition refers to the case of a one-sided analysis or, for a two-sided analysis, where calculating the **Upper Efficacy/Futility Bound.** The second condition is for the **Lower Efficacy/Futility Bound** for a two-sided analysis.

As implied from these conditions, the p-value scale is always assumed to **direction = higher**. This means if using the p-value boundary parameterization care should be taken at **Step 1: Simulation Inputs** that the inputs are consistent with that for the treatment effect (e.g. **Mean Difference**).

Score Scale The **Score Scale** (S_k) corresponds to setting the boundaries in terms of the score statistic. Score statistisc (and other increment based statistics such as the B-value) are widely used in the derivation of group sequential designs, though less used in practice. The Score statistic based on the (Fisher) information (I) will equal θI.

The conversion to the **Z-scale** is as follows:

$$Z_k = S_k / \sqrt{I_k}$$

The **Score Scale** has the same directionality as the Z-scale.

δ-**Scale** The **δ-scale** corresponds to setting the boundaries in terms of the treatment effect. The definition will depend on the endpoint of interest. For example, this could be mean difference for the two-sample Z-test, the risk difference for the chi-squared test or the log hazard ratio for the log-rank test. This is a common boundary scale requested by researchers.

The conversion to the **Z-scale** is as follows:

$$Z_k = \delta_k \sqrt{I_k}$$

The **δ-scale** has the same directionality as the Z-scale.

8.7.3.3 t-statistic Adjusted Boundaries (Endpoint of Interest = Means)

In clinical trials, the **t-test** is the most popular test for comparing means. However, the group sequential boundaries are calculated under the assumption of a (multvariate) Z-distribution process (subsubsection 7.2.1.1 for details) which corresponds to using the **Z-test.** While it is possible to construct exact boundaries for the **t-test** [Jennison and Turnbull, 1999, Liu and Li, 2014, Rom and McTague, 2020], this adds significant complication compared to constructing under the multivariate Z-distribution as the multivaritate t-distribution is significantly more complex.

However, Jennison and Turnbull [Jennison and Turnbull, 1999] showed that approximate **t-test** boundaries can be constructed based on the more commonly available Z-test boundaries. Based on their work, they state these boundaries are "remarkably accurate" for controlling the error rates at the desired level when using the **t-test.**

The **Boundary Decision** field uses these adjusted boundaries during simulation if **t-Distribution** is selected. Note that **Boundary Table** at **Step 3: Boundary Table** will be the original Z-distribution boundaries with the adjustment occuring within the simulation algorithm.

The method for generating these adjusted boundaries is as follows:

$$p_k = \Phi\left(Z_k\right)$$

$$Z(t)_k = T_{df}^{-1}\left(p_k\right)$$

where Φ is the standard normal distribution cumulative distribution function (CDF), $Z(t)_k$ are the t-distribution adjusted boundaries and T_{df}^{-1} is the inverse CDF (quantile function) for the central t-distribution.

Replace the boundaries in subsection 8.7.3 with these t-distribution adjusted boundaries and proceed otherwise the same.

8.7.4 Group Sequential Outputs

An overview of the statistics calculated in the **Simulation Report** is provided here. As per subsubsection 8.7.3.1, the outcome of the group sequential simulation should be a series of counts for how many simulations stopped at each look for efficacy and/or futility.

Efficacy (E) and futility (F) stopping counts objects contain the counts for each look k as follows:

$$E = E_1, E_2, \ldots E_{K-1}, E_K$$

$$F = F_1, F_2, \ldots F_{K-1}, F_K$$

Assuming that J equals the total number of simulations ran then we can calculate the percentage of trials which exited at each look for efficacy and futility as $E(\%) = 100(E/J)$ and $F(\%) = 100(F/J)$, where it assumed each element is divided by J.

The total % of subjects who stopped at a given look is therefore equal to $T(\%) = E(\%) + F(\%)$. Assuming pairwise addition, the $T(\%)$ object will have the following sequence: $T(\%) = T(\%)_1, T(\%)_2, \ldots T(\%)_{K-1}, T(\%)_K$ which will sum to 100%.

Based on the above we can calculate the power and average sample size $\left(\bar{N}\right)$ as follows:

$$Power = \sum_{k=1}^{K} E(\%)$$

$$\bar{N} = \sum_{k=1}^{K} \frac{T(\%)}{100} (N_k)$$

where N_k is the total sample size at look k.

9 Group Sequential Designs (Lan-DeMets Spending Function Only Tables), Interim Monitoring & Unblinded Sample Size Re-estimation

This chapter only provides information on the ***Group Sequential Design (Lan-DeMets Spending Function Only)*** *tables and their associated* ***Interim Monitoring & Unblinded Sample Size Re-estimation*** *tools.*

For information on the ***Group Sequential Design (Spending Function, Haybittle-Peto, Wang-Tsiatis, Unified Family, Custom Boundaries)*** *series of tables and the associated* ***Group Sequential Simulator Tool****, please refer to chapter 7.*

For reference, the Lan-DeMets Spending Function Only tables are MTT12 (Two Means), MTT40 (Two Poisson), MTT42 (Two Negative Binomial), MTE32 (Two Means Non-inferiority), MOT26 (One Mean), PTT12 (Two Proportions), POT8 (One Proportion - Alternative Variance), POT13 (One Proportion - Null Variance), STT12 (Two Survival - Fixed Follow-up, Constant Hazard), STT15 (Two Survival - Event-Driven, Constant Hazard), STT23 (Two Survival - Event-Driven, Piecewise Survival, Accrual Rates), STT25 (Two Survival - Event-Driven, Piecewise Survival, Accrual %).

The associated Interim Monitoring & Unblinded Sample Size Re-estimation tables are MTT25 (Two Means - linked with MTT12), PTT21 (Two Proportion - linked with PTT12) and STT17 (Two Survival - linked with STT12, STT15, STT23, STT25)

The *Spending Function, Haybittle-Peto, Wang-Tsiatis, Unified Family, Custom Boundaries tables are the GSTX series of tables including GST0 (Information-Based), GST1 (Two Means), GST2 (Two Proportions), GST3 (Two Survival - Event-Driven or Fixed Follow-up, Piecewise Survival, Accrual %)*

9.1 Introduction

This chapter provides an overview of the spending function only group sequential designs tables and associated interim monitoring and unblinded sample size re-estimation tool available for the two arm means, proportions and survival group sequential designs.

This section will cover the statistical theory behind the **Group Sequential Design (Lan-DeMets Spending Function Only)** series of tables and will give detailed description of how to design a group sequential trial in nQuery using these tables. It will

also summarize the theory and user interface of the nQuery Adapt tool for **Interim Monitoring & Unblinded Sample Size re-estimation**.

Note that much of theory and guidance here is also relevant for the Multi-arm Multi-Stages (MAMS) Group Sequential Design tables (MGT6, PGT4).

These Group Sequential Design and Interim Monitoring & Unblinded Sample Size Re-estimation features will only be available to users if an nQuery Advanced Pro license is active. Active packages are displayed in the Packages section on the Home tab. To purchase additional packages, see `www.statsols.com`.

9.2 Group Sequential Test Design

9.2.1 Background

Group sequential designs are an extension of fixed period designs in which data from the trial is analyzed at one or more stages prior to the conclusion of the trial. The trial can then be stopped early if there is strong evidence for or against the proposed treatment being effective based on data up to that point. Group sequential designs are one of the most widely used types of adaptive trial and provide the opportunity to stop a trial early for efficacy (strong interim evidence against the null hypothesis) and/or futility (strong interim evidence for the null hypothesis) and thus significantly reduce the economic and ethical costs over the equivalent fixed period design.

Note: Group Sequential Design is currently only available for users with an nQuery Advanced Pro license except for the Group Sequential Design tables for Two Means (MTT12), Two Proportions (PTT12) and Two Survival - Equal Followup (STT12) which are in nQuery Advanced (Core). Active packages are displayed in the Packages section in the Home tab. To purchase additional packages, see `www.statsols.com`.

9.2.2 Group Sequential Design Theory

In nQuery, the group sequential design tables' power and sample size calculations are performed using the Lan-DeMets alpha spending function approach [Demets and Lan, 1984, Demets and Lan, 1994]; for estimating boundary values. Building on the work of Lan and DeMets; Pampallona, Tsiatis, and Kim [Pampallona et al., 1995, Pampallona et al., 2001] later put forward the concept of using a beta spending approach to construct boundaries for futility where the evidence for the null is strong. These boundary values indicate the interim test values (test statistic, effect size, p-value) which would lead to the trial stopping early based on interim data. Boundary values can be estimated in a number of ways with nQuery providing bounds based on the O'Brien-Fleming [O'Brien and Fleming, 1979], Pocock [Pocock, 1977], Hwang-Shih-DeCani [Hwang et al., 1990] and Power Family spending functions. Each of these spending functions spend a certain proportion of the alpha error (Type I/efficacy) and/or beta error (Type II/futility) at each analysis or 'look' and then make the needed adjustments to the sample size and final errors to preserve the overall Type I and Type-2 errors. The "spent" alpha and beta values used at each look are calculated based upon the test hypothesis, the spending function chosen, the number of looks to be taken during the course of the study as well

as the overall Type I and Type-2 error rates. For a full introduction to group sequential methods, we recommend *Group Sequential Methods Applications to Clinical Trials* by Jennison & Turnbull (2000) [Jennison and Turnbull, 1999].

9.2.2.1 Spending Functions

There are four spending functions available to the user in nQuery for the efficacy and futility bounds. Note that nQuery also provides the option to manually input boundary values. As standard all alpha spending functions have the properties that the error spent at the start of the trial equals zero and the error spent at the final analysis equals the original desired error level i.e. the desired test significance level for alpha spending, one minus the power (as a proportion) for beta spending. Functionally the alpha and beta spending functions are the same.

The spending functions for alpha spending are summarised in Table 9.1 where $\alpha(\tau)$ is the cumulative alpha spent at the specified look, α is overall alpha error, τ is the information time (usually the sample size up to that look as a proportion of the total sample size), $z_{1\text{-}\alpha/2}$ is the inverse standard normal cumulative distribution assessed at "1-$\alpha/2$", Φ is the standard normal cumulative distribution function, ρ is the Power Family parameter and γ is the Hwang-Shih-DeCani gamma parameter.

Table 9.1: Spending Functions

Spending Function	Form
O'Brien-Fleming	$\alpha(\tau) = 2\left(1 - \Phi\left(\frac{z_{1-\alpha/2}}{\sqrt{\tau}}\right)\right)$
Pocock	$\alpha(\tau) = \alpha ln(1 + (e-1)\tau)$
Power Family	$\alpha(\tau) = \alpha\tau^{\rho}$
Hwang-Shih-DeCani	$\alpha(\tau) = \alpha\left[\frac{\left(1-e^{-\gamma\tau}\right)}{(1-e^{-\gamma})}\right]$

Most spending functions spend less error at the earlier looks, with the O'Brien-Fleming spending function being more conservative than the Pocock spending function (Power Family/Hwang-Shih-DeCani will depend on their free parameter). This is usually a desired characteristic as it means that the results of any interim analysis will only be considered significant (and thus ending the trial) at an early stage with an extreme result. It also means that the final analysis will be more comparable in terms of sample size and significance boundaries to an equivalent fixed term design.

9.2.2.2 Boundaries

The boundaries in nQuery represent the critical values at each look above or below which the trial would end early. These boundaries are usually constructed using the alpha and beta spending functions, though users are given the option of entering these manually. For the spending function approach, nQuery will automatically generate boundaries for the early rejection of the null hypothesis (if an efficacy alpha spending function is active), early finding for the null hypothesis (if a futility beta spending function is active) or both (if futility and efficacy are both active using a combination of both the alpha and beta spending functions).

Once these critical boundary statistics are generated, they can be compared during interim monitoring to the interim test statistics to decide whether to end the trial early. Essentially, if a test statistic crosses an efficacy boundary then it can be concluded that the experimental treatment shows a statistically significant effect and the trial can be stopped with rejection of the null hypothesis. If the test statistic crosses a futility boundary then this indicates with high probability that an effect will not be found, that the trial can be terminated by rejecting the alternative hypothesis. For futility bounds there are two options; either to have the boundaries binding, or non-binding. With binding boundaries, if the test statistic crosses the futility boundary, the test must be stopped, otherwise the type-1 error may become inflated. The reason for this is that there is an interaction between the efficacy and futility boundaries in their calculation that could cause the efficacy boundary to shift. In the case of non-binding boundaries; the efficacy boundaries are calculated as normal, that is, as if the futility boundaries did not exist. This eliminates the danger of inflating the Type I error if the futility boundary is overruled. The downside of the non-binding case is that it may increase the required sample size relative to the binding case.

In nQuery, boundary values are given on the standardized scale (i.e. Z-statistic scale) and will usually equal the treatment difference divided by its standard error. Examples for two independent sample design case are given in Table 9.2.2.2.

Table 9.2: Two Sample Group Sequential Standardized Statistics

Means	Proportions (Pooled)	Survival (Approx.)
$Z = \frac{\mu_2 - \mu_1}{\sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}}}$	$Z = \frac{\pi_2 - \pi_1}{\sqrt{\frac{\bar{\pi}(1-\bar{\pi})}{n_1} + \frac{\bar{\pi}(1-\bar{\pi})}{n_2}}}$	$Z = \frac{ln(HR)}{\sqrt{\frac{1}{E_1} + \frac{1}{E_2}}}$

For early stopping, we simply calculate the Z-statistic based on the current interim data and stop early if it is above the "upper" bound or below the "lower" (2-sided) or "futility" (1-sided) bound. Note that in nQuery; "upper", "lower" and "futility" are defined relative to the direction of the pre-specified effect size. For example, if the initial design assumes a negative difference ($\mu_1 > \mu_2$) then positive "upper" interim tests statistics would be those in which the interim difference is also negative and vice-versa. Similarly, "lower" results would be those in the opposite direction. Futility bounds can be above or below zero but the same guidance applies for the Z-statistic calculation.

9.2.2.3 Calculating Power or Sample Size

To calculate the power or sample size, we can use the drift parameter. This is the standardized Z-statistic defined above for the relevant test for the final look in the group sequential design. It also equals $\triangle\sqrt{I_x}$ where $\triangle$is the treatment effect (e.g. mean difference) and I_x is the maximum total information of the group sequential design.

To calculate the sample size, nQuery calculates the value for the drift parameter based on the values for the significance level, whether a one-sided or two-sided analysis is being used, the power, the number of looks and the spending function. The drift parameter is then set to equal to the standardized Z-statistic for the final look and via re-arrangement or iterative search, the sample size can be found.

To calculate the power, nQuery calculates the drift parameter by calculating the standardized Z-statistic based on the relevant information including the sample size. This drift is used to reverse-calculate the power via algorithm [Jennison and Turnbull, 1999] using the significance level, whether a one-sided or two-sided analysis is being used, the number of looks and the spending function.

9.2.3 Group Sequential Design in nQuery

nQuery provides an intuitive interface to make planning a group sequential design and finding the appropriate sample size or power easy. This section will outline the steps to plan a group sequential trial in nQuery.

9.2.3.1 Background

In nQuery, the vast majority of user actions and interface options are the same as for fixed term designs. This section will focus on the major additional issues associated with group sequential design in nQuery. See previous chapters for information on the shared table elements.

In nQuery, the inputs required for group sequential design can be split into two categories: fixed term parameters, group sequential trial (GST) parameters. The fixed term parameters are those which would be required to calculate the sample size or power for the equivalent fixed term design and thus will depend on the statistical test and data type. The GST parameters are those required to define the group sequential design such as the spending functions, number of interim looks etc. and will be effectively the same across different designs and data types. We will cover how both of these are entered and how to use nQuery for group sequential design in the following example.

9.2.3.2 Group Sequential Design Example

Main Table The main table is used to enter the fixed term parameters including the significance level, effect size and power among others. These will be very similar or the same as those for an equivalent fixed term design. In this example, the group sequential design is for a two sample t-test and thus the effect size is characterised by the mean difference and per-group standard deviations.

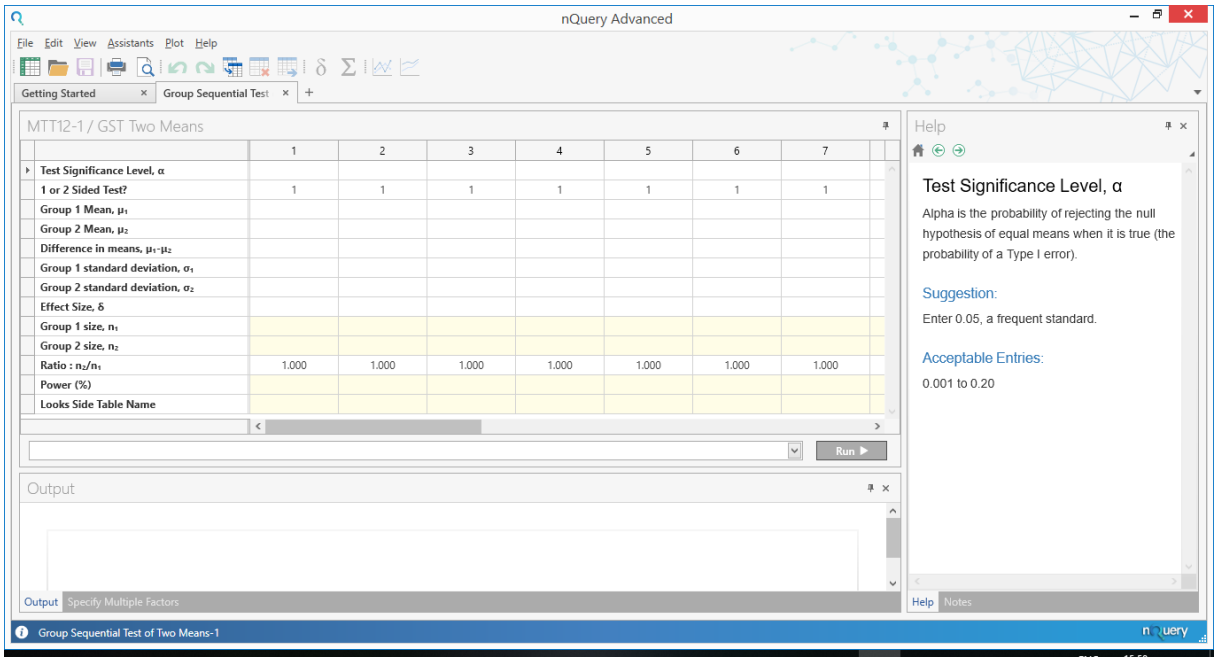


Figure 9.1: Two Means Group Sequential Design

The first thing we need to do is enter these fixed term design parameters. As these are effectively the same as for a fixed term design, please refer to previous chapters for guidance on filling these values. Here we will assume a treatment difference of -1 and per-group standard deviations of 2.5 for a 1-sided 5% significance test.

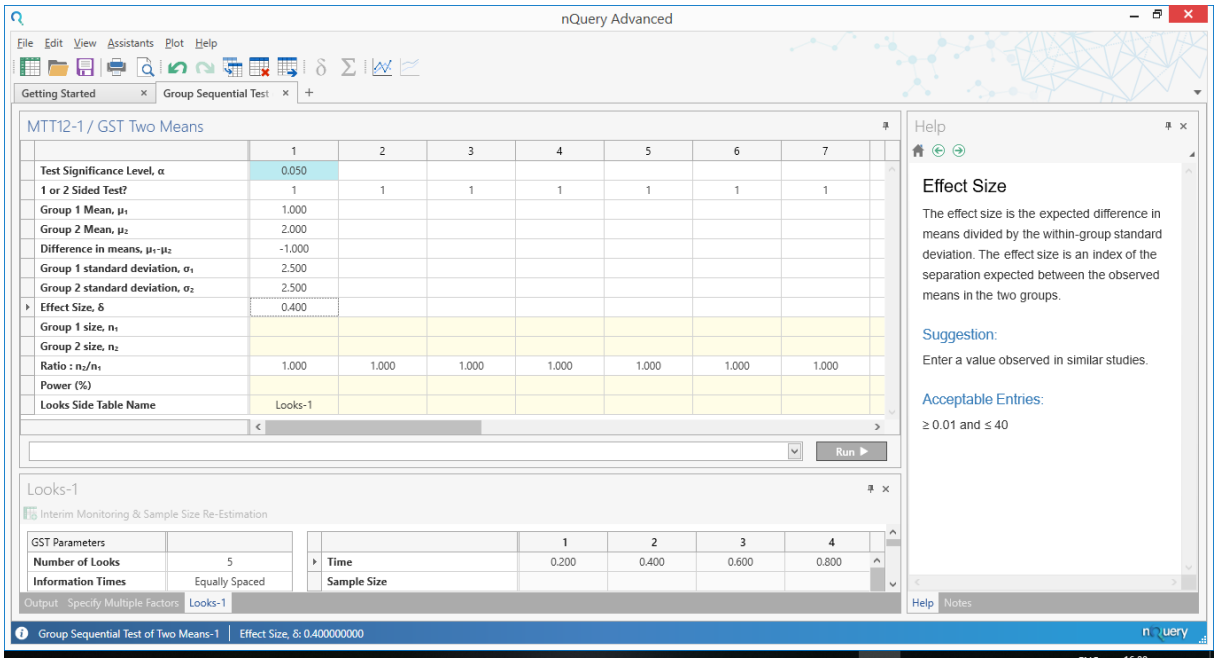


Figure 9.2: Example Fixed Term Parameters

We will leave the power and sample size empty for now as we want to define our group sequential design before calculating the sample size. To do this we will need to use the Looks side-table.

Looks Side-table The Looks side-table will automatically open below the main table for a specific column when any cell in the column is selected. It can also be manually opened using the "Compute Effect Size" options from the toolbar or Assistants file menu. For more details on what side-tables are and how they work in general, refer to subsection 1.7.4.

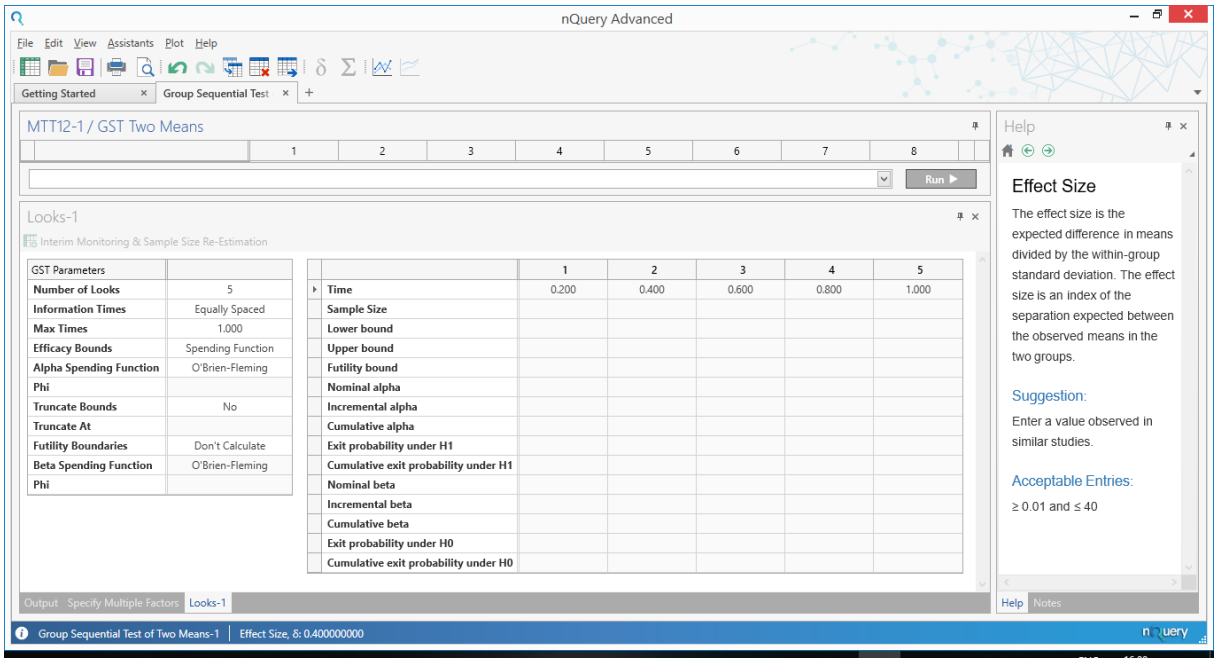


Figure 9.3: Looks Side-table

The Looks side-table can be split into two parts: the GST Parameters column (on the left) and the Looks table (on the right). The GST Parameters column defines the important features of the group sequential design. The Looks table will contain the important characteristics of the complete group sequential design as well as allowing some more complex study designs.

GST Parameters In the GST Parameters, there are 11 inputs settable to define the group sequential design operating characteristics. These can be summarised as follows:

1. Number of Looks (≥ 2): Set the total number of looks in group sequential design. As this is the total number of looks, the interim looks will equal this value minus one.
2. Information Times (Equally Spaced, User Input): Set whether the interim looks should be equally spaced or should be based on the user in-putted times (section 9.2.3.2)
3. Max Times (>0): Set the total maximum time. This will automatically re-scale the Time row in the Looks table when set. Note this is disabled when Information Times is set to User Input.
4. Efficacy Bounds (Spending Function, User Input, Don't Calculate): Set how the efficacy bounds will be calculated. Spending function will activate the Alpha Spending Function option, User Input will require editing the Upper Bound and Lower Bound rows of the Looks table (section 9.2.3.2), Don't Calculate will have no efficacy bounds and will only be usable if Futility Bounds is not set to Don't Calculate.

5. Alpha Spending Function (O'Brien-Fleming, Pocock, Power Family, Hwang-Shih-DeCani): Set the spending function used to calculate the efficacy bounds. For the Power Family and Hwang-Shih-DeCani options, the user will need to enter a value for the parameter row below this.
6. Power/HSD Parameter (>0 if Power Family, <3 if Hwang-Shih-DeCani): The free parameter for the Power Family or Hwang-Shih-DeCani efficacy spending function. Sometimes given the generic term of "Phi" in nQuery. See Table 9.1 for details.
7. Truncate Bounds (No, Yes): Set whether you want the efficacy bounds to be truncated at a specific user-defined value. If Yes is selected the Truncate at row will be active below.
8. Truncate at (>1): If Truncate Bounds is set to Yes, this defines the value at which the efficacy bounds are truncated. If an upper bound value in the Looks table is higher than this value then it will be set to this value. For lower bounds, it will be set to the minus version of this value.
9. Futility Bounds (Non-binding, Binding, Don't Calculate): Set how the futility bounds will be calculated. Non-binding and binding will activate the Alpha Spending Function option, Don't Calculate will have no futility bounds and will only be usable if Efficacy Bounds is not set to Don't Calculate. Non-binding allows futility bound contravention without error inflation, while binding does not allow this.
10. Beta Spending Function (O'Brien-Fleming, Pocock, Power Family, Hwang-Shih-DeCani): Set the spending function used to calculate the futility bounds. For the Power Family and Hwang-Shih-DeCani options, the user will need to enter a value for the parameter row below this.
11. Power/HSD Parameter (>0 if Power Family, <3 if Hwang-Shih-DeCani): The free parameter for the Power Family or Hwang-Shih-DeCani futility spending function. Sometimes given the generic term of "Phi" in nQuery. See Table 9.1 for details.

More detail on these are provided in the help cards and in subsection 9.2.2. In nQuery, the default values are for 5 look design with an efficacy bound using an O'Brien Fleming spending function. In this example, we will set these to have a two look equally spaced design (i.e. one interim analysis at 50% of the total sample size), an O'Brien-Fleming spending function for the efficacy bound and a Power Family spending function with a parameter equal to 1 (which is similar to Pocock spending function) for the non-binding futility bound.

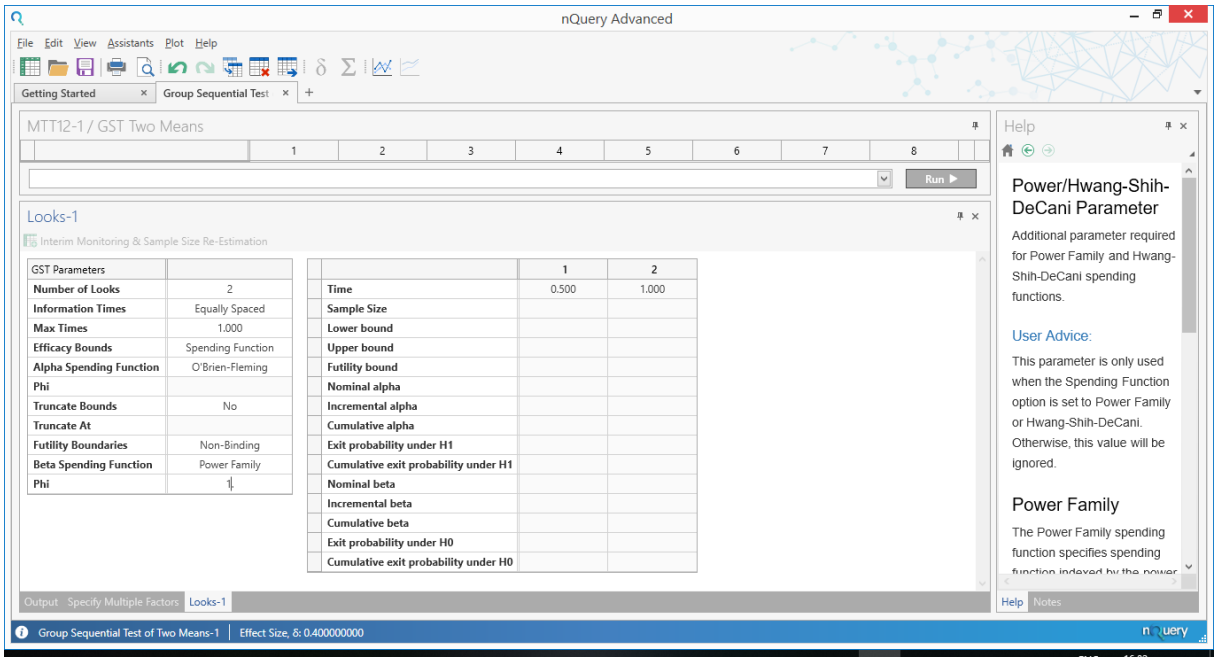


Figure 9.4: Example GST Parameters

Looks Table The Looks Table provides the information on the group sequential bounds and number of other useful parameters and additional information that characterises the complete group sequential design. In this table, each column corresponds to that Look. In this example, column 1 is the single interim look and column 2 is the final analysis. The Looks table contains the following rows:

1. Time: The Time at which each interim analysis will occur. By default, this will be the proportion of the total information at that look. The values in Time can be changed using the Max Times option (where each of these will be multiplied by the value in Max Times) or can be entered manually if Information Times is set to User Input
2. Sample Size: The cumulative sample size required at each look. The final entry will equal the calculated total sample size.
3. Lower Bound: The Lower Bound for efficacy below which we would end the trial early. The bounds are on the standardized test statistic scale. This will only be used for 2-sided designs with an active efficacy bound. These will be entered manually if Efficacy Bounds is set to User Input.
4. Upper Bound: The Upper Bound for efficacy above which we would end the trial early. The bounds are on the standardized test statistic scale. This will be only used with an active efficacy bound. These will be entered manually if Efficacy Bounds is set to User Input.
5. Futility Bound: The Futility Bound below which we would end the trial early for futility (can ignore if non-binding). The bounds are on the standardized test statistic scale. This will only be used for 1-sided designs with an active futility bound.
6. Nominal Alpha: This is the value of alpha (i.e. p-value) for these boundaries if they were used in a single stand-alone test.

7. Incremental Alpha: This is the amount of alpha (type I error) that is spent at this interim test since the last look. It is close to nominal alpha but differs slightly due to being adjusted for multiple testing.
8. Cumulative Alpha: This is total amount of alpha (type I error) that has been spent up to and including this look.
9. Exit Probability under H1: This is the percentage chance that the trial will stop, given the specified alternative hypothesis in the main table is true. This is chance for both the efficacy and futility bounds.
10. Cumulative Exit Probability under H1: This is the cumulative percentage chance that the trial will stopped at this or any previous look, given the specified alternative hypothesis in the main table is true. This is chance for both the efficacy and futility bounds.
11. Nominal Beta: This is the value of beta for these boundaries if they were used in a single stand-alone test.
12. Incremental Beta: This is the amount of beta error (type II error) that is spent at this interim test since the last look. It is close to nominal beta but differs slightly due to being adjusted for multiple testing.
13. Cumulative Beta: This is total amount of beta error (type II error) that has been spent up to and including this look.
14. Exit Probability under H0: This is the percentage chance that the trial will stop, given the specified null hypothesis (usually difference of zero) in the main table is true. This is chance for both the efficacy and futility bounds.
15. Cumulative Exit Probability under H0: This is the cumulative percentage chance that the trial will stopped at this or any previous look, given the specified null hypothesis (usually difference of zero) in the main table is true. This is chance for both the efficacy and futility bounds.

More information on these can be found in the table help cards when these rows are selected or in subsection 9.2.2. Unless a User Input option is set, this table will be read-only and will fill automatically once a power or sample size calculation occurs in the main table. In this example, set power to 80% in the main table. This will give a sample size of 87 in each group and following Looks table (Figure 9.5)

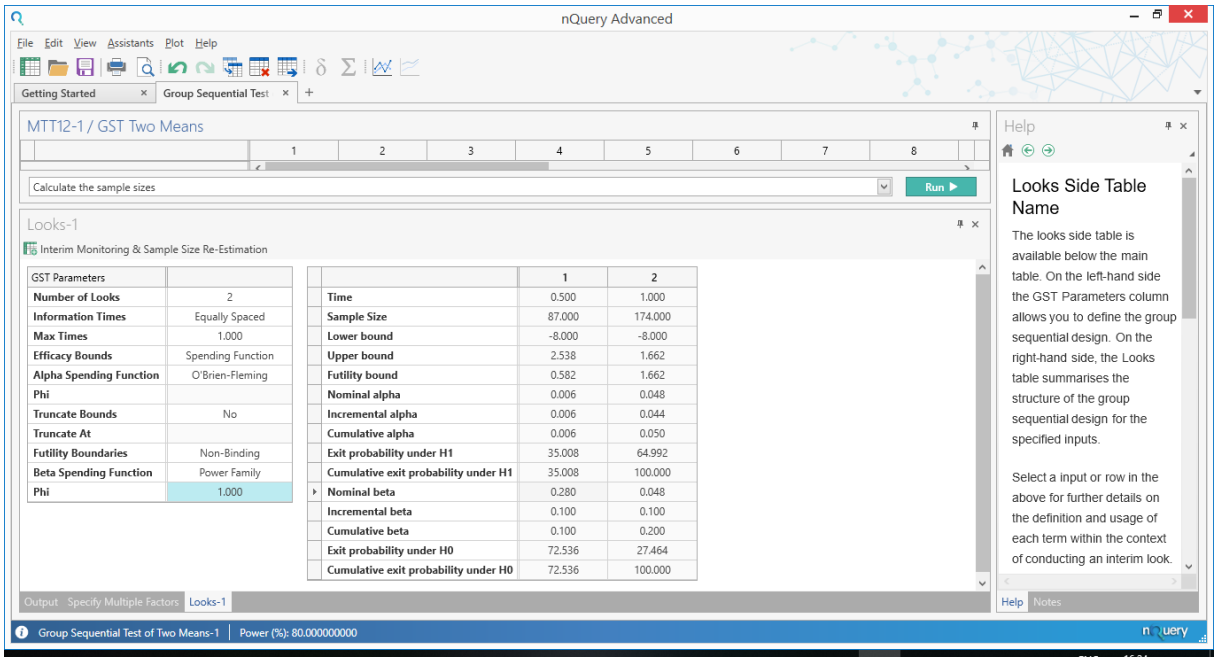


Figure 9.5: Example Looks Table

For practical purposes, the most important values are the Upper Bound, Futility Bound and Nominal Alpha. These are the values we will compare the interim test statistics (or p-values for nominal alpha) to decide whether to end the trial early or at the final analysis whether to reject the null hypothesis. The additional information provides useful context on the amount of error spent at each look and how likely the trial will end under the specified alternative hypothesis (i.e. the effect size in main table) or the null hypothesis.

As mentioned previously, certain elements of the Looks table will have to be set manually if Information Times or Efficacy Bounds are set to User Input. An example of these being set manually is given in Figure 9.6.

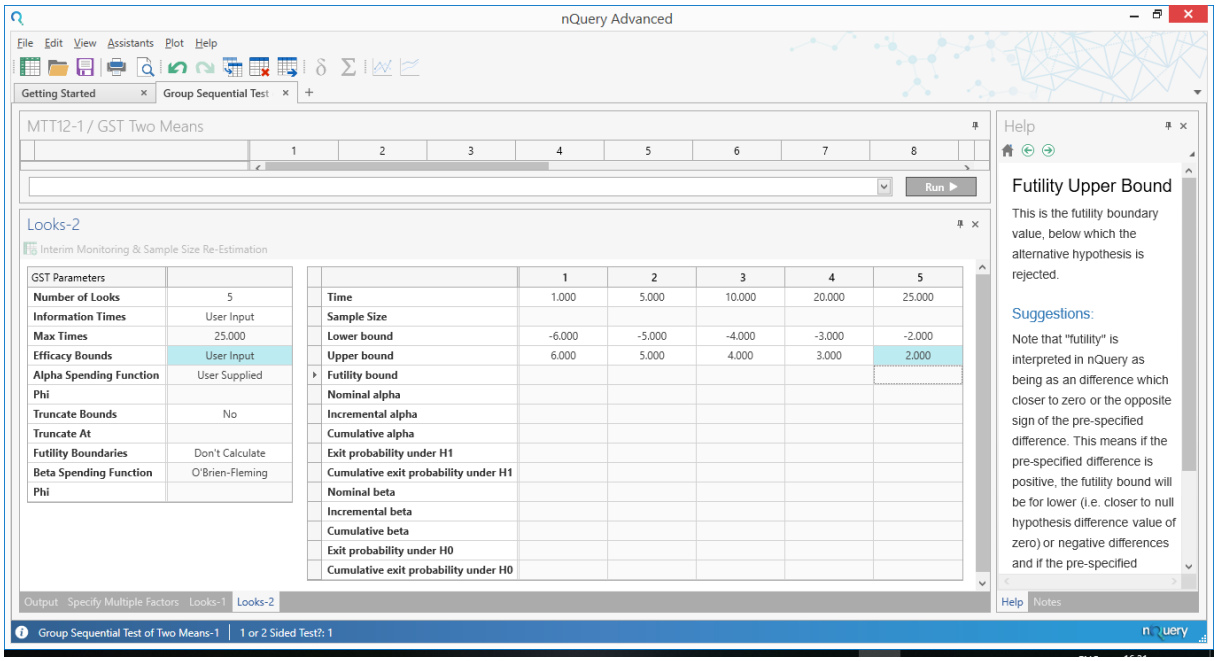


Figure 9.6: Custom Looks Table

9.3 Interim Monitoring and Unblinded Sample Size Re-estimation

9.3.1 Background

With nQuery Adapt, users will have access to the interim monitoring and sample size re-estimation tool. This tool will provide the opportunity to increase the sample size at an interim analysis if the interim information suggests a "promising" result but which is under-powered to find the current interim effect size if it were the true effect size. In group sequential designs and other similar designs, access to the interim data provides the opportunity to improve a study to better reflect the updated understanding of the study. One way to improve a group sequential design would be to use the interim effect size estimate not only to decide to whether to stop a trial early but to increase the sample size if the interim effect size is promising. This optionality gives the trialist the chance to power for a more optimistic effect size, thus reducing up-front costs, while still being confident of being able to find for a smaller but clinically relevant effect size by increasing sample size if needed.

Note: Interim Monitoring and Unblinded Sample Size Re-estimation is currently only available for users with an nQuery Advanced Pro license. Active packages are displayed in the Packages section in the Home tab. To purchase additional packages, see `www.statsols.com`.

9.3.2 Unblinded Sample Size Re-estimation Theory

nQuery provides unblinded sample size re-estimation methods based on two main approaches: Chen-DeMets-Lan method [Chen et al., 2004] and Cui-Hung-Wang method

[Cui et al., 1999]. The differences between this will be explored below but both of these methods are based on using the conditional power to define whether a result is "promising" and whether to increase and how much to increase the sample size.

9.3.2.1 Conditional Power

Conditional power is the probability that the trial will reject the null hypothesis at a subsequent look given the current test statistic and the assumed parameter values, which are usually assumed to equal their interim estimates. For "promising" trials where the conditional power falls between a lower bound, a typical value would be 50%, and the initial target power the sample size can be increased to make the conditional power equal the target study power.

The conditional power is calculated by assuming a set of "true" values for the fixed term parameters, the interim standardized test statistic and the proportion of information (i.e. sample size) used at the interim analysis. The generalized formula for the conditional power at look "k" for ending at look "k+1" is as follows [Jennison and Turnbull, 1999]:

$$CP\left(k\right) = \Phi\left(\frac{Z_k\sqrt{I_k} - z_{k+1}\sqrt{I_{k+1}} + \theta(I_{k+1} - I_k)}{\sqrt{I_{k+1} - I_k}}\right)$$

where Z_k is the interim standardized test statistic at time k, I_k is the information at time k, $z_{k+1}$is the target test statistic at look k+1, I_{k+1} is the information at time k+1 and θ is the "true" parameter value of interest

For unblinded sample size re-estimation, we will assume k is set to specified sample size re-estimation look and k+1 is the final look. This means the conditional power in nQuery is an approximation for the chance of rejecting the null at any subsequent look if k is not the penultimate look but practically there will be a negligible difference between this value and the "true" conditional power.

For unblinded sample size re-estimation, the information at a given look will equal the reciprocal of the squared standard error based on the "true" parameter values (e.g. for two means, the within-group standard deviations and sample sizes: $\left[\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}\right]$) and θ is the "true" parameter of interest (e.g. for two means, the mean difference). These "true" parameters are assumptions made by the user. Two common suggestions would be set these to either the interim estimates of these parameters or to set these to the assumed "true" values from the original design. It will be discussed later but it should be noted that the value of the interim test statistic, Z_k, will be treated the same for the unweighted (Wald) statistic and weighted (Cui-Hung-Wang) statistic.

9.3.2.2 Unblinded Sample Size Re-estimation Methods

Unblinded sample re-estimation increases the sample size in response to a "promising" result (i.e. effect size) given the interim data. Note that sample size decreases are also allowable but practically are greatly disfavoured by most sponsors and regulators. A "promising" result is one which is clinically relevant but which the current sample size is unlikely to be found significant given the current study design and trajectory. The definition of "promising" is tied typically to conditional power, though alternative metrics

such as Bayesian Predictive Power have been put forward. The sample size re-estimation is tied to the conditional power (and corresponding effect sizes) falling within a range defined as "promising". This range is defined by the study design but a typical range would be between 50% and the target power (e.g. 80% for our group sequential example). If the conditional power is based on the interim analysis, we can increase the sample size until the conditional power reaches the target level (typically the original target power level).

Thus by increasing the sample size, this "promising" result can be adequately powered for given the current available information to give the appropriate chance for finding significance at the final analysis (or any subsequent). However by allowing the study sample size to be changed based on the unblinded interim data there is the chance of increasing the overall error rate or introducing bias into a study. Two strategies for ensuring that the error rate is maintained will be discussed in this section: Chen-DeMets-Lan and Cui-Hung-Wang. Note that these methods change the method for calculating the standardized test statistics but that the group sequential bounds are unaffected and can be used as for a classic group sequential design.

Chen-DeMets-Lan The Chen-DeMets-Lan method [Chen et al., 2004] is a method of unblinded sample size re-estimation that requires minimal change from a group sequential trial. This method works by setting out a number of criteria related to the allowable conditions for increasing the sample size that ensures that the normal group sequential methods (bounds, test statistics etc.) can be used while ensuring the overall error rate is not inflated versus the original group sequential design. The two primary conditions which are required to ensure no error inflation are:

1. Sample Size Re-estimation is at the penultimate look
2. The conditional power at the penultimate look must lie between 50% and the original target power.

Chen-DeMets-Lan show that if these two conditions are met then the Type I error rate after increasing the sample size until the conditional power equals the original target power will not exceed the original target Type I error. For some conditions, the Type I error rate is lower than the original target Type I error but the conservativeness is very minor over this range. In addition, Gao, Ware and Mehta [Gao et al., 2008] and Mehta and Pocock [Mehta and Pocock, 2011] extended the work of Chen-DeMets-Lan to derive the exact lower bound for the conditional power which ensures Type I error control for any given group sequential or equivalent fixed term analysis. In basic terms, this is done by iteratively searching over the full range of conditional powers (and corresponding effect sizes), calculating the required sample size increase for each conditional power and then calculating the appropriate weighted test statistic (Cui-Hung-Wang) that ensures error control. For the range where this weighted statistic is lower than the original critical unweighted test statistic, the sample size can be increased while maintaining the Type I error.

After the sample size increase occurs, the final analysis is conducted as if it were a standard group sequential design and uses the pre-existing group sequential bound values and Wald test statistic calculation (subsection 9.2.2).

Cui-Hung-Wang The Cui-Hung-Wang method [Cui et al., 1999] is an extension of the generalized adaptive design approach of Muller and Schaefer for the case of sample size re-estimation. Under the Cui-Hung-Wang method, the user has full flexibility over which look sample size increases can occur, how many sample size increases occur, how large the sample size increase can be and the range of "promising" conditional powers allowable for sample size increases. This robustness to in-study changes gives the greatest operational flexibility possible regarding sample size. However, this method requires the usage of a weighted test statistic which differs from the classic standardized test statistic used in group sequential designs.

The Cui-Hung-Wang method uses a weighted test statistic based on the weighted combination of the incremental test statistics. Previously when discussing test statistics, we have been referring to the cumulative test statistics which are based on all the interim data up to that point. Incremental test statistics are those calculated based only on the data between the last look and the current look. However, the cumulative and incremental test statistics can be easily related for the traditional group sequential trial as follows:

$$Z_{Cumulative} = \frac{\sqrt{w_1}Z_1+\sqrt{w_2}Z_2+...+\sqrt{w_{k-1}}Z_{k-1}+\sqrt{w_k}Z_k}{\sqrt{w_1+w_2+...+w_{k-1}+w_k}}$$

where $Z_{1,2...,k\text{-}1,k}$are the respective incremental test statistics at each look and $w_{1,2...,k\text{-}1,k}$are the weights for each test statistics. The weights must sum to one.

For the classic group sequential test statistic, the weights will equal the proportion of the total sample size used for each incremental test statistic (e.g. for equally spaced 4 total look design they would equal 0.25, 0.25, 0.25, 0.25). The Cui-Hung-Wang and Chen-DeMets-Lan method differ in how these weights are affected by an increase in sample size during the study. Note that for both statistics, the bounds for the classic group sequential trial are used as before for accepting and rejecting the null hypothesis or for ending the trial early for efficacy or futility.

For the Chen-DeMets-Lan method, the weights used in this calculation are based on the actual (i.e. updated/increased) sample size for each incremental test statistic. Practically, this means that if a sample size occurs at the penultimate look, the weight placed on the final incremental test statistic will be increased so that the weight for the final cohort of data is proportional to the increased number of subjects between the penultimate and final look. Note that since the cumulative test statistic is equivalent to this version of the weighted sum of incremental test statistics, we can typically ignore the incremental tests statistics for practical purposes when using the Chen-DeMets-Lan or classic group sequential methods.

For the Cui-Hung-Wang method, the weights used in this calculation are based on the original proposed sample size for each incremental test statistic. This means that if a sample size increase occurs, subjects which are recruited after the sample size increase will be weighted less than subjects before the sample size re-estimation. However, this formulation ensures that the Type I error is retained regardless of the size of the sample size increase, when the sample size increase occurs and what range of conditional powers are considered "promising".

This robustness means that the Cui-Hung-Wang statistic provides a far greater level of operational control over the sample size re-estimation procedure. However, this comes at the cost of having to use a different test statistic than for the classic group sequential design

and the down-weighting of subjects after the sample size increase. Note the weighting issue is a source of debate and we refer to relevant papers for further details.

9.3.3 Unblinded Sample Size Re-estimation and Interim Monitoring in nQuery

This section will show how to conduct an unblinded sample size re-estimation and interim monitoring for a group sequential design in nQuery. We will cover two examples: one for the Chen-DeMets-Lan method and one for the Cui-Hung-Wang method.

9.3.3.1 Opening the Interim Monitoring and Sample Size Re-estimation Table

To open the Interim Monitoring and Sample Size Re-estimation table, we first must complete a group sequential design sample size or power calculation in a group sequential table with this feature available (see `www.statsols.com` for details on which tables have this feature in nQuery Adapt). In this section, we will take the completed example from subsubsection 9.2.3.2.

In short, this was a group sequential design with fixed term parameters of a mean difference of -1, common within-group standard deviations of 2.5, a one-sided 5% significance level and 80% power. The group sequential design was for a 2 look design (1 interim analysis), the interim look at 50% of subjects analysed, O'Brien-Fleming efficacy bounds and Power Family futility bounds with the Power Family parameter set to 1. Given this the overall sample size required was 174 (87 per group).

To open the Interim Monitoring & Sample Size Re-estimation tool, we select the "Interim Monitoring & Sample Size Re-estimation" button at the top of the Looks window. This option will be greyed out if a sample size or power calculation has not been completed in that column or if you do not have an nQuery Adapt license (see `www.statsols.com` and section 5.2 for details on purchasing and activating nQuery Adapt). This button is highlighted in Figure 9.7.

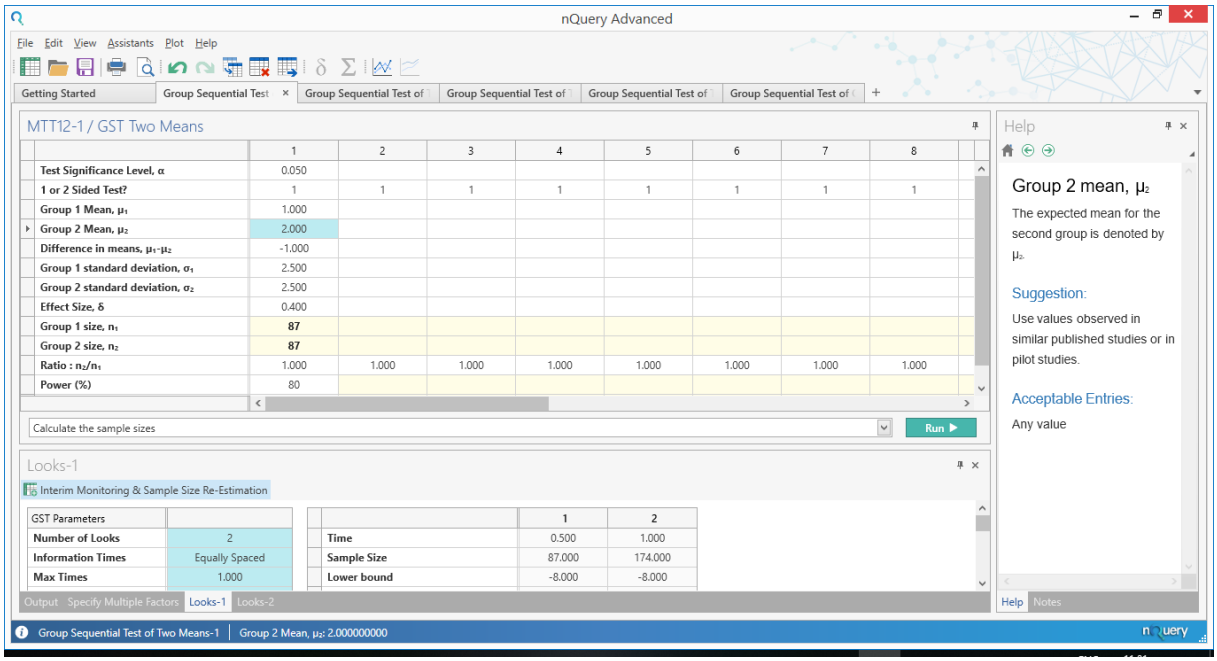


Figure 9.7: Opening Interim Monitoring and Sample Size Re-estimation Table

9.3.3.2 Interim Monitoring and Sample Size Re-estimation Table Introduction

The interim monitoring and sample size re-estimation table provides an intuitive approach for setting up a proposed sample size re-estimation and then allowing interim monitoring with that sample size re-estimation in mind. The basic structure of the interim monitoring and sample size re-estimation tables can be split into two main parts: the sample size re-estimation rules column and the interim monitoring tool. We will refer to the former as the "SSR Rules" and the latter as the "Monitoring Table" for short. We will summarise each of these in the following section.

When first opened the table will look as per Figure 9.8 for a two means group sequential design.

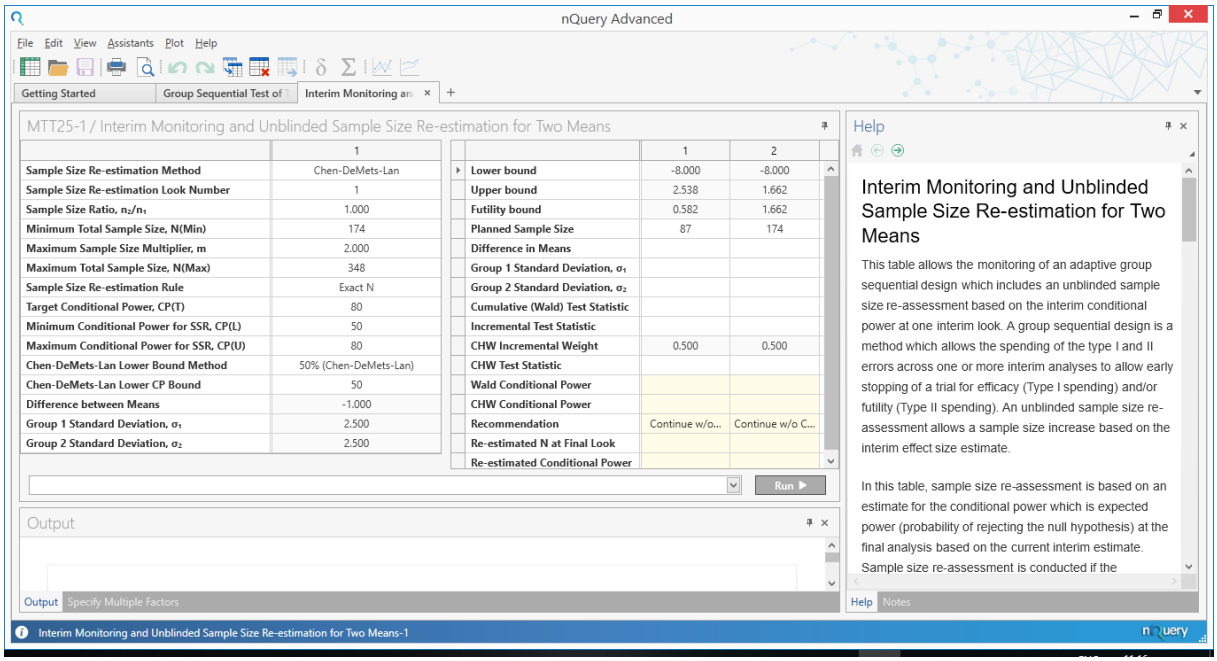


Figure 9.8: Interim Monitoring and Sample Size Re-estimation Table for Two Means GST

Setting up the Sample Size Re-estimation Rules To set up the rules that will define when and where a sample size re-estimation will occur, nQuery provides a large number of options to tailor the sample size re-estimation to the requirements of the user. These are set in the SSR Rules column (on the left in the main window). There are 12 inputs that can be edited by the user to define the sample size re-estimation rules. These are summarised below:

1. Sample Size Re-estimation Method (Chen-DeMets-Lan, Cui-Hung-Wang, None): Define the sample size re-estimation method desired for this study. The Chen-DeMets-Lan and Cui-Hung-Wang methods are summarised in subsubsection 9.3.2.2. In short, the Chen-DeMets-Lan method uses the standard group sequential test statistic but restricts sample size re-estimation to the penultimate look and for a certain range of conditional powers. The Cui-Hung-Wang method uses a different weighted test statistic from the group sequential design, based on the incremental test statistics weighted by the original planned sample size, and can be conducted for any look or conditional power. None will disable any sample size re-estimation (all subsequent options in this column can be ignored) and the tool will operate as a standard group sequential design monitoring table. This will default to the Chen-DeMets-Lan method.
2. Sample Size Re-estimation Look Number (If Chen-DeMets-Lan: Looks-1, if Cui-Hung-Wang: $<$ Looks): The look at which a sample size re-estimation will occur. Note that nQuery Adapt allows only a single sample size re-estimation. For the Chen-DeMets-Lan method, this must equal the total number of looks (including the final analysis) minus one. For the Cui-Hung-Wang method, this must be less than the total number of looks. Defaults to the number of looks minus one.
3. Sample Size Ratio ($>$0): The ratio between the group 1 and group 2 sample sizes. This will be assumed to be constant across all looks. Defaults to the sample size

ratio from the original group sequential design.

4. Minimum Total Sample Size (>2): The minimum total sample size allowable in this study. Changing this will automatically update the Planned Sample Size row in the Monitoring Table to reflect this value. Defaults to the sample size from the original group sequential design.
5. Maximum Sample Size Multiplier (>1): A multiplier for the minimum total sample size versus the maximum total size. Changing this will automatically update the Maximum Total Sample Size to reflect this value. Defaults to 2 (maximum sample size double minimum sample size).
6. Maximum Total Sample Size (>Minimum Total Sample Size): The maximum total sample size allowable in this study. If a sample size re-estimation occurs, this will be maximum allowable total sample size that will occur even if the target conditional power is not reached with this value. Defaults to twice the minimum total sample size.
7. Sample Size Re-estimation Rule (Exact N, Maximum N): The rule for how much the sample size should be increased by if the interim statistic gives a conditional power within the Minimum and Maximum Conditional Power for SSR value for the Sample Size Re-estimation Look Number column. Exact N will increase the total sample size until either the conditional power equals the Target Conditional Power or the Maximum Total Sample Size is reached. Max N will always increase the sample size to the Maximum Total Sample Size. The Max N rule may over-power the study but reduces the operational risk of study participants reverse-calculating the effect size using the "Exact N" calculated to restore the conditional power to the original target power.
8. Target Conditional Power (>Minimum Conditional Power for SSR, <100): This is the conditional power targetted by the sample size re-estimation increase if the Exact N rule is active in the Sample Size Re-estimation Rule row. The sample size is increased until this value is reached or the maximum sample size is reached. Defaults to the target power from the original group sequential design.
9. Minimum Conditional Power for SSR (<Target Conditional Power & Maximum Conditional Power for SSR): This is the minimum conditional power that would be considered "promising" and lead to a sample size re-estimation at the specified Look Number. For the Chen-DeMets-Lan method, this needs to be greater than the Chen-DeMets-Lan Lower CP Bound. Defaults to 50%.
10. Maximum Conditional power for SSR (>Minimum Conditional Power for SSR, <100): This is the maximum conditional power that would be considered "promising" and lead to a sample size re-estimation at the specified Look Number. Conditional powers above this value would have sufficient power and then a sample size increase would not be necessary. For the Chen-DeMets-Lan method, this should not be set higher than the power from the original group sequential design. Defaults to the target power from the original group sequential design.
11. Chen-DeMets-Lan Lower Bound Method (50% (Chen-DeMets-Lan), Derived (Mehta-Pocock)): Select the method used to the derive the allowable Minimum Conditional Power for SSR which can be used without leading to error inflation. Chen-DeMet-Lan sets this to 50% which holds for all group sequential designs. Derived (Mehta-Pocock) derives the lower bound which ensures the Type I error never exceeds the

level for the equivalent Cui-Hung-Wang test statistic and this value will always fall between 0% and 50%. Defaults to 50% (Chen-DeMets-Lan).

In addition to these parameters, the SSR Rules column will also include the fixed term parameters used to define the study effect size. These values can be useful for reference and if the user wishes to base conditional power calculations on these original design parameters rather than the interim estimates for these parameters. For the two means case, the relevant parameters are the difference in means and group 1 and group 2 standard deviations. Once we have set our SSR Rules, we can use the Monitoring Table to start entering our interim statistics and stop our trial early, implement a sample size increase if needed or find for or against the null hypothesis at our final look. More detail on all these rows is given in the Home and Help cards of the table.

9.3.3.3 Interim Monitoring Table

After the SSR Rules are set we need to enter our interim results to decide what action should be made at each look based on those results. To do this nQuery provides the Monitoring Table (on the right in the main window) which contains 16 rows and a number of columns equal to the total number of looks in the original group sequential design.

In this table each column corresponds to the respective interim look (e.g. column 1 is look 1, column 2 is look 2 etc.). To use this table we enter the required inputs in each column sequentially (i.e. complete column 1 before moving onto column 2 and so on) until the conditional power is calculated and Recommendation is made based on those inputs. We fill in each column in turn until either a recommendation is made to stop the trial early (ignorable if below non-binding futility bound) or the final column is filled and a recommendation is made to find for efficacy or futility.

There are 16 rows per column in the Monitoring Table for the Two Means case. These are summarised below:

1. Lower Bound (Read-only): The Lower Bound for efficacy below which we would end the trial early. The bounds are on the test statistic scale. These are inherited from the original group sequential design.
2. Upper Bound (Read-only): The Upper Bound for efficacy above which we would end the trial early. The bounds are on the standardized test statistic scale. These are inherited from the original group sequential design.
3. Futility Bound (Read-only): The Futility Bound below which we would end the trial early for futility (can ignore if non-binding). The bounds are on the test statistic scale. These are inherited from the original group sequential design.
4. Planned Sample Size (>2, >Planned Sample Size in Current Column - 1): The cumulative sample size analyzed at the current look. By default, this will equal the sample size at each look from the original group sequential design. This value can be changed in each column manually using the Minimum Total Sample option in the SSR rules or can be edited manually at any point by the user. This value will also be over-written by the cumulative test statistic side-table if the default value for the Cumulative Interim Total Sample Size (which defaults to this value) is changed and the Transfer Estimates option is set to Yes. If a sample size re-estimation is recommended these values will automatically update such that the sample size

increase will happen between the Sample Size Re-estimation Look and subsequent look and all other Planned Sample Sizes will increase accordingly.

5. Difference in Means ($\neq$0, Unique to Two Means): The "true" assumed value for the difference in means used for the conditional power calculation. Usually set to either the interim estimate for this parameter or the assumed parameter value from the original design. The Cumulative Test Statistic side-table will automatically set this to the Interim Difference Between Means if the Transfer Estimates option is set to Yes. The original design value for this parameter is available at the bottom of the SSR Rules column.
6. Group 1 Standard Deviation (>0, Unique to Two Means): The "true" assumed value for the group 1 standard deviation used for the conditional power calculation. Usually set to either the interim estimate for this parameter or the assumed parameter value from the original design. The Cumulative Test Statistic side-table will automatically set this to the Interim Group 1 Standard Deviation if the Transfer Estimates option is set to Yes. The original design value for this parameter is available at the bottom of the SSR Rules column.
7. Group 2 Standard Deviation (>0, Unique to Two Means): The "true" assumed value for the group 2 standard deviation used for the conditional power calculation. Usually set to either the interim estimate for this parameter or the assumed parameter value from the original design. The Cumulative Test Statistic side-table will automatically set this to the Interim Group 2 Standard Deviation if the Transfer Estimates option is set to Yes. The original design value for this parameter is available at the bottom of the SSR Rules column.
8. Cumulative (Wald) Test Statistic (Any Value): The standardized test statistic based on the interim data (see subsection 9.2.2) This is equivalent to the standard Z statistic for this data and is alternatively called the unweighted statistic (although its weighting is simply based on the empirical sample size rather than the initial sample size). This is the test statistic used for conditional power when the Chen-DeMets-Lan method or None options are selected from the Sample Size Re-estimation Method row in the SSR Rules column. This can be calculated using the Cumulative Test Statistic side-table based on the interim estimates for relevant effect size parameters (for two means, the mean difference and group 1 and 2 standard deviations). If this value falls above the Upper Bound or below the Lower Bound (2-sided), the trial should be ended early for efficacy. If this value falls below the Futility Bound, the trial can be ended early for futility.
9. Incremental Test Statistic (Any Value): The standardized test statistic (see subsection 9.2.2) based on the incremental data i.e. for the data between the last look and the current look. This is equivalent to the standard Z statistic for this incremental data. This incremental test statistics for all columns up to and including the current column are used to derive the Cui-Hung-Wang (CHW) Test statistic in combination with CHW Incremental Weights. The CHW test statistic is then used for conditional power when the Cui-Hung-Wang method is selected from the Sample Size Re-estimation Method row in the SSR Rules column. This can be calculated using the Incremental Test Statistic side-table based on the incremental estimates for relevant effect size parameters (for two means, the mean difference and group 1 and 2 standard deviations).

10. CHW Incremental Weight (Read-only): The incremental weights used in combination with the incremental test statistics to derive the Cui-Hung-Wang (CHW) Test Statistic. These will equal the original proposed incremental sample size used between each look and its prior look.
11. CHW Test Statistic (Any Value): The Cui-Hung-Wang Test weighted test statistic used for conditional power calculations when the Cui-Hung-Wang method selected from the Sample Size Re-estimation row of the SSR Rules. This will typically be auto-calculated using the incremental test statistic and CHW Incremental Weight column values (see section 9.3.2.2). However, these values can be entered manually if desired. If this value falls above the Upper Bound or below the Lower Bound (2-sided), the trial should be ended early for efficacy. If this value falls below the Futility Bound, the trial can be ended early for futility.
12. Wald Conditional Power (Read-only): The conditional power based on the "true" parameter estimates and the Cumulative (Wald) Test Statistic value based on the interim data. This will only be calculated if the Chen-DeMets-Lan and None options are selected from Sample Size Re-estimation Method row in SSR Rules. For the sample size re-estimation look column, if the conditional power falls between the Minimum Conditional Power for SSR and Maximum Conditional Power for SSR then a sample size re-estimation will automatically activate.
13. CHW Conditional Power (Read-only): The conditional power based on the "true" parameter estimates and the CHW Test Statistic value based on the interim data. This will only be calculated if the Cui-Hung-Wang option is selected from Sample Size Re-estimation Method row in SSR Rules. For the sample size re-estimation look column, if the conditional power falls between the Minimum Conditional Power for SSR and Maximum Conditional Power for SSR then a sample size re-estimation will automatically activate.
14. Recommendation (Read-only): This gives the recommendation for this look based on the relevant test statistic and conditional power. There are four recommendations that can be made at a given interim look: a) Stop for Efficacy - Stop trial early due to strong evidence for efficacy due to test statistic being beyond Upper (1-sided or 2-sided) or Lower Efficacy Bounds (2-sided only) b) Stop for Futility - Stop trial early due to strong evidence for futility due to test statistic being below Futility bound (1-sided only) c) Continue without (w/o) change - Continue until next look with no changes due to test statistic not being in the early stopping region or the conditional power falling within the lower and upper SSR conditional power bounds d) Add N & Continue - Add required additional sample size for "promising" design and continue trial until next look as conditional power fell between lower and upper SSR conditional power bound. At the final look, two recommendations can be made: "Find for Efficacy" (for 1-sided, test statistic above upper bound; for 2-sided, test statistic outside lower to upper bound range) or "Find for Futility" (for 1-sided, test statistic below upper bound; for 2-sided, test statistic inside lower to upper bound range) .
15. Re-estimate N at Final Look (Read-only): The recommended total sample size after a sample size re-estimation occurs. This will be empty unless a sample size re-estimation has been recommended in this column (Add N & Continue in Recommendation row). The increase in sample size will automatically place the additional sample size between the current look and the next look, with the Planned Sample

Size row automatically updated to reflect this. This pattern can be edited manually if desired in the Planned Sample Size row in the subsequent columns.

16. Re-estimated Conditional Power (Read-only): The conditional power based on the interim test statistic and "true" parameter values based on the sample size increase calculated in the Re-estimate N at Final Look row. This will be empty unless a sample size re-estimation has been recommended in this column (Add N & Continue in Recommendation row). For Exact N, this will equal the target conditional power approximately unless the maximum sample size is insufficient to restore the conditional power to the target conditional power.

More detail on these is given in the Home and Help cards of the table. Note that the difference in means and standard deviation rows are unique to the two mean design. Other designs will have the appropriate parameters instead but the basic workflow and assumptions are the same for other designs.

Note that in nQuery; "upper", "lower" and "futility" are defined relative to the direction of the pre-specified effect size. For example, if the initial design assumes a negative difference ($\mu_1 > \mu_2$) then positive "upper" interim tests statistics would be those in which the interim difference is also negative and vice-versa. Similarly, "lower" results would be those in the opposite direction. Futility bounds can be above or below zero but the same guidance applies for the Z-statistic calculation.

9.3.3.4 Monitoring Side-tables

In addition to these tables, nQuery provides two side-tables which make calculating and entering the required inputs easier for the "true" parameter values and the test statistics required in the Monitoring Table. These two side-tables are the Cumulative Test Statistic side-table and the Incremental Test Statistic Side-Table.

These side-tables allow the user to enter relevant interim/incremental effect size estimates and calculate the relevant test statistic and transfer this into the Monitoring Table. The Cumulative Test Statistic side-table will automatically open in the window if the "true" parameter values or Cumulative (Wald) Test Statistic rows are selected in a column and the Incremental Test Statistic side-table will automatically open in the window below the main table if the Incremental Test Statistic row is selected. Functionally, these work the same as side-tables seen in other tables (see section 3.1).

The calculations in both side-tables are identical and based on the relevant standardized test statistic calculations from subsection 9.2.2. They differ in that the Cumulative Test Statistic side-table requires the user input the cumulative interim estimates (i.e. based on all the data up to and including the current look) and the Incremental Test Statistic side-table requires the user input the incremental estimates (i.e. based only on the data from the last look to the current look). In addition, the Cumulative Test Statistic side-table gives the option to transfer the relevant interim effect size parameters and sample size into the relevant rows of the Monitoring Table by setting the Transfer Estimates option to Yes.

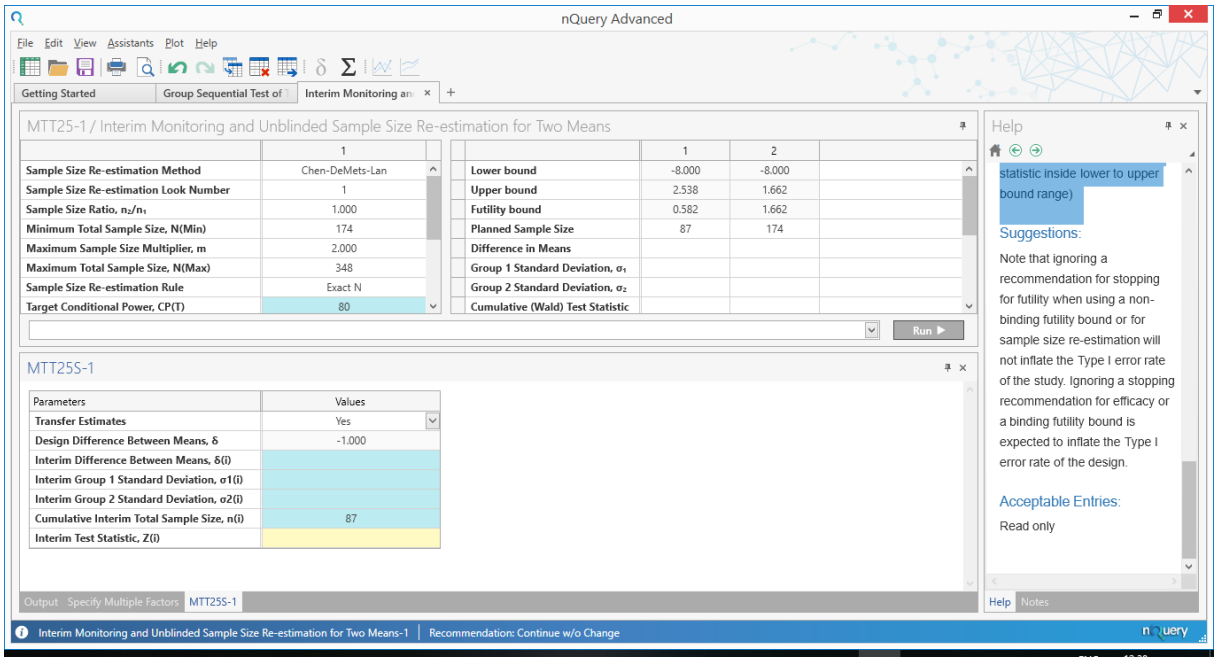


Figure 9.9: Cumulative Test Statistic Side-Table for Two Means

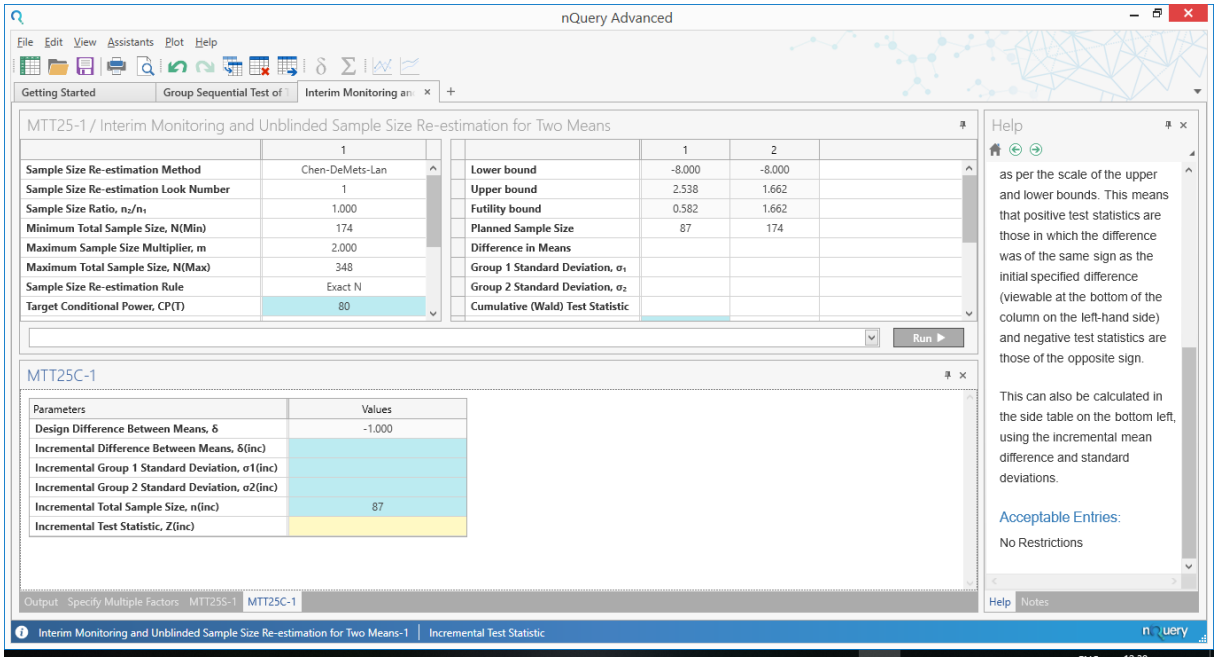


Figure 9.10: Incremental Test Statistic Side-Table for Two Means

The Cumulative Test Statistic side-table can help calculate the cumulative (Wald) test statistic for the Chen-DeMets-Lan method while also automatically assigning the "true" parameter values for conditional power as being equal to their interim estimates. The Incremental Test Statistic side-table can help calculate the incremental test statistics needed to calculate the Cui-Hung-Wang (CHW) test statistic in combination with the pre-set CHW Incremental Weights. The functionality of both will be explored further in the worked example that follows.

Note that in nQuery; "upper", "lower" and "futility" are defined relative to the direction of the pre-specified effect size. For example, if the initial design assumes a negative difference ($\mu_1 > \mu_2$) then positive "upper" interim tests statistics would be those in which the interim difference is also negative and vice-versa. Similarly, "lower" results would be those in the opposite direction. Futility bounds can be above or below zero but the same guidance applies for the Z-statistic calculation. Thus these side-tables will provide the Design effect (e.g. difference in means). Cumulative/Incremental effects (e.g. differences) which have the same sign as the design effect will give a positive test statistic and those of the opposite sign will give a negative test statistic.

9.3.4 Interim Monitoring and Sample Size Re-estimation Worked Examples

9.3.4.1 Chen-DeMets-Lan Worked Example

For this example, we will use the group sequential design from subsubsection 9.2.3.2 and have a Chen-DeMets-Lan sample size re-estimation based on the default rules used by the Interim Monitoring and Sample Size Re-estimation table. For reference, this was a group sequential design with fixed term parameters of a mean difference of -1, common within-group standard deviations of 2.5, a one-sided 5% significance level and 80% power. The group sequential design was for a 2 look design (1 interim analysis), the interim look at 50% of subjects analysed, O'Brien-Fleming efficacy bounds and Power Family futility bounds with the Power Family parameter set to 1. This gave an overall sample size of 174 (87 per group).

These default rules will give a sample size re-estimation at the penultimate look (i.e. Look 1 for two look design), the minimum sample size will equal our original sample size (174), the maximum sample size will be twice our original sample size (348), we will only increase sample size if needed until the target conditional power (equalling our initial target power of 80%) is reached and will only increase the sample size if the conditional power is between 50% (Chen-DeMets-Lan lower bound) and 80% (target power) at Look 1. Before we enter our interim data, our table will look as per Figure 9.8.

We will now enter the relevant inputs in column 1 of the monitoring table. Let us assume that the interim data suggests a 25% reduction from our initial estimate of the effect size (i.e. -0.75 mean difference, assuming standard deviations are the same). We could enter the relevant mean difference and standard deviations manually and also calculate the cumulative test statistic manually and enter it here. However, we will use the Cumulative Test Statistic Side-Table to calculate these automatically instead. When we select the "Difference in Means" row in column 1, this side-table will open automatically in the window below the main table. In this side-table, we leave the Transfer Estimates option as Yes so that our entered interim estimates will be set to be the true values for the conditional power calculations. We will also leave the Cumulative Sample Size as its default value of the Planned Sample Size for this column. We then enter our interim estimates for the difference in means and the group 1 and 2 standard deviations. In this case, these are -0.75, 2.5 and 2.5 respectively. The side-table will automatically calculate the Cumulative Test Statistic and transfer it and the interim parameter estimates into the main table.

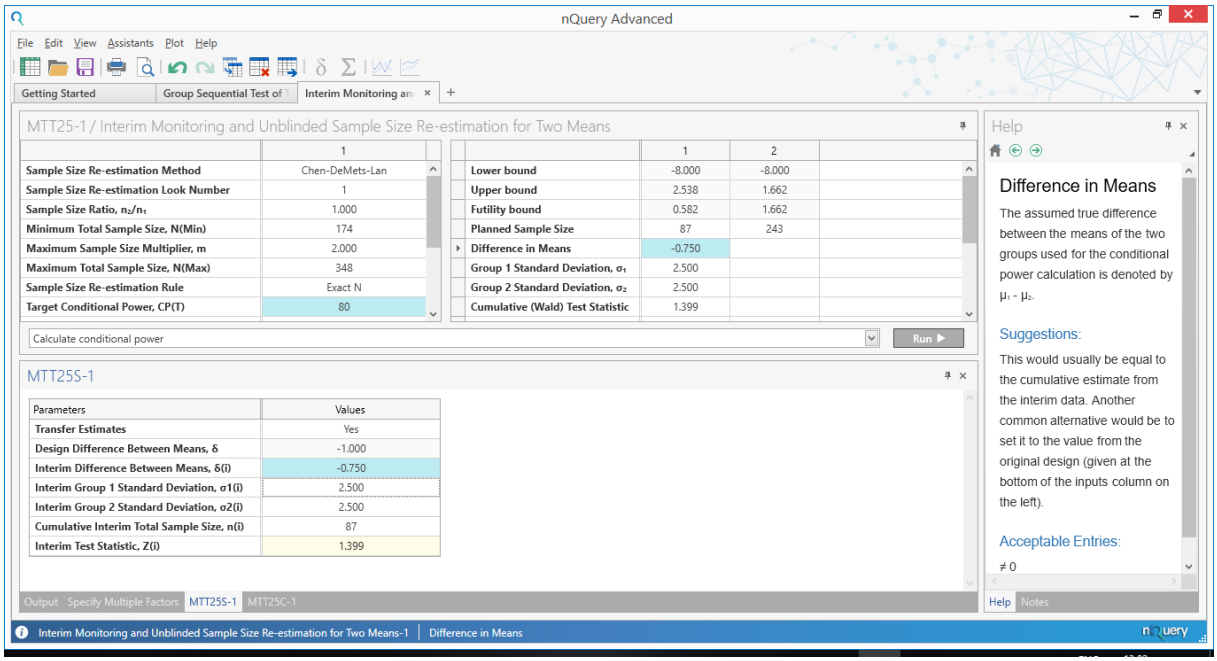


Figure 9.11: Chen-DeMets-Lan Side-Table Example

Note that in nQuery; "upper", "lower" and "futility" are defined relative to the direction of the pre-specified effect size. For example, if the initial design assumes a negative difference ($\mu_1 > \mu_2$) then positive "upper" interim tests statistics would be those in which the interim difference is also negative and vice-versa. Similarly, "lower" results would be those in the opposite direction. Futility bounds can be above or below zero but the same guidance applies for the Z-statistic calculation. Thus these side-tables will provide the Design effect (e.g. difference in means). Cumulative/Incremental effects (e.g. differences) which have the same sign as the design effect will give a positive test statistic and those of the opposite sign will give a negative test statistic. Thus, in this case entering -0.75 returns an interim test statistic of 1.399 but a value of 0.75 would have returned a test statistic of -1.399.

Once these values have been transferred, the conditional power is automatically calculated in this column in the Monitoring Table. In this case, these interim results give a conditional power of 67.28% which falls between our Conditional Power Sample Size Re-estimation range of 50% to 80%. Thus nQuery gives a recommendation of "Add N & Continue" in the Recommendation row in column 1 and nQuery automatically calculates the required total sample size to increase the conditional power to 80%. In this case, this corresponds to an increase in the total sample size from 176 to 243, giving an updated conditional power of 80.06%. The Planned Sample Size in column 2 is updated automatically to reflect this.

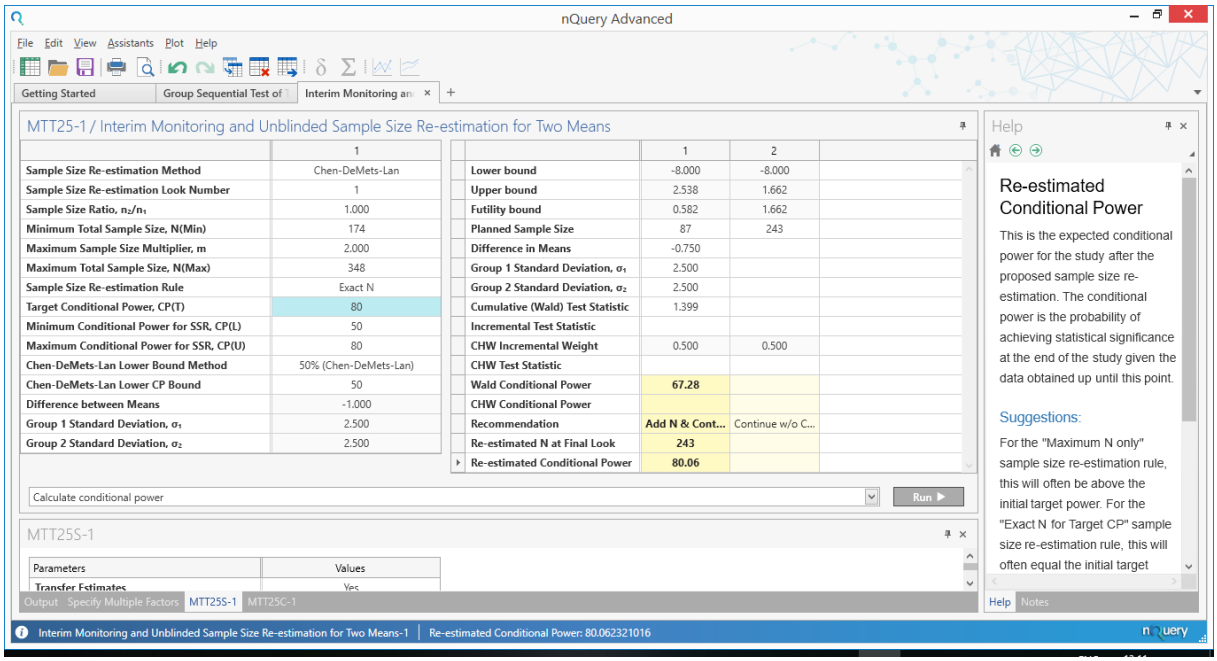


Figure 9.12: Chen-DeMets-Lan Sample Size Re-estimation Example

We can now complete our interim monitoring by entering our estimates at the end of our (now larger) study. Assume that the final analysis has the same difference in means (-0.75) and per-group standard deviations (2.5). We can use the Cumulative Test Statistic Side-table as before and calculate a test statistic of 2.338. As this test statistic value is greater than the Upper Bound (1.662) at the final analysis, we find for efficacy for this study at the final look.

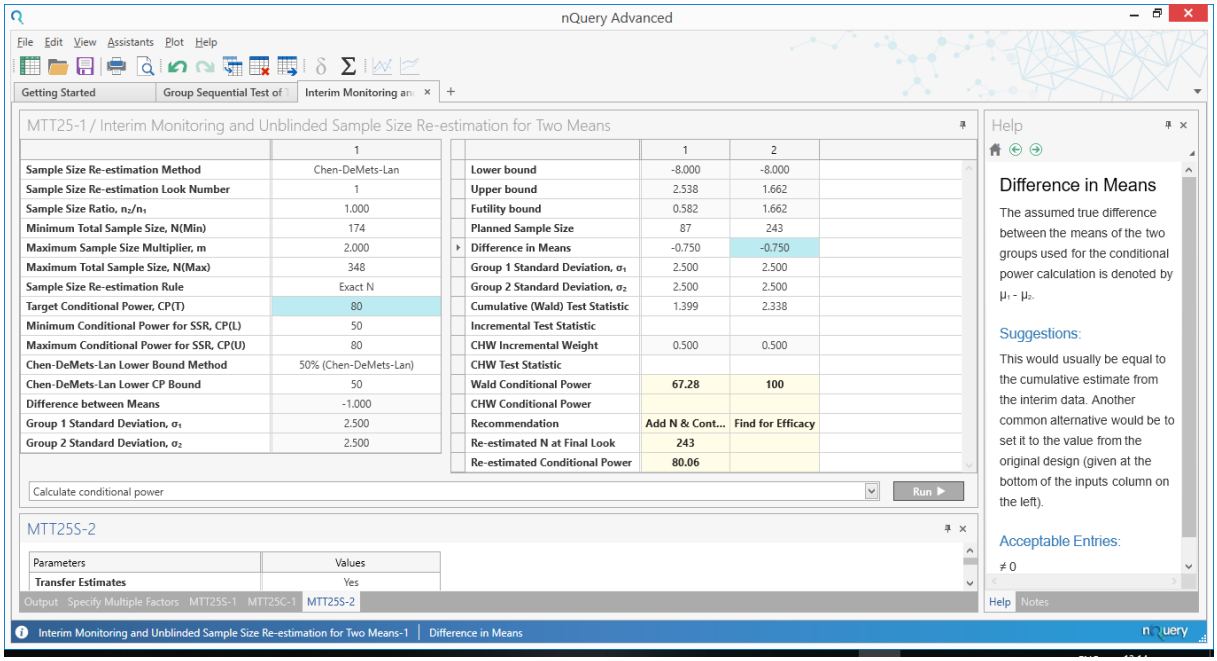


Figure 9.13: Chen-DeMets-Lan Completed Design Example

9.3.4.2 Cui-Hung-Wang Worked Example

For this example, we will assume the same group sequential design.

For reference, this was a group sequential design with fixed term parameters of a mean difference of -1, common within-group standard deviations of 2.5, a one-sided 5% significance level and 80% power. The group sequential design was for a 2 look design (1 interim analysis), the interim look at 50% of subjects analysed, O'Brien-Fleming efficacy bounds and Power Family futility bounds with the Power Family parameter set to 1. This gave an overall sample size of 174 (87 per group).

In this case we assumed a 50% reduction in our difference in means versus the original study design (-0.5 difference in means).

For this sample size re-estimation we will also make some additional changes to the previous example. In this example we will increase the sample size multiplier to 3 (maximum N equal to 522), use a Max N rule for sample size increases (i.e. N always increased to the maximum N) and decrease the lower bound for the conditional power to 30%. This will give SSR Rules inputs as in Figure 9.14.

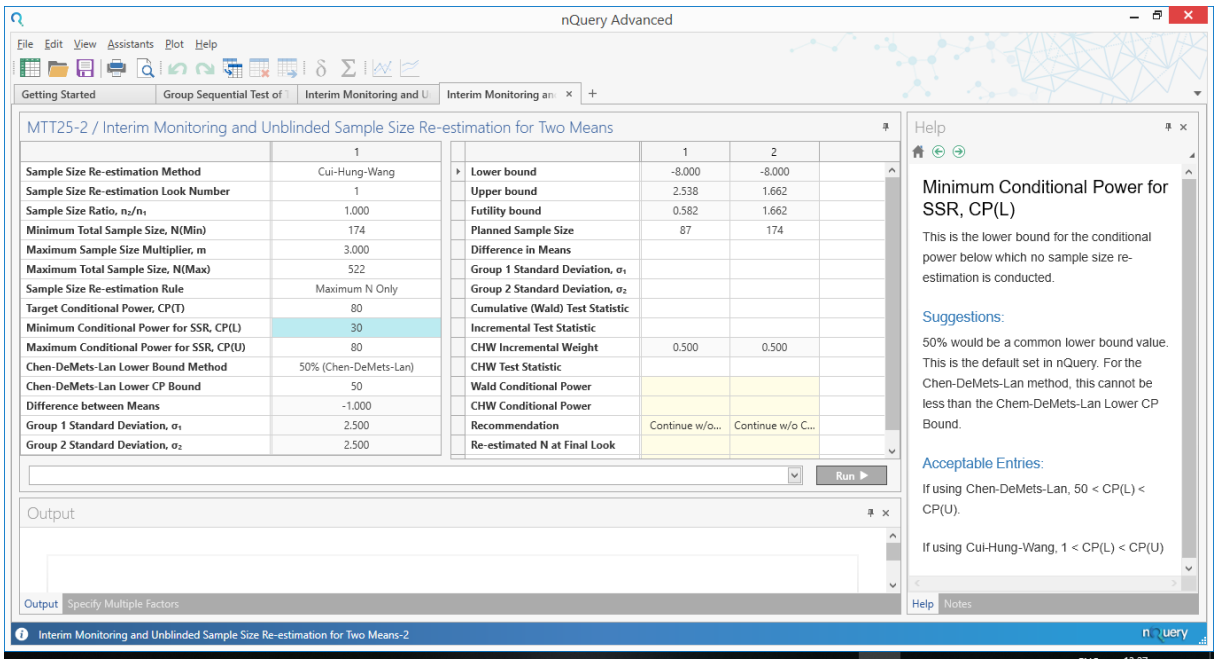


Figure 9.14: Cui-Hung-Wang Example Rules Setup

We will now enter the relevant inputs in column 1 of the monitoring table. In this case, we will enter our interim estimates for the design parameters in column 1 (difference in means of -0.5, per-group standard deviations equal to 2.5). We will then use the Incremental Test Statistic Side-Table to calculate the Incremental Test Statistic. When we select the "Incremental Test Statistic" row in column 1, this side-table will open automatically in the window below the main table. In this side-table, we will leave the Incremental Sample Size as its default value of the Planned Sample Size for this column. For designs with a greater number of columns this would equal the Planned Sample Size in the current column minus the Planned Sample Size in the prior column. We then enter our incremental estimates for the difference in means and the group 1 and 2 standard deviations. In this case, these are

-0.5, 2.5 and 2.5 respectively. The side-table will automatically calculate the Incremental Test Statistic and transfer it into the main table.

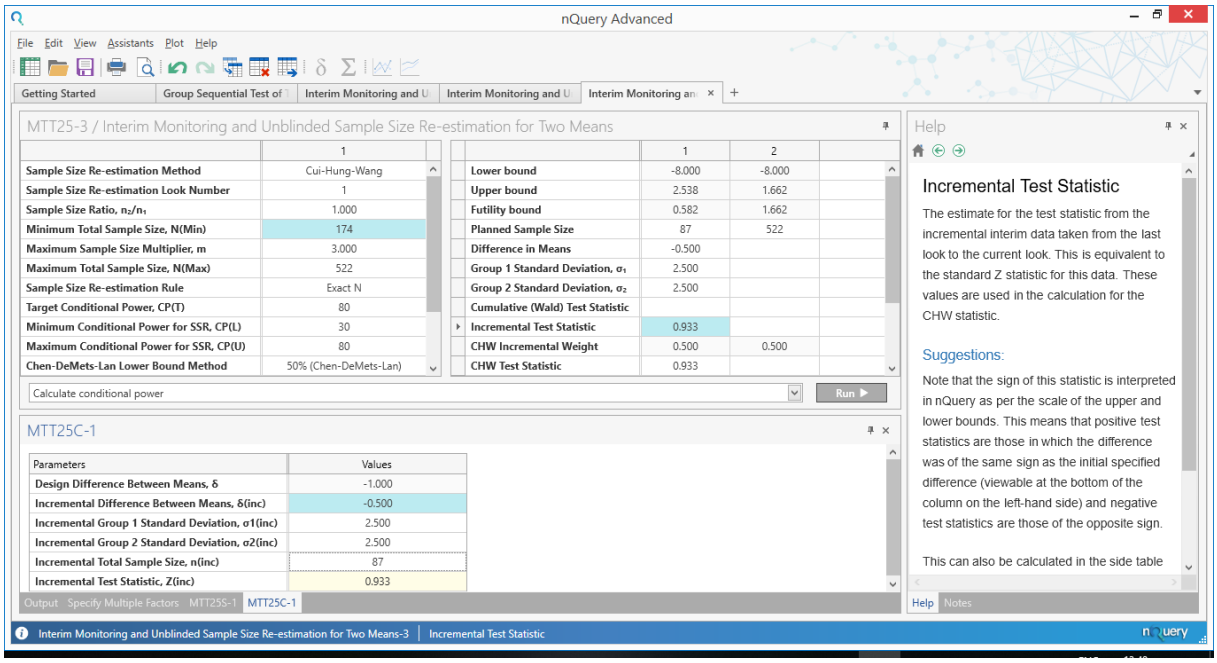


Figure 9.15: Cui-Hung-Wang Side-Table Example

Note that in nQuery; "upper", "lower" and "futility" are defined relative to the direction of the pre-specified effect size. For example, if the initial design assumes a negative difference ($\mu_1 > \mu_2$) then positive "upper" interim tests statistics would be those in which the interim difference is also negative and vice-versa. Similarly, "lower" results would be those in the opposite direction. Futility bounds can be above or below zero but the same guidance applies for the Z-statistic calculation. Thus these side-tables will provide the Design effect (e.g. difference in means). Cumulative/Incremental effects (e.g. differences) which have the same sign as the design effect will give a positive test statistic and those of the opposite sign will give a negative test statistic. Thus, in this case entering -0.5 returns an interim test statistic of 0.933 but a value of 0.5 would have returned a test statistic of -0.933. It is important to note that for the looks before the sample size re-estimation look that the Cumulative and CHW tests statistics should be identical. You may want to calculate both at each look to confirm this.

Once these values have been transferred, the conditional power is automatically calculated in this column in the Monitoring Table. In this case, these interim results give a conditional power of 31.38% which falls between our Conditional Power Sample Size Re-estimation range of 30% to 80%. Note that no sample size re-estimation would have occurred with the default range. Thus nQuery gives a recommendation of "Add N & Continue" in the Recommendation row in column 1 and nQuery automatically sets this sample size to the maximum sample size of 522. In this case, this gives an updated conditional power of 75.24%. Note that this conditional power is lower than the target conditional power. With the Exact N rule, the result would have been the same in this case as the target conditional power was not reached with this maximum sample size. The Planned Sample Size in column 2 is updated automatically to reflect this.

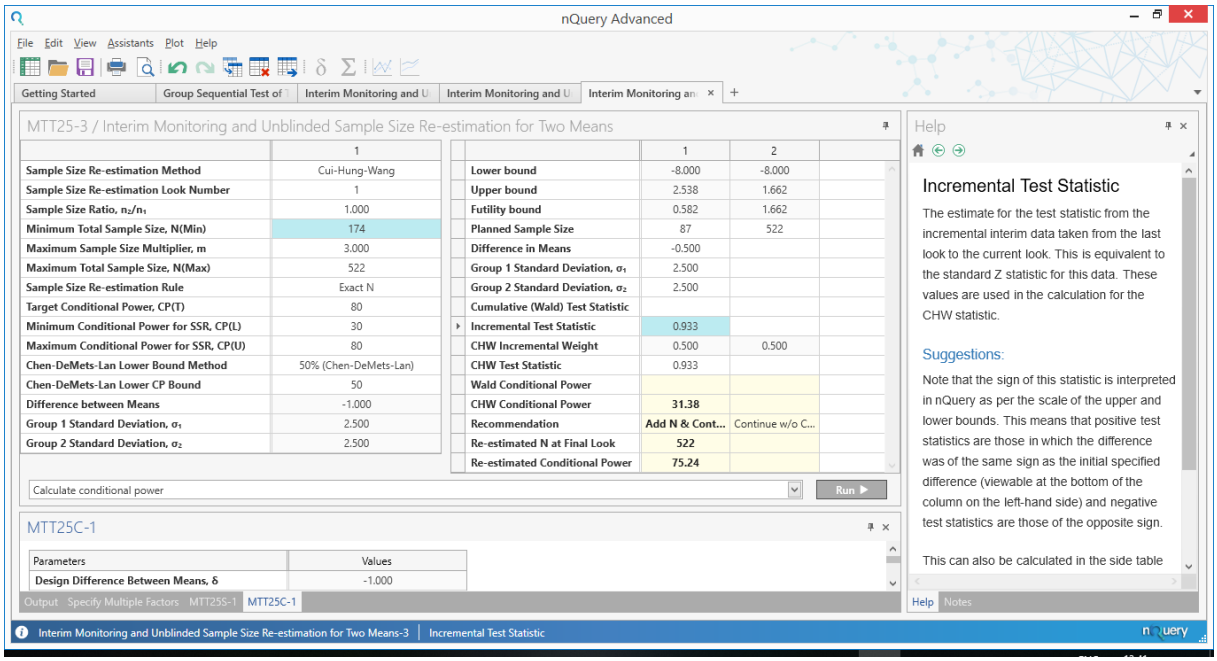


Figure 9.16: Cui-Hung-Wang Sample Size Re-estimation Example

We can now complete our interim monitoring by entering our estimates at the end of our (now larger) study. Assume that the final analysis has the same difference in means (-0.5) and per-group standard deviations (2.5). We can enter these parameter values in column 2 and use the Incremental Test Statistic Side-table as before and calculate a CHW test statistic of 2.134 based on an incremental test statistic of 2.086. As this test statistic value is greater than the Upper Bound (1.662) at the final analysis, we find for efficacy for this study at the final look.

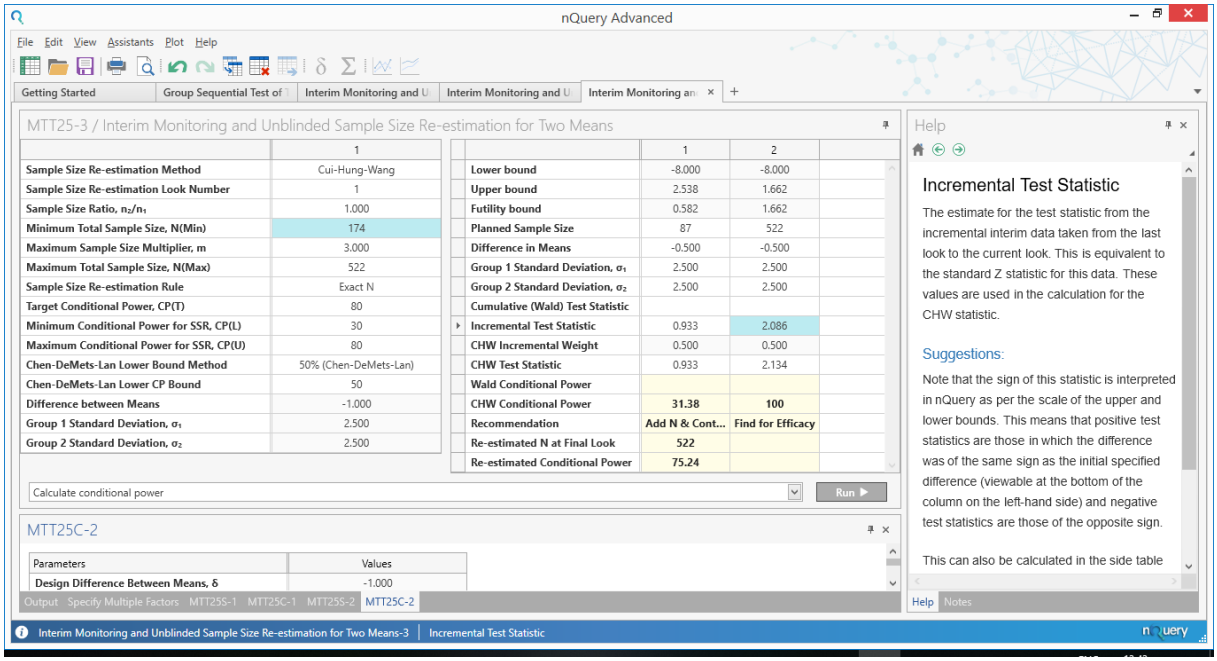


Figure 9.17: Cui-Hung-Wang Completed Design Example

10 Multiple Comparisons Procedure - Modelling (MCP-Mod)

nQuery has the facility to calculate the sample size or power needed for the "Proof-of-Concept" (PoC) stage of an MCP-Mod trial. As the MCP-Mod methodology has two main purposes (PoC, dose-finding (DF)) different criteria can be used to calculate the required sample size or power.

One approach is to concentrate on the PoC step of the procedure, calculating the sample size needed to ensure a minimum power level for detecting PoC under an assumed placebo and maximum dose-response and an assumed set of dose-response models. The focus here and in nQuery is on this approach.

Another strategy is to focus on the dose-estimating part of the method. This would find the sample size needed for a prespecified minimum precision (i.e. confidence interval width) for the dose-response estimates. This approach is not explored here.

This section will give a background to MCP-Mod, the underlying theory and derivations and the methods employed in nQuery. A demonstration of how to design an MCP-Mod trial in nQuery is also included.

Note: MCP-Mod is currently only available for users with an nQuery Advanced Pro license. Active packages are displayed in the Packages section in the Home tab. To purchase additional packages, see `www.statsols.com`.

10.1 Multiple Comparison Procedures and Modelling (MCP-Mod) Design

10.1.1 Background

MCP-Mod is a type of Phase II trial design methodology used in dose-response studies. Phase II studies have the following two main goals:

1. Proof-of-Concept (PoC): The goal here is to establish that changes in dose lead to significance changes in the efficacy (and/or safety) endpoint and that at least one dose is of clinical interest.
2. Dose-finding (DF): The second goal is to select one or more effective (and safe) doses for evaluation in confirmatory (Phase III) clinical trials or equivalent studies.

Historically, the proof-of-concept and dose finding objectives have often been evaluated in separate trials with proof-of-concept established first and then a dose-finding study used to select doses of interest for further evaluation. In this framework, the proof-of-concept trial was referred to as the Phase IIa trial and the dose-finding trial was referred to as

the Phase IIb trial, with the proof-of-concept and dose-response studies using different statistical methods. For proof-of-concept Phase IIa trials a common approach was the multiple comparison procedure (MCP) and for dose-finding Phase IIb trials a common approach was parametric dose-response modelling (Mod).

Under the Multiple Comparison Procedure (MCP) strategy, one evaluates the statistical significance of a contrast test between doses while preserving the family wise error rate (FWER). PoC is established when at least one contrast is statistically significant. If PoC is established, the minimum effective dose (MED) is found. The MED is the lowest dose that is considered statistically (significant) and clinically superior to placebo. The MCP approach regards the dose as a qualitative factor and generally makes few, if any, assumptions about the underlying dose response relationship. However, inferences about the target dose are restricted to the discrete, possibly small, set of doses used in the trial.

The modeling approach is primarily used to estimate the true dose-response curve. Doses that achieve desired clinical effects are estimated via inverse regression methods, which can also be used to evaluate the precision (i.e. confidence intervals) of the estimated doses. The dose is taken to be a quantitative factor, allowing greater flexibility for target dose estimation including potentially doses not evaluated directly in the study. However, the validity of the modelling approach strongly depends on choosing the appropriate parametric dose-response model (e.g. linear, Emax, Beta). Note that modelling can also be used for PoC by testing the significance of the parametric fitted dose-response model versus a flat dose-response null model. However, this approach is less robust than MCP due to the sensitivity to model choice as mentioned previously.

The MCP-Mod methodology was designed to provide a unified strategy to the analysis of data from dose-response studies which combines strengths of the multiple comparison procedure and modelling approaches by having the flexibility of modeling for dose estimation, while preserving the robustness to model misspecification associated with MCP.

The basic idea behind MCP-Mod was first proposed in [Tukey, 1985]. They proposed the use of several trend tests simultaneously and to adjust the resulting p-values for multiplicity. [Bretz et al., 2005] formalized the MCP-Mod procedure and so users are recommended to see this paper for more details on the basic methodology. A more detailed description of the method and it's practical implementation, including power analysis, can be found in [Pinheiro et al., 2006].

10.1.2 MCP-Mod Theory

10.1.2.1 MCP-Mod Model

The notation used to represent the dose-response model is presented here. Let Y denote the observed response for a given set of patients assigned to one of a set of k doses which we will denote as d where $d = d_1, \ldots, d_k$. We will consider the following dose-response model:

$$Y_{ij} = \mu_{d_i} + \epsilon_{ij}, \epsilon_{ij} \sim N(0, \sigma^2), i = 1, \ldots, k.j = 1, \ldots, n_i$$

Where $\mu_{d_i} = f(d_i, \theta)$ denotes the mean response at dose d_i, θ represents the vector of model parameters, i represents the dose group and j represents the patient within dose group i. Let $\mu = \mu_{d_1}, \ldots, \mu_{d_k}$ denote the mean dose response vector.

10.1.2.2 MCP-Mod Test (MCP)

Instead of prespecifying a single dose-response model, MCP-Mod uses a set of candidate models covering a suitable range of dose-response shapes. Each of the models in the candidate set is tested using appropriate contrasts and employing an MCP that preserves the FWER. PoC is established if at least one of the model tests is significant. Once PoC is verified, the "best" model(s) among the candidate set is chosen to fit the data and to produce estimated doses using modeling techniques, while still ensuring the appropriate FWER. The "best" model can be evaluated using a model fit statistic such as the lowest MCP p-value or the AIC.

The procedure requires that a set of M candidate models be chosen. Let $f_m(d, \theta_m)$ and $f_m^0(d, \theta_m^0), m = 1, \ldots, M$ denote the model and standardized model functions respectively, where θ_m and θ_m^0 are the parameters of model m under the unstandardized and standardized model functions respectively.

The hypothesis of interest for each of the dose-response models is $H_0^m : c_m^{'}\mu = 0$, where $c_m = (c_m 1, \ldots, c_m k)$ is the optimal contrast vector for model m, and $\sum_{i=1}^k c_m i = 0$. Therefore each candidate models is tested using the following contrast test,

$$T_m = \frac{\sum_{i=1}^k c_{mi}\bar{Y_i}}{S\sqrt{\sum_{i=1}^k c_{mi}^2/n_i}}, m = 1, \ldots, M.$$

where $\bar{Y_i} = \sum_{i=1}^k Y_{ij}/n_i$ is the arithmetic mean response in dose group i, $S^2 = \sum_{i=1}^k \sum_{j=1}^{n_i}(Y_{ij} - \bar{Y_i})^2/v$ is the pooled variance estimator, with $v = \sum_i n_i - k$ degrees of freedom.

Each contrast test can thus be considered as a decision procedure determining whether the given dose-response shape is statistically significant, based on the observed data. The contrast coefficients, c_m are optimal in the sense that they maximize the power to detect the underlying model.

The final detection of a significant dose-response signal (i.e demonstrating PoC), is based on the maximum contrast test statistic, $T_{max} = maxT_1, \ldots, T_M$. Under the null hypothesis of no dose effect the mean response at each dose should be equal. Under this assumption and the dose-response model formulation, it follows that the contrast test statistics follow a multivariate t-distribution with v degrees of freedom. PoC is hence established if

$$T_{max} \geq q_{1-\alpha}$$

where $q_{1-\alpha}$ is the α significance level multiplicity adjusted critical value (i.e., the relevant quantile of the central multivariate t distribution).

10.1.2.3 MCP-Mod Power and Sample Size

Sample size is based on MCP contrast test for the models in the candidate set outlined in subsubsection 10.1.2.2. This method is outlined in Pinheiro et al (2006). Under this sample size procedure, the power of the MCP procedure is determined by the distribution of the maximum contrast test statistic under the alternative hypothesis that the m^{th} dose-response model is the true response.

Under the alternative hypothesis, these contrast test statistics have a non-central multivariate t-distribution. Given the contrast test outlined previously the power for each candidate model m in MCP procedure is defined as

$$(1-\beta)_m = P\left(max_l T_l \geq q_{1-\alpha} | \mu = \mu_m\right) = 1 - P\left(T_1 < q_{1-\alpha} \ldots T_m < q_{1-\alpha} | \mu = \mu_m\right)$$

For sample size determination, it is useful to consider the vector of power values per candidate model. It follows from the model specification and the properties of the multivariate t distribution that the contrast test statistics T_l are jointly distributed as non-central multivariate t distribution with $k(n-1)$ degrees of freedom, the correlation matrix derived from the contrast coefficients (see Pinehiero et al 2006) and per model non-centrality parameters of $\delta_{ml} = \sqrt{n} c_l' \mu_m / \sigma$.

The calculation of quantiles of the non-central multivariate t-distribution is required and in nQuery the calculation of these quantiles is done using the Separation-of-Variables Method as discussed in Genz and Bretz (2002).

For practical purposes, a single summary measure of power is needed for sample size determination. Multiple options are available but the chosen function should be monotonically increasing. In nQuery, three choices of summary function are given. These are the Mean (unweighted), Minimum, and Median. nQuery provides the per-model power so the manual calculation of other summary functions is possible.

10.1.2.4 Dose-Response Models

The list of available dose-response models is given below. Note that most of these models require the pre-specification by the user of 1-3 additional parameters to fully define the model. The definition of each model including these additional parameters is given below with additional parameters given in brackets with model name e.g. **Emax*(ED50)*** indicates ED50 is required unique input for Emax model. These additional parameters alongside the placebo effect, maximum effect, standard deviation and specified dose-levels given by the user elsewhere (see section 10.2) define the model effects.

Note some common terminology including d (dose response at specific dose), E_0 (placebo dose response for most models, basal effect for logistic model), E_{max} (maximum dose response, for models other than the Beta and Quadratic models this will equal response at last dose). $f\left(d, \theta\right)$ is the unstandardized model and $f^0\left(d, \theta^0\right)$ is standardized model.

- **Linear**: This model assumes a positive linear relationship between E_0 and E_{max} on the original dose scale (i.e. between response at placebo and largest dose).δ is the linear slope parameter and this is derived automatically from the model definitions via simultaneous equations.

$$f\left(d, \theta\right) = E_0 + \delta d$$

$$f^0\left(d, \theta^0\right) = d$$

- **Linear Log-Dose (*Off*):** This model assumes a positive linear relationship between E_0 and E_{max} on the log-dose scale (i.e. between response at placebo and largest dose). The Off parameter is provided to prevent issues with doses equal to zero.

This is typically set to a small value such as 0.01 times the maximum dose. δ is the linear slope parameter and this is derived automatically from the model definitions via simultaneous equations.

$$f\left(d,\theta\right)=E_0+\delta\log\left(d+Off\right)$$

$$f^0\left(d,\theta^0\right)=\log\left(d+Off\right)$$

- **Emax (*ED50*)**: A positive monotonic concave dose-response curve model. Also known as the hyperbolic Emax model, in contrast to the more flexible sigmoidal Emax model (see below). ED_{50} is the expected dose at which we would expect 50% of the maximum dose response to occur.

$$f\left(d,\theta\right)=E_0+E_{max}\frac{d}{ED_{50}+d}$$

$$f^0\left(d,\theta^0\right)=\frac{d}{ED_{50}+d}$$

- **Sigmoidal Emax (*ED50, h*)**: A positive monotonic concave dose-response curve model. It is similar to the Emax model (see above) but has an additional parameter, h, (often called the Hill parameter/coefficient) which characterizes the slope of the dose-response curve at the ED_{50} dose. A Hill parameter value of one is equivalent to the (hyperbolic) Emax model with values lower than one implying a shallower slope than the Emax model and values higher than one implying a steeper slope than the Emax model.

$$f\left(d,\theta\right)=E_0+E_{max}\frac{d^h}{ED_{50}+d^h}$$

$$f^0\left(d,\theta^0\right)=\frac{d^h}{ED_{50}+d^h}$$

- **Logistic (*ED50, δ*)**: A positive monotonic concave dose-response curve model. It is closely related to the sigmoidal Emax model which is equivalent to a logistic model on the log(dose) scale, with this Logistic model being on the original dose scale. It requires the specification of ED50 (the dose giving half the maximum dose response effect) and δ which controls for the slope of the curve. Higher δ imply a steeper dose-response curve.

$$f\left(d,\theta\right)=E_0+E_{max}/\left\{1+\exp\left[\left(ED_{50}-d\right)/\delta\right]\right\}$$

$$f^0\left(d,\theta^0\right)=1/\left\{1+\exp\left[\left(ED_{50}-d\right)/\delta\right]\right\}$$

- **Exponential (*δ*)**: A positive monotonic convex dose-response curve model. It requires the specification of the parameter δ which controls the convexity of the model with higher values implying a faster increase in response with increase in dose. E_1 is a slope parameter and this is derived automatically from the model

definitions via simultaneous equations.

$$f\left(d,\theta\right)=E_0+E_1\left(\exp\left(\frac{d}{\delta}\right)-1\right)$$

$$f^0\left(d,\theta^0\right)=\exp\left(\frac{d}{\delta}\right)-1$$

- **Beta (*a, b, Scale*)**: A flexible model that can be used to model non-monotonic dose-response curves. It requires the specification of three parameters. "a" and "b" are the first and second shape parameters for the Beta model and the distributional assumptions of the Beta distribution in terms of shape can be applied here. The scale parameter is used to characterise the range of the Beta function (e.g. scale of 100 would re-scale Beta Distribution to [0,100] rather than the standard [0,1]). The scale parameter should be greater than the largest dose with a value of 1.2 times the maximum dose being a useful default.

$$f\left(d,\theta\right)=E_0+E_{max}B\left(a,b\right)\left(\frac{d}{Scale}\right)^a\left(1-\frac{d}{Scale}\right)^b,B\left(a,b\right)=\frac{\left(a+b\right)^{a+b}}{a^ab^b}$$

$$f^0\left(d,\theta^0\right)=B\left(a,b\right)\left(\frac{d}{Scale}\right)^a\left(1-\frac{d}{Scale}\right)^b$$

- **Quadratic (δ)**: A flexible model which assumes a quadratic dose-response relationship and can be used to model non-monotonic dose-response curves. It requires only the specification of the parameter δ. δ represents a ratio of the quadratic model parameters, $\beta_1$and β_2,and is defined below. Note that the concave version of the quadratic model has been implemented in nQuery which imposes the restriction that $\beta_2$is negative. Note that, through the formulation below, specifying a negative value for δ will result in a positive value being found for $\beta_1$and vice versa.

$$f\left(d,\theta\right)=E_0+\beta_1d+\beta_2d^2$$

$$f^0\left(d,\theta^0\right)=d+\delta d^2,\delta=\frac{\beta_2}{|\beta_1|}\&\beta_2<0$$

β_2 here represents the curvature of the dose-response relationship and $\beta_1$represents the slope of the curve. The values for the$\beta_1$and $\beta_2$parameters of the quadratic model are found through the following equations:

$$\beta_2=-|4\delta^2(ME-PE)|$$

$$\beta_1=\frac{\beta_2}{\delta}$$

where ME represents the maximum response effect expected to be observed in the dose-range and PE represents the effect at placebo.

10.2 MCP-Mod Demonstration

10.2.1 Background

In nQuery the layout for MCP-Mod is similar to that of most other tables in nQuery. See chapter 1 for an introduction to using nQuery. This section will focus on the additional issues associated with the MCP-Mod table by demonstrating a detailed example of using the table in nQuery.

In nQuery, the inputs required for the MCP-Mod design can be split into three separate categories.

The first of these categories consists of the general test design parameters such as power and the placebo effect. These are equivalent to the main table inputs seen in standard nQuery tables.

The other two categories are the dose levels being assessed in the study and the candidate models selected and their per-model inputs (see subsubsection 10.1.2.4) and outputs e.g. power. These are both contained in the mandatory side-table. See section 3.1 for general guidance on side-tables.

In this section we will consider an example which relates to a real Phase II design in the development program of a drug for the indication of generalized anxiety disorder (GAD). Five active doses are to be used in the study: 10, 25, 50, 100, and 150mg, with an additional placebo arm (corresponding to a 0mg dose). This is the same example considered in section 2 of Pinheiro et al. (2006). Further details will be provided as we complete the example.

10.2.2 Main Table (General Design Parameters)

The main table (as discussed in previous chapters of this manual) is used to enter the common parameters which apply to each model. These are the test significance level, whether to use a one or two sided test, the placebo effect, the maximum treatment effect and common standard deviation (equivalent to the residual standard deviation in our model and practically the standard deviation of responses within a dose-level).

Alongside these common parameters, the number of doses and number of models need to be specified. This will set the number of columns in the doses input table and candidates models specification table contained in the side table. See subsection 10.2.3 for details.

Figure 10.1 illustrates how the main table will appear on the initial opening of the table in nQuery.

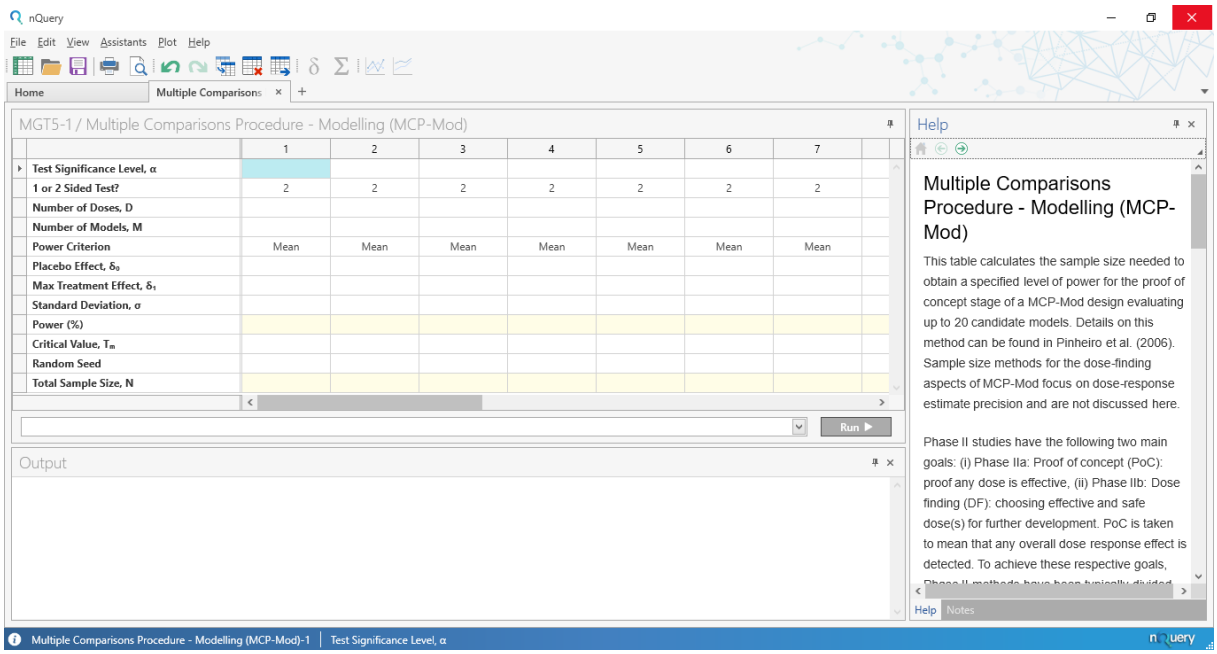


Figure 10.1: MCP-Mod Design Main Table

The first step required is to specify the desired significance level (α), whether a one or two sided test is required and the number of doses and candidate models of interest. Select the power criteria (mean, minimum or median power) and then specify the expected placebo effect, the maximum effect, and the common standard deviation. If one wishes to solve for the total sample size then specify the target power. If one wishes to solve for power, then specify the total sample size here or specify the individual sample sizes per dose group in the Dose Level Side table, as discussed in section 5.2.3.1 below.

In this example, considered here we will assume a significance level of 0.05, 80% power, a residual standard deviation of 1, a one sided test, a placebo Effect of 0, a maximum treatment effect of 0.4, 6 doses (5 doses and the placebo dose), a candidate set of 6 models and use the "Mean" power criteria. The power value will be left empty for now and entered after the side-table section is complete.

Optionally, the user can also enter a random seed and critical value. The random seed is used for the simulations used for the multivariate t-distribution method implemented in nQuery. If left blank this will default to a value based on the system time. Setting this option to a specific value allows the user to generate the exact same results for a given set of inputs. In this example, we will set the seed to 1234 to allow exact replication of this example.

The critical value is the critical multivariate t-statistic for the multivariate t-distribution CDF ($q_{1-\alpha}$). To use the optimal t-statistic set the test significance level to desired level and this will make the Critical Value read-only. To use a custom test statistic do not enter the significance level and enter the critical value. As we have entered the significance level, the optimal contrasts will be used here.

For more information on these parameters, see the help cards in the software. The Critical Value parameter will be calculated automatically for us. The completed main table is shown in Figure 10.2.

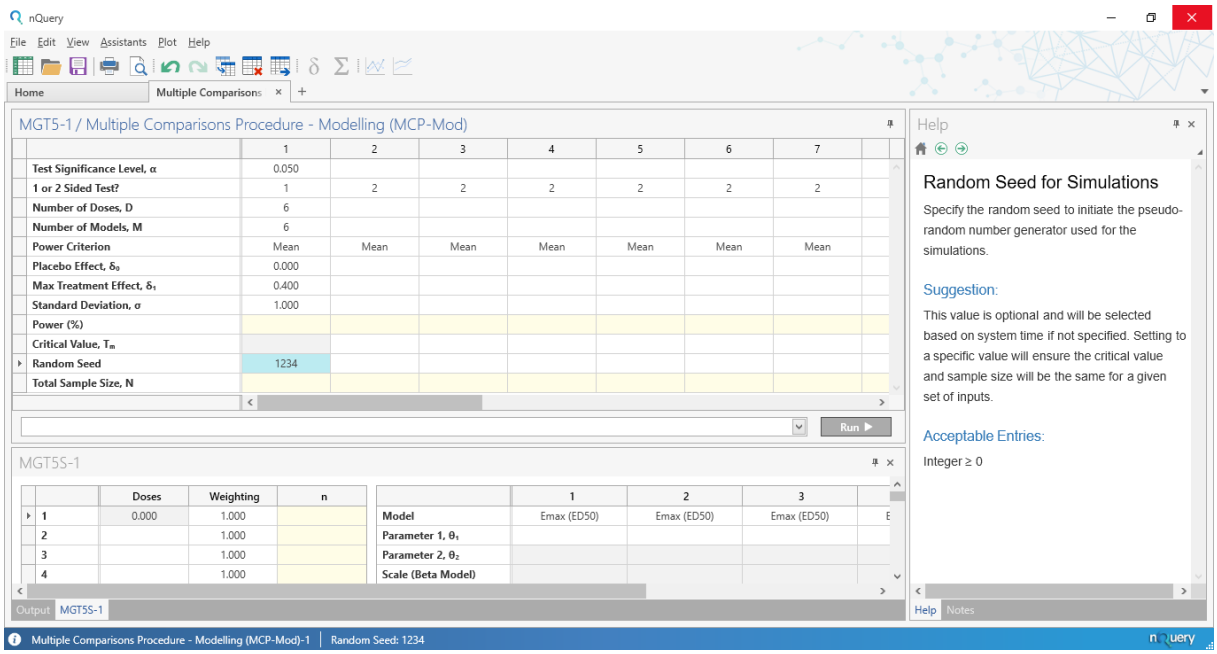


Figure 10.2: Completed MCP-Mod Main Table

10.2.3 Side-Table (Dose Levels and Candidate Models)

After the number of doses and number of models is specified in a column, the MCP-Mod side-table will automatically appear below the main table window. See subsection 10.2.3 for general guidance on side-tables. In this example, upon opening the side-table will be as per Figure 10.3.

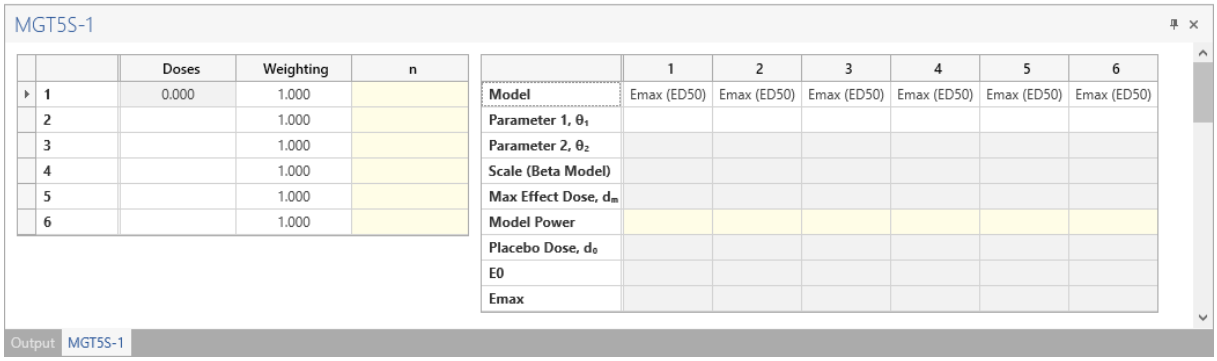


Figure 10.3: MCP-Mod Side-Table

The table on the left-hand side is the Doses Table where the dose levels of interest will be entered. On the right-hand side is the Model Specification Table where candidate models are selected and model specific inputs and outputs are provided.

10.2.3.1 Doses Table

On the left-hand side of the side-table, the planned dose levels table is provided as per Figure 10.4. This table specifies which doses will be considered in this trial and sample size weightings applied to each dose level.

		Doses	Weighting	n
▸	1	0.000	1.000	
	2		1.000	
	3		1.000	
	4		1.000	
	5		1.000	
	6		1.000	

Figure 10.4: Dose Levels Table

In this table, enter the proposed study dose levels (how much/concentration of the proposed treatment given to each dose level) in the first "Doses" column. Note that the first row entry in the Doses column is automatically set to 0 as this represents the placebo dose (i.e. no treatment given) which is required for this method. It is recommended that doses are entered in increasing order down the column but nQuery will automatically adjust if a non-increasing set of dose levels is given. In this example we will assume the following set of doses: 0, 10, 25, 50, 100, 150 (mg).

Next, enter the sample size weightings per dose level in the second "Weighting" column. By default all entries in this column will equal one, corresponding to equal sample size per dose level. The proportion of the total sample size in a given dose level is given by $W_i / \sum W_i$ where W_i is the weighting per dose level.

If solving for power, one may enter the individual dose group sample sizes in the third column. Otherwise, once a sample size determination is complete the third column, "n", will automatically be filled with the per-dose sample sizes. For this example, assume equal sample size per column and leave the default "1's" inputs. The final dose levels tables will be filled as per Figure 10.5.

		Doses	Weighting	n
	1	0.000	1.000	
	2	10.000	1.000	
	3	25.000	1.000	
	4	50.000	1.000	
	5	100.000	1.000	
✎	6	150.	1.000	

Figure 10.5: Completed MCP-Mod Dose Levels Table

10.2.3.2 Model Specification Table

On the right-hand side of the side-table, the model specification table is provided as per Figure 10.6. This table specifies which candidate set of models will be considered and where any additional parameters required per-model are inputted. After a sample size determination, it contains the per-model outputs including model power, minimum effect dose level (d_0), maximum effect dose level (d_m), the minimum dose effect (E_0) and

maximum dose effect (E_{max}). Note that the maximum and minimum dose levels will automatically be calculated for most models after the Dose Levels table is filled. The major exceptions are the Beta model and the Quadratic model where the maximum effect dose level is not known pre-calculation.

	1	2	3	4	5	6
Model	Emax (ED50)	Emax (ED50)	Emax (ED50)	Emax (ED50)	Emax (ED50)	Emax (ED50)
Parameter 1, θ_1						
Parameter 2, θ_2						
Scale (Beta Model)						
Max Effect Dose, d_m	150.000	150.000	150.000	150.000	150.000	150.000
Model Power						
Placebo Dose, d_0	0.000	0.000	0.000	0.000	0.000	0.000
E0						
Emax						

Figure 10.6: Model Specification Table

In this table, the desired candidate models are selected in each column using the drop down menu in the Model row of the model specification table. After a model is selected, 0 to 3 (equal to the number of parameters given in brackets beside model name) of the rows will become available to edit depending on the model selected. Column cells that require inputs for calculations will be white and those not required for the given model will be grey. Note that the same model can be selected multiple times, characterized with different model specific parameters, except for the Linear model which has no additional inputs. Details on the models available and the model specific parameters required are given in subsubsection 10.1.2.4.

In this example we will consider the following set of candidate models, with the corresponding parameter values assumed for each model given in brackets after each model:

- Linear
- Emax (ED50 = 25)
- Logistic (ED50 = 50, δ = 10.88111)
- Exponential (δ = 85)
- Beta (a = 0.33, b = 2.31, Scale = 200)
- Beta (a = 1.39, b = 1.39, Scale = 200)

The completed model specification table is given in Figure 10.7.

	1	2	3	4	5	6
Model	Linear	Emax (ED50)	Logistic (ED50, δ)	Exponential (δ)	Beta (a, b, Scale)	Beta (a, b, Scale)
Parameter 1, θ_1		25.000	50.000	85.000	0.330	1.390
Parameter 2, θ_2			10.881		2.310	1.390
Scale (Beta Model)					200.000	200.000
Max Effect Dose, d_m	150.000	150.000	150.000	150.000	150.000	150.000
Model Power						
Placebo Dose, d_0	0.000	0.000	0.000	0.000	0.000	0.000
E0						
Emax						

Figure 10.7: Completed Model Specification Table Example

In this example, after the final parameter which is required in the model specification table is entered (e.g. "Scale" in column 6), the calculation will not run as the Power row has not been filled in the main table. However, if the main table had been fully filled the calculation would occur automatically. Note that if you do not want every edit to this side-table to automatically start the calculation, leaving one or more of the mandatory inputs in the main table empty is recommended. Once a calculation is complete the per-model power, placebo dose, maximum effect dose, E0 and Emax will be calculated automatically in this table. Note that some models will also calculate additional parameters such as the slope parameter for the linear and exponential models.

10.2.4 Results

In this example, the last input is 80% in the Power row in the main table After this is entered, the calculation will start. After the calculation is complete the entire table in nQuery will be as per Figure 10.8. Note that this method (due to the computation of multivariate t-distribution) may take some time to run.

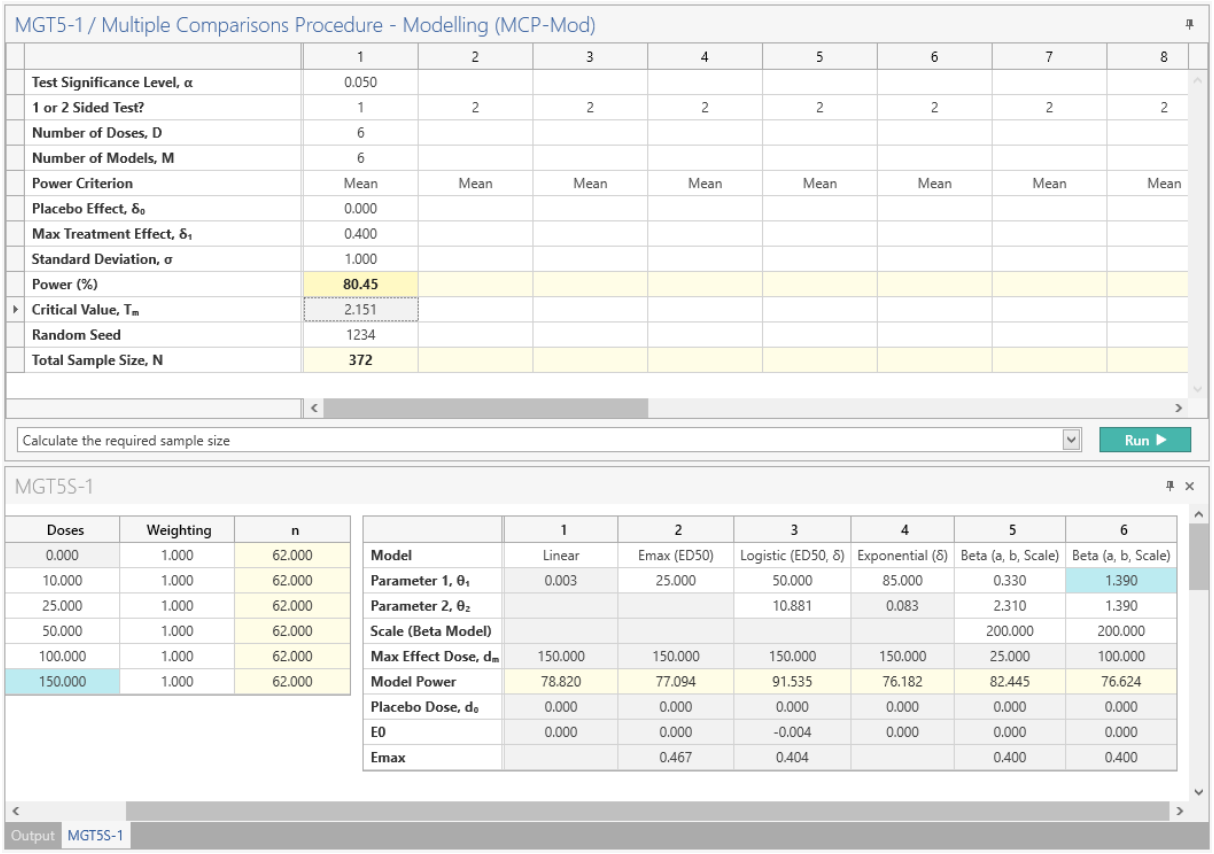


Figure 10.8: Completed MCP-Mod Example

This example results in a sample size of 372 and thus a per dose group sample size of 62 as per Pinheiro [Pinheiro et al., 2006]. The exact mean power is automatically updated to 80.44% for this sample size. The per-model powers and other parameters are given in the model specification table in the side-table. The per-model powers ranged from 76.139% for the exponential model to 91.522% for the logistic model. Note the maximum effect dose is the final dose for all models except the Beta models, with the first Beta model having its maximum effect (i.e. the maximum dose effect specified in the main table) at the 25mg dose and the second Beta model having its maximum effect at the 100mg dose. These are found automatically by evaluating the Beta model at each specified dose level and finding the maximum effect dose from the results.

Using a custom critical value will have a shorter calculation time so the optimal critical value can be used in other examples directly if the significance level and model specification were unchanged.

11 nQuery Predict

nQuery Predict is a tool to predict the timing of key clinical trial enrollment and event milestones both before or during a trial. Predictions are generated via simulation using a variety of statistical models based on interim trial data or pre-trial estimates of accrual, event and dropout rates.

This chapter will consist of two sections. In section 11.1, enrollment and event milestone prediction is described at a high level with a technical background provided on how simulations are generated for all the available methods in nQuery Predict. In section 11.2, fully worked demonstrations are provided for each of the main enrollment and event milestone prediction types with guidance on setting up a prediction, the user interface and the main results and outputs for a milestone prediction.

Note: nQuery Predict is currently only available for users with an nQuery Advanced Expert license. Active packages are displayed in the Packages section in the Home tab. To purchase additional packages, go to `www.statsols.com`.

11.1 Trial Milestone Prediction

nQuery Predict focusses on prediction for two primary milestone types: enrollment and events. Enrollment prediction focusses on when the required number of subjects will be enrolled into the study. Event prediction focusses on when the required number of events in a survival (time-to-event) trial will occur in a study. Terms which are used directly in the nQuery Predict user interface are **highlighted in bold.**

11.1.1 Enrollment Prediction

11.1.1.1 Background

The majority of clinical trials have a pre-specified target for enrollment, often derived using a sample size determination calculation. After an enrollment target is set there is a practical requirement for trialists and sponsors to estimate how long it will take to enroll the target sample size. This requires knowledge of the expected accrual rate and accrual pattern using data from prior trials or expert elicitation. Statistical methods can be applied using this knowledge to make informed inferences about the likely length of the accrual period and resulting study length. These inferences can then be used in the logistics of planning a trial.

However, it is very common for pre-trial projections of accrual rates to be inaccurate. To combat this, interim data can be used to generate more accurate estimates of the accrual rate and pattern and this information can be used to update the expected accrual period

and study length. This provides trialists with the knowledge they may need to adjust stakeholder expectations or to get a trial back on track by making on-going changes to the trial e.g. by opening new sites (e.g. hospitals).

nQuery Predict uses simulation from common parametric statistical distributions to model the recruitment process and generate estimates of how long recruitment will likely need to continue to achieve a **Target Sample Size**. Enrollment prediction is available for the following scenarios:

- Enrollment Prediction using Subject-level Data Only
- Enrollment Prediction using Subject and Site-level Data
- Enrollment Prediction using Summary Data

Data-level predictions (**Subject-level Data Only, Subject and Site-level Data**) assume the predictions are being made while the trial is on-going based on interim trial data. Data-level prediction assume the user is providing a subject-level dataset where each column corresponds to a required subject-level user input and each row corresponds to an individual subject. If site-level data is being used, each column corresponds to required site-level user input and each row corresponds to an individual site.

Summary Data (also known as **Fixed Parameters**) prediction can be made pre-trial or while the trial is on-going. **Summary Data** assumes the user inputs fixed single parameter estimates to set up the prediction.

For enrollment prediction using **Subject-level Data Only**, the data is required to include the column **Arrival Time** for each subject up until the current time (i.e. time of last accrual).

For enrollment predicting using **Subject and Site-level Data**, the subject data is required to include the **Arrival Time** and **Site ID** for each subject. The site data is required to include the **Site ID** for each site, the expected future enrollment rate per site (**Accrual Rate/Site**), the **Enrollment Cap** per site (i.e. maximum number of subjects that can be recruited from that site) and **Site Initiation Time** (i.e. opening time) for currently **Opened Sites**. Optionally, the **Start Time** and **End Time** for the **Site Initiation Period** for currently **Unopened Sites** can be provided. Note that all **Site ID** values contained in the subject-level data must be contained in the **Site ID** values in the site-level data but not vice-versa (as site-level data can contain unopened sites or open sites which have not enrolled a subject at the **Current Time**).

For Summary Data, the **Current Sample Size** and **Current Time** are required. For pre-trial prediction, these are both set to zero.

The following statistical models are available for generating enrollment times:

- Poisson (Constant)
- Poisson (Non-Homogenous)

The **Poisson** model assumes a constant event rate where the timing of each event is independent from each other. The **Poisson** model is assumed to be a global enrollment process for the **Subject-level Data Only** and **Summary Data** cases. For **Subject and Site-level Data**, an individual Poisson process is specified for each individual site.

11.1.1.2 Technical Details

Poisson Enrollment Generation Poisson enrollment generation is created by sampling the expected inter-arrival time between each accrual. These can be shown to follow the exponential distribution for a Poisson process [Ahrens and Dieter, 1972]. The probability distribution function (pdf) and generating model are as follows :

$$f(x) = \lambda \exp(-\lambda x)$$

$$x = -ln(u)/\lambda$$

$$\lambda = \frac{n}{t}$$

where $f(x)$ is the pdf, λ is the Poisson rate, x is the random inter-arrival time generated, u is a value generated from a standard uniform distribution ($U(0,1)$) and n is the sample size accrued up to current time, t. The definition of λ given in the third equation above is the default value given in nQuery Predict for the Poisson accrual rate.

For subject-level data only or Summary Data, the number of inter-arrival times generated equals the **Target Sample Size** minus the **Current Sample Size**. The total length of the remaining accrual period after the **Current Time** is given by the sum of all the inter-arrival times generated to simulate the necessary number of subjects. Each subject's arrival time after the **Current Time** equals the cumulative sum of inter-arrival times until and including that subject's inter-arrival time. These times relative to the study start are calculated by adding the **Current Time** to them e.g. **Total Accural Period Length = Cumulative Sum(x) + Current Time.**

For subject and site-level data, inter-arrival times are generated for each site up to the smaller of the **Enrollment Cap** minus the **Current Sample Size** in a site or the total number of required simulated subjects (**Target Sample Size - Current Sample Size**). The effective arrival time for each subject is the cumulative sum within each site of the inter-arrival times up until and including that subject's inter-arrival time. The effective arrival times across all sites are then compared with only the lowest required number of arrival times (i.e. target sample size minus current sample size) used.

Non-Homogenous Poisson Enrollment For subject-level or summary data, the user can specify **piecewise accrual rates** and the enrollment process will be modelled using a non-homogenous Possion process.

The enrollment times are simulated using the Inversion Method based on Çinlar [Cinlar, 2013]:

$$A(t) = \int_0^t a(t')dt'$$

where $A(t)$ is the expected number of subjects enrolled in the interval $[0, t)$ and $a(t)$ is the enrollment rate at time t.

In nQuery, $a(t)$ will be a piecewise constant function. If P pieces are required, then it is represented by vectors $\boldsymbol{a}$ and $\boldsymbol{t}$, both of length P, where $\boldsymbol{a}_i$ is the accrual rate between times between times $\boldsymbol{t}_{i-1}$ and $\boldsymbol{t}_i$, for $i \in \{2, ..., P\}$

If $A(t)$ strictly increases monotonically, then it will have an inverse, $A^{-1}()$ that generates a stationary unit Poission process $u_1, u_2, u_3, ..., u_N$, where N is the target number of enrollments.

i.e.

$$u_j = \sum_{i=1}^{j} x_i$$

where x_i is a randomly generated value that is exponentially distributed with rate 1, for $j \in \{1, ..., N\}$

From this, the enrollment times are calculated as follows:

$$\tau_i = A^{-1}(u_i)$$

where τ_i is the enrollment time of the i^{th} subject, $i \in \{1, ..., N\}$

Site Opening Time Generation For unopened sites, the site opening time is generated using a uniform distribution between the specified site initiation start time and end time. This gives a site initiation times as follows:

$$OT = ST + (ET - ST)u$$

where OT is the simulated opening time for a site, ST is the specified site initiation window start time, ET is the specified site initiation window end time and u is a value generated from a standard uniform distribution ($U(0, 1)$).

11.1.2 Events Prediction

11.1.2.1 Background

In survival analysis (also referred to as time-to-event analysis), the primary endpoint of interest is the length of time until a subject experiences an event of interest. Common events of interest are death (overall survival - OS) or disease progression (progression free survival - PFS).

Unlike other common endpoints, the follow up per subject is unknown a priori since a subject's follow up time will depend on when the endpoint of interest occurs for a subject i.e. their survival time. Importantly, the inference at the end of the study will primarily be based on the subjects who have had the event of interest since subjects who dropout or are censored will not have an explicit time to event. Therefore the study length will depend on when the required number of events occurs. This milestone **Target Number of Event**s is often derived from a power analysis for example. In survival analysis the power is related to the number of events with the sample size an estimate of the number of

subjects needed to achieve that number of events given study constraints such as accrual and event rates.

From a milestone event prediction perspective, this requires the modelling of both the enrollment process (unless enrollment is complete at the time of an interim analysis) and the survival process. For the survival process, there are number of potential models available. In addition, competing processes which prevent a subject from having the event of interest in the future, such as dropout or competing events, may also be modelled.

The choice of administrative right-censoring for subject who do not have the event of interest or any competing event during the study is also an important consideration. Two common choices are an event-driven (also known as variable follow up) design and a fixed follow up design. In the event-driven design, the study is continued until the required number of events has occurred at which point the remaining subjects in the study are right-censored. In a fixed follow up design, each subject has a fixed maximum follow up period and if they do not have the event during this period then they are administratively right-censored.

Given the additional complexity of generating simulations for the enrollment, event and dropout/competing event processes, a wider number of scenarios and models are available for events prediction. Enrollment simulation, where needed, is conducted as per subsection 11.1.1. This gives the following scenarios for events prediction:

- Blinded Events Prediction with Enrollment Ongoing using Subject-level Data Only
- Blinded Events Prediction with Enrollment Ongoing using Subject and Site-level Data
- Blinded Events Prediction with Enrollment Ongoing using Summary Data
- Unblinded Events Prediction with Enrollment Ongoing using Subject-level Data Only
- Unblinded Events Prediction with Enrollment Ongoing using Subject and Site-level Data
- Unblinded Events Prediction with Enrollment Ongoing using Summary Data
- Blinded Events Prediction with Enrollment Complete using Subject-level Data
- Blinded Events Prediction with Enrollment Complete using Summary Data
- Unblinded Events Prediction with Enrollment Complete using Subject-level Data
- Unblinded Events Prediction with Enrollment Complete using Summary Data

Data-level predictions (**Subject-level Data Only, Subject and Site-level Data**) assume the predictions are being made while the trial is on-going based on interim trial data. Data-level prediction assume the user is providing a subject-level dataset where each column corresponds to a required subject-level user input and each row corresponds to an individual subject. If site-level data is being used, each column corresponds to required site-level user input and each row corresponds to an individual site.

Summary Data (also known as **Fixed Parameters**) prediction can be made pre-trial or while the trial is on-going. **Summary Data** assumes the user inputs fixed single parameter estimates to set up the prediction.

Blinded Events and **Unblinded Events** refers to whether the treatment assignment for each subject is assumed to be known (and will be used for event milestone prediction) by

the trialist. **Unblinded**, also known as a comparative analysis, assumes treatment assignment is known and **Blinded Events**, also known as non-comparative, assumes treatment assignment is unknown. If **Blinded Events** is selected, the event (and dropout) model will assume a "global" event process for all subjects. If **Unblinded Events** is selected, separate event process models are used to individually model the two treatment groups.

Enrollment Ongoing indicates that enrollment is still happening at the point that the current prediction is being made. **Enrollment Complete** indicates that the enrollment process is complete at the time the current prediction is being made. **Enrollment Complete** means that **Subject and Site-level Data** cannot be used as site-level data is only used for modelling the enrollment process and has no input on the event model.

If using **Subject-level Data** (with or without site-level data), columns for the **Arrival Time** per subject, the **Status Indicator** and **Time on Study** are required for each subject.

The **Arrival Time** is time from the start of the study until when a subject entered the study and is the same as for the Enrollment Prediction case.

The **Status Indicator** column indicates whether a subject has the **Event Status, Dropout Status** or **Censored Status** at the current time. The value in the **Status Indicator** column which corresponds to each status is set by the user and can be manually inputted for any status that has not occurred at the **Current Time** (see subsection 11.2.7 for details).

Event Status indicates a subject has had the event of interest (e.g. death) at the current time.

Dropout Status indicates a subject had dropped out at the current time. **Dropout Status** can also be used to indicate subjects who have had a "competing" event which prevents the subject from having the event of interest in the future.

The **Censored Status** (also referred to as **Available Status**) indicates a subject who has neither had the event of interest or a dropout event and therefore would be censored if the study was to end at the **Current Time**. These subjects are still available to have the event of interest (or dropout) and therefore will have a predicted event (and dropout) time simulated for them.

The **Time on Study** column gives the value for how long a subject was in the study. The definition will depend on whether they have a **Event/Dropout Status** or **Censored Status**. For subjects who have the **Event Status** or **Dropout Status** for their **Status Indicator**, the **Time on Study** will be the length of time from their **Arrival Time** until they have had an event or dropped out. For subjects who have the **Censored Status** for their **Status Indicator**, the **Time on Study** is the length of time from their **Arrival Time** until the **Current Time**.

If using **Subject-level Data** (with or without **Site-level Data**) alongside **Unblinded Events,** a **Treatment ID** column is required which indicates which treatment group each subject is in. The two groups are named the **Control Group** and **Treatment Group** and the value in the **Treatment ID** column which corresponds to each of these groups is set by the user (see subsection 11.2.7 for details).

As per enrollment prediction, if using **Subject and Site-level Data** when **Enrollment Ongoing** then the subject data is required to include the **Site ID** column. The site data is required to include the **Site ID** for each site, the expected future enrollment rate

per site (**Accrual Rate/Site**), the **Enrollment Cap** per site (i.e. maximum number of subjects that can be recruited from that site) and **Site Initiation Time** (i.e. opening time) for currently **Opened Sites**. Optionally, the **Start Time** and **End Time** for the **Site Initiation Period** for currently **Unopened Sites** can be provided. Note that all **Site ID** values contained in the subject-level data must be contained in the **Site ID** values in the site-level data but not vice-versa (as site-level data can contain unopened sites or open sites which have not enrolled a subject at the **Current Time**).

For **Summary Data** with **Blinded Events**, the **Current Sample Size, Current Number of Events, Current Number of Dropouts** and **Current Time** are required. The **Current Number Censored** (i.e. available) is automatically calculated for the user by subtracting the **Current Events** and **Current Number of Dropouts** from the **Current Sample Size.**

For **Summary Data** with **Unblinded Events**, the **Current Sample Size (Control), Current Sample Size (Treatment), Current Number of Events (Control), Current Number of Events (Treatment), Current Number of Dropouts (Control), Current Number of Dropouts (Treatment)** and **Current Time** are required. **(Current/Treatment)** in brackets indicates the treatment group. The **Current Number Censored (Control)** (i.e. available) is automatically calculated for the user by subtracting the **Current Number of Events (Control)** and **Current Number of Dropouts (Control)** from the **Current Sample Size (Control).** The **Current Number Censored (Treatment)** (i.e. available) is automatically calculated for the user by subtracting the **Current Number of Events (Treatment)** and **Current Number of Dropouts (Treatment)** from the **Current Sample Size (Treatment).**

The following models are available for generating survival times:

- Exponential
- Piecewise Exponential (available only for Subject-level Data Only, Subject and Site-level Data)
- Weibull (available only for Subject-level Data Only, Subject and Site-level Data)

The **Exponential** model assumes a constant hazard (event) rate over time where events are independent from time on study. The **Piecewise Exponential** model assumes a piecewise survival curve where there are pre-specified time periods which have individual differing exponential hazard rates. The **Weibull** model is a more flexible model than the **Exponential** which allows the hazard rate to change over time and depend on how long a subject has been in the study (see subsubsection 11.1.2.2 for details).

The following models are available for generating dropout times:

- Exponential
- Piecewise Exponential (available only for Subject-level Data Only, Subject and Site-level Data)

The dropout models work the same as the event models.

For the **Enrollment Ongoing** case, the same models are used as for **Enrollment Prediction** above. See subsection 11.1.1 for details.

11.1.2.2 Technical Details

Constant Exponential Event Prediction Exponential event times are generated directly from the exponential distribution [Ahrens and Dieter, 1972]. Note that in nQuery Predict this refers to the model where **Response Distribution = Exponential** and **Number of Hazard Pieces = 1** at the **Event & Dropout Information** step of **Setup** (see subsection 11.2.7)

The probability distribution function (pdf) and generating model are as follows:

$$f(x) = \lambda \exp(-\lambda x)$$

$$x = -ln(u)/\lambda$$

$$\lambda_i = \frac{E_i}{F_i}$$

where $f(x)$ is the pdf, λ is the exponential hazard rate, x is the random survival time generated, u is a value generated from a standard uniform distribution ($U(0,1)$), E_i is the number of events that have occurred in the group of interest and F_i is the total follow up time (i.e. sum of follow up) for all subjects in the group of interest up until the current time.

The definition of λ given in the third equation above is the default value given in nQuery Predict for the event **Hazard Rate**. For **Blinded Events**, the total events and total follow up for all subjects is used to calculate a global exponential hazard rate applied to all subjects. For **Unblinded Events**, the events and total follow up for each group are used to calculate an exponential hazard rate for each group separately.

The survival time generated here, x, is survival time from the **Current Time** when the prediction is generated. If interim data was used, for subjects who were still available to have the event in that data (**Censored Status**) their time-to-event will equal the survival time generated using this model plus their **Time on Study** up until the current time. For the time of event relative to the study start (rather than time-to-event after **Arrival Time**), add the time-to-event (i.e. **Time on Study** + x) and **Arrival Time.**

Piecewise Exponential Event Prediction Piecewise exponential event times are generated using the memoryless independent increments method. Note that in nQuery Predict this refers to the model where **Response Distribution = Exponential** and **Number of Hazard Pieces > 1** at the **Event & Dropout Information** step of **Setup** (see subsection 11.2.7)

In the piecewise exponential model, there are K sequential independent time periods (the first of which starts at the current study time (defined as ($\tau_1 = 0$)) with an independent exponential hazard rate which applies over each pre-specified time period. Each time period has a length equal to $\tau_{i+1} - \tau_i$.

$$P = 1, 2, ..., K$$

$$\mathrm{T} = \tau_1, \tau_2, ...\tau_K, \tau_{K+1}; \tau_1 = 0, \tau_{K+1} = \infty$$

$$\mathit{\Lambda} = \lambda_1, \lambda_2, ..., \lambda_K$$

$$L = l_1 = \tau_2 - \tau_1, l_2 = \tau_2 - \tau_1, ...l_K = \tau_K - \tau_{K+1} = \infty$$

$$X = x_1, x_2, ..., x_K$$

$$x_i = -ln(u_i)/\lambda_i$$

$$\begin{cases} x = \tau_i + x_i & x_i \leq L_i \\ Repeat_{i+1} & x_i > L_i \end{cases}$$

where P is sequential periods from 1 to K, T is the start time (τ_i) of each time period (first period starts at 0, $K+1$ "starts" at infinity), Λ is the exponential hazard rates (λ_i) assigned to each time period starting at time τ_i, L is the length of the each time period (this equals the start time of the next period minus the start time of the current period ($\tau_{i+1} - \tau_i$)), X is the random survival time generated (x_i) for each period, u_i is a value generated from a standard uniform distribution ($U(0,1)$) for each period and $Repeat_{i+1}$ indicates that the step above should be repeated for the $(i+1)^{th}$ case.

In the memoryless method, an exponential survival time (x_1) is first randomly generated for the first time period ($P = 1$) and its corresponding exponential hazard rate (λ_1). If the generated survival time (x_1) for the first period is less than or equal to the length of the first time period ($l_1 = \tau_2 - \tau_1 = \tau_2$) i.e. ($x_1 \leq l_1$) then we stop the algorithm and set the overall survival time equal to the start time of the first period plus the generated survival time for the first period i.e. ($x = \tau_1 + x_1 = x_1$).

However, if the first survival time exceeds the length of the first time period i.e. ($x_1 > l_1$), it is assumed the subject survived at least up until the start of the next (second) period (τ_2) and the algorithm continues. Next for the second time period ($P = 2$), an exponential survival time is generated for the second time period (x_2) with its corresponding exponential hazard rate (λ_2). If the generated survival time (x_2) for the second period is less than or equal to the length of the first time period ($l_2 = \tau_3 - \tau_2$) i.e. ($x_2 \leq l_2$) then the algorithm stops and the overall survival time is set equal to the start time of the second period plus the generated survival time for the second period i.e. ($x = \tau_2 + x_2$).

However, if the second survival time exceeds the length of the second time period i.e. ($x_2 > l_2$), it is assumed the subject survived at least up until the next ($P = 3$) period's start time (τ_3)and the algorithm continues. These steps are continued until either the algorithm stops due to the generated survival time in a given period being less than or equal to the length of that time period i.e. ($x_i \leq l_i$) or until the K^{th} period is reached at which point the overall survival equals the final period start time plus the final generated survival time i.e. ($x = \tau_K + x_K$).

In nQuery Predict the piecewise exponential default is the same as the **Constant Exponential**, with time period starts (τ_i) that increase from zero in increments of one for each additional number of hazard pieces (time periods) specified with the hazard rate equal to the default from the constant exponential hazard rate case (see section 11.1.2.2) in each period.

The survival time generated here (x) is the survival time from the **Current Time** i.e. the time when the prediction is generated. If interim data was used, for subjects who were still available to have the event in that data (**Censored Status**) their time-to-event will equal the survival time generated using this model plus their **Time on Study** up until the current time. For the time of event relative to the study start (rather than time-to-event after **Arrival Time**), add the time-to-event (i.e. **Time on Study** + x) and **Arrival Time.**

Note that there are alternative methods proposed for the generation of piecewise exponential survival times such as the CDF method ([Walke, 2010]).

Weibull Event Prediction Weibull survival times are generated from Weibull distribution. As the hazard rate changes over time for a subject, the calculation of survival time will differ for subjects who were already in the study and available to have the event (**Status Censored**) at the time of the current prediction (conditional) and subjects who will enter at or after the current prediction time (unconditional).

For subjects who are in the study at the time of the prediction, the conditional survival time is calculated as follows:

$$x = \frac{1}{\mu}\left[(\mu T)^{\nu} - \ln(1-u)\right]^{\frac{1}{\nu}} - T$$

where x is the generated survival time from the current time, μ is Weibull scale parameter, ν is the Weibull shape parameter, T is the time spent on the trial (**Time on Study**) up until the current time and u is a value generated from a standard uniform distribution ($U(0,1)$).

For subjects who are enrolled at or after the current prediction time, the unconditional survival time is calculated as follows:

$$x = \frac{1}{\mu}\left(-\ln(1-u)\right)^{\frac{1}{\nu}}$$

where x is the generated survival time from the current time, μ is Weibull scale parameter, ν is the Weibull shape parameter and u is a value generated from a standard uniform distribution ($U(0,1)$).

Note that if the Weibull shape parameter (ν) is equal to one then the Weibull distribution reduces to an exponential distribution with rate equal to the Weibull scale parameter (μ). When the shape parameter is less than one, this indicates that the event rate reduces over time and when the shape parameter is greater than one, this indicates that the event rate will increase over time.

nQuery Predict will provide the best fit Weibull model by default based on the interim subject-level data. The two parameter estimates can be derived via maximum likelihood estimation using numerical optimization over the Weibull likelihood function below:

$$L(\mu,\nu) = \prod_{i=1}^{n} \left[(\mu\nu)(\mu t_j)^{\nu-1}\right]^{\delta_j} e^{-(\mu t_j)^{\nu}}$$

where $L(\mu,\nu)$ is the likelihood function, μ is Weibull scale parameter, ν is the Weibull shape parameter, t_j is the length of time a subject has been in the study (**Time on Study**) and δ_j is an indicator function which equals 1 for subjects who had the event of interest (**Status Event**) and zero otherwise. Note that nQuery applies optimization over the log-likelihood, an example of which can be found in [Nielsen, 2011].

Dropout Generation The exponential and piecewise exponential models are available for the dropout process. These work the same as for the event generation methods outlined above.

11.2 nQuery Predict Demonstration

This section will demonstrate how to create milestone predictions using nQuery Predict. The demonstration is split into nine subsections as follows:

1. Creating an nQuery Predict Workspace (subsection 11.2.1)
2. nQuery Predict Workspace Layout (subsection 11.2.2)
3. Dataset Management (subsection 11.2.3)
4. nQuery Predict Example Datasets (subsection 11.2.4)
5. Select the Type of Prediction (see subsection 11.2.5)
6. Enrollment Prediction Demonstration (subsection 11.2.6)
7. Event Prediction Demonstration (subsection 11.2.7)
8. Results Output Summary (Reports/Plots/Tables) (subsection 11.2.8)
9. Other Features (subsection 11.2.9)

Creating an nQuery Predict Workspace (subsection 11.2.1) gives an overview of how to create a new nQuery Predict workspace both with and without interim data.

nQuery Predict Workspace Layout (subsection 11.2.2) gives an overview for the layout of an nQuery Predict workspace and the primary purpose of each of the main user interface elements.

Dataset Management (subsection 11.2.3) gives an overview of how to open, edit, upload and remove datasets within a nQuery Predict workspace.

nQuery Predict Example Datasets (subsection 11.2.4) gives an overview of the example subject (SubjectData.csv) and site-level (SiteData.csv) datasets provided with nQuery and a basic introduction to the required fields needed in nQuery Predict, alongside other important information such as range restrictions and optional values.

Select the Type of Prediction/Setup Introduction (see subsection 11.2.5) gives an overview of Step 1 of the Setup stage of a prediction where the **Target, Input** and **Enrollment Status** are specified. A brief introduction to the **Setup** stage of the nQuery Predict workspace is also provided

Enrollment Prediction Demonstration (subsection 11.2.6) gives an overview of enrollment milestone prediction using Subject Data Only, using Subject + Site Data or using Summary Data inputs.

Event Prediction Demonstration (subsection 11.2.7) gives an overview of event milestone prediction for survival (time-to-event) analysis using Subject Data Only, using Subject + Site Data or using Summary Data inputs and with or without enrollment being complete.

Results Output Summary (subsection 11.2.8) gives a high-level overview of the outputs from prediction including the **Reports, Plots** and **Tables** available. Note that prediction-specific details for different prediction types are provided in the **Prediction Demonstration** sections above.

Other Features (subsection 11.2.9) gives an overview of other features available in an nQuery Predict workspace such as exporting results and error checking.

The first five subsections are common across all predictions. Enrollment Prediction Demonstration and Event Prediction Demonstration will have different **Setup** steps and results (**Reports/Plots/Tables**) depending on choices at the **Select Type of Prediction** step. These are broken up further into predictions using an **Input** of **Subject Data Only, Subject + Site Data** or **Summary Data** (Fixed Parameters), and **Enrollment Status** (Event Prediction Only). **Results Summary** and **Other Features** have both common and prediction-specific elements which are both highlighted.

11.2.1 Creating an nQuery Predict Workspace

The nQuery Predict Workspace is a tab in which a user will setup, run and view the results of their milestone prediction. To create a new nQuery Prediction Workspace the user can select the "Create Prediction" button in the Home Screen tab in top-left Home quadrant (1), select the Predict menu in the file menu at the top of the software window (2) or select the Predict toolbar icon  in the toolbar (3). These three options are highlighted in Figure 11.1.

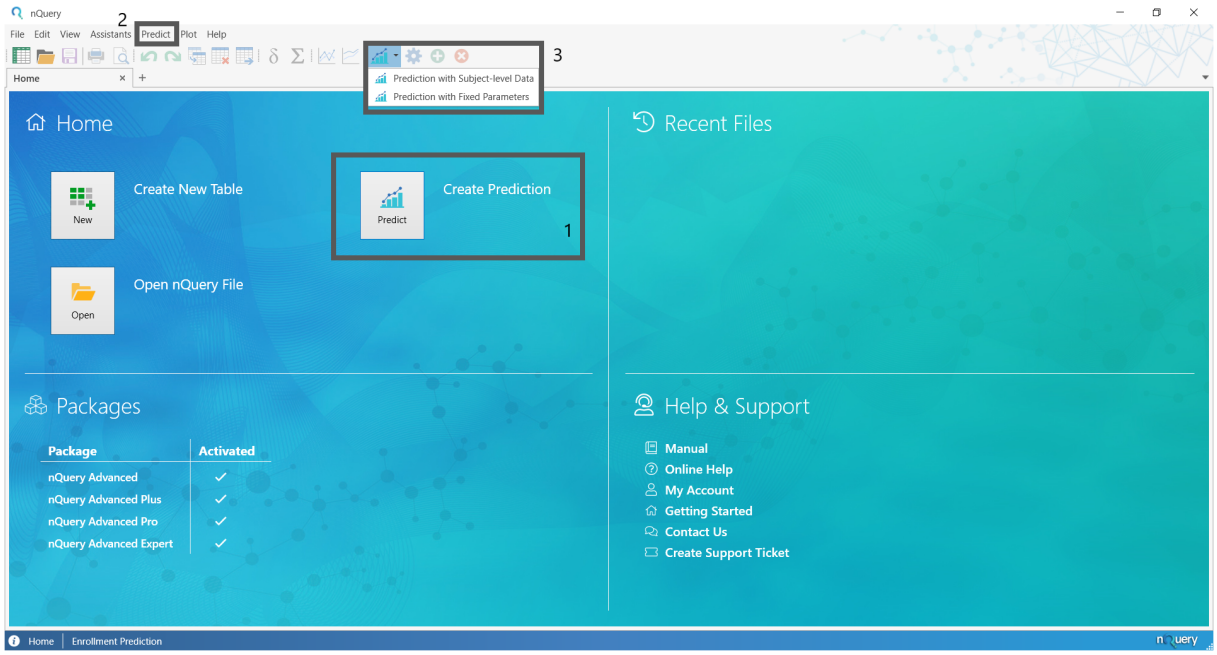


Figure 11.1: nQuery Predict Workspace Creation Options

If the Predict > New Prediction file menu or New Prediction toolbar option are used the user is presented with the option to either create a "Prediction with Subject-level Data" or "Prediction with Fixed Parameters". These two methods are described below.

11.2.1.1 Prediction with Subject-level Data

If "Prediction with Subject-level Data" is selected, the "New Prediction - Import Datasets" window is opened. This window is also shown if the "Create Prediction" button is selected from the Home tab. This is shown in Figure 11.2.

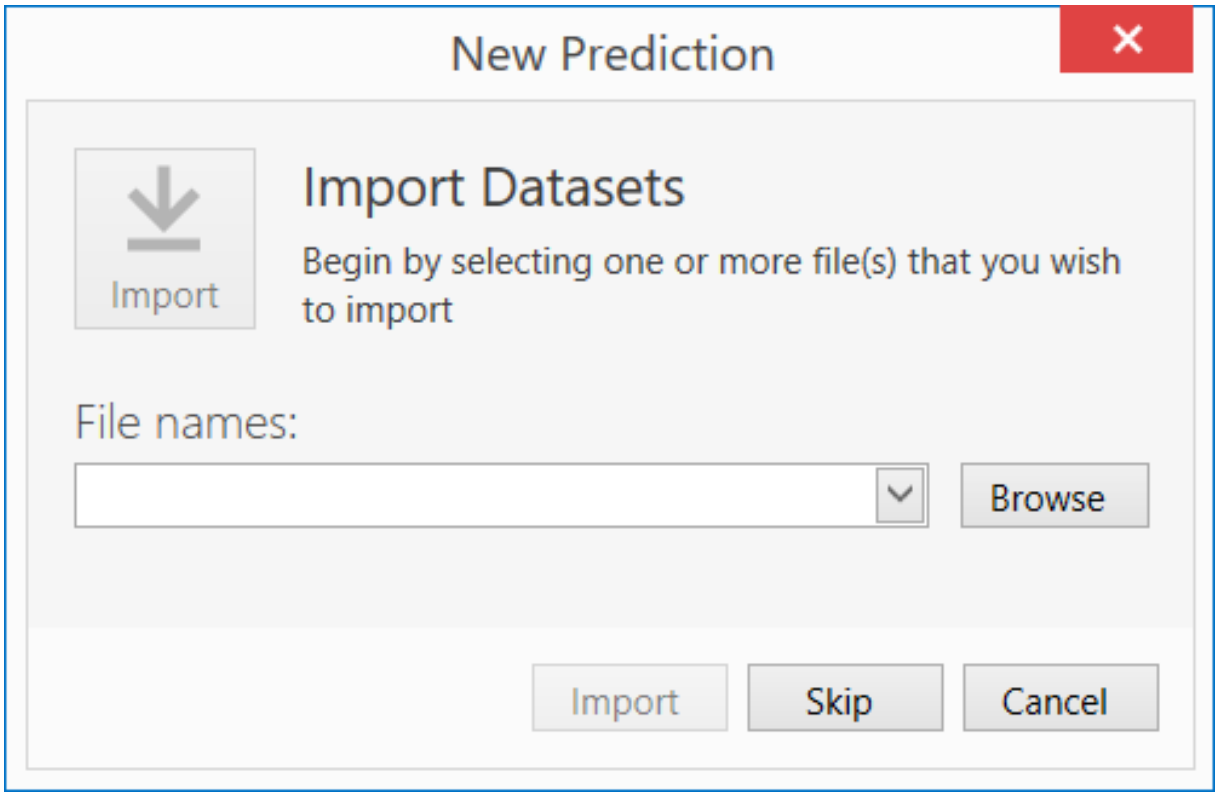


Figure 11.2: New Prediction - Import Datasets Window

In the "New Prediction - Import Datasets" window, the user can import csv files containing the required interim data for milestone prediction. To import datasets, select the Browse button to open the Open window, shown in Figure 11.3.

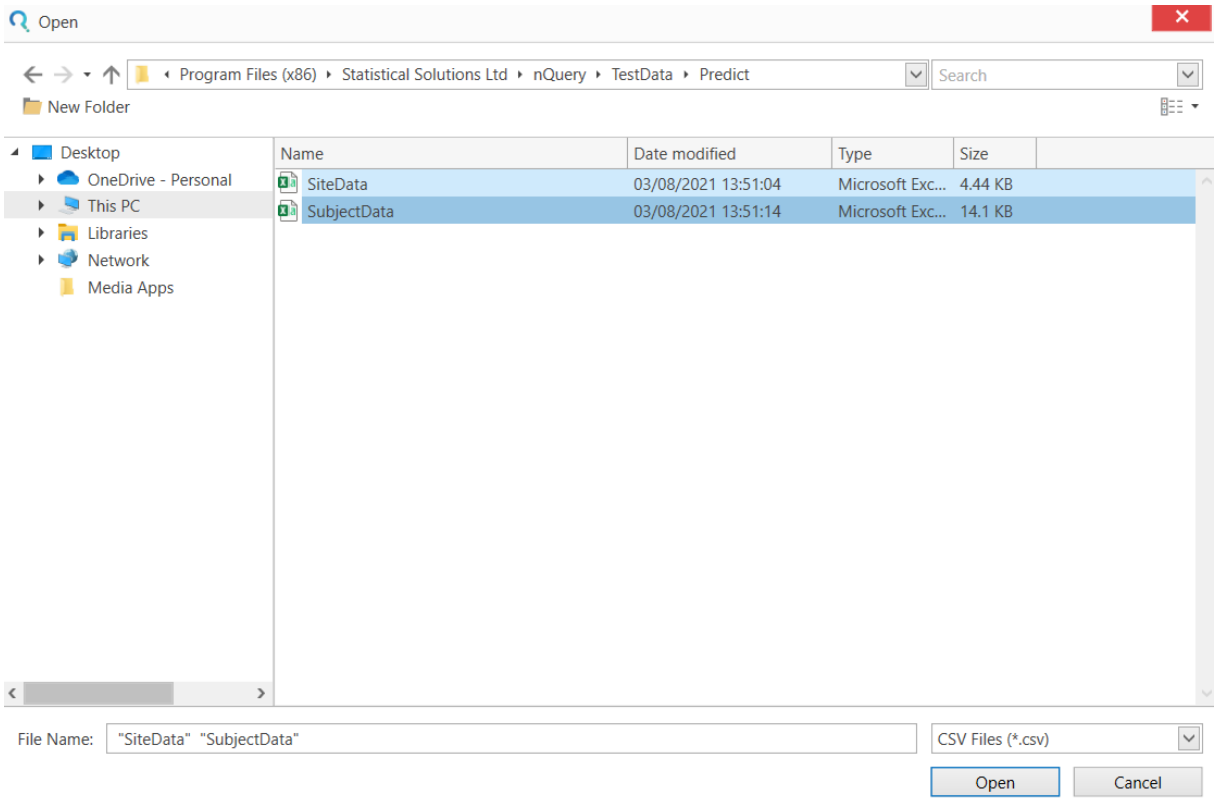


Figure 11.3: Open Window for nQuery Predict Data

nQuery Predict comes with an example subject-level dataset (named SubjectData.csv) and site-level dataset (named SiteData.csv). These simulated datasets were created based on available summary data from a real clinical trial. These datasets can be found in the nQuery installation folder which by default is C:\Program Files (x86)\Statistical Solutions Ltd\nQuery\TestData\Predict. All demonstration examples in the remainder of this chapter will use these example files.

To find a file the user can use the Navigation Pane on the left of the Open window, enter the file location directly in the Address Bar at the top or use the Search field in the top-right to find a file within the current folder and subfolders.

To open a file, the user first selects the required file(s) in the main window. To select multiple files, select a first file then select another file while holding down SHIFT (to select all files between the first and second file) or CTRL (to select multiple individual files). All files currently selected will be displayed in the File Name field at the bottom of the Open window. When the required files are selected, select Open in the bottom-right to return to the "New Prediction - Import Datasets" window.

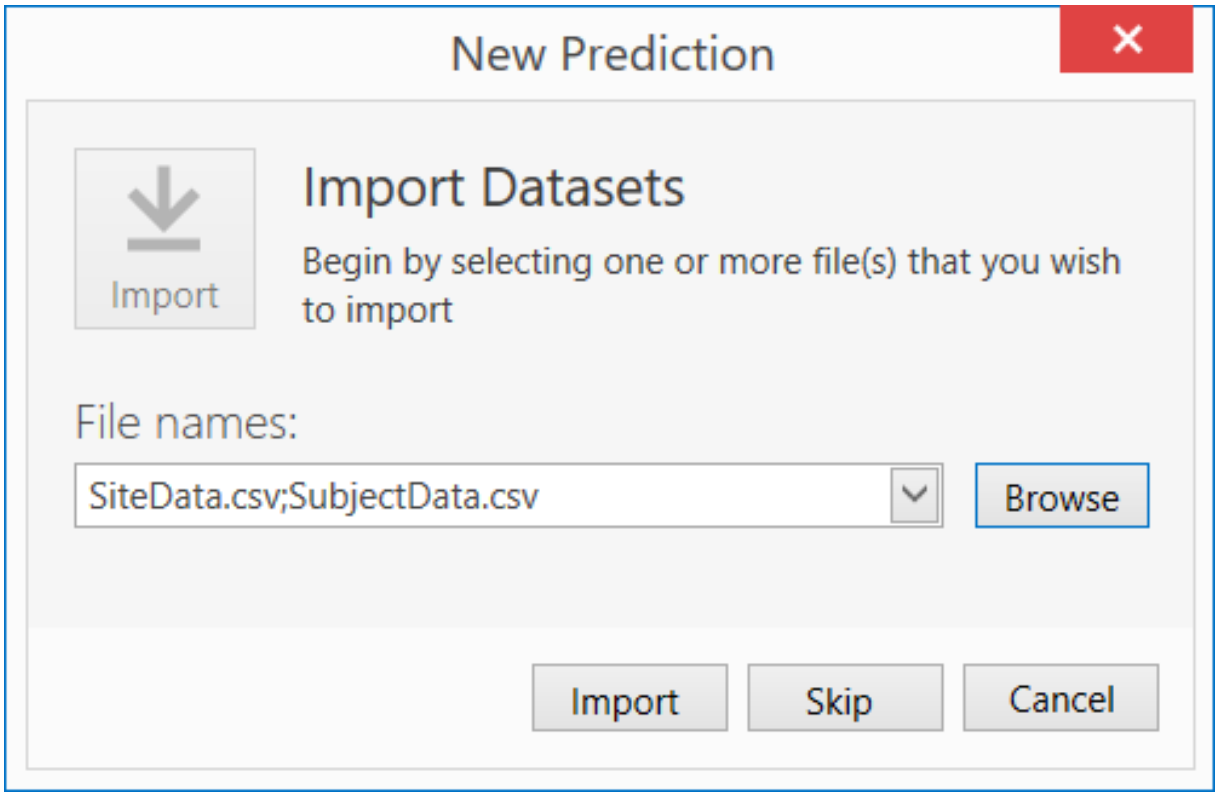


Figure 11.4: New Prediction - Import Datasets Complete Example

To create the nQuery Predict workspace, select the Import button. The new nQuery Predict workspace will be as per Figure 11.5.

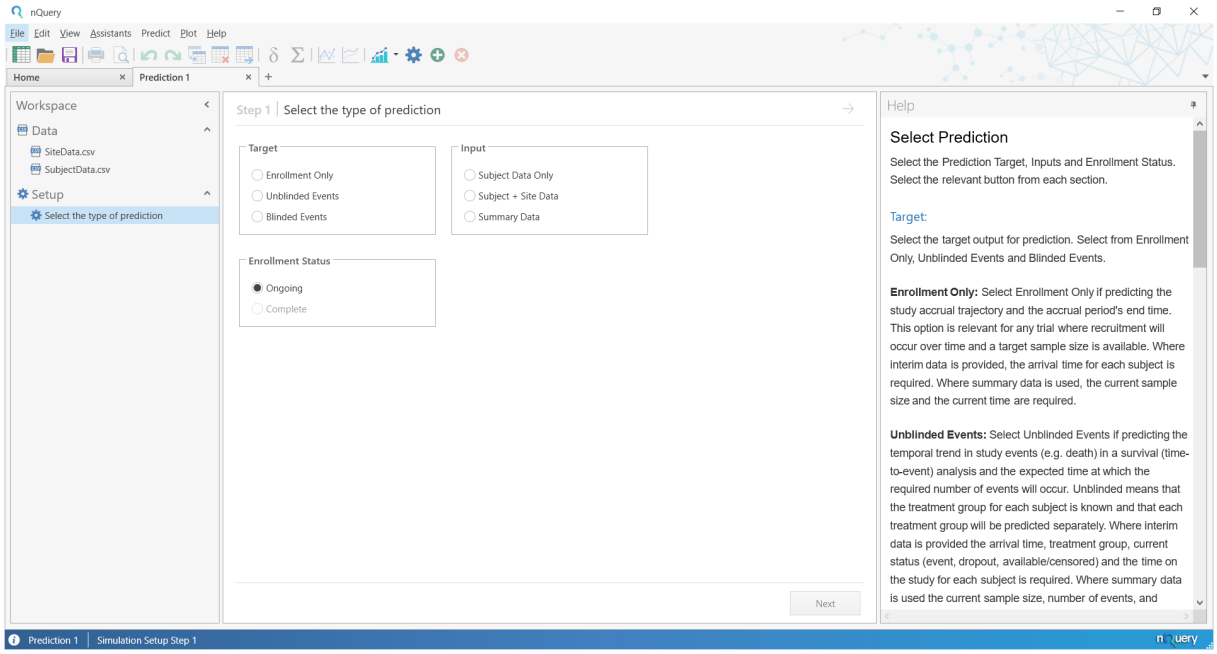


Figure 11.5: New nQuery Predict Workspace with Data

11.2.1.2 Prediction with Fixed Parameters

If "Prediction with Fixed Parameters" is selected an nQuery Predict workspace will immediately open. Selecting the Skip button on the "New Prediction - Import Datasets" window (see Figure 11.2) will also open an empty workspace.

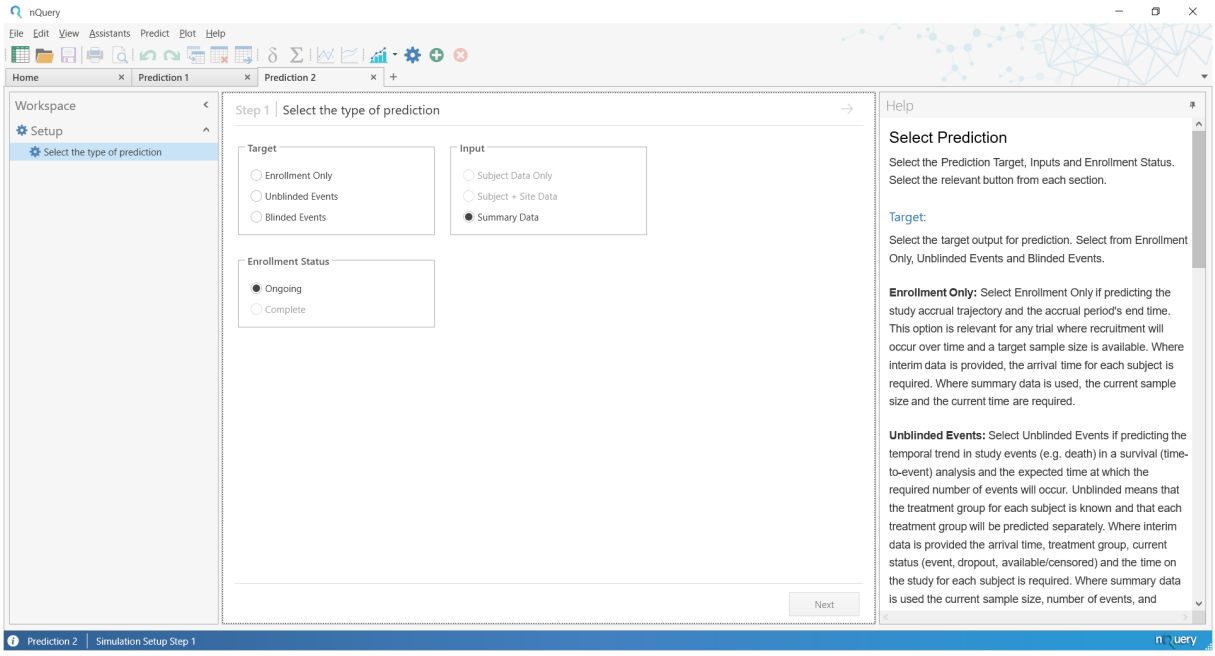


Figure 11.6: New nQuery Predict Workspace without Data

If this method is used the workspace will not contain any data and therefore the Subject Data Only and Subject + Site Data Input Options will not be available (see subsection 11.2.5). To add datasets after a workspace is open, the Add Dataset option from the Predict file menu or toolbar can be used (see subsection 11.2.3).

11.2.2 nQuery Predict Workspace Layout

11.2.2.1 nQuery Predict Workspace Layout Overview

An nQuery Predict workspace will consist of three primary user interface elements: the Workspace Navigation Bar (1), the Main Display Window (2) and the Help Window (3). These are numbered in Figure 11.7.

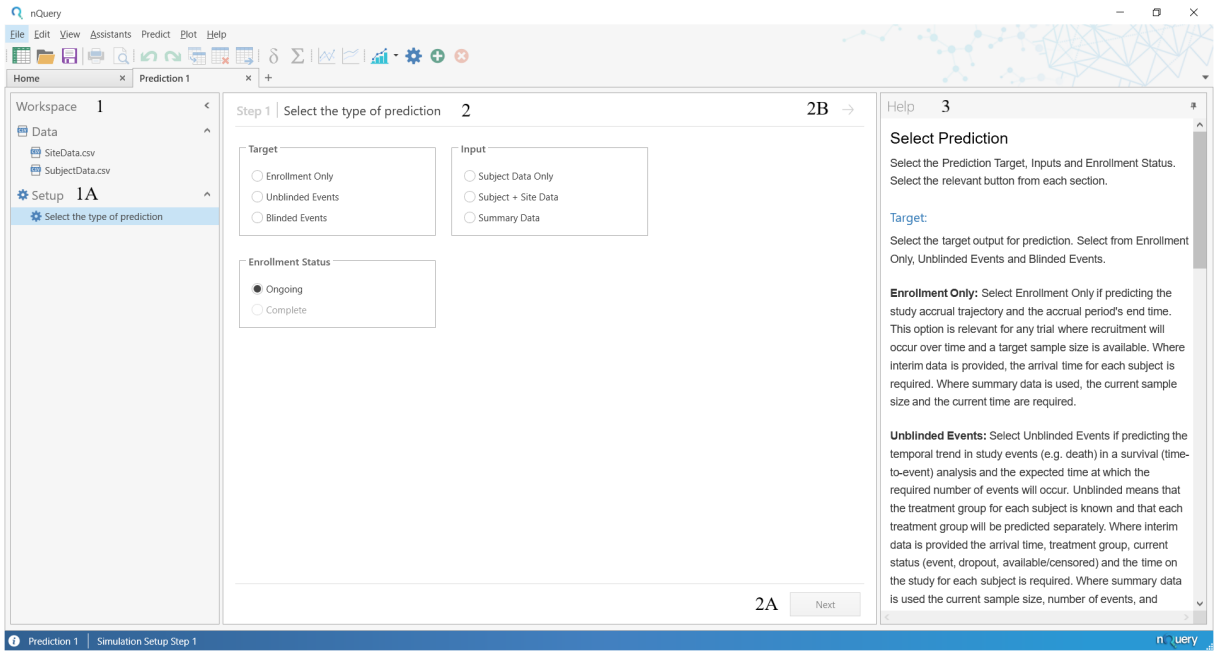


Figure 11.7: nQuery Predict Workspace Layout

The Workspace Navigation Bar (1) is used to navigate to a specific element (**Data, Setup** step**, Report, Plot, Table**) of the current nQuery Predict Workspace at any time. Elements are organized under headers with an example header (**Setup**) highlighted as per 1A in Figure 11.7. A specific element can be selected from under a given header. Header elements can opened and collapsed by selecting the header name. In Figure 11.7, the **Select the Type of Prediction** step can be selected from the **Setup** header or the **SubjectData.csv** or **SiteData.csv** datasets can be selected from the **Data** header.

The following elements are potentially available, depending on the current prediction stage, in the Workspace Navigation Bar: **Data, Setup, Reports, Plots, Tables.** Details for **Data** are given in subsection 11.2.3. Details for **Setup** are given in subsection 11.2.5, subsection 11.2.6 and subsection 11.2.7. Details for **Reports, Plots** and **Tables** are given in subsection 11.2.8, subsection 11.2.6 and subsection 11.2.7.

The Main Display Window (2) displays the current element selected and is where the user can input values and view results. During the **Setup** stage, the user can select the Next button (2A) or Right-Arrow buttons (2B) to move to the next step (note subsequent **Setup** steps will have a corresponding adjacent Back and Left-Arrow buttons to go back to prior step) and users can select and enter values in the main fields (e.g. for the current **Select the Type of Prediction** step, radio buttons can be select from the **Target, Input** and **Enrollment Status** fields). Details on what is displayed in the Main Display Window for a given element will be shown in the sections below.

The Help Window (3) provides context and guidance on all of the elements currently displayed in Main Display Window. The Help will include definitions, context, suggested values and tips.

11.2.2.2 Editing the nQuery Predict Workspace Layout

There are three primary ways to change the default layout of an nQuery Predict Workspace: collapsing the Workspace Navigation Bar, unpinning the Help Window and changing the width of the Main Display Window.

To collapse the Workspace Navigation Bar, select the < button to the right of the main "Workspace" header at the top-right of the Workspace Navigation Bar. When the Workspace Navigation Bar is collapsed, elements can be shown and selected by clicking the named bar (name will be the same as the current element shown in the Main Display Window) on the left-hand side of the nQuery Predict Workspace. To uncollapse the Workspace Navigation Bar, select the > button at the top of the named bar on the left-hand side.

To unpin the Help window, select the button on the right of Help Window header in the top-right. When the Help Window is unpinned, the Help Window will not be displayed unless the cursor is placed over the Help section in the top-right of the nQuery Predict Workspace after which the Help Window will be displayed until a different element is selected in the nQuery Predict Workspace. To repin the Help Window, select the button when the Help Window is open.

To change the width of the Main Display Window, move the cursor over the left-hand edge (if the Workspace Navigation Bar is not collapsed) or right-hand edge (if the Help Window is displayed) of the Main Display Window until the cursor changes to a two-way arrow (↔) and click and drag the cursor to change the Main Display Window width.

An example workspace where the Workspace Navigation Bar is collapsed and Help Window is unpinned and unselected is shown in Figure 11.8, with the user interface items referenced above highlighted in yellow.

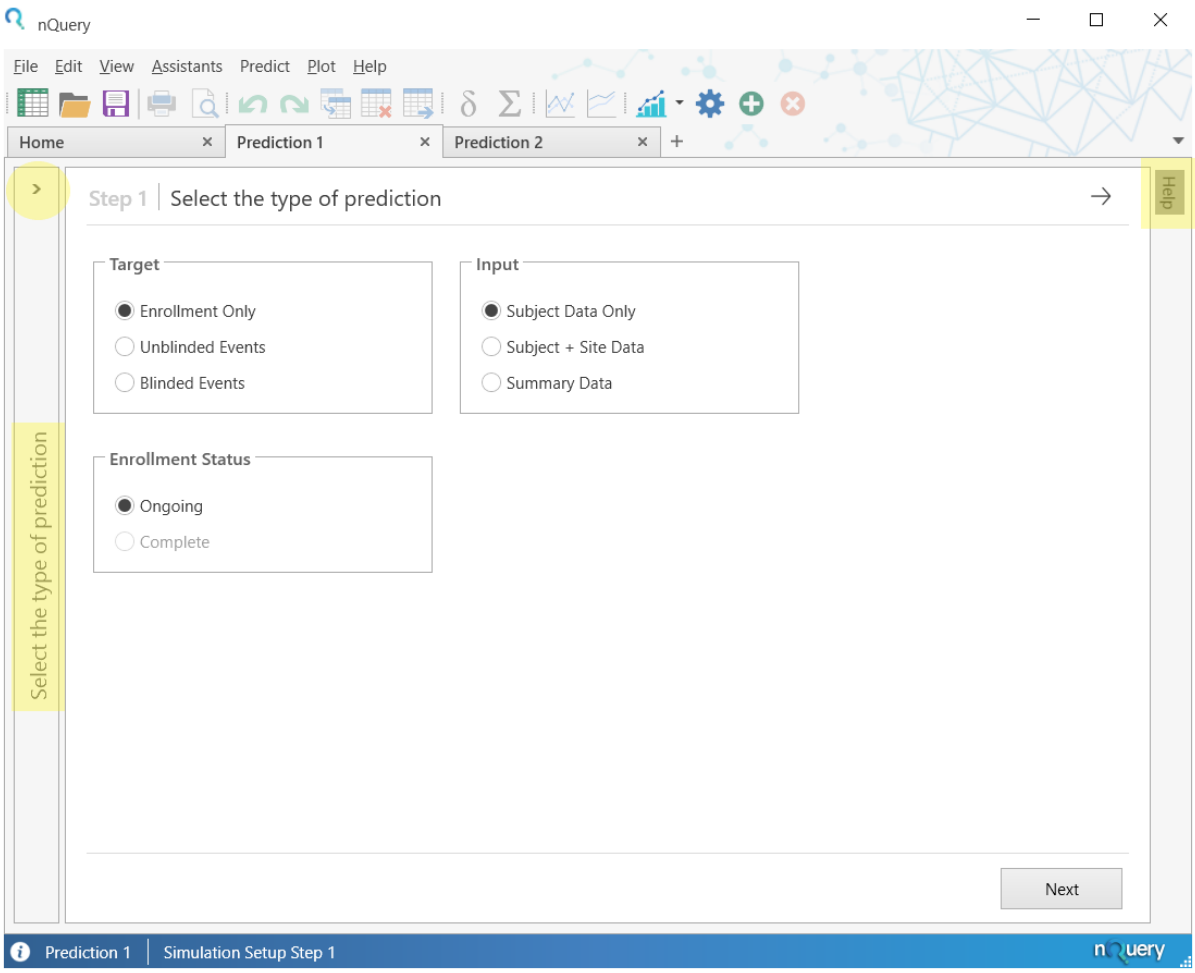


Figure 11.8: Collapsed nQuery Predict Workspace

11.2.3 Dataset Management

11.2.3.1 Viewing and Editing Datasets

To view any dataset in the current nQuery Predict workspace, select that dataset from the **Data** header in the Workspace Navigation Bar (subsection 11.2.2) on the left-hand side of the workspace which has been highlighted in Figure 11.9.

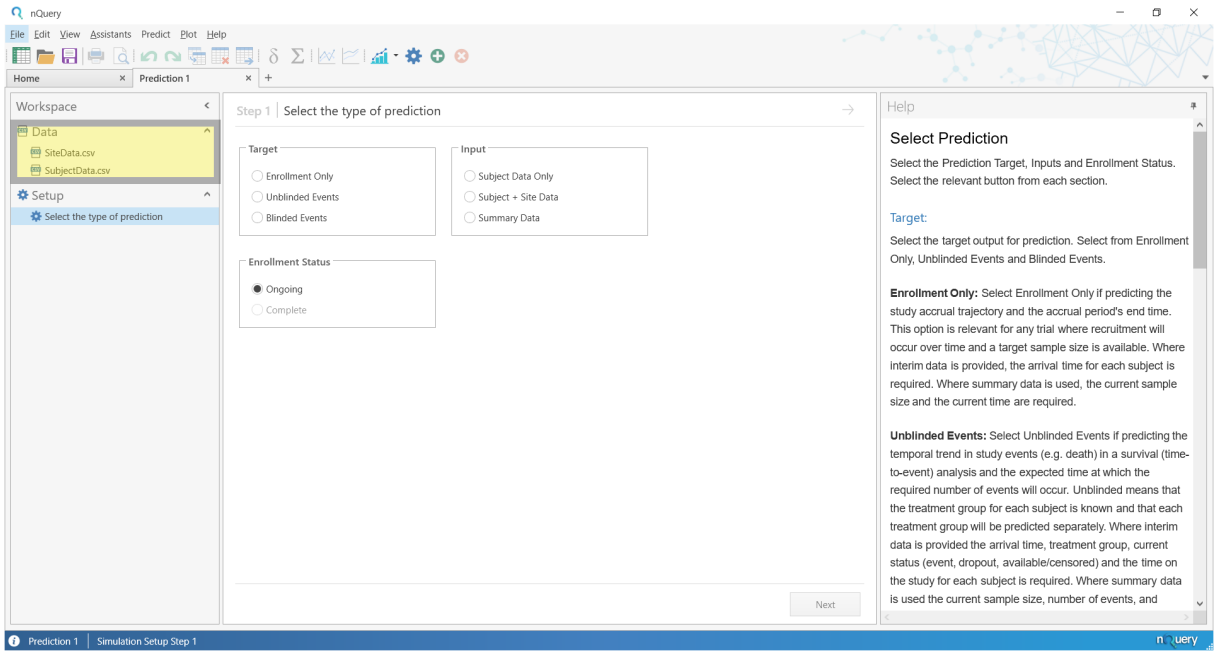


Figure 11.9: nQuery Predict Workspace with Highlighted Data field

After selecting a dataset from the Data field, the selected dataset will be displayed in the main nQuery Predict workspace window. An example with the SubjectData.csv file is shown in Figure 11.10.

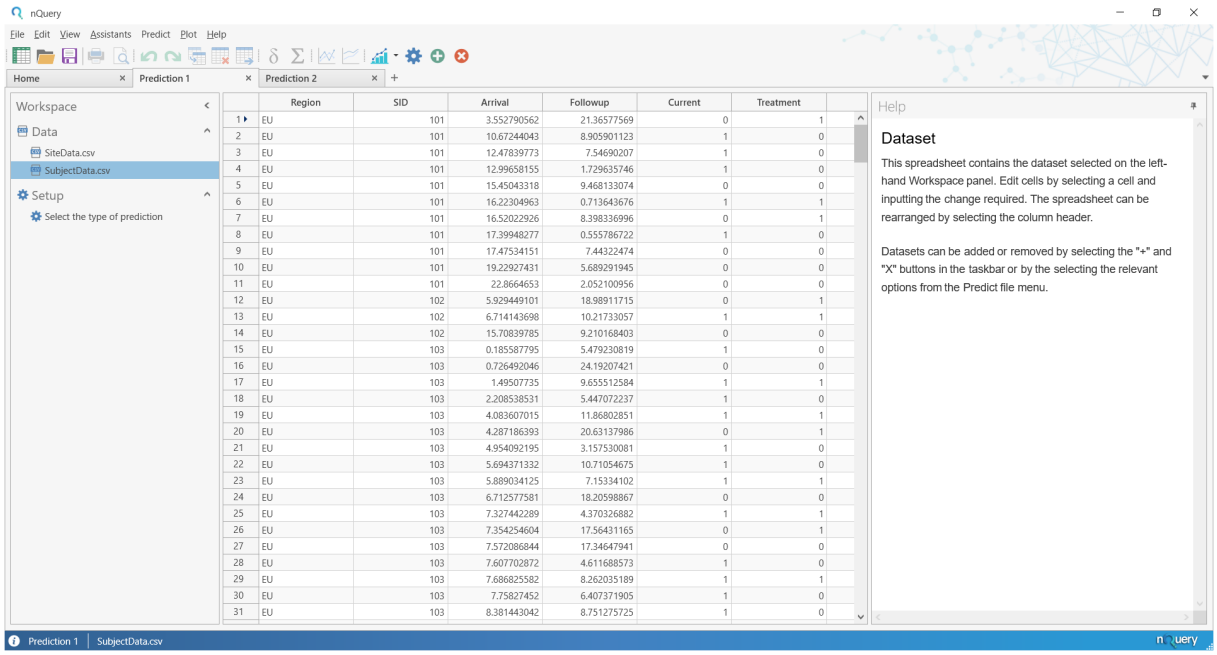


Figure 11.10: nQuery Predict Workspace Displaying SubjectData Example Dataset

When a dataset is displayed, the user can edit cells and sort columns. To edit a cell, double-click a cell and enter the new required input. Note that nQuery automatically detects whether a column is a non-numeric category, integer or real numeric value based on the values in that column. This is to reduce the number of options shown during the

Subject-level Data (Step 2 in **Setup** when **Input = Subject Data Only** or **Subject + Site Level Data**) and Site-level Data (Step 3 in **Setup** if **Subject + Site Data** selected from **Input**) drop-down menus. If the user enters a real value into a category or integer column, an out of range error will be displayed in that cell (see subsection 2.2.1).

To sort a column from low to high for a numeric column or A to Z for a alphanumeric column, select the column header containing the column name at the top of the required column. To sort the column from high to low (or Z to A) select the column header a second time. When the dataset has been sorted by a column, an up (if low to high/A to Z) or down arrow (if high to low/Z to A) will be shown to the right of the column header.

An example where the SubjectData has been sorted by the **Arrival** column from low to high and an edit is underway in the first row cell is shown in Figure 11.11.

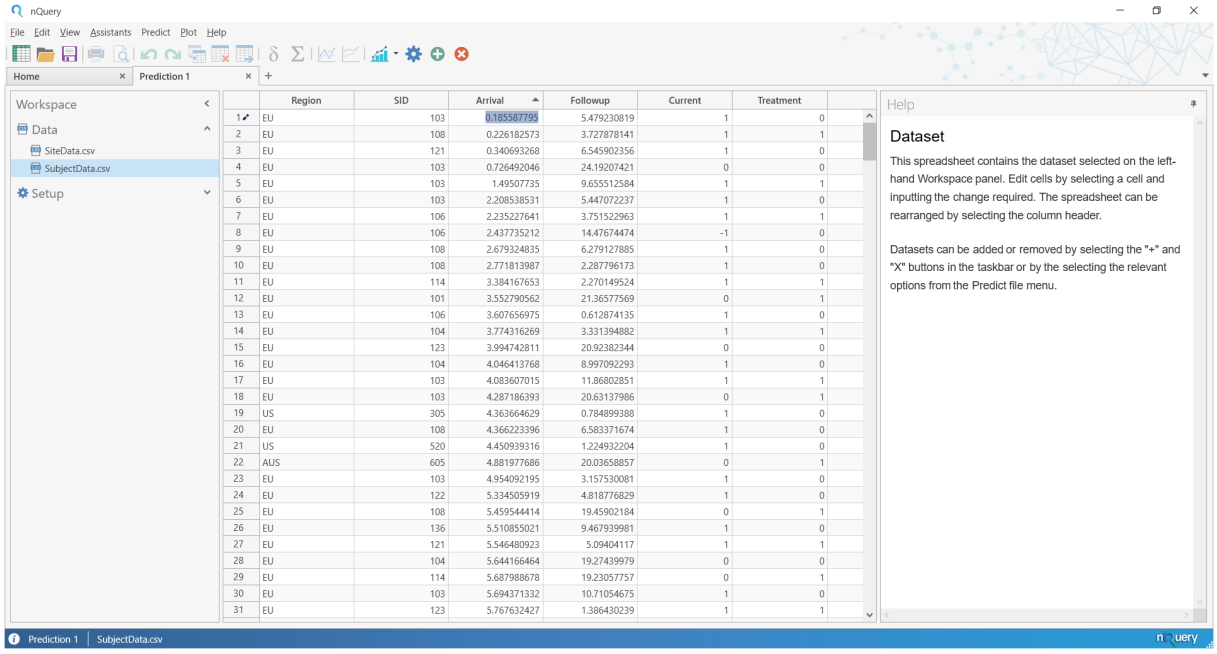


Figure 11.11: nQuery Predict Workspace with SubjectData Column Sort and Cell Edit

11.2.3.2 Adding and Removing Datasets

After an nQuery Predict workspace is open, datasets can be added or removed from the workspace by using the **Add Dataset** and **Remove Dataset** options. These two options are available from the Predict file menu or by selecting the **Add Dataset** or **Remove Dataset** buttons from the Toolbar menu.

Selecting **Add Dataset** will open the "New Prediction - Import Datasets" window. See subsubsection 11.2.1.1 for details on how the Import Datasets window works. The only difference for the **Add Dataset** option is the lack of the **Skip** button as this is not required for an existing workspace.

Selecting **Remove Dataset** while you have a dataset selected in the current workspace will remove that dataset from the workspace's Data field. Note that there is no additional prompt before the dataset is removed.

11.2.4 nQuery Predict Example Datasets

Before providing a demonstration of using nQuery Predict to create milestone predictions, a brief overview of the example datasets is provided here.

These datasets can be found in the nQuery installation folder which was specified during installation. By default, the datasets would be located in the following folder: C:\Program Files (x86)\Statistical Solutions Ltd\nQuery\TestData\Predict

These datasets are artificial but have been created to have summary characteristics similar to data from a real clinical trial.

The simulated data was based on the data available at the interim analysis of a group sequential survival analysis which had a **Target Number of Events** of 374 events, with subjects followed until this target events was reached at which point any remaining subjects were administratively right-censored. The one interim analysis was planned when 50% of the **Target Number of Events** was reached i.e. 187 events.

To achieve this **Target Number of Events**, it was assumed a **Target Sample Size** of 460 would be needed. The study plan was to accrue subjects over the first 30 months of the trial (giving an expected **Accrual Rate** of $460/30 = 15.3333$). There were 127 sites (hospitals) available for subject recruitment in the study plan.

It was expected that an overall **Study Duration** of 40 months would be needed to reach the **Target Number of Events** given that accrual process and expected **Event Hazard Rates**.

The interim analysis data simulated here occurs 24.9 (83% of planned accrual period length) months (i.e. **Current Time = 24.9**) into the study when 187 (50%) of the target events have occurred. At this point, 402 (87.4%) of the subjects have been accrued, with 118 out of the total possible 127 sites open.

11.2.4.1 SubjectData.csv

The SubjectData.csv is a comma-separated values (.csv) file which has six columns and 402 rows. Each row corresponds to an individual subject and each column is a characteristic for each subject. The columns in order from left to right, alongside a description and context, are as follows:

- **Region** (Region - Any Input Type): The **Region** the subject/site is from. 3 distinct values: EU (European Union), US (United States), AUS (Australasia)
- **SID** (**Site ID** - Any Input Type, all values must be in **Site-Level Data Site ID** column): The **Site ID** of the site from which a subject was recruited. 93 distinct integer values ranging from 101 to 623. See subsubsection 11.2.4.2 for details on the example **Site-Level Dataset: SiteData.csv**
- **Arrival** (**Arrival Time** - Numeric Values ≥ 0): The **Arrival Time** (start of the study is time = 0) in months at which a subject was recruited. 402 distinct real numeric values ranging from 0.185587795 (first arrival) to 24.91856625 (last arrival, also is **Current Time**)
- **Followup** (**Time on Study** - Numeric Values $\geq$ **Arrival Time** in row): The length of time in months a subject has been followed for since arrival (i.e. **Time on Study**).

402 distinct real numeric values ranging from 0 (just arrived) to 24.19207421 (months on study). Note that **Followup** definition depends on **Current** column, where **Followup** equals the **Time on Study** before subject had an event (**Event Status: Current = 1**) or dropped out (**Dropout Status: Current = -1**) but **Followup** equals time from **Arrival** until the **Current Time** for subjects who are still available to have the event in the future (**Censored Status : Current = 0**)

- **Current** (**Status Indicator** - Any Input Type with minimum one, maximum three distinct values: The current status of a subject (i.e. **Status Indicator**). 3 distinct integer values: -1 = Subject has dropped out at **Current Time**, 0 = Subject is available (i.e. has neither had event or dropped out) at **Current Time**, 1 = Subject has have event of interest (death) at **Current Time**
- **Treatment** (**Treatment ID** - Any Input Type with two distinct values): The treatment group (i.e. **Treatment ID)** a subject was assigned to. 2 distinct integer values: 0 = Subject is in **Control Group**, 1 = Subject is in **Treatment Group**

11.2.4.2 SiteData.csv

The SiteData.csv is comma-separated values file which has seven columns and 127 rows. Each row corresponds to an individual site and each column is a characteristic for each site. The columns in order from left to right, alongside a description and context, are as follows:

- **Region** (Region - Any Input Type): The **Region** the subject/site is from. 3 distinct values: EU (European Union), US (United States), AUS (Australasia)
- **SID** (**Site ID** - Any Input Type, must include all **Site ID** values from **Subject-Level Dataset Site ID** column): The site ID for a site. 127 distinct integer values ranging from 101 to 623. Note that if **Input = Subject + Site Data**, the Site ID column for the Site Data must contain all Site IDs given in the corresponding subject-level Site ID column. However, the Site Data Site ID can contain values not included in the Subject Data Site ID for sites which are unopened or have not recruited a subject at the **Current Time**.
- **Cap** (**Enrollment Cap** - Integer > 0): The **Enrollment Cap** in a site i.e. the maximum number of subjects that can recruited from a site. Integer values ranging from 5 to 72.
- **Open Time** (**Site Initiation Time: Opened Sites** - Numeric Value ≥ 0) : The time at which a site opened (study start is time = 0) i.e. **Site Initiation Time** for **Open Sites**. Real numeric values ranging from 0 to 19.375. Note that 9 rows do not have a value for **Open Time**. These are the 9 unopened sites at the **Current Time**. If a given site has a **Site Initiation Time for Open Sites** and **Start and End Time for Site Initiation window for Unopened Sites**, it is assumed the site is **Open** and only this value is used.
- **Rate** (**Accrual Rate/Site** - Numeric Value ≥ 0): The planned accrual rate (i.e. **Accrual Rate/Site**) in a site. The accrual rate is the number of subjects recruited per unit time (months in this case). Real numeric values ranging from 0.045541405 to 2.224390244. Note that for open sites which have recruited a minimum of one subject, the default accrual rate for a site given in **Accrual Options Setup** step will be based on the actual rate rather than the planned rate given here

- **Start** (**Site Initiation Time: Unopened Sites (Optional): Start Time - Current Time**$\leq$ Numeric Value $\leq$ **End Time**): The **Start Time** of the **Site Initiation** window for **Unopened Sites** to open. Nine real numeric values between 25.1 and 25.51. Note that 118 rows do not have a value for **Start** as these sites are already open at the **Current Time**. If a given site has a **Site Initiation Time for Open Sites** and **Start and End Time for Site Initiation window for Unopened Sites**, it is assumed the site is **Open** and this value is ignored.
- **End** (**Site Initiation Time: Unopened Sites (Optional): EndTime** - Numeric Value $\geq$ **Start Time**): The **End Time** of the **Site Initiation** window for **Unopened Sites** to open. Nine real numeric values between 25.3 and 26.11. Note that 118 rows do not have a value for **End** as these sites are already open at the **Current Time**. If a given site has a **Site Initiation Time for Open Sites** and **Start and End Time for Site Initiation window for Unopened Sites**, it is assumed the site is **Open** and this value is ignored.

If there is an input from the Site Data which is incompatible with the Subject Data provided (for example Open Time > Current Time, Enrollment Cap > subjects recruited in Site at Current Time), these will be highlighted in the **Accrual Infos/Sites** table at the **Accrual Options** step of **Setup** (see subsection 11.2.6 and subsection 11.2.7).

11.2.5 Select the Type of Prediction/Setup Introduction

The **Select the Type of Prediction** is the first step of the **Setup** stage of the creating a milestone prediction in nQuery Predict. The **Select the Type of Prediction** step selects the specific characteristics needed to setup the appropriate prediction for a study. There are three sections at this step: **Target, Input and Enrollment Status**. The **Select the Type of Prediction** step in the nQuery Predict workspace is shown in Figure 11.12.

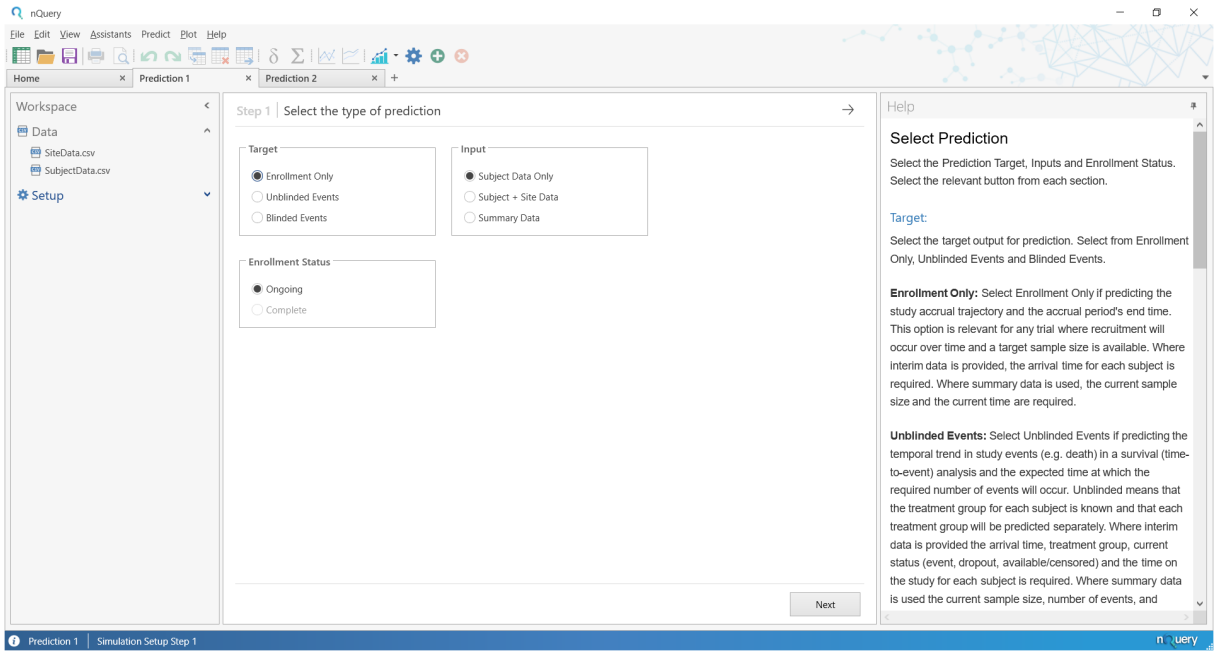


Figure 11.12: Select a Type of Prediction Step

The appropriate **Setup** is chosen by selecting the required radio button to the left of the appropriate option in each section. A brief introduction on using the **Setup** field and three sections of the **Setup the Type of Prediction** step are provided next.

11.2.5.1 Target

The **Target** section specifies what will be the target of the milestone prediction. The three options for **Target** are as follows:

- Enrollment Only
- Unblinded Events
- Blinded Events

Enrollment Only will select a milestone prediction where the objective is to project the length of time (**Accrual Duration**) required to enroll a **Target Sample Size**. When **Subject-level Data** is used (**Input = Subject Data Only** or **Subject + Site Data**), this will require an **Arrival Time** per subject. For **Summary Data Input**, this will require the **Current Sample Size** and **Current Time**

Unblinded Events will select a milestone prediction where the objective is to project the length of time (**Study Duration**) required to achieve a **Target Number of Events** when the treatment group assignment for each subject is known. When a **Subject-level Data** is used (**Input = Subject Data Only** or **Subject + Site Data**), this will require the **Arrival Time, Time on Study, Status Indicator (Event Status, Dropout Status, Censored Status)** and **Treatment ID (Control Group, Treatment Group)**. For **Summary Data Input,** the **Current Sample Size (Control), Current Sample Size (Treatment), Current Number of Events (Control), Current Number of Events (Treatment), Current Number of Dropouts (Control), Current Number of Dropouts (Treatment)** and **Current Time** are required. **(Current/Treatment)** in brackets indicates the treatment group.

Blinded Events will select a milestone prediction where the objective is to project the length of time (**Study Duration**) required to achieve a **Target Number of Events** when the treatment group assignment for each subject is unknown. When a **Subject-level Data** is used (**Input = Subject Data Only** or **Subject + Site Data**), this will require the **Arrival Time, Time on Study** and **Status Indicator (Event Status, Dropout Status, Censored Status)**. For **Summary Data Input,** the **Current Sample Size, Current Number of Events, Current Number of Dropouts** and **Current Time** are required.

11.2.5.2 Input

The **Input** section specifies what will be the input type used to generate the milestone prediction. The three options for **Input** are as follows:

- Subject Data Only
- Subject + Site Data
- Summary Data

Subject Data Only means the milestone prediction will be based on subject-level interim data only for the enrollment and/or event process. The specific fields required in the Subject Data will depend on the choice of **Target** (see subsubsection 11.2.5.1).

Subject + Site Data Only means the milestone prediction will be based on subject-level and site-level interim data. The specific fields required in the Subject Data will depend on the choice of **Target** (see subsubsection 11.2.5.1) and will be the same as for **Subject Data Only** with the addition of a **Site ID** field to link the **Subject-Level Data** and **Site-Level Data**. The Site Data fields will be same for all predictions as the Site Data is only used for enrollment modelling. **Subject + Site Data** is not available if **Enrollment Status** is set to **Complete**.

Summary Data means the milestone prediction will be based on fixed parameter estimates made either pre-trial or based on summary statistics from an on-going trial. The specific fields required will depend on the choice of **Target** (see subsubsection 11.2.5.1). For a pre-trial milestone prediction, enter zero for all allowable fields at the second **Fixed Parameters** step.

11.2.5.3 Enrollment Status

The **Enrollment Status** section specifies if enrollment is complete in a survival analysis trial at the time that the milestone prediction will be generated. The two options for **Enrollment Status** are as follows:

- Ongoing
- Complete

Ongoing means that the enrollment process is still ongoing at the time at which the milestone prediction is being generated. In this case, the **Accrual Options** step of **Setup** will be included to set the **Target Number of Events** and define the **Accrual Model** used to generate future simulated subjects that will be enrolled into the study.

Complete means that the enrollment process is complete at the time at which the milestone prediction is being generated. In this case, the **Accrual Options** step summarizes the accrual process up to the **Current Time** but since enrollment is complete, the **Target Number of Events** and **Accrual Model** inputs are not required at the **Accrual Options** step. **Complete** is only available if **Target** equals **Unblinded Events** or **Blinded Events.**

11.2.5.4 Setup Introduction

During the **Setup** stage the user will be required to specify the desired inputs to generate simulations for the milestone prediction. The specific subsequent steps will depend on the selections made at the **Select the type of Prediction** step (see subsection 11.2.6 and subsection 11.2.7 for details) but there are five broad categories of step. These are, in order inputted by the user, known as:

- Data Field Selection: Select fields from Dataset which correspond the required inputs for milestone prediction if **Input = Subject Data Only** or **Subject + Site Data**

- Fixed Parameters: Input fixed parameter estimates if **Input = Summary Data**
- Accrual Options: Select a model and edit options to specify how accrual simulations will be generated. This step will differ depending if **Input = Subject Data Only** or **Subject + Site Data**. If **Enrollment Status = Complete**, this step will provide a summary of accrual up to the **Current Time** only
- Event and Dropout Information: Select a model and edit options to specify how event and dropout simulations will be generated if **Target = Unblinded Events** or **Blinded Events**
- Simulation Controls: Edit the options for the overall simulation such as the number of simulations, random seed and additional tables desired. See subsubsection 11.2.9.4 for details

The **Setup** stage involves completing the required steps in order. To move to the next step, the user must fill in all required information and then select the Next button in the bottom left of the Main Window or the → button in the top-right of the Main Window. These options will be greyed out until all required information at a given step has been entered, though most stages after Data Field Selection/Fixed Parameters will have defaults based on fitting the models to the provided information (information on the models available and their nQuery Predict defaults is given in section 11.1). At the final **Simulation Controls** step, the Next button will be replaced with a Run button which when selected will start the milestone prediction simulation .

Once a step is complete, the user can also go forward and backwards within the **Setup** stage by using the Next/Back buttons in the bottom-right of the Main Window or the →/← buttons in the top-right of the Main Window.

The user can navigate to a specific step by selecting the desired step from under the **Setup** heading in the Workspace Navigation Bar on the left-hand side (see subsection 11.2.2 for details).

When a simulation has been completed, the Workspace Navigation Bar's **Setup** heading can be used to change any of the **Setup** inputs. To make changes return to any step of the **Setup** stage, edit the desired simulation inputs in that step, select the Next or → button at that step and then re-run the simulation after selecting Run at the final **Simulation Controls** step.

Note that changing any option at the **Select the type of prediction** step of **Setup** will reset the prediction and delete all subsequent steps and any user inputs made at those steps.

11.2.6 Enrollment Prediction Demonstration

Enrollment milestone prediction is the projection of how long a study will take to recruit a **Target Sample Size**. In nQuery Predict, there are three main approaches to enrollment milestone prediction:

- Enrollment Prediction using Subject-level Data only (subsubsection 11.2.6.1)
- Enrollment Prediction using Subject and Site-level Data (subsubsection 11.2.6.2)
- Enrollment Prediction using Summary Data (subsubsection 11.2.6.3)

Each of these scenarios will be demonstrated using the SubjectLevel.csv and SiteLevel.csv datasets provided with nQuery Predict. See subsection 11.2.4 for details on these datasets.

Each demonstration will start with demonstration using the default values given by nQuery Predict, followed by additional scenarios taken from the context these datasets were taken from and which use additional options available in nQuery Predict.

The additional options covered in each demo are as follows:

- Subject-level Data only: Editing **Target Sample Size** and future **Accrual Rate**
- Subject and Site-level Data: Editing **Target Sample Size**, removing and editing individual **Sites**
- Summary Data: Editing **Target Sample Size**, **Pre-Trial** enrollment prediction

For these demonstrations, it is assumed the appropriate nQuery Workspace has been created as per the **Creating a nQuery Predict Workspace** section above (subsection 11.2.1).

11.2.6.1 Enrollment Prediction using Subject-Level Interim Data Only

Setup **Enrollment Only** milestone prediction using **Subject-level Data Only** means that the prediction will project the expected length of the accrual period needed to recruit a specified **Target Sample Size** using subject-level interim data alone.

In the **Setup** for this prediction, first in the **Select the type of Prediction** step select **Enrollment Only** from the **Target** field and **Subject Data Only** from the **Input** field. **Enrollment Status** must be **Ongoing** for enrollment milestone prediction. These selections are shown in Figure 11.13. Select the Next button in the bottom-right or → button in the top-right of the Main Window to move to the next step of the prediction **Setup** stage.

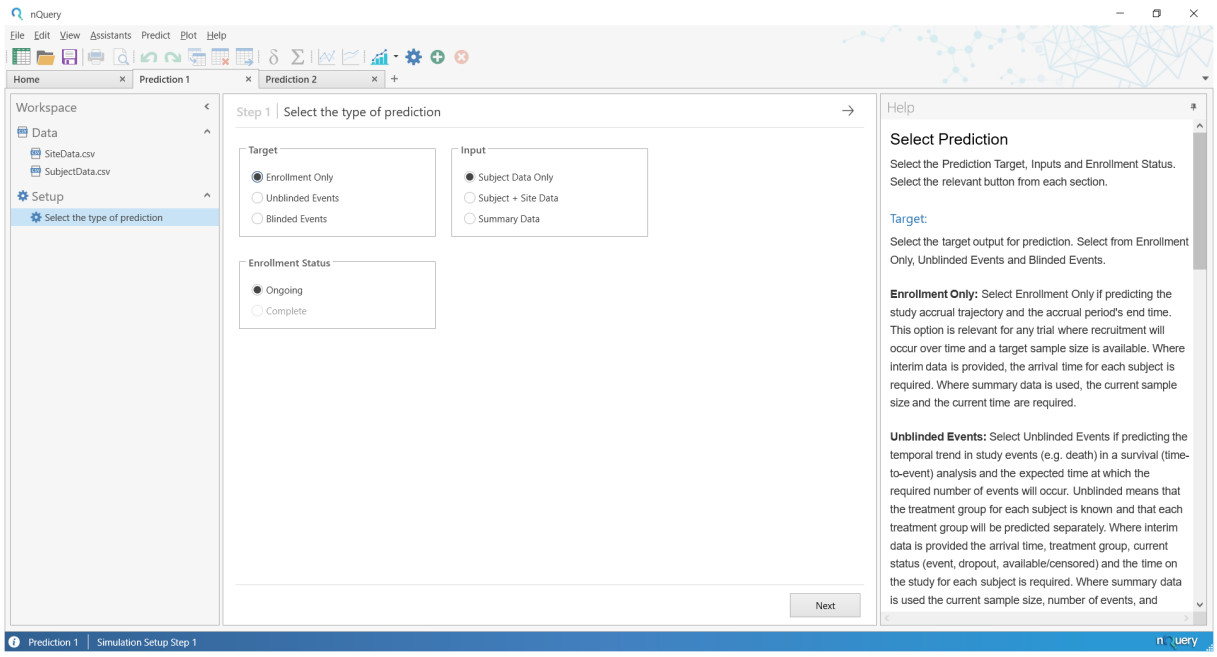


Figure 11.13: Select the Type of Prediction Setup Step for Enrollment Prediction using Subject-level Data

The next step is the **Subject-level Data** step. The **Subject-level Data** step is a Data Field Selection step. The **Subject-level Data** is the dataset where each row corresponds to a specific subject enrolled in the study.

Data Field Selection steps are steps in which the required dataset in the current Workspace is selected and columns in the selected dataset are assigned to the required fields for that prediction problem. The options in a given Data Field Selection field are opened by selecting the button on the right of each field which is found to the right of the field name e.g. **Select Data**. Each field will have specific requirements (e.g. numeric only, two distinct values only) and nQuery Predict only displays options which are consistent with those fields.

In this prediction there are two fields which are as follows:

- Select Dataset: Select the dataset that is the Subject-level Data from the datasets in the current workspace
- Arrival Time: The arrival time column contains the length of time since the study start (Time = 0) until a subject entered the study. Each subject's Arrival Time should be greater than or equal to zero

For this prediction, in the **Select Dataset** field select **SubjectData.csv** and in the **Arrival Time** field select **Arrival**. These selections are shown in Figure 11.14. Select the Next or → button to move to the next **Setup** step.

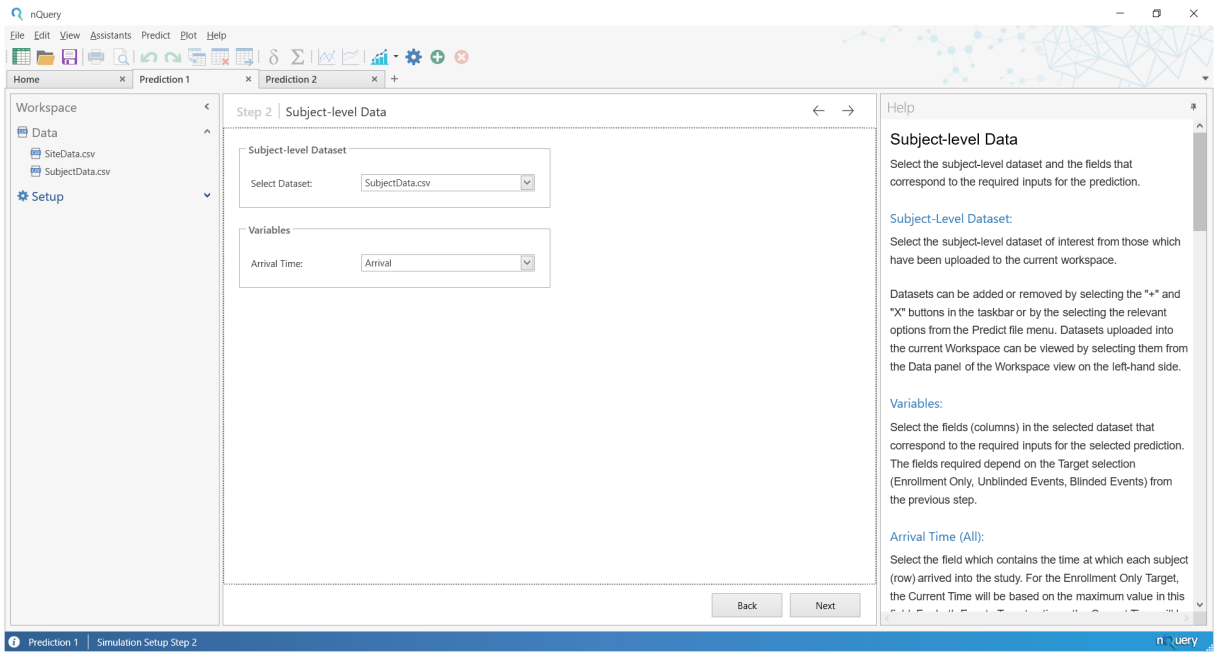


Figure 11.14: Subject-level Data Setup Step for Enrollment Prediction using Subject-level Data

The next step is the **Accrual Options** step which specifies the **Target Sample Size, Accrual Model** and future **Accrual Rate**. The **Accrual Options** step, and its defaults, for this demonstration are shown in Figure 11.15.

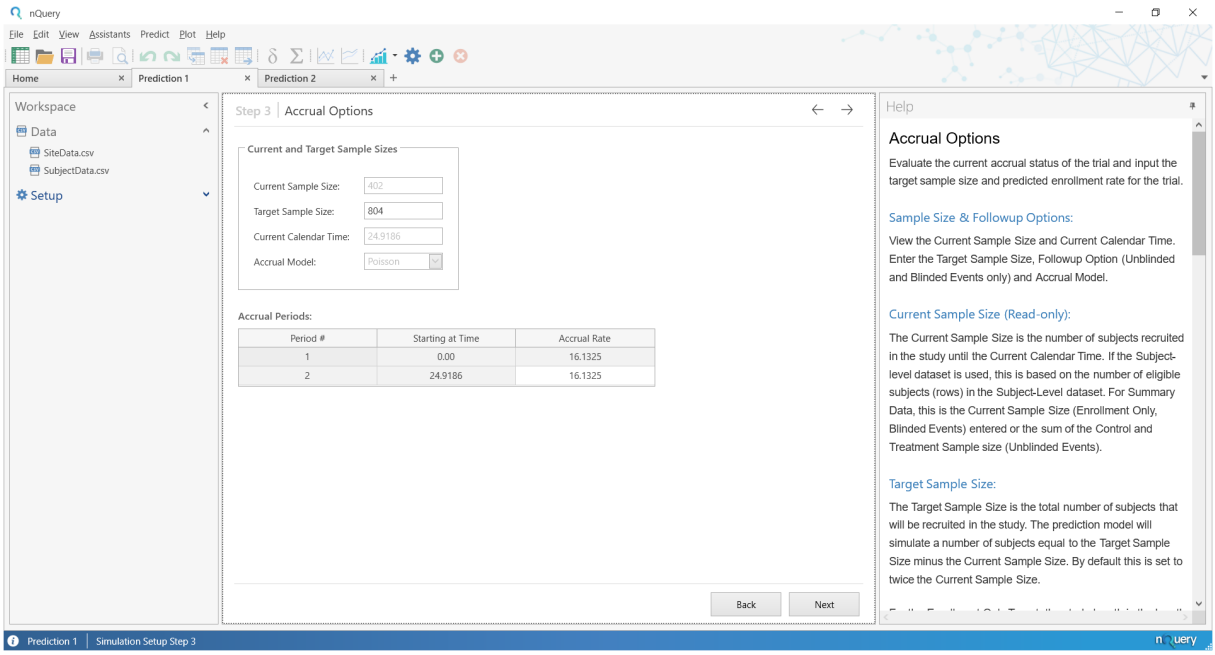


Figure 11.15: Accrual Options Setup Step for Enrollment Prediction using Subject-level Data

The **Accrual Options** step consists of two main elements: the **Current and Target Sample Sizes** input fields and the **Accrual Periods** table.

The **Current and Target Sample Sizes** input fields provides information on study enrollment based on the subject-level data and allows the user to edit the **Target Sample Size** and select the **Accrual Model**. The following fields are provided in this prediction:

- Current Sample Size (Read-only): Sample Size recruited into a study so far. Equals the number of rows in the Subject-level Data
- Target Sample Size (Editable, Integer > Current Sample Size): Total number of subjects that will be recruited in this study. The number of simulated subjects equals the Total Sample Size minus the Current Sample Size
- Current Time (Read-only): The length of time that has passed since the study started. Equals the maximum Arrival Time value
- Accrual Model (Editable): The statistical model that will be used to generate simulated enrollments

In nQuery Predict, the **Target Sample Size** defaults to twice the **Current Sample Size** and the **Accrual Model** defaults to **Poisson.** In this demonstration, the **Current Sample Size** equals 402 and therefore the default **Target Sample Size** is $402\,(2) = 804$.

The **Accrual Periods** table contains information on the **Accrual Rate** up the **Current Time** and allows the user to edit the future **Accrual Rate** used to generate enrollment simulations. The **Accrual Periods** has three columns ,with each row corresponding to a time period, with the columns defined as follows:

- Period #: A numeric ID for the current time period. Increases in increments of one for each subsequent row

- Starting at Time: The starting time for the current time period row. The first row will equal 0 (rate from study start to Current Time) and the second row will equal the Current Time
- Accrual Rate: The accrual rate is the average number of subjects recruited per unit time (months). The accrual rate in the first row will equal the accrual rate up to the Current Time

For the **Poisson Accrual Model**, the **Accrual Periods** table will consist of two time period rows. The first row will correspond to the information provided by the user regarding the study up until the **Current Time.** The second row will correspond to the inputs used to generate future enrollments. By default the **Accrual Rate** in the future second row will equal the **Accrual Rate** from the first row i.e. the accrual rate up until the **Current Time.** For the inputs used in this demonstration, this **Accrual Rate** column values in each row equal 16.13254936. The user can edit the **Accrual Rate** for generating future enrollments by editing the second cell of the **Accrual Rate** column.

For now, the default values will be used for **Target Sample Size** (804), **Accrual Model** (Poisson) and **Accrual Rate** (16.13254936) as per Figure 11.15. Select the Next or → button to move to the next **Setup** step.

The final step is the **Simulation Controls** step. The **Simulation Controls** step consists of three sections: Simulation Controls, Output for All Trials and Output Options.

Simulation Controls (top-left) sets the **Number of Simulations**, **Refresh Frequency** and **Random Seed**

Output For All Trials (bottom-left) sets the Percentiles desired in the **Percentile Summary** table in the **Simulation Summary** report for key simulation outputs such as study length and sample size.

Output Options (right) selects which additional datasets the user wants in the **Tables** field of the simulation results. Additional datasets will be summary statistics for each simulation and outputs from a set number of individual of simulations.

The **Simulation Controls** step is described in detail in subsubsection 11.2.9.4. In this demonstration, the defaults will be used which corresponds to 1000 simulations with the default percentiles (5%, 25%, 50%, 75%, 95%) and with the "Save summary statistics for every simulation run" **Output Options** table active. The **Simulation Controls** defaults for this demonstration are shown in Figure 11.16. To start the milestone prediction, Select the Run (where Next button was in previous steps) or → button.

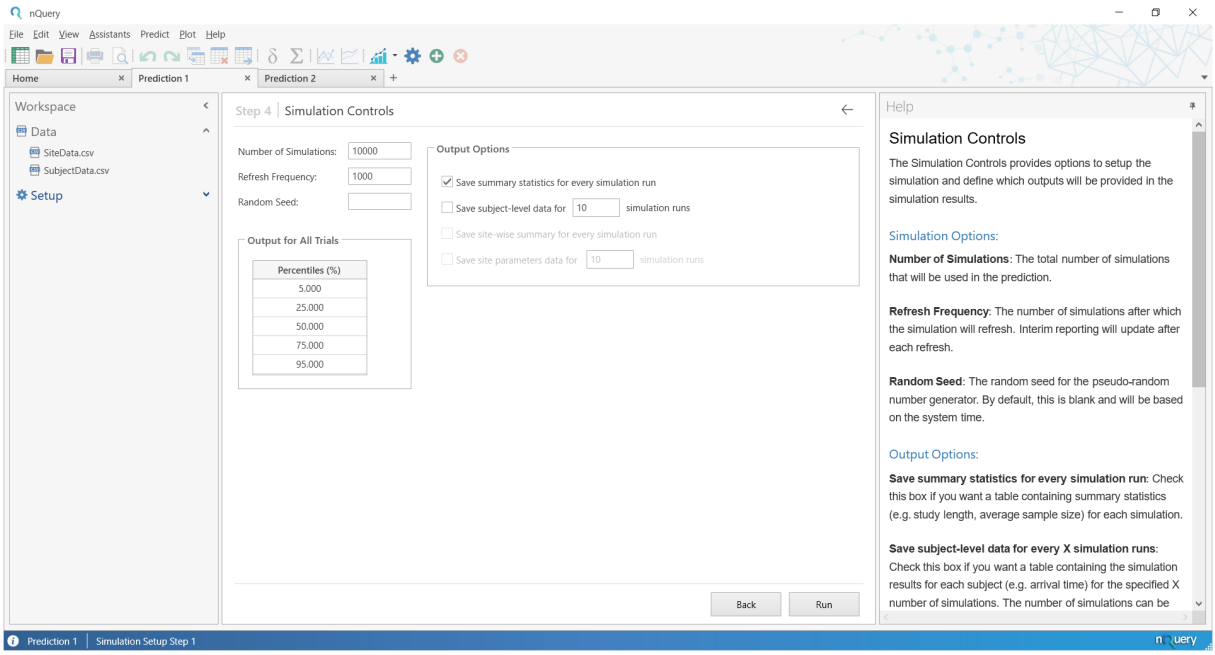


Figure 11.16: Simulation Controls Setup Step for Enrollment Prediction using Subject-level Data

Results While a milestone prediction is being run, a **Simulation in Progress** window will be displayed. The **Simulation in Progress** window provides updated information on key simulation metrics while the simulation is ongoing. An example for this demonstration is given in Figure 11.17.

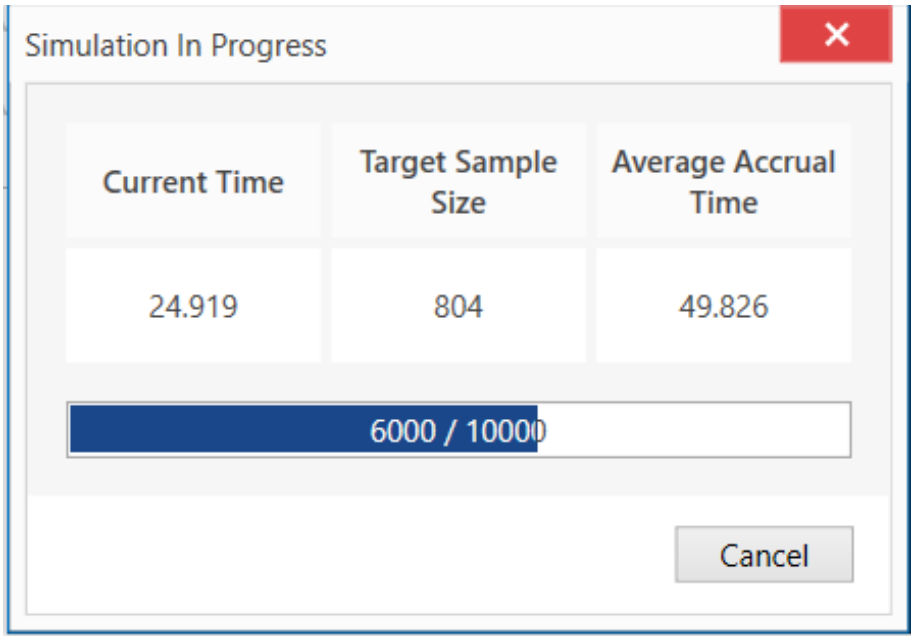


Figure 11.17: Simulation in Progress Window for Enrollment Prediction using Subject-level Data

Once the simulation is complete, the results will automatically be added to the Workspace Navigation Bar on the left and the first element under the **Plots** header will be displayed.

In this demonstration, the **Enrollment Prediction Plot** will be displayed. This is shown in Figure 11.18.

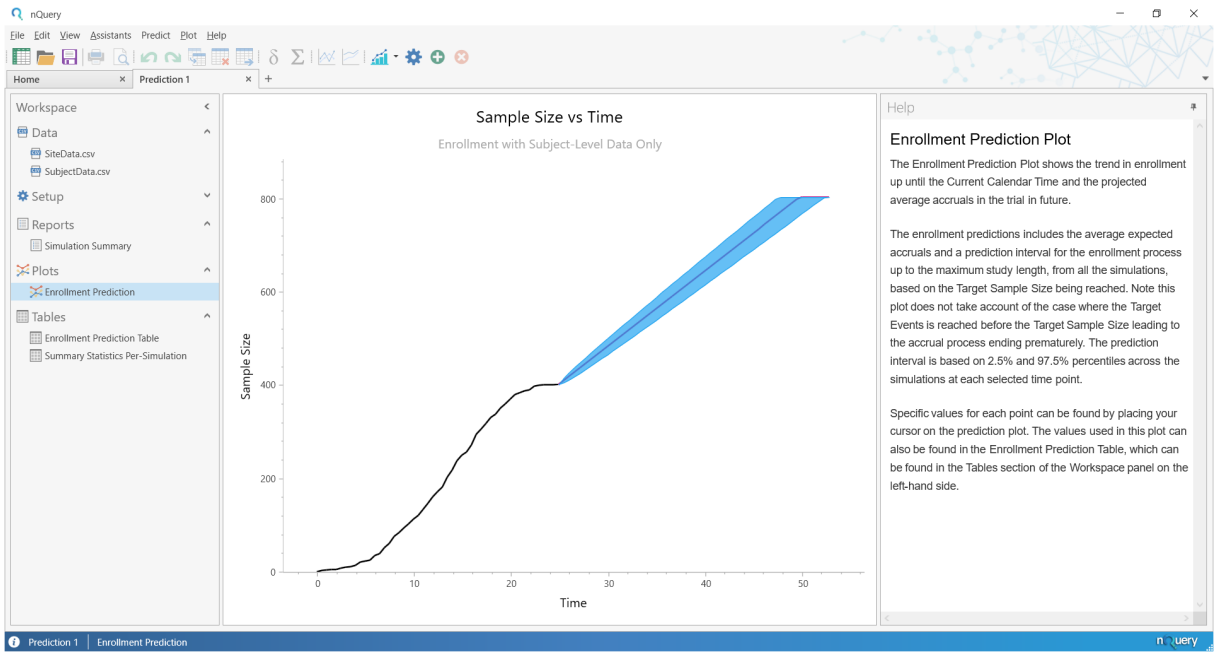


Figure 11.18: Enrollment Prediction Plot for Enrollment Prediction using Subject-level Data

The results of a nQuery Predict milestone prediction can be divided into three categories: **Reports, Plots** and **Tables**. A high-level summary of the results in nQuery Predict is provided in subsection 11.2.8 with demonstration specific elements highlighted here.

For this demonstration the **Reports** header contains the **Simulation Summary** report, the **Plots** header contains the **Enrollment Prediction** plot and the **Tables** header contains the **Enrollment Prediction Table** and **Summary Statistics Per-Simulation**. To select any result element, select it from the appropriate header in the Workspace Navigation Bar on the left (see subsection 11.2.2 for details on the Navigation Bar).

The **Simulation Summary** provides a tabular summary of the inputs and outputs from the current milestone prediction simulation. The **Simulation Summary** for this demonstration is shown in Figure 11.19.

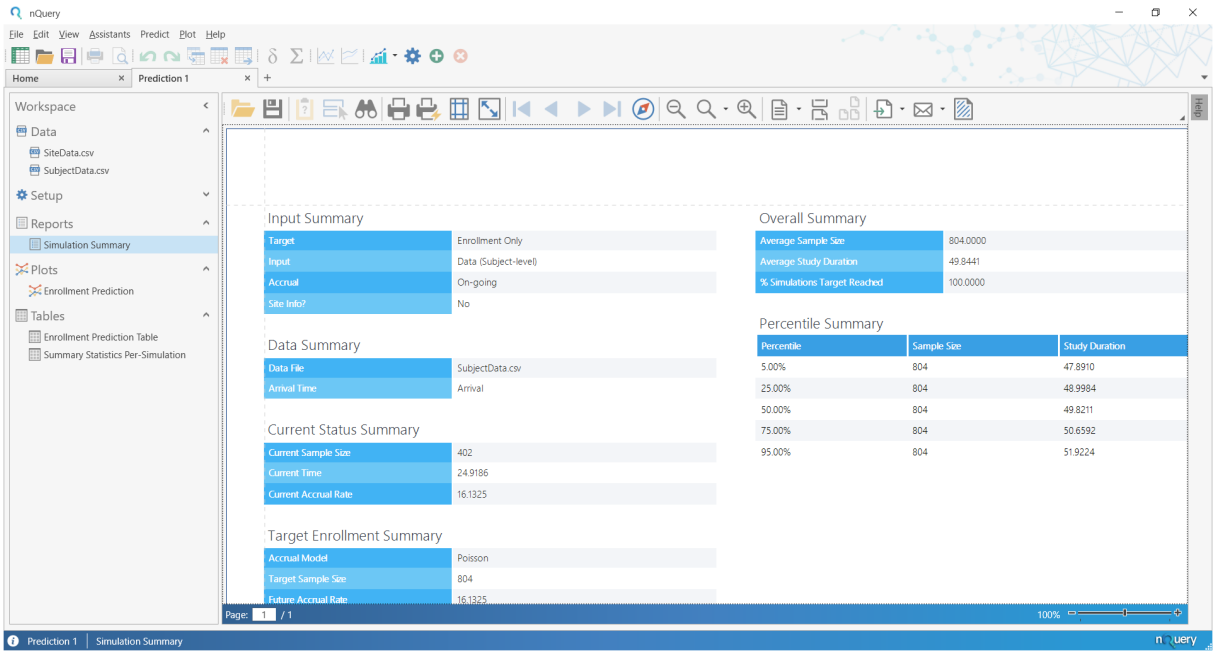


Figure 11.19: Simulation Summary Report for Enrollment Prediction using Subject-level Data

In the **Simulation Summary** report, the left-hand column provides a summary of inputs used to generate the current simulation and the right-hand column provides the results of the current simulation. In this demonstration, we will skip the left-hand Inputs column and focus on the main results in the right-hand column and the main report options.

The results column (on the right) is shown in Figure 11.20. For this demonstration, the **Overall Summary** shows that the **Target Sample Size** of 804 was reached in every simulation with an **Average Accrual Duration** over all the simulations of 49.8441. The **Percentile Summary** shows that 90% of predictions had an **Accrual Duration** between 47.8910 (5% Percentile) and 51.9224 (95% Percentile), 50% a duration between 48.9984 (25% Percentile) and 50.6592 (75% Percentile) and a median (50% Percentile) duration of 49.8211.

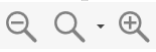
Overall Summary

Average Sample Size	804.0000
Average Study Duration	49.8441
% Simulations Target Reached	100.0000

Percentile Summary

Percentile	Sample Size	Study Duration
5.00%	804	47.8910
25.00%	804	48.9984
50.00%	804	49.8211
75.00%	804	50.6592
95.00%	804	51.9224

Figure 11.20: Simulation Summary Report Results for Enrollment Prediction

To edit the **Simulation Summary report there a** number of buttons available at the top of the report. For full detail on the **Simulation Summary** report and options to edit the report see subsubsection 11.2.8.2. However the Zoom options  , Page Layout and Setup options  and Export option  will be the more commonly used options.

The **Enrollment Prediction** plot provides a visual summary of enrollment simulation from the study start to when the **Target Sample Size** was reached in all simulations. The X-axis is **Time** (relative to study start) and the Y-axis is **Sample Size** (enrolled at Time X-axis value). When the cursor is placed over the **Enrollment Prediction** plot, information on the **Sample Size** enrolled at a given **Time** is shown as per Figure 11.21.

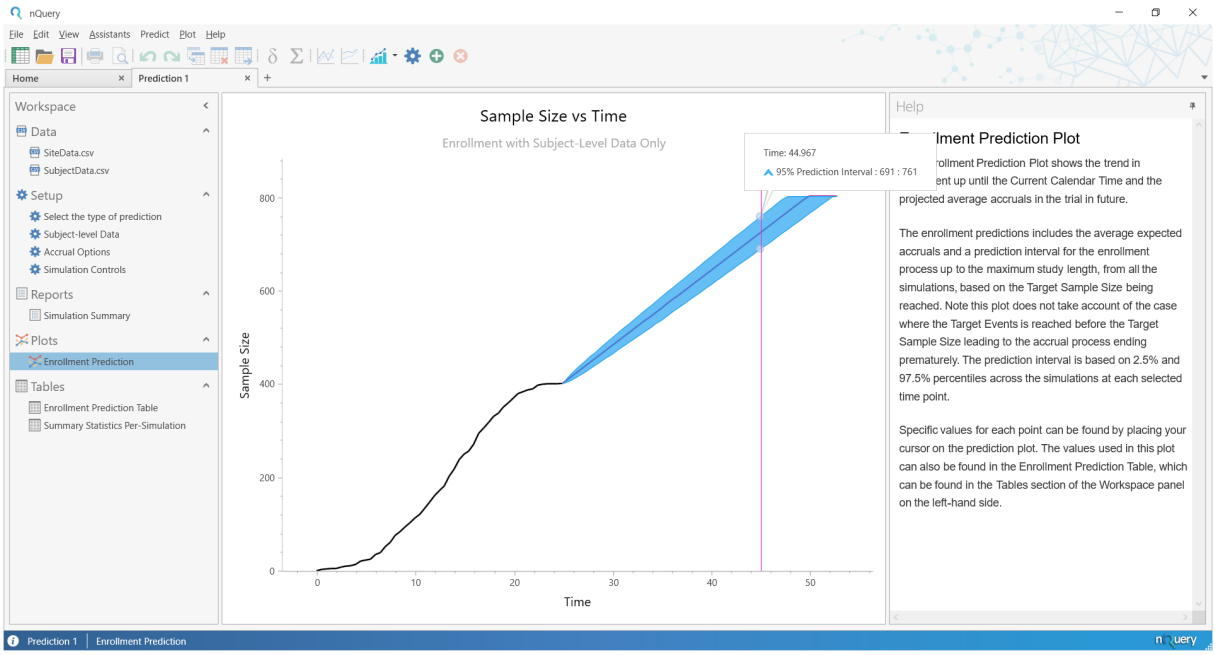
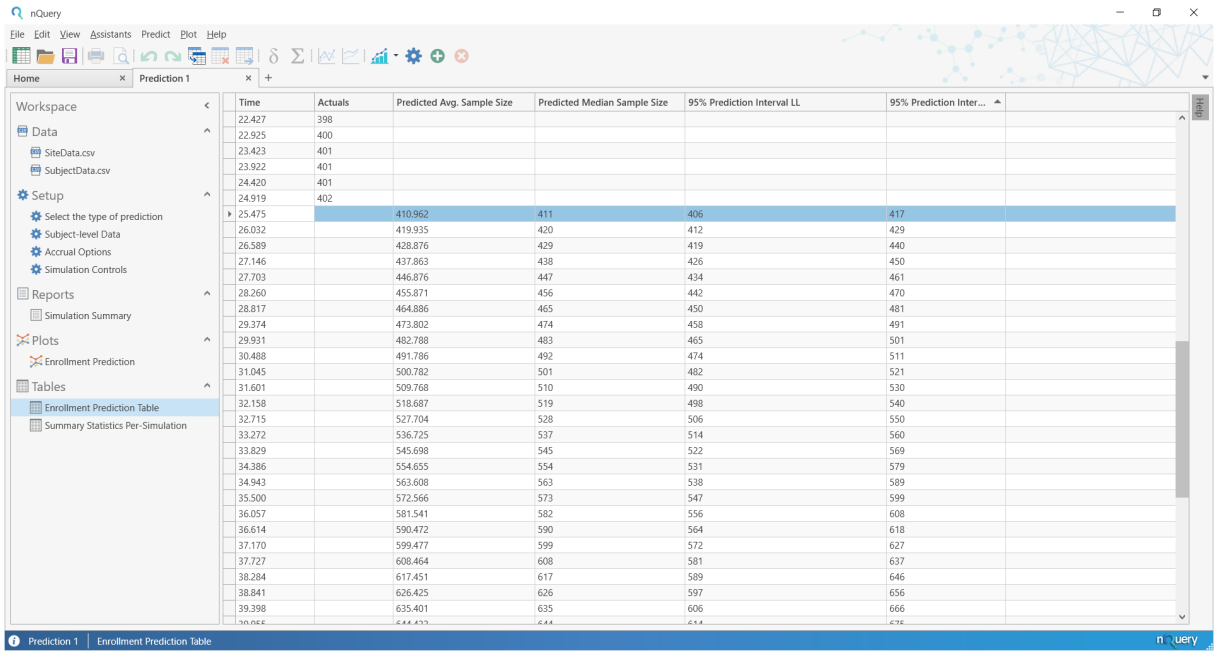


Figure 11.21: Enrollment Prediction Plot for Enrollment Prediction using Subject-level Data

The **Enrollment Prediction** plot consists of two parts: from Time = 0 to **Current Time** and from **Current Time** to the **Maximum Time**. The first part is a black line which plots the accrual pattern from the user inputs provided. The second part is a blue conic section with a grey line where the blue conic section plots the 95% prediction interval for the **Sample Size** enrolled at a given **Time** across all simulations and the grey line is the average **Sample Size** enrolled at a given time. The 95% prediction interval indicates the 95% of predictions had a sample size that fell between the lower and upper limit at a given time.

The **Enrollment Prediction Table** is the table used to create the **Enrollment Prediction** plot, which by default consists of ~100 rows (50 pre-simulation and 50 post-simulation). It consists of five columns: **Time, Actual, Predicted Avg. Sample Size, Predicted Median Sample Size, 95% Prediction Interval LL, 95% Prediction Interval UL**. The **Enrollment Prediction Table** for this demonstration at the start of the simulated period is given in Figure 11.22.



Time	Actuals	Predicted Avg. Sample Size	Predicted Median Sample Size	95% Prediction Interval LL	95% Prediction Inter...
22.427	398				
22.925	400				
23.423	401				
23.922	401				
24.420	401				
24.919	402				
25.475		410.962	411	406	417
26.032		419.935	420	412	429
26.589		428.876	429	419	440
27.146		437.863	438	426	450
27.703		446.876	447	434	461
28.260		455.871	456	442	470
28.817		464.886	465	450	481
29.374		473.802	474	458	491
29.931		482.788	483	465	501
30.488		491.786	492	474	511
31.045		500.782	501	482	521
31.601		509.768	510	490	530
32.158		518.687	519	498	540
32.715		527.704	528	506	550
33.272		536.725	537	514	560
33.829		545.698	545	522	569
34.386		554.655	554	531	579
34.943		563.608	563	538	589
35.500		572.566	573	547	599
36.057		581.541	582	556	608
36.614		590.472	590	564	618
37.170		599.477	599	572	627
37.727		608.464	608	581	637
38.284		617.451	617	589	646
38.841		626.425	626	597	656
39.398		635.401	635	606	666

Figure 11.22: Enrollment Prediction Table for Enrollment Prediction using Subject-level Data

Time is the time value relative to the study start time of zero. **Actual** is the actual sample size achieved at a pre-simulation **Time** row. **Predicted Avg. Sample Size** is the predicted average (mean) sample size enrolled at a post-simulation **Time** row. **Predicted Median Sample Size** is the predicted median sample size enrolled at a post-simulation **Time** row. **95% Prediction Interval LL** is the lower limit for the 95% prediction interval for the sample size enrolled at a post-simulation **Time** row. **95% Prediction Interval UL** is the upper limit for the 95% prediction interval for the sample size enrolled at a post-simulation **Time** row.

The **Summary Statistics Per-Simulation Table** provides the summary statistics achieved for primary outputs in each simulation. For this demonstration this includes the **Simulation ID, Current Time, Current Sample Size, Target Sample Size, Accrual Duration.** The **Summary Statistics Per-Simulation Table** for this demonstration is shown in Figure 11.23.

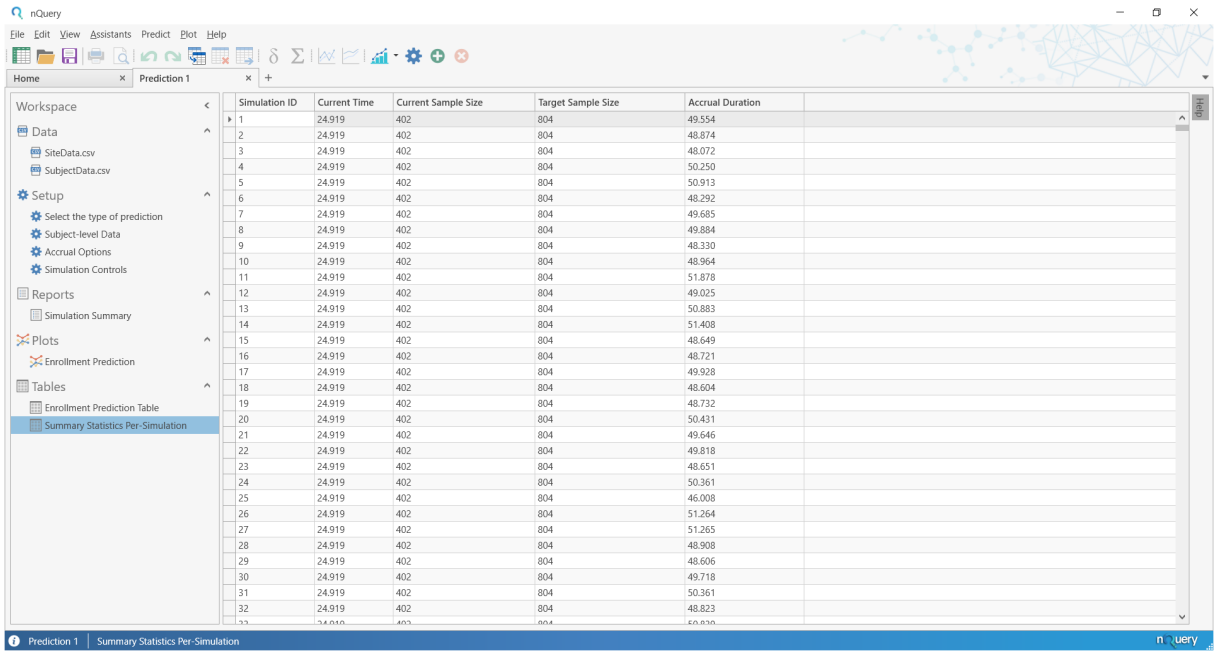


Figure 11.23: Summary Statistics Per-Simulation Table for Enrollment Prediction using Subject-level Data

Simulation ID is in order of simulation from 1 up to **Number of Simulations**, **Current Time, Current Sample Size** and **Target Sample Size** summarize the user inputs and are constant, and the **Accrual Duration** is the length of time needed to achieve the **Target Sample Size** in that simulation.

Alternative Scenarios The demonstration has focused on the default inputs using **SubjectData.csv** up to this point. However, as noted in the data summary given in subsection 11.2.4 the study from which the example data was simulated had an original sample size target of 460 (402 enrolled in **SubjectData.csv**). Additionally, in the **Enrollment Prediction Plot** there is noticeable "kink" where the accrual rate was slowing down for the final 4-5 months before the current time.

To explore this additional information, we will investigate two additional scenarios

- Scenario A: **Target Sample Size = 460** using default **Accrual Rate**
- Scenario B: **Target Sample Size = 460** using slower "updated" **Accrual Rate**

Scenario A The only changes required compared to the first demonstration is to change the **Target Sample Size** to 460 at the **Accrual Options** step. The simplest way to do this is to select the **Setup** header in the Workspace Navigation Bar on the left and then select the **Accrual Options** drop down option. Then edit the **Target Sample Size** 460 in the **Current and Target Sample Sizes** section in the top-left and select the Next or $\rightarrow$ button. At the next **Simulation Controls** step, we will add a single simulation run by selecting the checkbox beside the **Save subject-level data for (x) simulation runs** and replace the default of 10 runs with 1 runs at the "(x)" spot. An edited down summary of the **Setup** changes is provided in Figure 11.24.

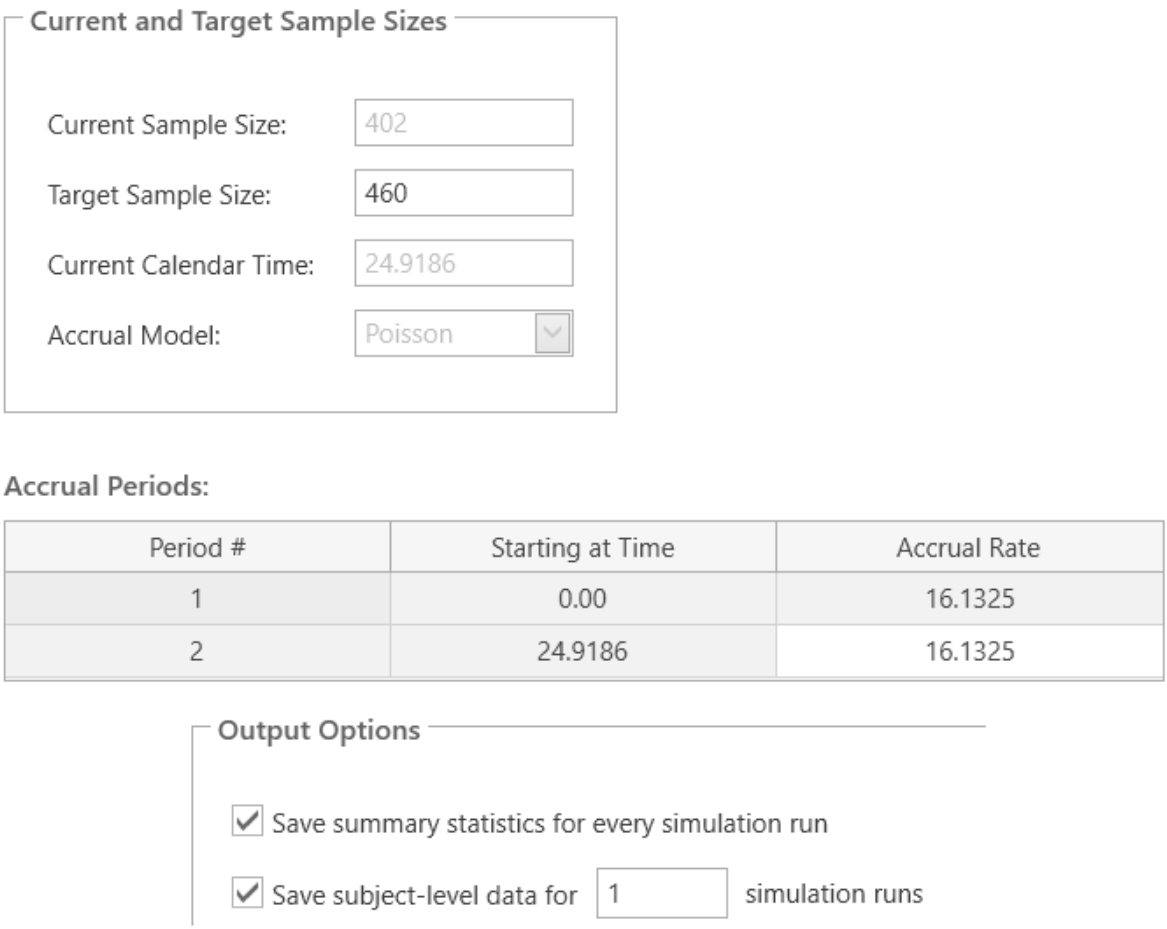


Figure 11.24: Scenario A Setup Changes for Enrollment Prediction using Subject-level Data

To run the simulation again with the new Scenario A, select the Run/$^{\rightarrow}$ button. The main results of this Scenario A simulation are shown in Figure 11.25.

Overall Summary

Average Sample Size	460.0000
Average Study Duration	28.5155
% Simulations Target Reached	100.0000

Percentile Summary

Percentile	Sample Size	Study Duration
5.00%	460	27.7693
25.00%	460	28.1827
50.00%	460	28.4985
75.00%	460	28.8238
95.00%	460	29.3238

Figure 11.25: Scenario A Results for Enrollment Prediction using Subject-level Data

For Scenario A, the **Overall Summary** shows that the **Target Sample Size** of 460 was reached in every simulation with an **Average Accrual Duration** over all the simulations of 28.5155. The **Percentile Summary** shows that 90% of predictions had an **Accrual Duration** between 27.7693 (5% Percentile) and 29.3238 (95% Percentile), 50% a duration between 28.1827 (25% Percentile) and 28.8238 (75% Percentile) and a median (50% Percentile) duration of 28.4985.

Given that the original target accrual period length was 30 months, this indicates that if the average accrual rate over the entire period up to the current time was being maintained that the accrual period would around 1.5 months less than expected.

The **Per-Simulation Subject-level Data Table** was also generated here and is shown for Scenario A in Figure 11.26 with the first simulated subject (and their **Arrival Time**) in the first simulation (**Simulation ID = 1**) highlighted. Note that the order of the Subject ID is based on **Arrival Time** order.

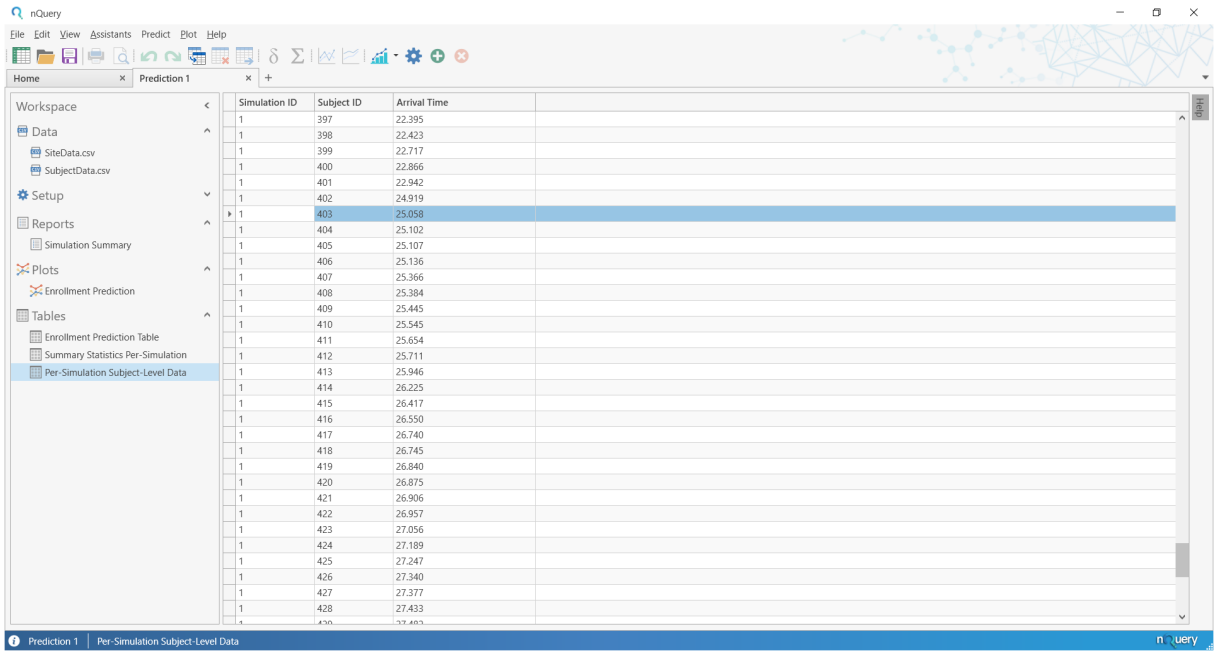


Figure 11.26: Per-Simulation Subject-level Data Table for Subject-level Data

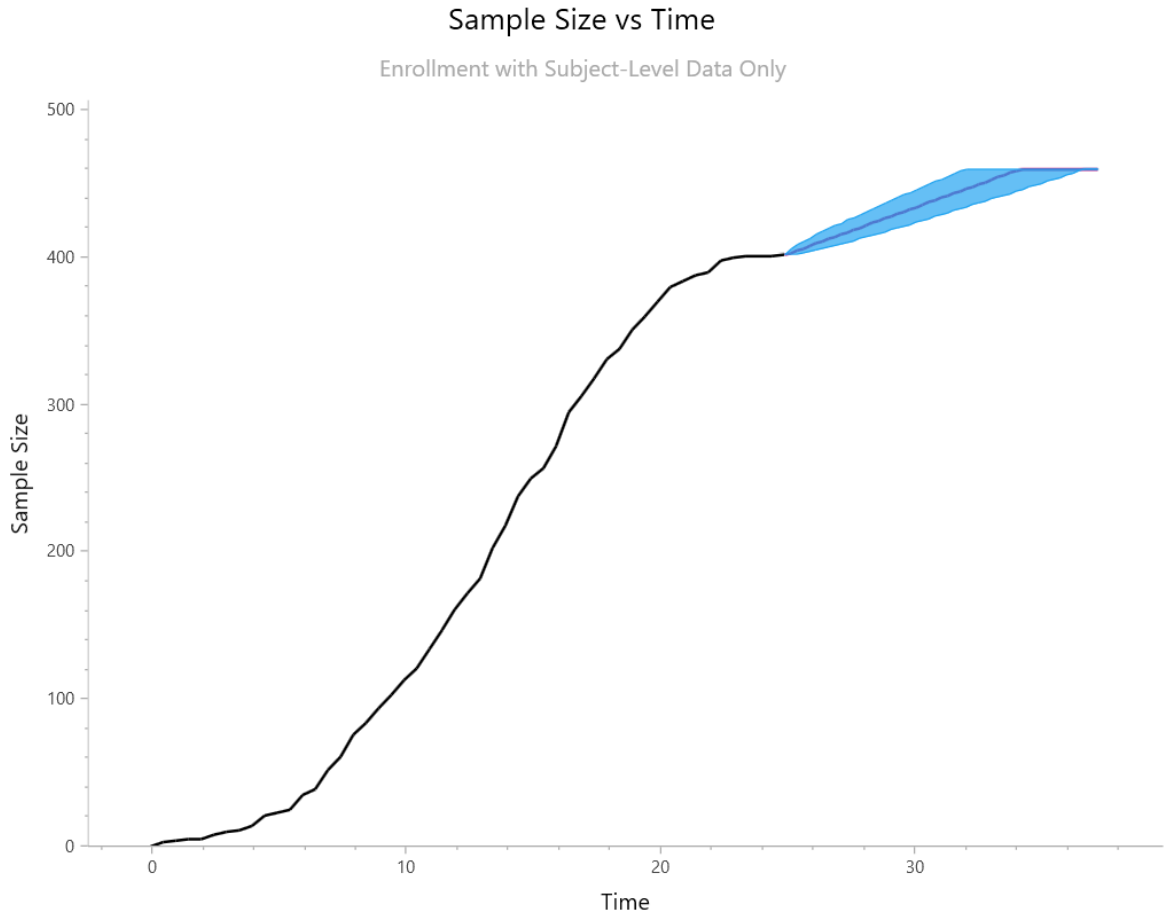
Scenario B Scenario A assumed the **Accrual Rate** would continue at average rate over the entirety of the period up until this simulation was made. However, there is evidence that in the last five months there was a significant reduction in the **Accrual Rate**, perhaps reflecting a wind down of the enrollment process.

To evaluate this scenario, we note that 31 subjects where recruited after 20 months of the accrual period is passed. The remaining accrual period after 20 months to the current time equals 4.9186 (24.9816 (Current Time) - 20). This gives an average accrual rate over this period of ($31/4.9186 \approx 6.3$). This is significantly lower than the average 16.13 **Accrual Rate** over the entire period up to now.

To evaluate this scenario, select **Accrual Options** from under the **Setup** header in the Workspace Navigation Bar on the left then change the **Accrual Rate** in the **Period # = 2** row to 6.3 at the **Accrual Options** step by and then select the Next or → button. At the next **Simulation Controls** step, select the Run or → button to simulate Scenario B. The changes and results for Scenario B are summarized in Figure 11.27.

Accrual Periods:

Period #	Starting at Time	Accrual Rate
1	0.00	16.1325
2	24.9186	6.30



Overall Summary

Average Sample Size	460.0000
Average Study Duration	34.1373
% Simulations Target Reached	100.0000

Percentile Summary

Percentile	Sample Size	Study Duration
5.00%	460	32.2229
25.00%	460	33.3058
50.00%	460	34.0726
75.00%	460	34.9239
95.00%	460	36.2008

Figure 11.27: Scenario B for Enrollment Prediction with Subject-level Data

For Scenario B, the **Overall Summary** shows that the **Target Sample Size** of 460 was reached in every simulation with an **Average Accrual Duration** over all the simula-

tions of 34.1373 with the **Percentile Summary** showing that 90% of predictions had a **Accrual Duration** between 32.2229 and 36.2008, 50% a duration between 33.3058 and 34.9239 with a median duration of 34.0726.

Given that the original target accrual period length was 30 months, this indicates that if the reduced accrual rate over approximately last five months were to continue then the accrual period may be approximately 4 months longer than expected. This may indicate that action is needed to get the trial back on track compared to Scenario A where the trial was assumed to be ahead of schedule.

11.2.6.2 Enrollment Prediction using Subject and Site-level Interim Data

Setup **Enrollment Only** milestone prediction using **Subject + Site-level Data** means that the prediction will project the expected length of the accrual period needed to recruit a specified **Target Sample Size** using subject-level and site-level interim data.

In the **Setup** for this prediction, first in the **Select the type of Prediction** step select **Enrollment Only** from the **Target** field and **Subject + Site Data** from the **Input** field. **Enrollment Status** must be **Ongoing** for enrollment milestone prediction. These selections are shown in Figure 11.28. Select the Next button in the bottom-right or → button in the top-right of the Main Window to move to the next step of the prediction **Setup** stage.

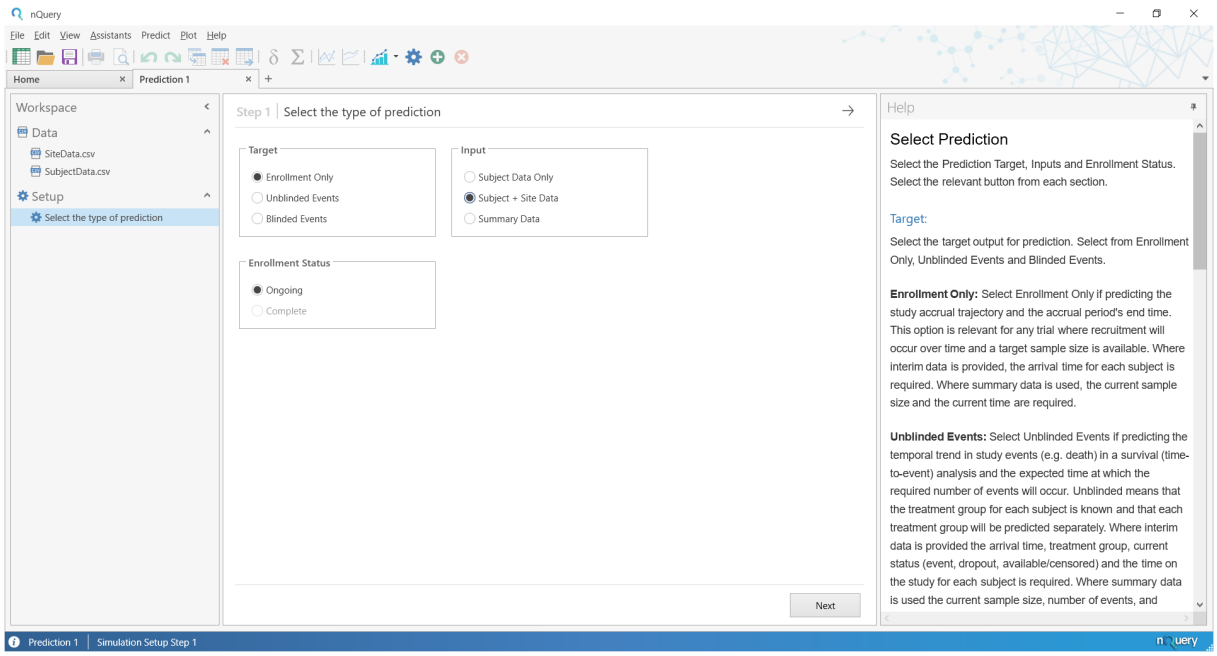


Figure 11.28: Select the Type of Prediction Setup Step for Enrollment Prediction using Subject + Site-level Data

The next step is the **Subject-level Data** step. The **Subject-level Data** step is a Data Field Selection step. The **Subject-level Data** is the dataset where each row corresponds to a specific subject enrolled in the study.

Data Field Selection steps are steps in which the required dataset in the current Workspace is selected and columns in the selected dataset are assigned to the required fields for that

prediction problem. The options in a given Data Field Selection field are opened by selecting the button on the right of each field which is found to the right of the field name e.g. **Select Data**. Each field will have specific requirements (e.g. numeric only, two distinct values only) and nQuery Predict only displays options which are consistent with those fields.

In this prediction there are three fields which are as follows:

- Select Dataset: Select the dataset that is the Subject-level Data from the datasets in the current workspace
- Arrival Time: The arrival time column contains the length of time since the study start (Time = 0) until a subject entered the study. Each subject's Arrival Time should be greater than or equal to zero
- Site ID: Site ID of site from which a subject was recruited. Site IDs here must correspond to Site ID values contained in the Site-level Data Site ID column

For this prediction, in the **Select Dataset** field select **SubjectData.csv,** in the **Arrival Time** field select **Arrival** and in the **Site ID** field select **SID.** These selections are shown in Figure 11.29. Select the Next or → button to move to the next **Setup** step.

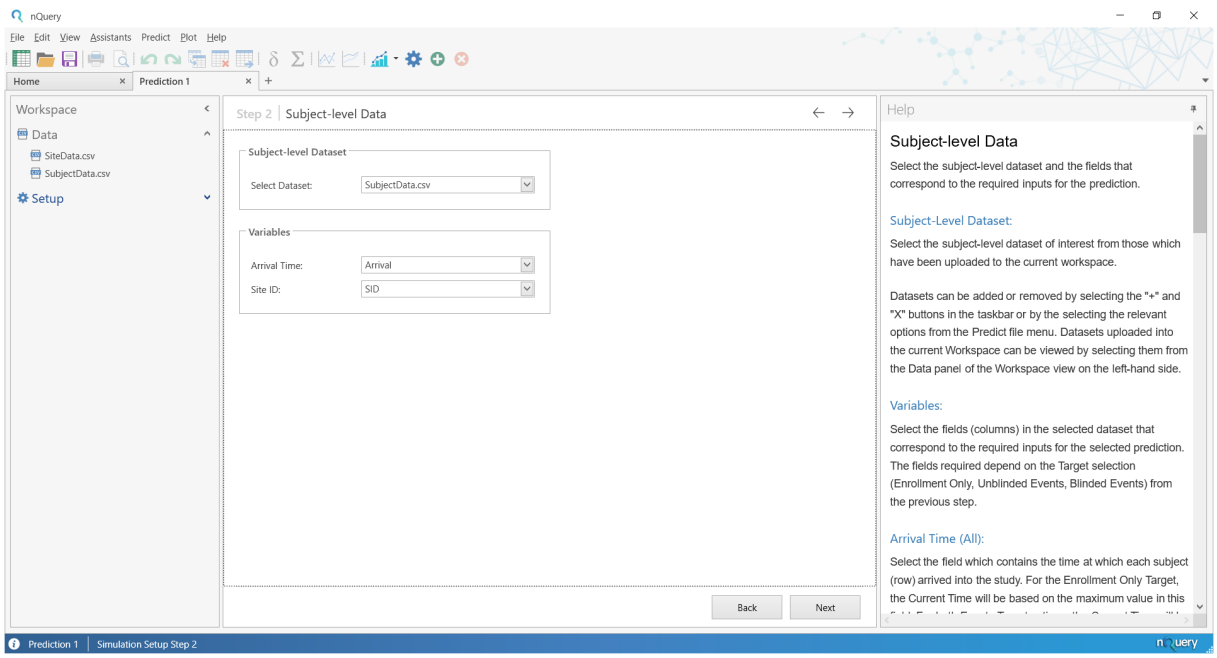


Figure 11.29: Subject-level Data Setup Step for Enrollment Prediction using Subject + Site-level Data

The next step is the **Site-level Data** step. The **Site-level Data** step is a Data Field Selection step as per the **Subject-level Data** step. The **Site-level Data** is the dataset where each row corresponds to a specific site.

The **Site-level Data** step fields are the same for all predictions. These fields are:

- Select Dataset: Select the dataset that is the Site-level Data from the datasets in the current workspace
- Site ID: Site ID for each site. Each row should have a distinct Site ID and Site IDs from Subject-level Data must be included in the list of Site IDs selected here

- Accrual Rate/Site: The planned accrual rate (subjects recruited per unit time) in a site. Each site's Accrual Rate/Site should be a numeric value greater than zero
- Enrollment Cap: The maximum number of subjects that can be recruited from that site. Each site's Enrollment Cap should be an integer greater than the higher of zero and the No. of Accruals (see below)
- Site Initiation Time (Opened Sites): The time at which a site was open and able to start enrolling subjects. Each site's Site Initiation Time should be a numeric value less than the Current Time
- Start Time (Unopened Sites): The start time of the window during which an unopened site could open. Optional field for unopened sites, should be numeric value greater than or equal to the Current Time
- End Time (Unopened Sites): The start time of the window during which an unopened site could open. Optional field for unopened sites, should be numeric value greater than or equal to the Start Time (Unopened Sites) for that site

For this prediction, in the **Select Dataset** field select **SiteData.csv,** in the **Site ID** field select **SID**, in the **Accrual Rate/Site** field select **Rate**, in the **Enrollment Cap** field select **Cap**, in the **Site Initiation Time** field select **OpenTime**, in the **Start Time** field select **Start** and in the **End Time** field select **End.** These selections are shown in Figure 11.30. Select the Next or → button to move to the next **Setup** step.

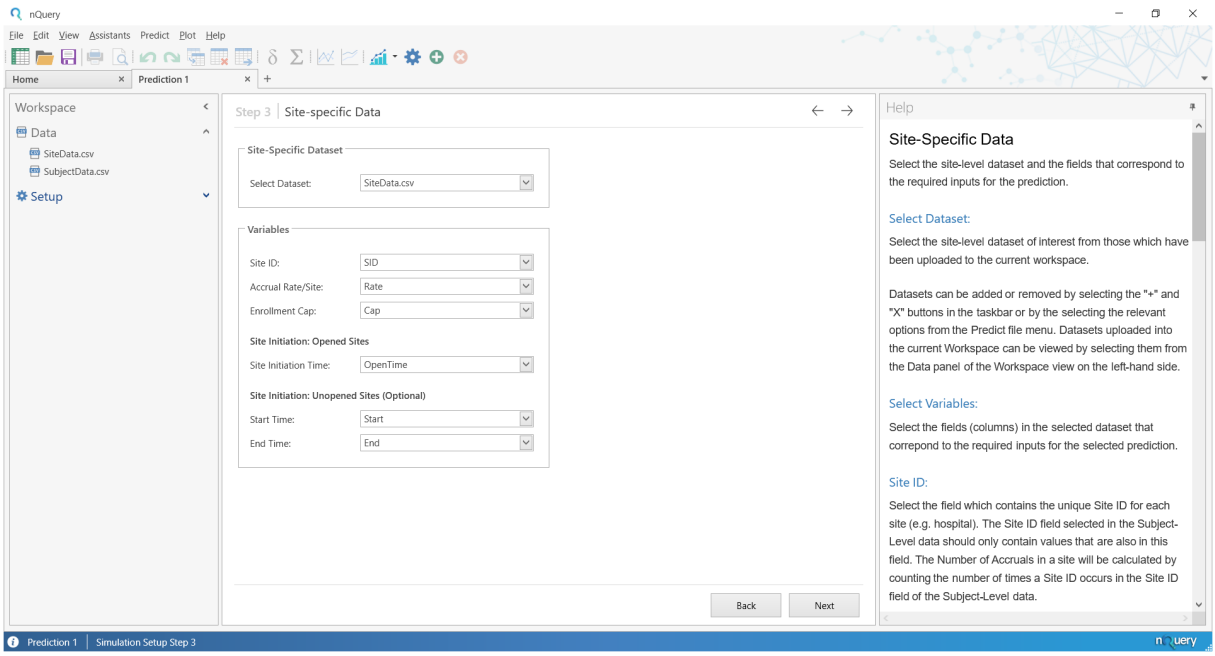


Figure 11.30: Site-level Data Setup Step

The next step is the **Accrual Options** step. When **Site-level Data** is used, the **Accrual Options** consists of two tabs: **Sample Size & Followup Options** and **Accrual Options/Site**. A given tab can be opened by selecting the grey tab name at the top of the main window, just below the **Step 4 | Accrual Options** name. These tabs are highlighted in Figure 11.31.

The **Sample Size & Followup Options** tab provides overall information about the trial up until the current time alongside the **Target Sample Size** and **Accrual Model.** The **Sample Size & Followup Options** tab for this demonstration is shown in Figure 11.31.

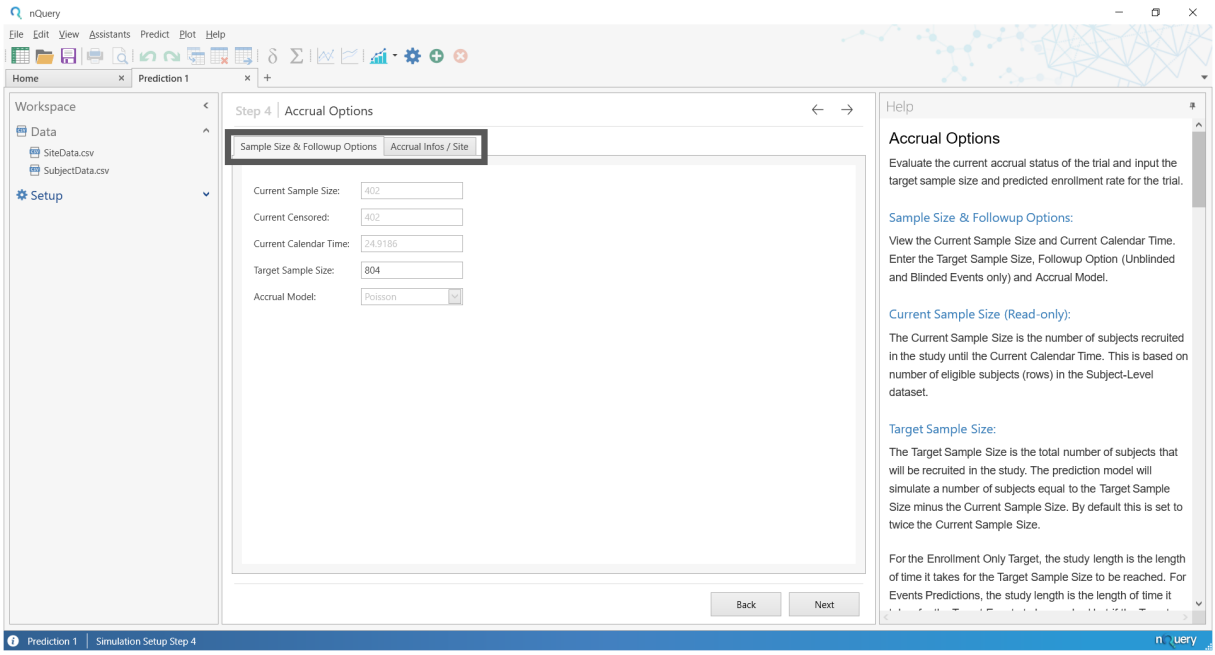


Figure 11.31: Accrual Options Step Sample Size & Followup Options tab for Site-level Data

The **Sample Size & Followup Options** fields are:

- Current Sample Size (Read-only): Sample Size recruited into a study so far. Equals the number of rows in the Subject-level Data
- Current Time (Read-only): The length of time that has passed since the study started. Equals the maximum Arrival Time value
- Target Sample Size (Editable): Total number of subjects that will be recruited in this study. The number of simulated subjects equals the Total Sample Size minus the Current Sample Size
- Accrual Model (Editable): The statistical model that will be used to generate simulated enrollments

In nQuery Predict, the **Target Sample Size** defaults to twice the **Current Sample Size** and the **Accrual Model** defaults to **Poisson.** In this demonstration, the **Current Sample Size** equals 402 and therefore the default **Target Sample Size** is $402\,(2) = 804$.

To open the **Accrual Options/Site** tab select the tab at the top of the main window with that name. This is shown in Figure 11.32

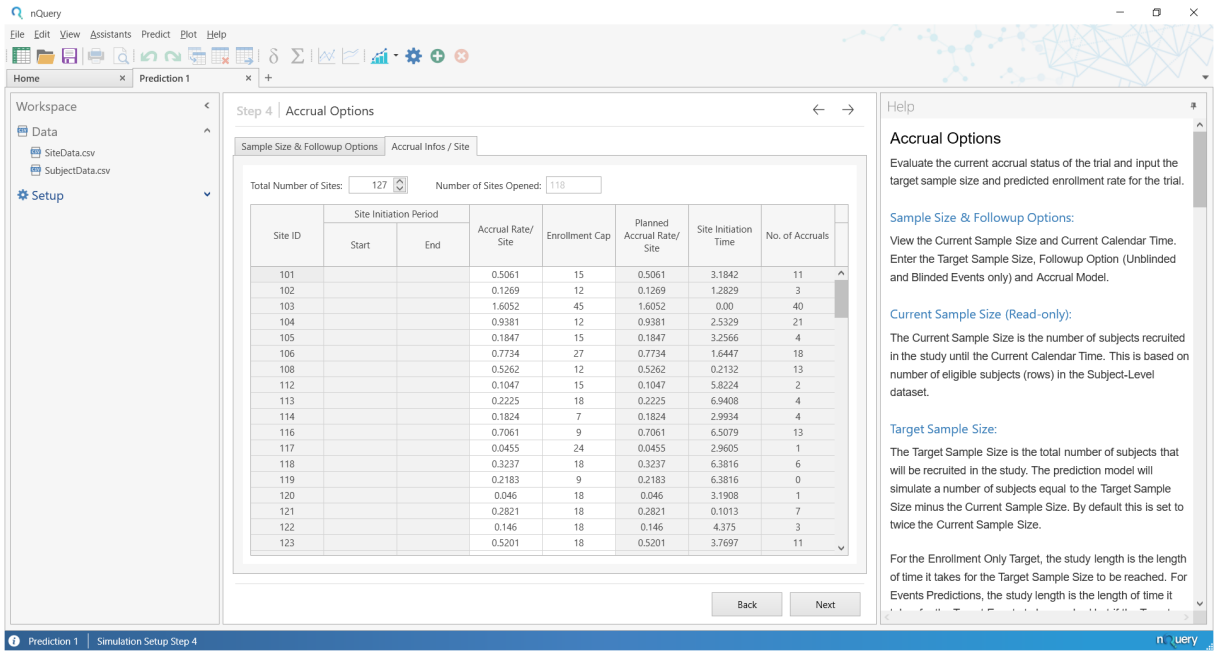


Figure 11.32: Accrual Options Step Accrual Options/Site tab for Site-level Data

The **Accrual Options/Site** tab has three main elements: the **Total Number of Sites** field, the **Number of Sites Open** field and the **Site Accrual Table**.

The **Total Number of Sites** and **Number of Sites Open** field are found at the top of tab window. The **Total Number of Sites** field sets the total number of sites that will be used to simulate subjects in this milestone prediction and by default is equal to the number of rows/sites in the **Site-level Data**.

The **Number of Sites Open** field is the number sites that are already open at the time the simulation is being performed and is the number of sites which had a **Site Initiation Time** in the site-level data. The **Total Number of Sites** must always be greater than or equal to the **Number of Sites Open**.

The **Site Accrual Table** consists of eight columns with each row corresponding to required information for each site. The columns are defined as follows:

- Site ID (Read-only for Open Sites, Editable for Unopened Sites): Site ID for a site. Taken directly from Site-level Data. All Site ID must be unique and include all Site ID in the subject-level Site ID field
- Site Initiation Period - Start Time (Editable for Unopened Sites, Numeric $\geq$ Current Time): Start time for window during which unopened site can open. Not used for open sites
- Site Initiation Period - End Time (Editable for Unopened Sites, Numeric $\geq$ Start Time): End time for window during which unopened site can open. Not used for open sites
- Accrual Rate/Site (Editable, Numeric > 0): The accrual rate (subjects recruited per unit time) that will be used to simulate subjects for that site
- Enrollment Cap (Editable, Numeric $\geq$ No. of Accruals) The maximum number of subjects that can be recruited in a site. This must be greater than the No. of Accruals in a site

- Planned Accrual Rate/Site (Read-only): The original planned accrual rate in a site. Taken from Site-level Data
- Site Initiation Time (Read-only): The site initiation time for opened sites. Taken from Site-level Data. Not used for unopened sites
- No. of Accruals (Read-only): The number of subjects that have been enrolled in an open site at the current time. Not used for unopened sites

Site ID, Site Initiation Period (Start Time, End Time), Enrollment Cap, Planned Accrual Rate/Site and **Site Initiation Time** are taken directly from the **Site-level Data**.

For sites which have already recruited subjects (i.e. **No. of Accruals** > 0), the default **Accrual Rate/Site** is calculated using the **No. of Accruals** and **Site Initiation Time** using the following relationship:

$$R = \frac{\#A}{(CT - SIT)}$$

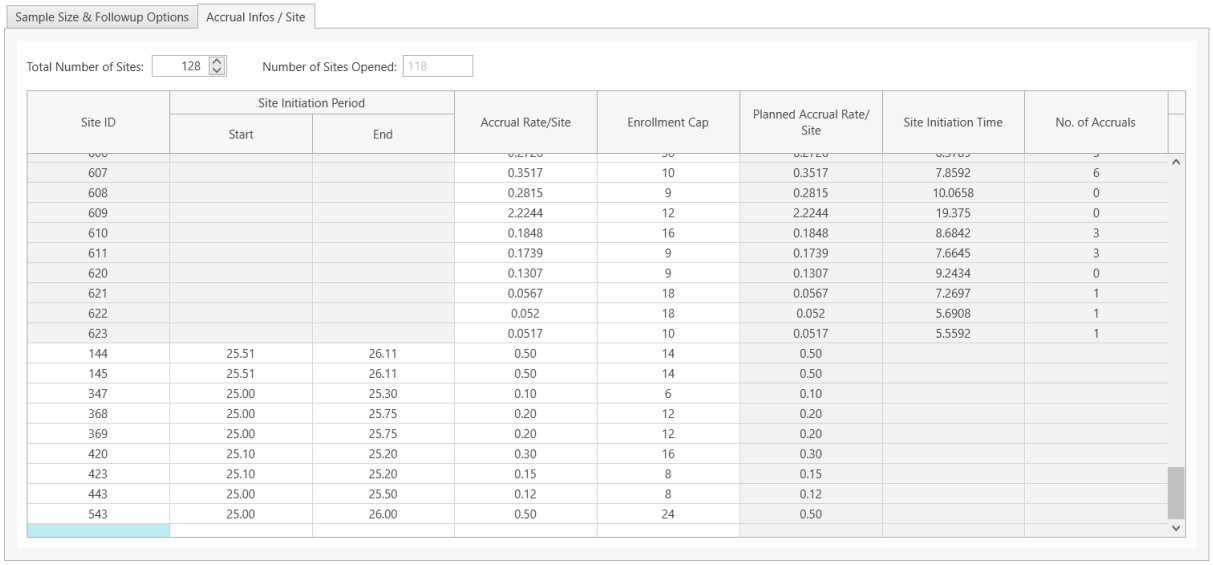
where R is the **Accrual Rate/Site**, $\#A$ is the **No. of Accruals** in a site, CT is the **Current Time** and SIT is the **Site Initiation Time** for that site.

For sites which are unopened sites or which have not recruited a subject (i.e. **No. of Accruals** $= 0$), the **Planned Accrual Rate/Site** from the **Site-level Data's Accrual Rate** field is used.

The **No. of Accruals** is calculated by counting the number of times each **Site ID** value occurred in the **Subject-level Data's Site ID** column.

As referenced above, the inputs for the **Site Accrual Table** for each site depend on whether a site is open or unopened. Unopened sites are automatically placed at the bottom of the **Site Accrual Table**.

The user can also add additional sites (rows) by increasing the **Total Number of Sites** field above the original value derived from the number of rows in the **Site-level Data**. This will add a blank row at the bottom of the **Site Accrual Table**. Note **Setup** cannot continue until all new rows are filled appropriately. An example of **Site Accrual Table** with the unopened sites from the **SiteLevel.csv** data alongside one blank new site by increasing **Total Number of Sites** to 128 is provided in Figure 11.33.



Site ID	Site Initiation Period		Accrual Rate/Site	Enrollment Cap	Planned Accrual Rate/ Site	Site Initiation Time	No. of Accruals
	Start	End					
607			0.3517	10	0.3517	7.8592	6
608			0.2815	9	0.2815	10.0658	0
609			2.2244	12	2.2244	19.375	0
610			0.1848	16	0.1848	8.6842	3
611			0.1739	9	0.1739	7.6645	3
620			0.1307	9	0.1307	9.2434	0
621			0.0567	18	0.0567	7.2697	1
622			0.052	18	0.052	5.6908	1
623			0.0517	10	0.0517	5.5592	1
144	25.51	26.11	0.50	14	0.50		
145	25.51	26.11	0.50	14	0.50		
347	25.00	25.30	0.10	6	0.10		
368	25.00	25.75	0.20	12	0.20		
369	25.00	25.75	0.20	12	0.20		
420	25.10	25.20	0.30	16	0.30		
423	25.10	25.20	0.15	8	0.15		
443	25.00	25.50	0.12	8	0.12		
543	25.00	26.00	0.50	24	0.50		

Figure 11.33: Unopened and New Sites in Site Accrual Table

For this demonstration, assume the **Total Number of Sites** is reset to its default of 127. Select the Next or → button to move to the next **Setup** step.

The final step is the **Simulation Controls** step. The **Simulation Controls** step consists of three sections: Simulation Controls, Output for All Trials and Output Options.

Simulation Controls (top-left) sets the **Number of Simulations**, **Refresh Frequency** and **Random Seed**

Output For All Trials (bottom-left) sets the Percentiles desired in the **Percentile Summary** table in the **Simulation Summary** report for key simulation outputs such as study length and sample size.

Output Options (right) selects which additional datasets the user wants in the **Tables** field of the simulation results. Additional datasets will be summary statistics for each simulation and outputs from a set number of individual of simulations.

The **Simulation Controls** step is described in detail in subsubsection 11.2.9.4. In this demonstration, the defaults will be used which corresponds to 1000 simulations with the default percentiles (5%, 25%, 50%, 75%, 95%) and with the "Save summary statistics for every simulation run" **Output Options** table active. The **Simulation Controls** defaults for this demonstration are shown in Figure 11.34. To start the milestone prediction, Select the Run (where Next button was in previous steps) or → button.

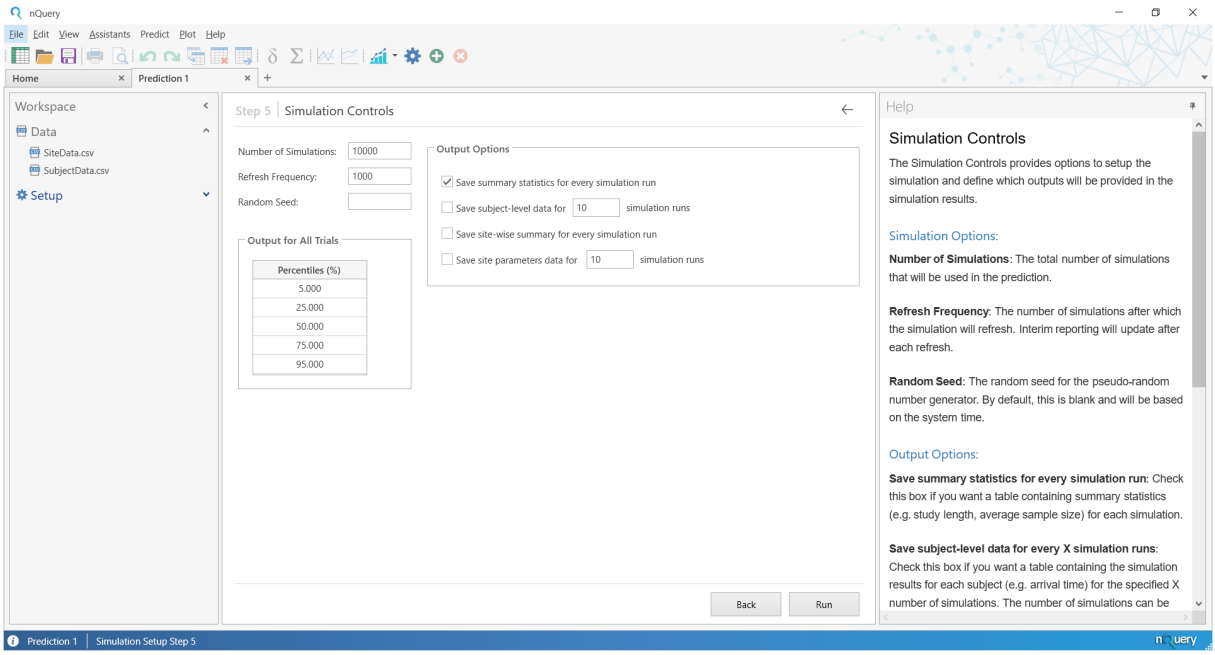


Figure 11.34: Simulation Controls Setup Step for Enrollment Prediction using Subject + Site-level Data

Results While a milestone prediction is being run, a **Simulation in Progress** window will be displayed. The **Simulation in Progress** window provides updated information on key simulation metrics while the simulation is ongoing. An example for this demonstration is given in Figure 11.35.

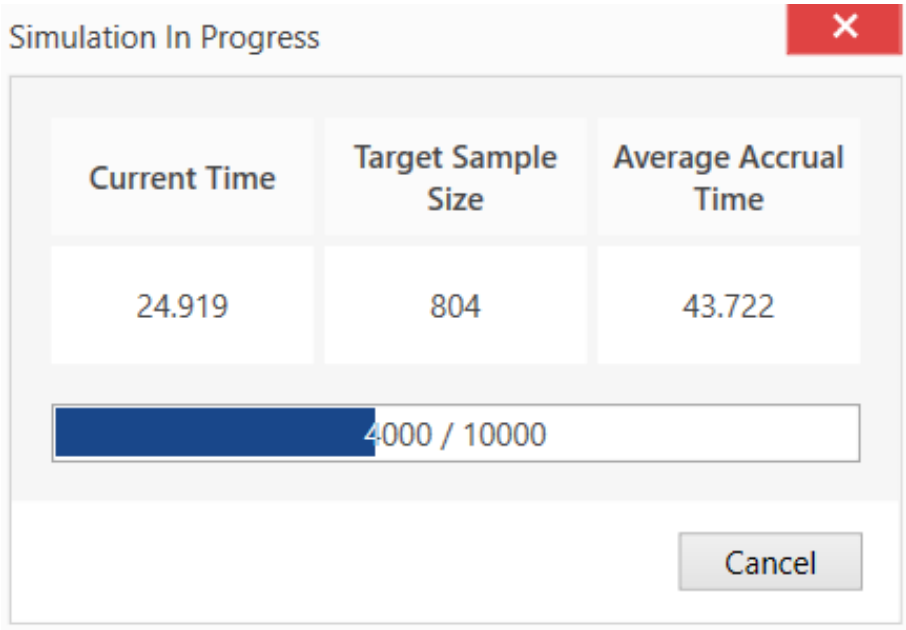


Figure 11.35: Simulation in Progress Window for Enrollment Prediction using Subject + Site-level Data

Once the simulation is complete, the results will automatically be added to the Workspace Navigation Bar on the left and the first element under the **Plots** header will be displayed.

In this demonstration, the **Enrollment Prediction Plot** will be displayed. This is shown in Figure 11.36.

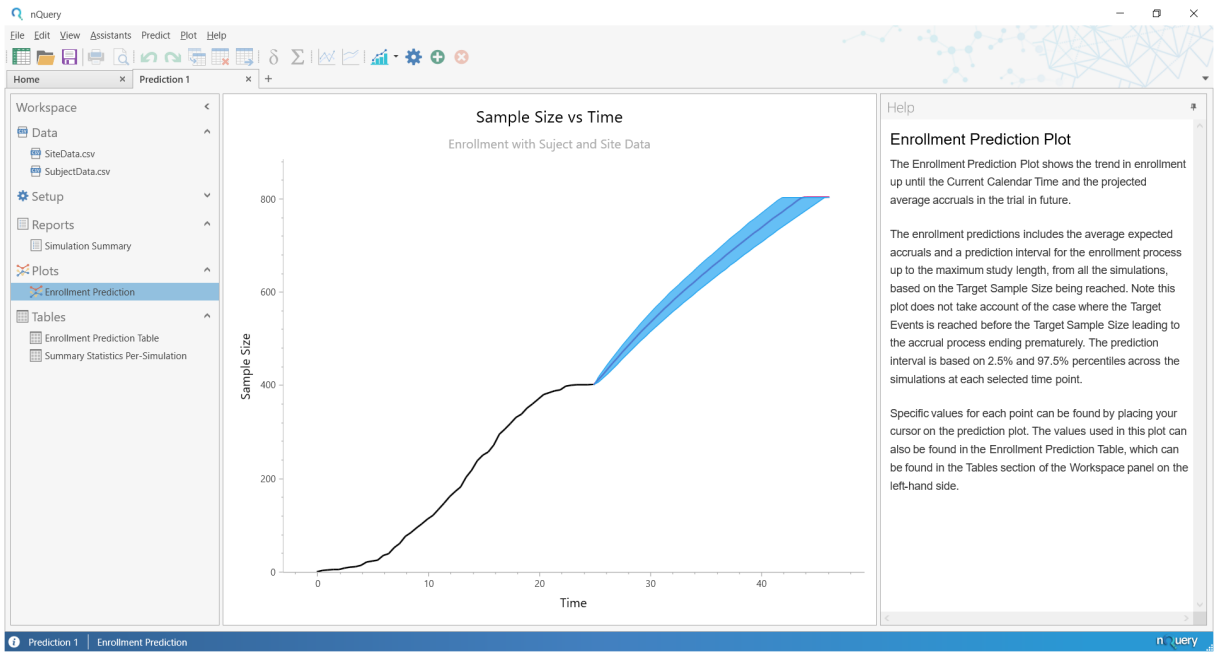


Figure 11.36: Enrollment Prediction Plot for Enrollment Prediction using Subject + Site-level Data

The results of a nQuery Predict milestone prediction can be divided into three categories: **Reports, Plots** and **Tables**. A high-level summary of the results in nQuery Predict is provided in subsection 11.2.8 with demonstration specific elements highlighted here.

For this demonstration the **Reports** header contains the **Simulation Summary** report, the **Plots** header contains the **Enrollment Prediction** plot and the **Tables** header contains the **Enrollment Prediction Table** and **Summary Statistics Per-Simulation**. To select any result element, select it from the appropriate header in the Workspace Navigation Bar on the left (see subsection 11.2.2 for details on the Navigation Bar).

The **Simulation Summary** provides a tabular summary of the inputs and outputs from the current milestone prediction simulation. The **Simulation Summary** for this demonstration is shown in Figure 11.37.

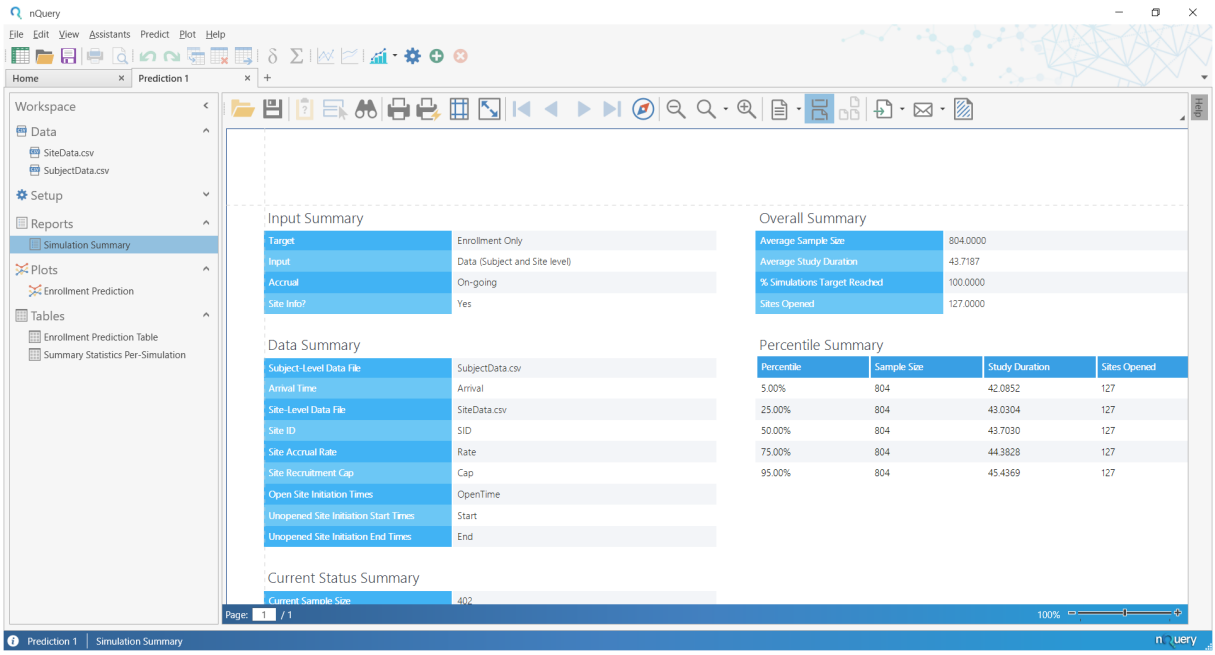


Figure 11.37: Simulation Summary Report for Enrollment Prediction using Subject + Site-level Data

In the **Simulation Summary** report, the left-hand column provides a summary of inputs used to generate the current simulation and the right-hand column provides the results of the current simulation. In this demonstration, we will skip the left-hand Inputs column and focus on the main results in the right-hand column and the main report options.

The results column (on the right) is shown in Figure 11.38. For this demonstration, the **Overall Summary** shows that the **Target Sample Size** of 804 was reached in every simulation with an **Average Accrual Duration** over all the simulations of 43.7187. All 127 **Sites Opened** in all simulations. The **Percentile Summary** shows that 90% of predictions had an **Accrual Duration** between 42.0852 (5% Percentile) and 45.4369 (95% Percentile), 50% a duration between 43.0304 (25% Percentile) and 44.3828 (75% Percentile) and a median (50% Percentile) duration of 43.7030.

Overall Summary

Average Sample Size	804.0000
Average Study Duration	43.7187
% Simulations Target Reached	100.0000
Sites Opened	127.0000

Percentile Summary

Percentile	Sample Size	Study Duration	Sites Opened
5.00%	804	42.0852	127
25.00%	804	43.0304	127
50.00%	804	43.7030	127
75.00%	804	44.3828	127
95.00%	804	45.4369	127

Figure 11.38: Simulation Summary Report Results for Enrollment Prediction with Subject + Site-level Data

To edit the **Simulation Summary report there a** number of buttons available at the top of the report. For full detail on the **Simulation Summary** report and options to edit the report see subsubsection 11.2.8.2. However the Zoom options  , Page Layout and Setup options  and Export option  will be the more commonly used options.

The **Enrollment Prediction** plot provides a visual summary of enrollment simulation from the study start to when the **Target Sample Size** was reached in all simulations. The X-axis is **Time** (relative to study start) and the Y-axis is **Sample Size** (enrolled at Time X-axis value). When the cursor is placed over the **Enrollment Prediction** plot, information on the **Sample Size** enrolled at a given **Time** is shown as per Figure 11.39.

Figure 11.39: Enrollment Prediction Plot for Enrollment Prediction using Subject + Site-level Data

The **Enrollment Prediction** plot consists of two parts: from Time = 0 to **Current Time** and from **Current Time** to the **Maximum Time**. The first part is a black line which plots the accrual pattern from the user inputs provided. The second part is a blue conic section with a grey line where the blue conic section plots the 95% prediction interval for the **Sample Size** enrolled at a given **Time** across all simulations and the grey line is the average **Sample Size** enrolled at a given time. The 95% prediction interval indicates the 95% of predictions had a sample size that fell between the lower and upper limit at a given time.

The **Enrollment Prediction Table** is the table used to create the **Enrollment Prediction** plot, which by default consists of ~100 rows (50 pre-simulation and 50 post-simulation). It consists of five columns: **Time, Actual, Predicted Avg. Sample Size, Predicted Median Sample Size, 95% Prediction Interval LL, 95% Prediction Interval UL**. The **Enrollment Prediction Table** for this demonstration at the start of the simulated period is given in Figure 11.40.

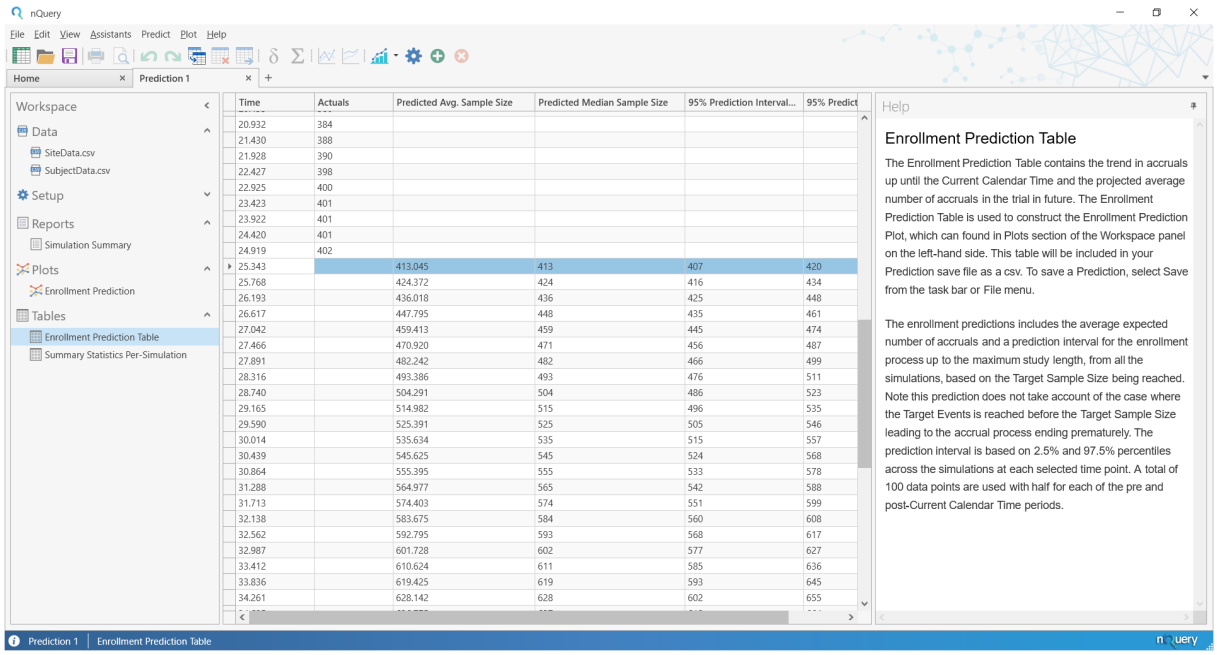


Figure 11.40: Enrollment Prediction Table for Enrollment Prediction using Subject + Site-level Data

Time is the time value relative to the study start time of zero. **Actual** is the actual sample size achieved at a pre-simulation **Time** row. **Predicted Avg. Sample Size** is the predicted average (mean) sample size enrolled at a post-simulation **Time** row. **Predicted Median Sample Size** is the predicted median sample size enrolled at a post-simulation **Time** row. **95% Prediction Interval LL** is the lower limit for the 95% prediction interval for the sample size enrolled at a post-simulation **Time** row. **95% Prediction Interval UL** is the upper limit for the 95% prediction interval for the sample size enrolled at a post-simulation **Time** row.

The **Summary Statistics Per-Simulation Table** provides the summary statistics achieved for primary outputs in each simulation. For this demonstration this includes the **Simulation ID, Current Time, Current Sample Size, Target Sample Size, Accrual Duration.** The **Summary Statistics Per-Simulation Table** for this demonstration is shown in Figure 11.41.

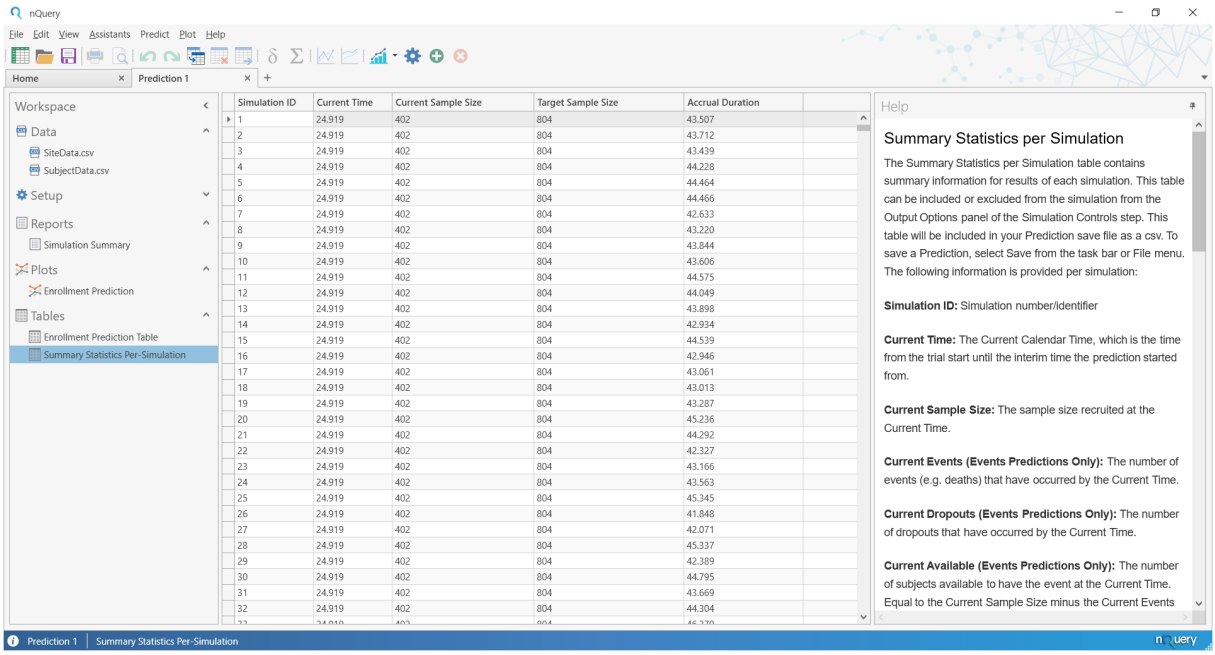


Figure 11.41: Summary Statistics Per-Simulation Table for Enrollment Prediction using Subject + Site-level Data

Simulation ID is in order of simulation from 1 up to **Number of Simulations**, **Current Time, Current Sample Size** and **Target Sample Size** summarize the user inputs and are constant, and the **Accrual Duration** is the length of time needed to achieve the **Target Sample Size** in that simulation.

Alternative Scenarios The demonstration has focused on the default inputs using **SubjectData.csv** up to this point. However, as noted in the data summary given in subsection 11.2.4 the study from which the example data was simulated had an original sample size target of 460 (402 enrolled in **SubjectData.csv**).

However, note that the percentage of the **Target Sample Size** enrolled $(100(402/406) = 87.5)$ at the **Current Time** of 24.9186 months is higher than the percentage of the targetted accrual period length (30 months) used so far $(100\,(24.9186/30) = 83.1\%)$. This could indicate that the planned number of new sites (9) may be higher than necessary and an adjustment may be made to reduce this number and stagger their opening times to avoid being in the process of opening sites when enrollment is complete.

To explore this additional information, we will investigate two additional scenarios

- Scenario A: **Target Sample Size = 460** using defaults for each site
- Scenario B: **Target Sample Size = 460** using less unopened sites and opening them over a longer period

Scenario A The change required compared to the first demonstration is to change the **Target Sample Size** to 460 in the **Sample Size & Followup Options** tab of the **Accrual Options** step. The simplest way to do this is to select the **Setup** header in the Workspace Navigation Bar on the left and then select the **Accrual Options** drop

down option. Then edit the **Target Sample Size** 460 in the **Sample Size & Followup Options tab** in the top-left and select the Next or → button.

At the **Simulation Controls** step, we will add the three additional tables under the **Output Options** field by selecting the checkbox beside each. We will replace the default of 10 with 1 (at "(x)" spot) for **Save subject-level data for (x) simulation runs** and **Save site parameters data for (x) simulation runs**. An edited down summary of the **Setup** changes is provided in Figure 11.42.

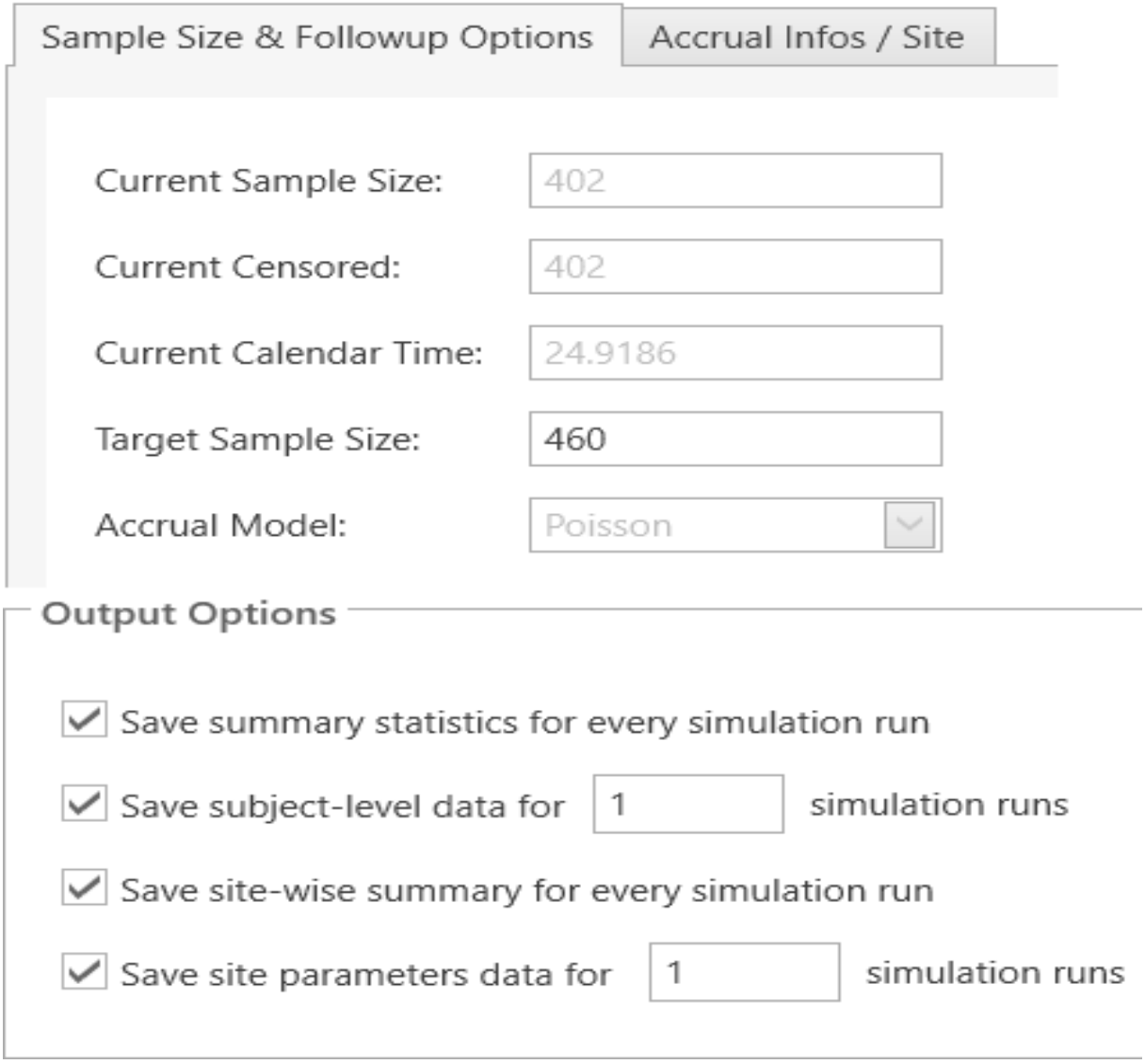
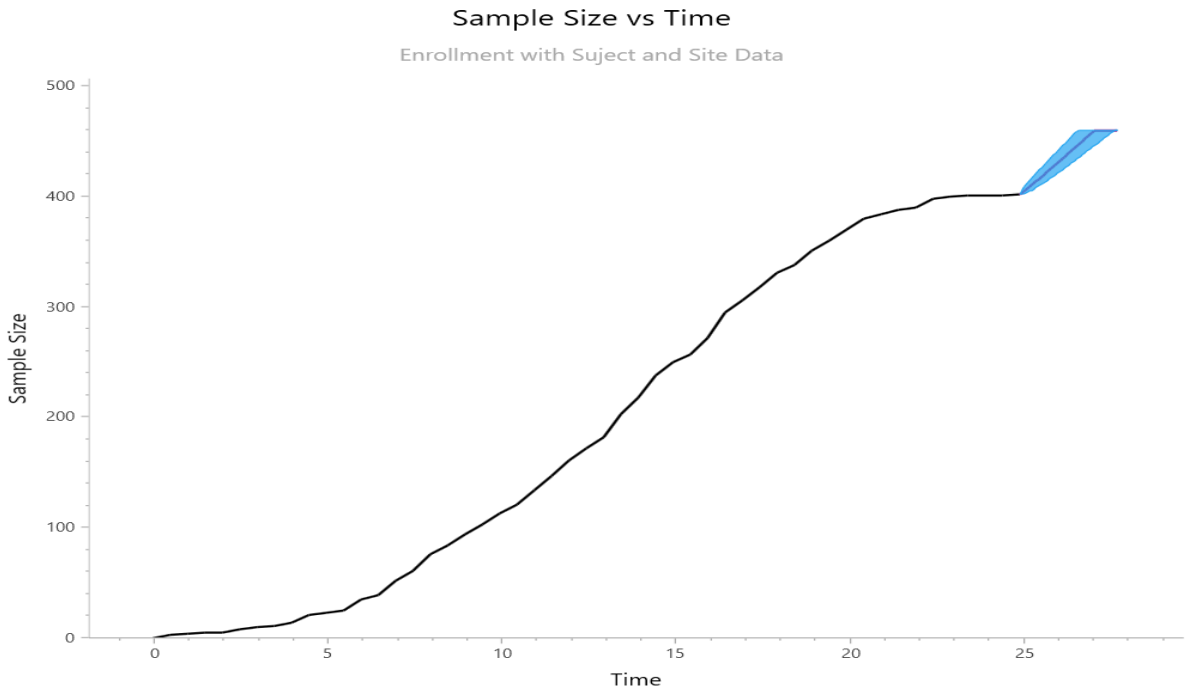


Figure 11.42: Scenario A Setup Changes for Enrollment Prediction using Subject + Site-level Data

To run the simulation again with the new Scenario A, select the Run/→ button. The main results of this Scenario A simulation are shown in Figure 11.43.



Overall Summary

Average Sample Size	460.0000
Average Study Duration	27.0594
% Simulations Target Reached	100.0000
Sites Opened	127.0000

Percentile Summary

Percentile	Sample Size	Study Duration	Sites Opened
5.00%	460	26.6307	127
25.00%	460	26.8680	127
50.00%	460	27.0472	127
75.00%	460	27.2409	127
95.00%	460	27.5243	127

Figure 11.43: Scenario A Results for Enrollment Prediction using Subject + Site-level Data

For Scenario A, the **Overall Summary** shows that the **Target Sample Size** of 460 was reached in every simulation with an **Average Accrual Duration** over all the simulations of 27.0594. The **Percentile Summary** shows that 90% of predictions had an **Accrual Duration** between 26.6307 (5% Percentile) and 27.5243 (95% Percentile), 50% a duration between 26.8680 (25% Percentile) and 27.2409 (75% Percentile) and a median (50% Percentile) duration of 27.0472.

Given that the original target accrual period length was 30 months, this indicates that if the average accrual rate over the entire period up to the current time was being maintained that the accrual period would around 3 months less than expected.

The **Per-Simulation Subject-level Data Table** was also generated here and is shown for Scenario A in Figure 11.44 with the first simulated subject (and their **Arrival Time** and **Site ID** for the site they were generated from) in the first simulation (**Simulation ID = 1**) highlighted. Note that the order of the Subject ID is based on **Arrival Time** order.

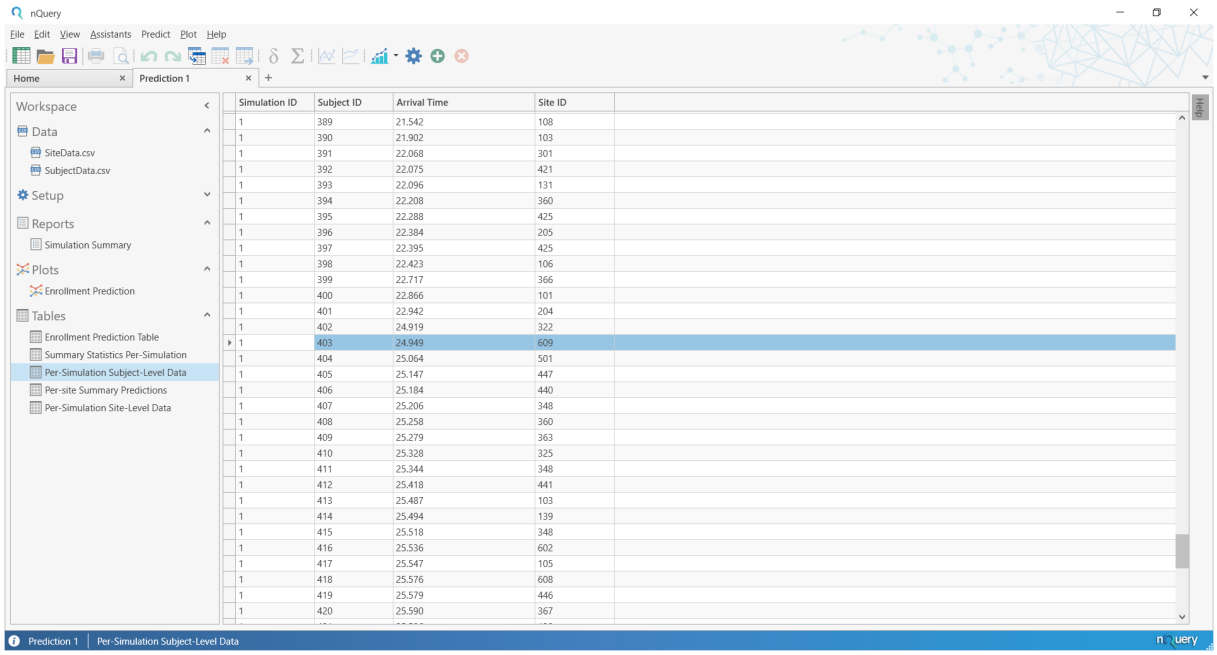


Figure 11.44: Per-Simulation Subject-level Data Table for Subject + Site-level Data

The **Per-Site Summary Predictions Table** was also generated here and is shown for Scenario A in Figure 11.45. The **Per-Site Summary Predictions Table** contains the following columns:

- Site ID: Site ID for a site
- Avg. Accrual: The average number of subjects enrolled from this site across all simulations
- Avg. Max Time: The average time of the final enrollment in a site
- Avg. Start Time: The average site initiation time for a site. This is from the Site-level Data for open sites and generated randomly for unopened sites
- Avg. Duration: The average length of time a site was open and enrolling subjects
- Avg. Rate: The average accrual rate for a site during the period it was open
- Times Open: The number of simulations in which the site opened before enrollment was complete

Note that **Times Opens** will equals the number of simulations except for unopened sites with any generated start times higher than a given simulation's **Accrual Duration**.

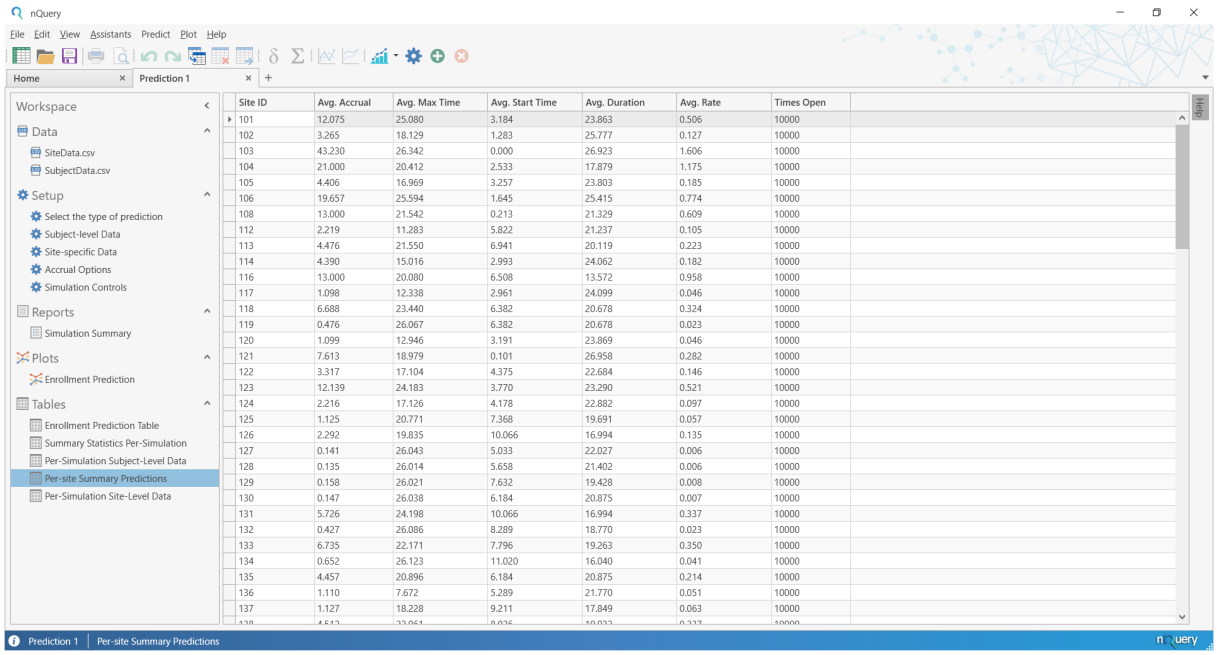


Figure 11.45: Per-Site Summary Predictions for Scenario A

The **Per-Simulation Site-level Data Table** was also generated here and is shown for Scenario A in Figure 11.46. The **Per-Simulation Site-level Data Table** contains the following columns:

- Simulation ID: The simulation number
- Site ID: Site ID for a site
- Site Activation Time: Time after study start when site become open to enroll subjects. Taken from Site-level Data for open sites, generated for unopened sites
- True Enrollment Rate: The user specified enrollment rate for a site
- Accruals: Total number of subjects enrolled from a site in a simulation
- Observed Enrollment Rate: The actual enrollment rate (subjects enrolled per unit time) achieved in a site in a simulation
- Final Enrollment Time: Time of the final enrollment in a site in a simulation
- Enrollment Duration: The length of time a site was open in a simulation
- Site Open: Indicator of whether site opened in a simulation. Tick = Open, X = Did not open

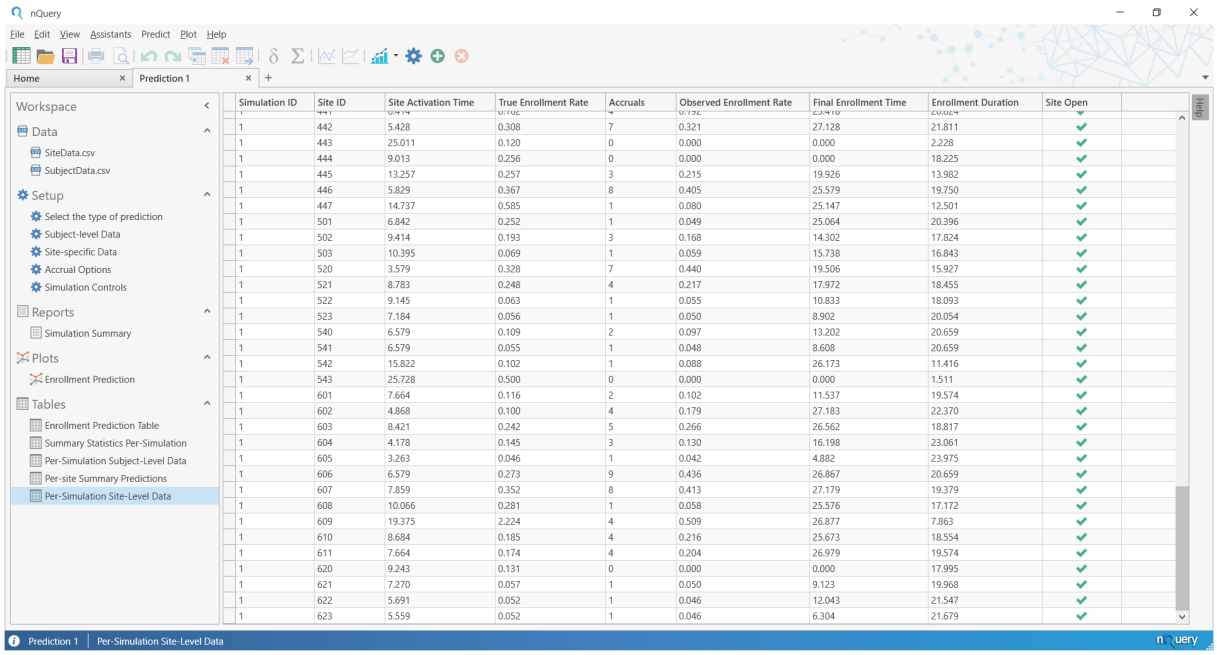


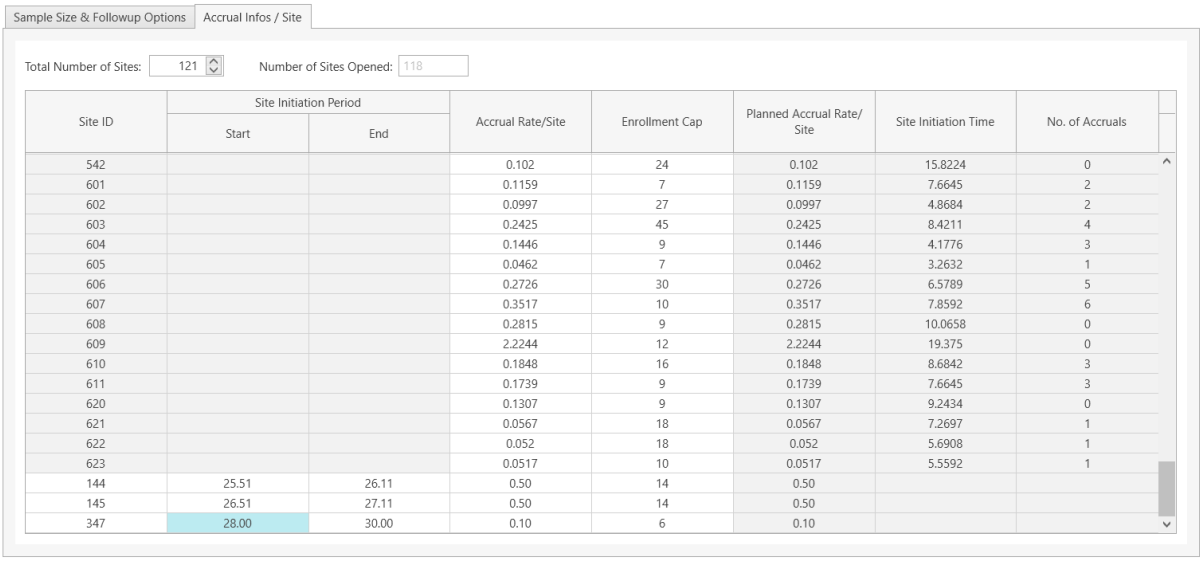
Figure 11.46: Per-Simulation Site-level Data Table for Scenario A

Scenario B Scenario A assumed that an additional 9 sites would open after the **Current Time**, as per the original study plan. Given that the enrollment is ahead of schedule in Scenario A, it was decided to reduce the number of planned unopened sites to 3 with Site ID 144, 145, 347 being retained.

Site ID 144 (expected accrual rate of 0.5 per month) would retain their current opening window of 25.51 - 26.11 months, the **Site ID 145** (expected accrual rate of 0.5 per month) window was shifted up by one month to 26.51-27.11 months and the smaller **Site ID** 347 (expected accrual rate of 0.1 per month) shifted up to a reserve position with an opening window of 28-30 months and was expected to be unneeded.

To evaluate this scenario, select **Accrual Options** from under the **Setup** header in the Workspace Navigation Bar. In **Accrual Options**, open the **Accrual Infos/Sites** tab. Change the **Total Number of Sites** to 121. In the **Site Accrual Table**, scroll down to the unopened sites.

The **Site ID** = 144 row is unchanged. In the **Site ID** = 145 row, change the **Start** column value to 26.51 and the **End** column value to 27.11. In the **Site ID** = 347 row, change the **Start** column to 28 and the **End** column to 30. The updated **Accrual Infos/Sites** tab for Scenario B is shown in Figure 11.47.



Site ID	Site Initiation Period		Accrual Rate/Site	Enrollment Cap	Planned Accrual Rate/ Site	Site Initiation Time	No. of Accruals
	Start	End					
542			0.102	24	0.102	15.8224	0
601			0.1159	7	0.1159	7.6645	2
602			0.0997	27	0.0997	4.8684	2
603			0.2425	45	0.2425	8.4211	4
604			0.1446	9	0.1446	4.1776	3
605			0.0462	7	0.0462	3.2632	1
606			0.2726	30	0.2726	6.5789	5
607			0.3517	10	0.3517	7.8592	6
608			0.2815	9	0.2815	10.0658	0
609			2.2244	12	2.2244	19.375	0
610			0.1848	16	0.1848	8.6842	3
611			0.1739	9	0.1739	7.6645	3
620			0.1307	9	0.1307	9.2434	0
621			0.0567	18	0.0567	7.2697	1
622			0.052	18	0.052	5.6908	1
623			0.0517	10	0.0517	5.5592	1
144	25.51	26.11	0.50	14	0.50		
145	26.51	27.11	0.50	14	0.50		
347	28.00	30.00	0.10	6	0.10		

Figure 11.47: Scenario B Accrual Infos/Sites Tab

Next or → button. At the next **Simulation Controls** step, select the Run or → button to simulate Scenario B. The results for Scenario B are summarized in Figure 11.48.

Overall Summary

Average Sample Size	460.0000
Average Study Duration	27.1852
% Simulations Target Reached	100.0000
Sites Opened	119.8660

Percentile Summary

Percentile	Sample Size	Study Duration	Sites Opened
5.00%	460	26.7222	119
25.00%	460	26.9806	120
50.00%	460	27.1730	120
75.00%	460	27.3722	120
95.00%	460	27.6869	120

Figure 11.48: Scenario B for Enrollment Prediction with Subject + Site-level Data

For Scenario B, the **Overall Summary** shows that the **Target Sample Size** of 460 was reached in every simulation with an **Average Accrual Duration** over all the simulations of 27.1852 with the **Percentile Summary** showing that 90% of predictions had an

Accrual Duration between 26.7222 and 27.6869, 50% a duration between 26.9806 and 27.3722 with a median duration of 27.1730.

Note that number of sites ranged from 119 to 120 with an average of 119.8660 sites opened across all simulations. In the **Per-Site Summary Predictions Table** for this demonstration Site 144 opened in every simulation (0.681 subjects enrolled on average), Site 145 opened in 8547 simulations (0.222 subjects enrolled on average) and Site 346 opened 3 times (<0.001 subjects enrolled on average).

Given that Scenario A had an **Average Study Duration** of 27.0594 this indicates the new sites had a minimal impact on reaching the **Target Sample Size** and perhaps no further sites were needed or that sites could be closed. In nQuery Predict "Closing" opened sites at the **Current Time** could be achieved by setting the **Enrollment Cap** equal to **No. of Accruals** in the **Site Accrual Table.**

11.2.6.3 Enrollment Prediction using Summary Data

Setup **Enrollment Only** milestone prediction using **Summary Data** means that the prediction will project the expected length of the accrual period needed to recruit a specified **Target Sample Size** using summary data.

In the **Setup** for this prediction, first in the **Select the type of Prediction** step select **Enrollment Only** from the **Target** field and **Summary** from the **Input** field. **Enrollment Status** must be **Ongoing** for enrollment milestone prediction. These selections are shown in Figure 11.49. Select the Next button in the bottom-right or → button in the top-right of the Main Window to move to the next step of the prediction **Setup** stage.

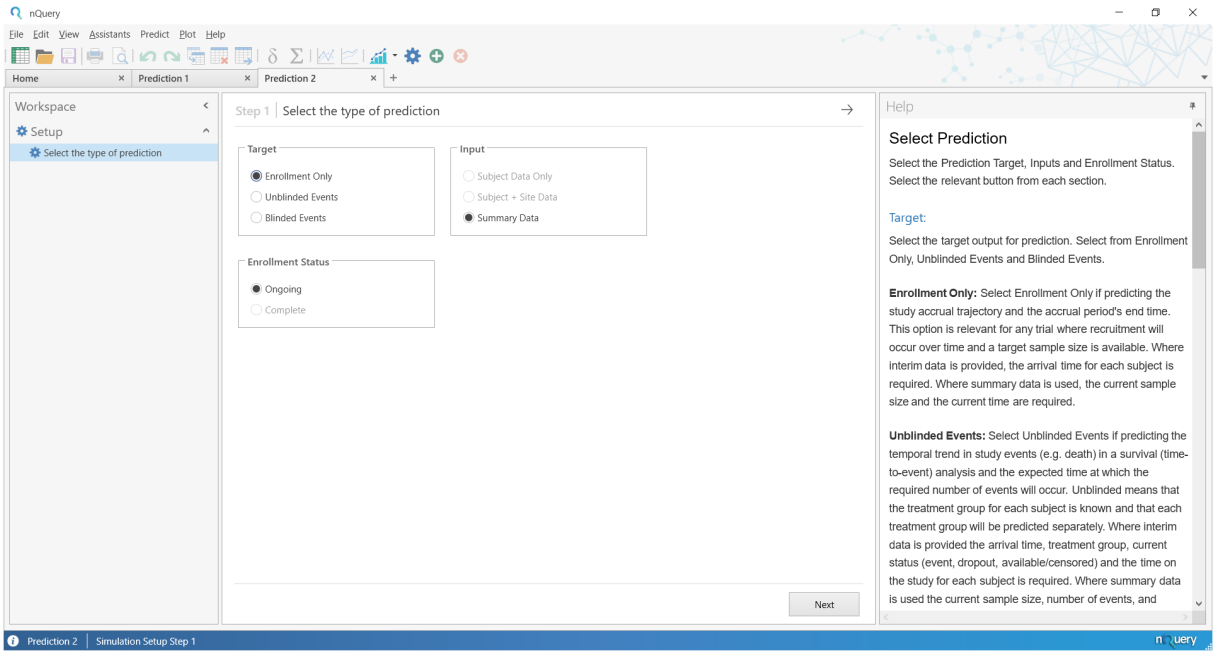


Figure 11.49: Select the Type of Prediction Setup Step for Enrollment Prediction using Summary Data

The next step is the **Fixed Parameters** step. For this demonstration, there is a **Current Sample Size and Calendar Time** section which contains two fields which are as follows:

- Current Sample Size: The sample size enrolled into the study at the Current Time
- Current Time: The length of time the study has been on-going since the study began

For this demonstration, inputs are selected which mirror those from **SubjectData.csv** used in the examples above. This would give a **Current Sample Size** of 402 and a **Current Time** of 24.9186. The **Fixed Parameters** step with these values inputted is shown in Figure 11.50. After all fields all filled, select the Next or → button to move to the next **Setup** step.

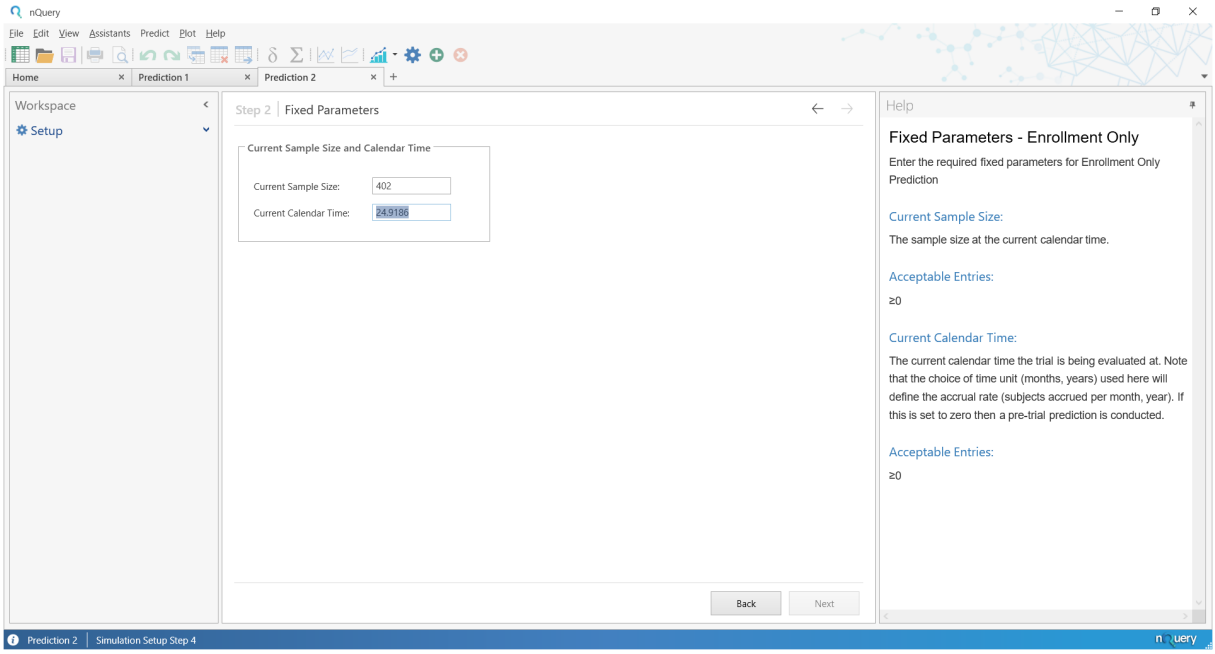


Figure 11.50: Fixed Parameters Setup Step for Enrollment Prediction using Summary Data

The next step is the **Accrual Options** step which specifies the **Target Sample Size, Accrual Model** and future **Accrual Rate**. The **Accrual Options** step, and its defaults, for this demonstration are shown in Figure 11.51.

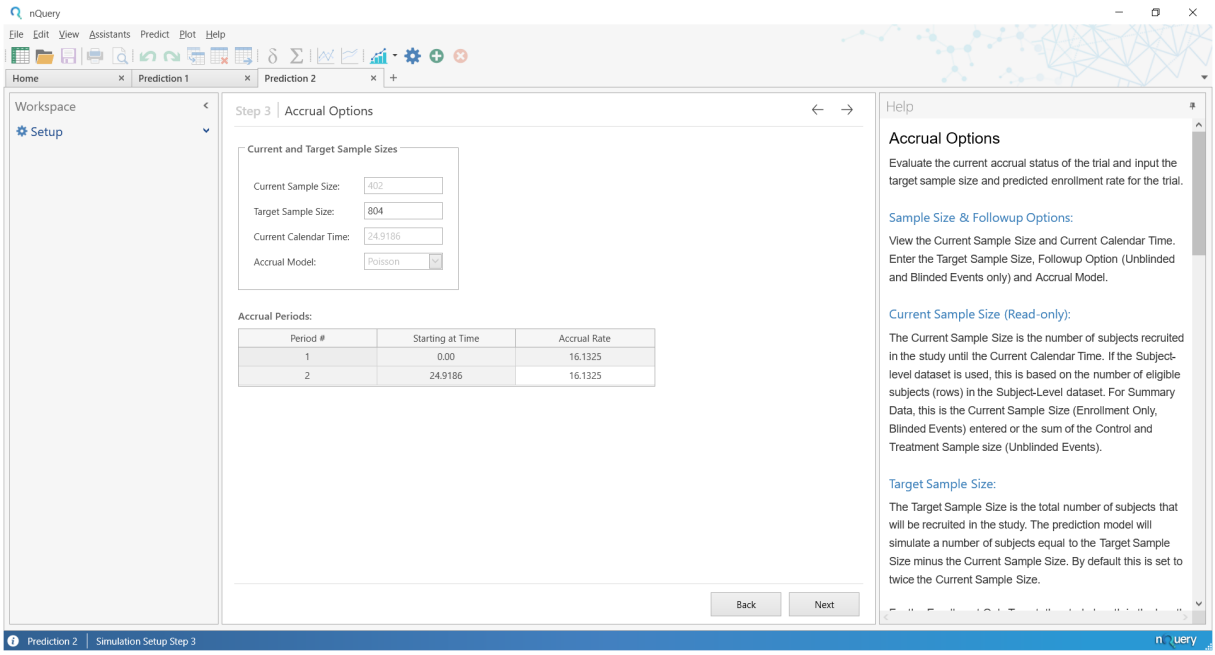


Figure 11.51: Accrual Options Setup Step for Enrollment Prediction using Summary Data

The **Accrual Options** step consists of two main elements: the **Current and Target Sample Sizes** input fields and the **Accrual Periods** table.

The **Current and Target Sample Sizes** input fields provides information on study enrollment based on the **Fixed Parameters** step inputs and allows the user to edit the **Target Sample Size** and select the **Accrual Model**. The following fields are provided in this prediction:

- Current Sample Size (Read-only): Sample Size recruited into a study so far. Taken from Fixed Parameters step
- Target Sample Size (Editable): Total number of subjects that will be recruited in this study. The number of simulated subjects equals the Total Sample Size minus the Current Sample Size.
- Current Time (Read-only): The length of time that has passed since the study started. Taken from Fixed Parameters step
- Accrual Model (Editable): The statistical model that will be used to generate simulated enrollments

In nQuery Predict, the **Target Sample Size** defaults to twice the **Current Sample Size** and the **Accrual Model** defaults to **Poisson.** In this demonstration, the **Current Sample Size** equals 402 and therefore the default **Target Sample Size** is $402\,(2) = 804$.

The **Accrual Periods** table contains information on the **Accrual Rate** up the **Current Time** and allows the user to edit the future **Accrual Rate** used to generate enrollment simulations. The **Accrual Periods** has three columns ,with each row corresponding to a time period, with the columns defined as follows:

- Period #: A numeric ID for the current time period. Increases in increments of one for each subsequent row

- Starting at Time: The starting time for the current time period row. The first row will equal 0 (rate from study start to Current Time) and the second row will equal the Current Time
- Accrual Rate: The accrual rate is the average number of subjects recruited per unit time (months). The accrual rate in the first row will equal the accrual rate up to the Current Time

For the **Poisson Accrual Model**, the **Accrual Periods** table will consist of two time period rows. The first row will correspond to the information provided by the user regarding the study up until the **Current Time.** The second row will correspond to the inputs used to generate future enrollments. By default the **Accrual Rate** in the future second row will equal the **Accrual Rate** from the first row i.e. the accrual rate up until the **Current Time.** For the inputs used in this demonstration, this **Accrual Rate** column values in each row equal 16.13254936 (**Current Sample Size/Current Time**). The user can edit the **Accrual Rate** for generating future enrollments by editing the second cell of the **Accrual Rate** column.

For now, the default values will be used for **Target Sample Size** (804), **Accrual Model** (Poisson) and **Accrual Rate** (16.13254936) as per Figure 11.51. Select the Next or → button to move to the next **Setup** step.

The final step is the **Simulation Controls** step. The **Simulation Controls** step consists of three sections: Simulation Controls, Output for All Trials and Output Options.

Simulation Controls (top-left) sets the **Number of Simulations**, **Refresh Frequency** and **Random Seed**

Output For All Trials (bottom-left) sets the Percentiles desired in the **Percentile Summary** table in the **Simulation Summary** report for key simulation outputs such as study length and sample size.

Output Options (right) selects which additional datasets the user wants in the **Tables** field of the simulation results. Additional datasets will be summary statistics for each simulation and outputs from a set number of individual of simulations.

The **Simulation Controls** step is described in detail in subsubsection 11.2.9.4. In this demonstration, the defaults will be used which corresponds to 1000 simulations with the default percentiles (5%, 25%, 50%, 75%, 95%) and with the "Save summary statistics for every simulation run" **Output Options** table active. The **Simulation Controls** defaults for this demonstration are shown in Figure 11.52. To start the milestone prediction, Select the Run (where Next button was in previous steps) or → button.

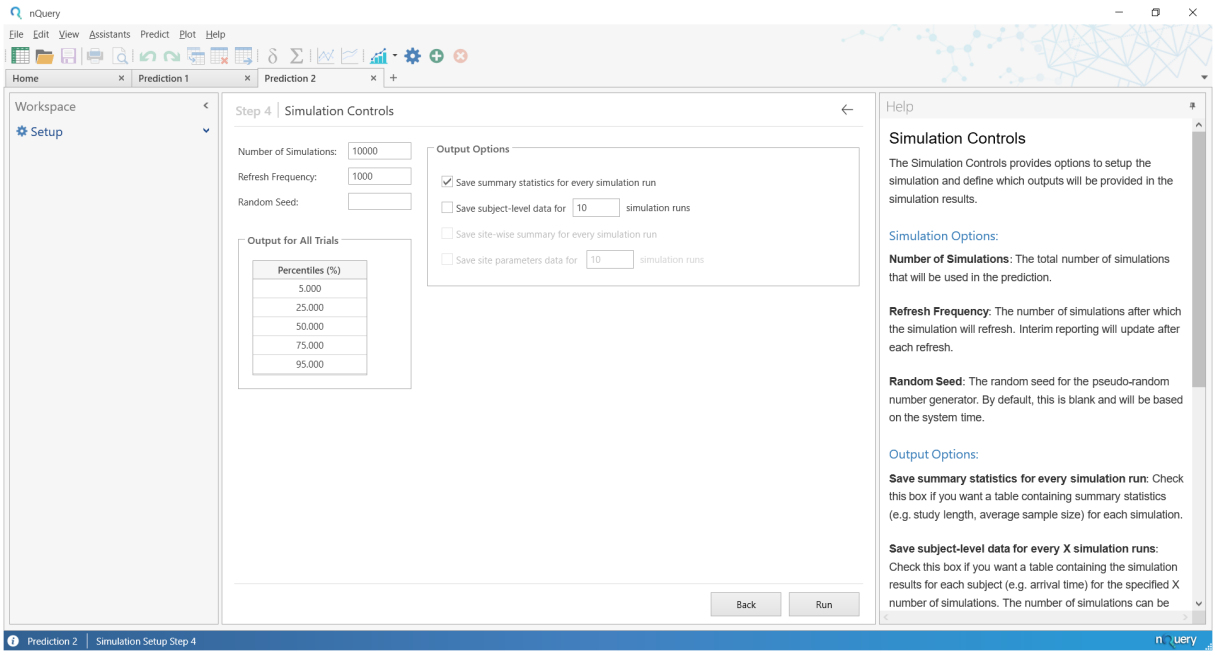


Figure 11.52: Simulation Controls Setup Step for Enrollment Prediction using Summary Data

Results While a milestone prediction is being run, a **Simulation in Progress** window will be displayed. The **Simulation in Progress** window provides updated information on key simulation metrics while the simulation is ongoing. An example for this demonstration is given in Figure 11.53.

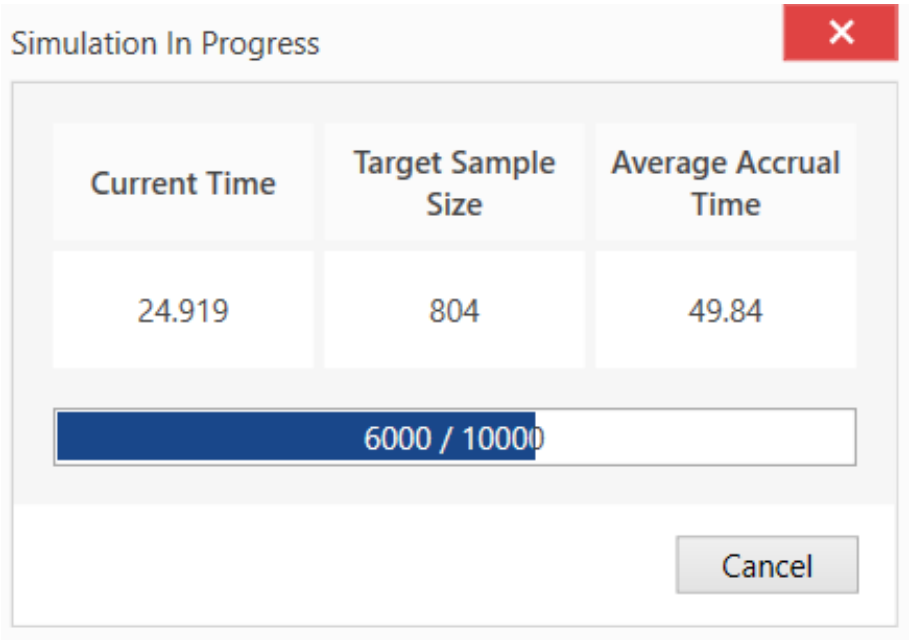


Figure 11.53: Simulation in Progress Window for Enrollment Prediction using Summary Data

Once the simulation is complete, the results will automatically be added to the Workspace Navigation Bar on the left and the first element under the **Plots** header will be displayed.

In this demonstration, the **Enrollment Prediction Plot** will be displayed. This is shown in Figure 11.54.

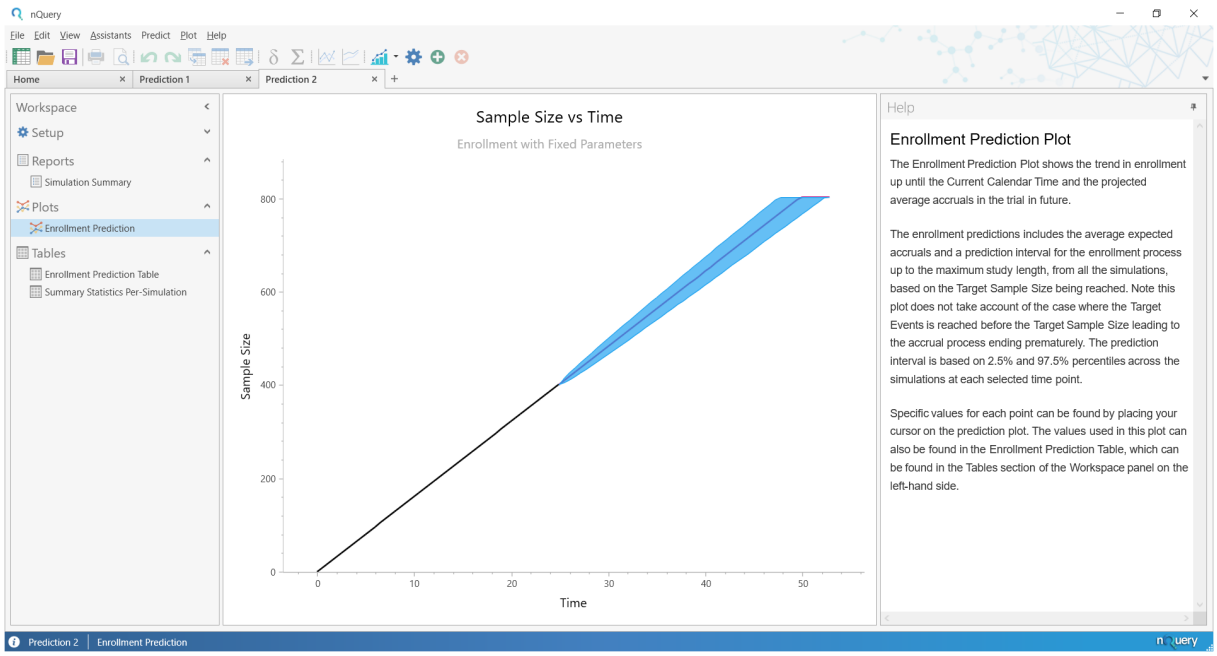


Figure 11.54: Enrollment Prediction Plot for Enrollment Prediction using Summary Data

The results of a nQuery Predict milestone prediction can be divided into three categories: **Reports, Plots** and **Tables**. A high-level summary of the results in nQuery Predict is provided in subsection 11.2.8 with demonstration specific elements highlighted here.

For this demonstration the **Reports** header contains the **Simulation Summary** report, the **Plots** header contains the **Enrollment Prediction** plot and the **Tables** header contains the **Enrollment Prediction Table** and **Summary Statistics Per-Simulation**. To select any result element, select it from the appropriate header in the Workspace Navigation Bar on the left (see subsection 11.2.2 for details on the Navigation Bar).

The **Simulation Summary** provides a tabular summary of the inputs and outputs from the current milestone prediction simulation. The **Simulation Summary** for this demonstration is shown in Figure 11.55.

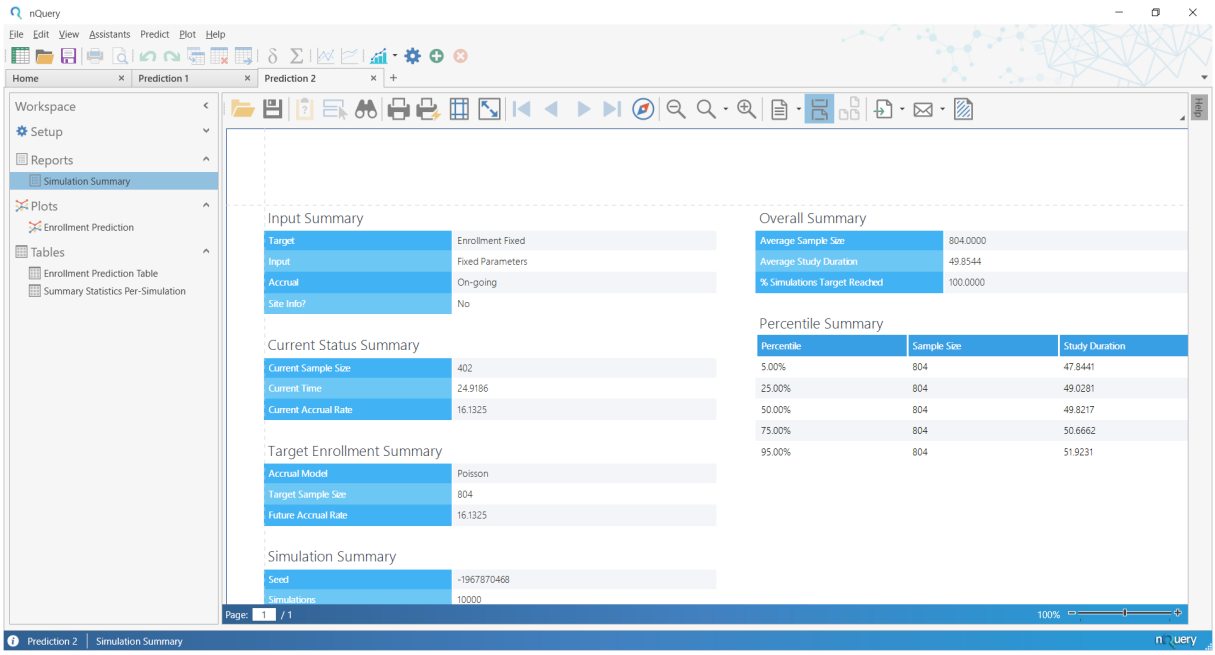


Figure 11.55: Simulation Summary Report for Enrollment Prediction using Summary Data

In the **Simulation Summary** report, the left-hand column provides a summary of inputs used to generate the current simulation and the right-hand column provides the results of the current simulation. In this demonstration, we will skip the left-hand Inputs column and focus on the main results in the right-hand column and the main report options.

The results column (on the right) is shown in Figure 11.56. For this demonstration, the **Overall Summary** shows that the **Target Sample Size** of 804 was reached in every simulation with an **Average Accrual Duration** over all the simulations of 49.8544. The **Percentile Summary** shows that 90% of predictions had a **Accrual Duration** between 47.8441 (5% Percentile) and 51.9231 (95% Percentile), 50% a duration between 49.0281 (25% Percentile) and 50.6662 (75% Percentile) and a median (50% Percentile) duration of 49.8217.

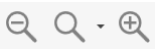
Overall Summary

Average Sample Size	804.0000
Average Study Duration	49.8544
% Simulations Target Reached	100.0000

Percentile Summary

Percentile	Sample Size	Study Duration
5.00%	804	47.8441
25.00%	804	49.0281
50.00%	804	49.8217
75.00%	804	50.6662
95.00%	804	51.9231

Figure 11.56: Simulation Summary Report Results for Enrollment Prediction using Summary Data

To edit the **Simulation Summary report there a** number of buttons available at the top of the report. For full detail on the **Simulation Summary** report and options to edit the report see subsubsection 11.2.8.2. However the Zoom options  , Page Layout and Setup options  and Export option  will be the more commonly used options.

The **Enrollment Prediction** plot provides a visual summary of enrollment simulation from the study start to when the **Target Sample Size** was reached in all simulations. The X-axis is **Time** (relative to study start) and the Y-axis is **Sample Size** (enrolled at Time X-axis value). When the cursor is placed over the **Enrollment Prediction** plot, information on the **Sample Size** enrolled at a given **Time** is shown as per Figure 11.57.

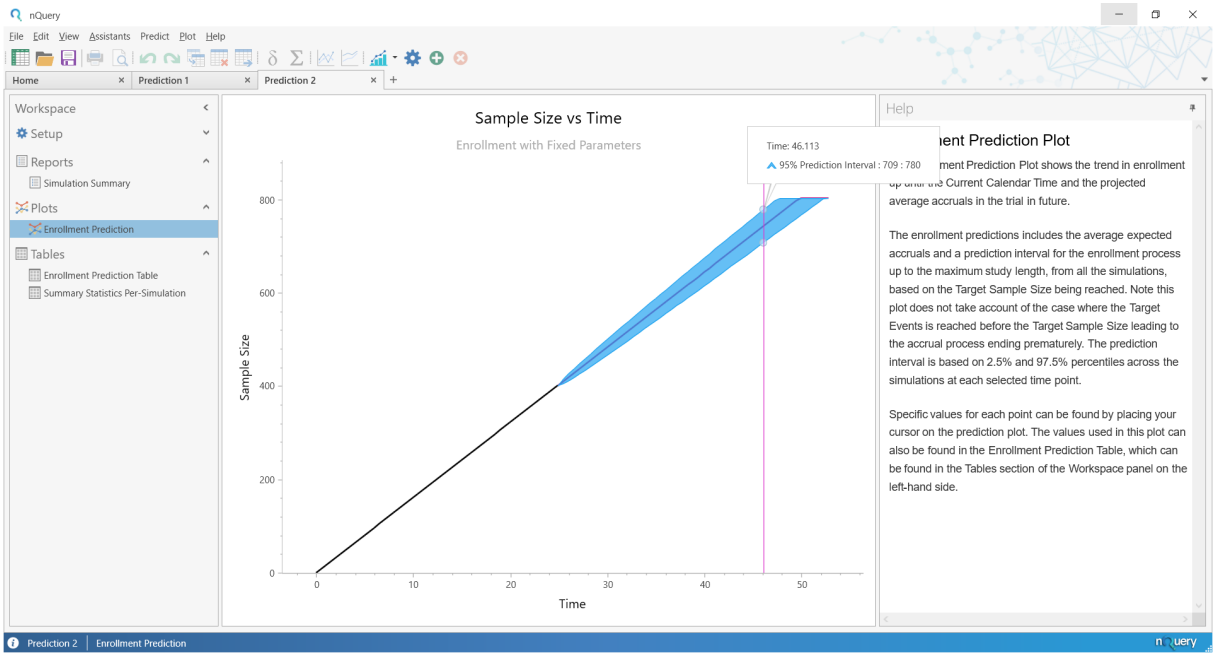


Figure 11.57: Enrollment Prediction Plot for Enrollment Prediction using Summary Data

The **Enrollment Prediction** plot consists of two parts: from Time = 0 to **Current Time** and from **Current Time** to the **Maximum Time**. The first part is a black line which gives the hypothetical accrual pattern based on the **Fixed Parameters** step, in this case a constant linear increase in **Sample Size.**

The second part is a blue conic section with a grey line where the blue conic section plots the 95% prediction interval for the **Sample Size** enrolled at a given **Time** across all simulations and the grey line is the average **Sample Size** enrolled at a given time. The 95% prediction interval indicates the 95% of predictions had a sample size that fell between the lower and upper limit at a given time.

The **Enrollment Prediction Table** is the table used to create the **Enrollment Prediction** plot, which by default consists of ~100 rows (50 pre-simulation and 50 post-simulation). It consists of five columns: **Time, Actual, Predicted Avg. Sample Size, Predicted Median Sample Size, 95% Prediction Interval LL, 95% Prediction Interval UL**. The **Enrollment Prediction Table** for this demonstration at the start of the simulated period is given in Figure 11.58.

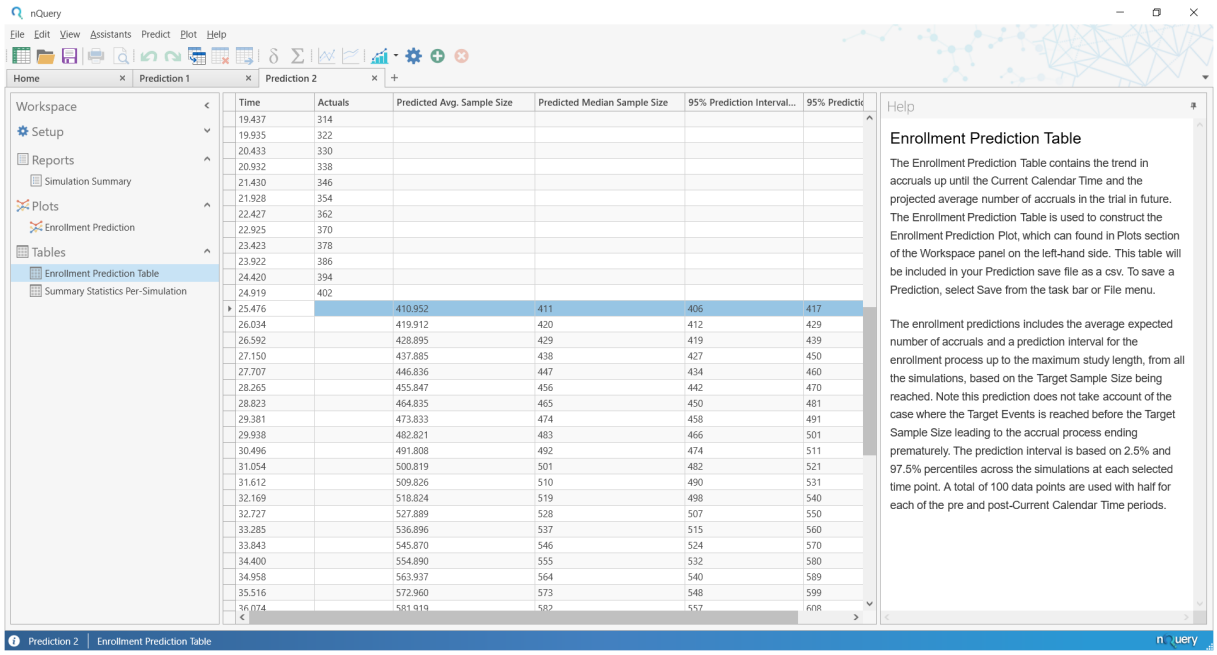


Figure 11.58: Enrollment Prediction Table for Enrollment Prediction using Summary Data

Time is the time value relative to the study start time of zero. **Actual** is the actual sample size achieved at a pre-simulation **Time** row. **Predicted Avg. Sample Size** is the predicted average (mean) sample size enrolled at a post-simulation **Time** row. **Predicted Median Sample Size** is the predicted median sample size enrolled at a post-simulation **Time** row. **95% Prediction Interval LL** is the lower limit for the 95% prediction interval for the sample size enrolled at a post-simulation **Time** row. **95% Prediction Interval UL** is the upper limit for the 95% prediction interval for the sample size enrolled at a post-simulation **Time** row.

The **Summary Statistics Per-Simulation Table** provides the summary statistics achieved for primary outputs in each simulation. For this demonstration this includes the **Simulation ID, Current Time, Current Sample Size, Target Sample Size, Accrual Duration.** The **Summary Statistics Per-Simulation Table** for this demonstration is shown in Figure 11.59.

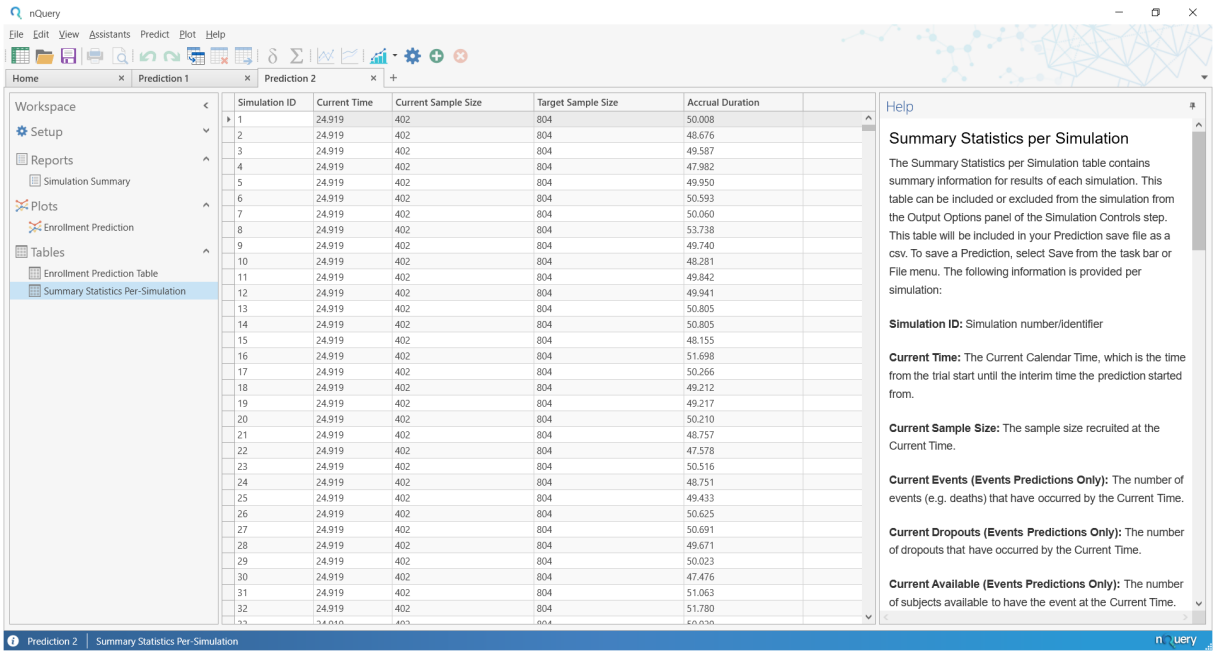


Figure 11.59: Summary Statistics Per-Simulation Table for Enrollment Prediction using Summary Data

Simulation ID is in order of simulation from 1 up to **Number of Simulations**, **Current Time, Current Sample Size** and **Target Sample Size** summarize the user inputs and are constant, and the **Accrual Duration** is the length of time needed to achieve the **Target Sample Size** in that simulation.

Alternative Scenarios The demonstration has focused on the default inputs using **Fixed Parameters** based on **SubjectData.csv** up to this point. However, as noted in the data summary given in subsection 11.2.4, the study from which the example data was simulated had an original sample size target of 460 (402 enrolled in **SubjectData.csv**). In addition, the pre-trial enrollment plan (460 enrolled over 30 months) can be simulated in nQuery Predict.

To explore this additional information, we will investigate two additional scenarios

- Scenario A: **Target Sample Size = 460** using default **Accrual Rate**
- Scenario B: Pre-trial plan of 460 enrolled in 30 months

Scenario A The only changes required compared to the first demonstration is to change the **Target Sample Size** to 460 at the **Accrual Options** step. The simplest way to do this is to select the **Setup** header in the Workspace Navigation Bar on the left and then select the **Accrual Options** drop down option. Then edit the **Target Sample Size** 460 in the **Current and Target Sample Sizes** section in the top-left and select the Next or $\rightarrow$ button. At the next **Simulation Controls** step, we will add a single simulation run by selecting the checkbox beside the **Save subject-level data for (x) simulation runs** and replace the default of 10 runs with 1 runs at the "(x)" spot. An edited down summary of the **Setup** changes is provided in Figure 11.60.

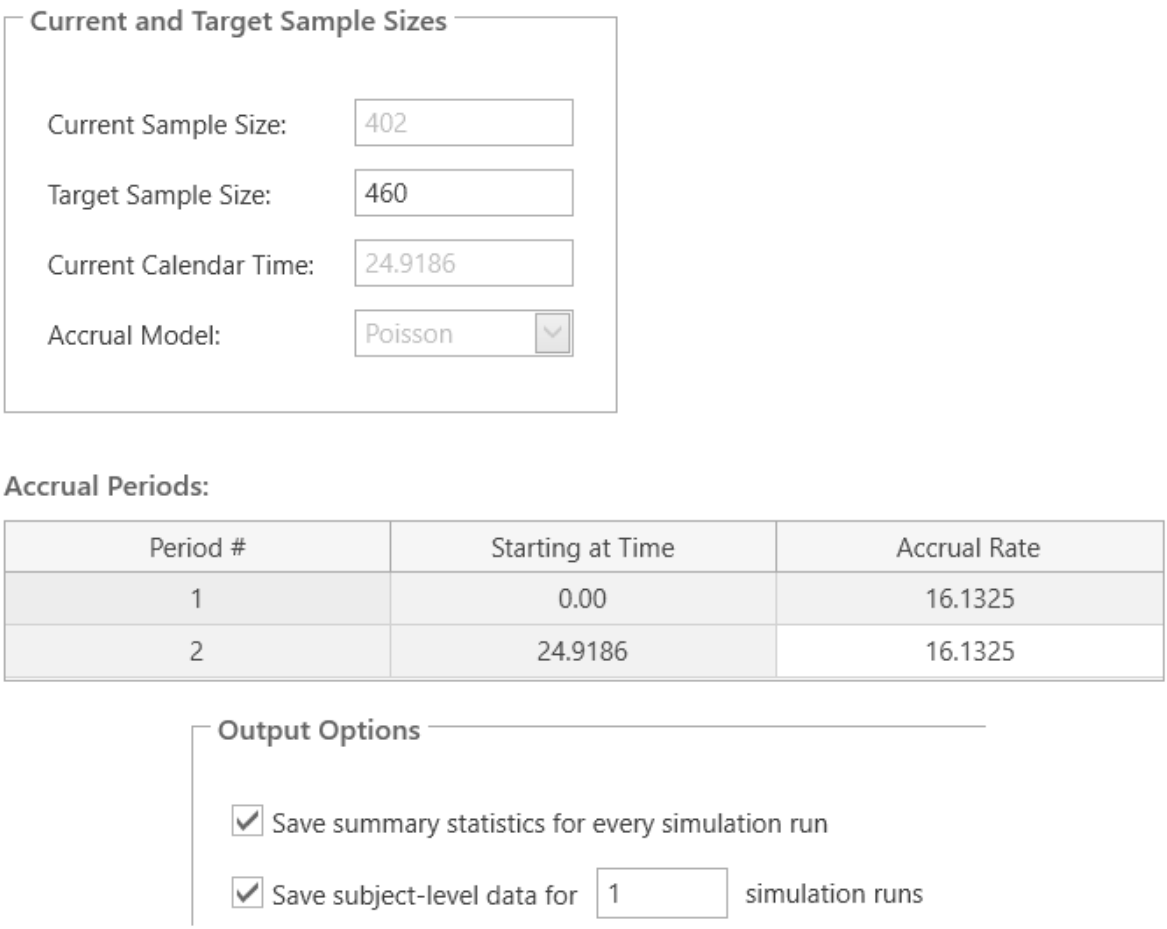


Figure 11.60: Scenario A Setup Changes for Enrollment Prediction using Summary Data

To run the simulation again with the new Scenario A, select the Run/$^{\rightarrow}$ button. The main results of this Scenario A simulation are shown in Figure 11.61.

Overall Summary

Average Sample Size	460.0000
Average Study Duration	28.5144
% Simulations Target Reached	100.0000

Percentile Summary

Percentile	Sample Size	Study Duration
5.00%	460	27.7499
25.00%	460	28.1831
50.00%	460	28.4979
75.00%	460	28.8238
95.00%	460	29.3381

Figure 11.61: Scenario A Results for Enrollment Prediction using Summary Data

For Scenario A, the **Overall Summary** shows that the **Target Sample Size** of 460 was reached in every simulation with an **Average Accrual Duration** over all the simulations of 28.5144. The **Percentile Summary** shows that 90% of predictions had an **Accrual Duration** between 27.7499 and 29.3381, 50% a duration between 28.1831 and 28.8238 and a median duration of 28.4979.

Given that the original target accrual period length was 30 months, this indicates that if the average accrual rate over the entire period up to the current time was being maintained that the accrual period would around 1.5 months less than expected.

The **Per-Simulation Subject-level Data Table** was also generated here and is shown for Scenario A in Figure 11.62 with the first simulated subject (and their **Arrival Time**) in the first simulation (**Simulation ID = 1**) highlighted. Note that the order of the Subject ID is based on **Arrival Time** order. Note that the **Subject ID** field starts at 403 as the hypothetical subjects enrolled before the **Current Time** are not retrospectively simulated.

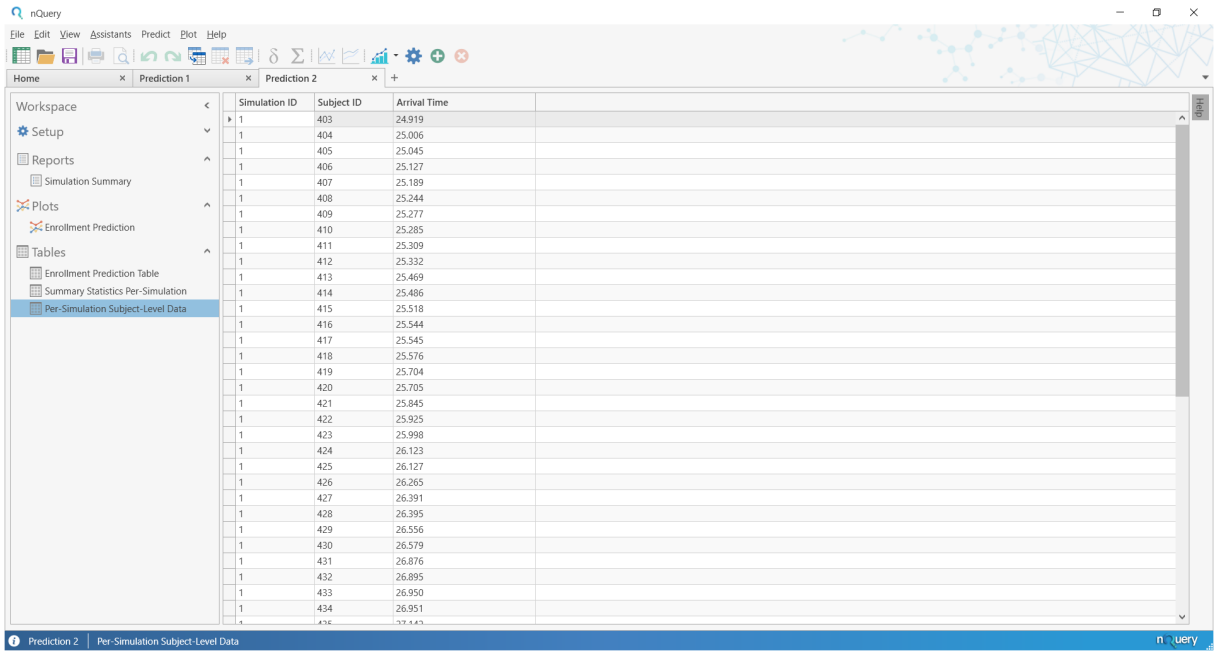


Figure 11.62: Per-Simulation Subject-level Data Table for Summary Data

Scenario B Before the trial began, the planned accrual period length was 30 months with a **Target Sample Size**

To replicate this pre-study plan, create a new empty nQuery Predict Workspace by selecting **Predict > New Prediction >Prediction with Fixed Parameters** from the file menu.

In the **Select the Type of Prediction** step, select **Enrollment Only** from **Target** and **Summary Data** from **Input** as before. Select the Next or → button to continue.

In the **Fixed Parameters** step, set **Current Sample Size** and **Current Time** to zero. Select the Next or → button to continue.

In the **Accrual Options** step, set the **Target Sample Size** to 460 in the **Current and Target Sample Sizes** field. In the **Accrual Periods** table, set the **Period #2 Accrual Rate** equal to 15.3333 (Target Sample Size/Planned Accrual Period Length = 460/30). These **Accrual Options** inputs are shown in Figure 11.63. Select the Next or → button to continue.

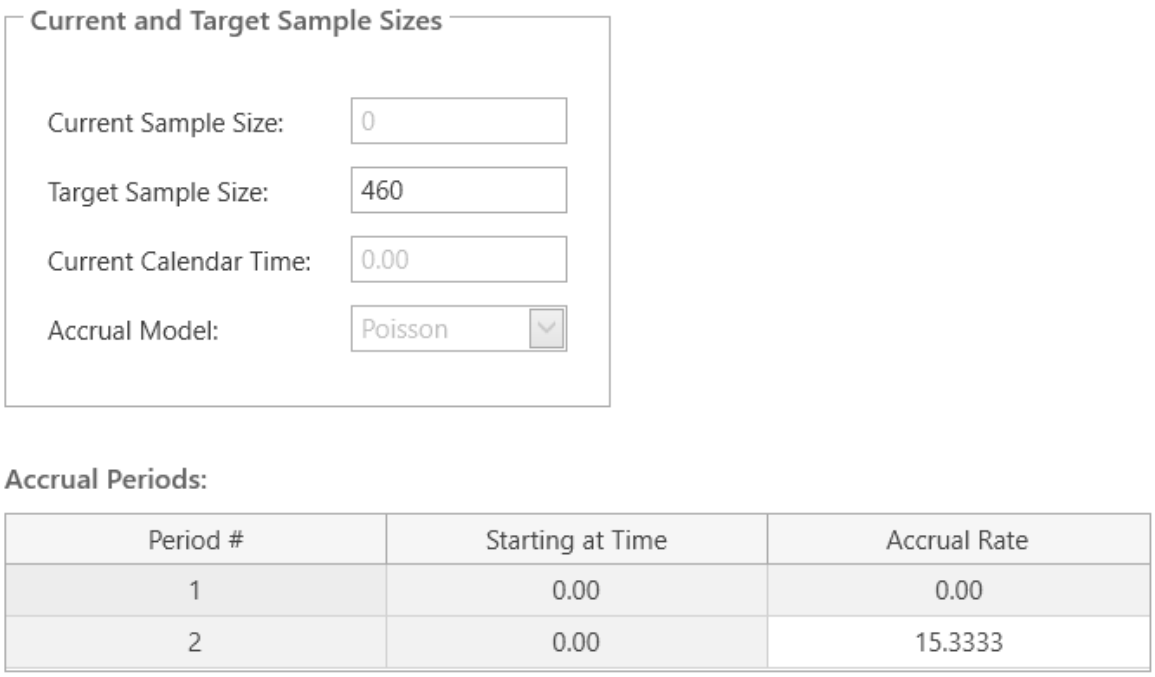
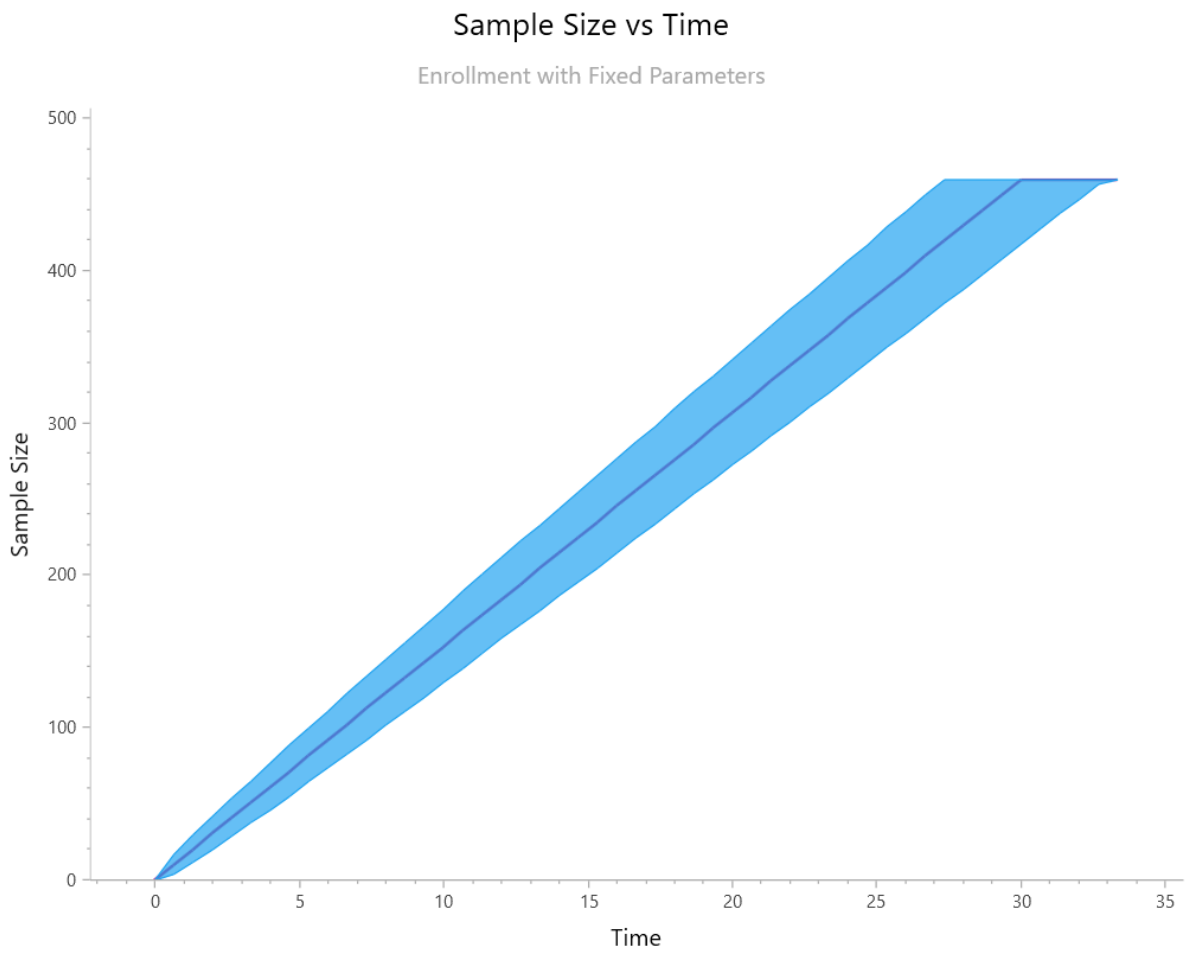


Figure 11.63: Accrual Options Step for Pre-Trial Enrollment Only Scenario B

At the **Simulation Controls** step, select the Run or → button to simulate Scenario B. The results for Scenario B are summarized in Figure 11.64.



Overall Summary

Average Sample Size	460.0000
Average Study Duration	30.0025
% Simulations Target Reached	100.0000

Percentile Summary

Percentile	Sample Size	Study Duration
5.00%	460	27.7095
25.00%	460	29.0589
50.00%	460	29.9660
75.00%	460	30.9309
95.00%	460	32.4217

Figure 11.64: Pre-Trial Enrollment Only Prediction Results

For Scenario B, the **Overall Summary** shows that the **Target Sample Size** of 460 was reached in every simulation with an **Average Accrual Duration** over all the simulations of 30.0025 with the **Percentile Summary** showing that 90% of predictions had an **Accrual Duration** between 27.7095 and 32.4217, 50% a duration between 29.0589 and 30.9309 with a median duration of 29.9660. This gives a baseline understanding of the

likely outcome for the enrollment process pre-trial under a simple **Poisson** process.

11.2.7 Events Prediction Demonstration

Event milestone prediction is the projection of how long a survival (time-to-event) study will take to recruit a **Target Number of Events.** In nQuery Predict, there are two main approaches to event milestone prediction:

- Blinded Events Prediction
- Unblinded Events Prediction

Blinded events prediction is where prediction is made without knowledge of treatment group assignment. Unblinded events prediction is where prediction is made with knowledge of treatment group assignment.

Within each approach, examples will be shown for when **Input** is **Subject Data Only, Subject + Site Data** or **Summary Data** and for when **Enrollment Status** is **Ongoing** or **Complete.** The combinations shown in the examples in each sections will be as follows:

- Blinded Events Prediction with Subject Data Only with Enrollment Ongoing
  - See subsubsection 11.2.7.1
- Unblinded Events Prediction with Subject + Site Data with Enrollment Ongoing
  - See subsubsection 11.2.7.2
- Blinded Events Prediction with Subject Data Only with Enrollment Complete
  - See subsubsection 11.2.7.3
- Unblinded Events Prediction with Summary Data with Enrollment Ongoing
  - See subsubsection 11.2.7.4
- Blinded Events Prediction with Summary Data Pre-Trial
  - See subsubsection 11.2.7.5

These five examples will cover the major changes in workflow depending on the other options selected at the **Select the Type of Prediction** step.

Each of these scenarios will be demonstrated using the SubjectLevel.csv and SiteLevel.csv datasets provided with nQuery Predict. See subsection 11.2.4 for details on these datasets.

Each demonstration will start with demonstration using the default values given by nQuery Predict, followed by additional scenarios taken from the context these datasets were taken from and which use additional options available in nQuery Predict.

The additional options covered in each demo are as follows:

- Blinded Events, Subject Data Only, Enrollment Ongoing: Editing **Target Sample Size**, **Weibull Event Model**, **Fixed Followup** design
- Unblinded Events, Subject + Site Data, Enrollment Ongoing: Editing **Target Sample Size**, removing and "closing" sites, **Weibull Event Model**
- Blinded Events, Subject Data Only, Enrollment Complete: Editing **Target Number of Events**, **Piecewise Exponential Event Model**

- Unblinded Events, Summary Data, Enrollment Ongoing: Editing **Exponential Model Hazard Rates**
- Blinded Events, Summary Data, Pre-Trial: **Unblinded Events Pre-Trial**, editing **Exponential Model Hazard Rates**

For these demonstrations, it is assumed an nQuery Workspace with the two example datasets has been created as per the **Creating a nQuery Predict Workspace** section above (subsection 11.2.1).

11.2.7.1 Blinded Events Prediction with Subject Data Only and Enrollment Ongoing

Setup **Blinded Events** milestone prediction using **Subject-level Data Only** means that the prediction will project the expected length of the accrual period and study needed to achieve a specified **Target Number of Events** using subject-level interim data alone.

In the **Setup** for this prediction, first in the **Select the type of Prediction** step select **Blinded Events** from the **Target** field, **Subject Data Only** from the **Input** field and **Ongoing** from the **Enrollment Status** field.

These selections are shown in Figure 11.65. Select the Next button in the bottom-right or → button in the top-right of the Main Window to move to the next step of the prediction **Setup** stage.

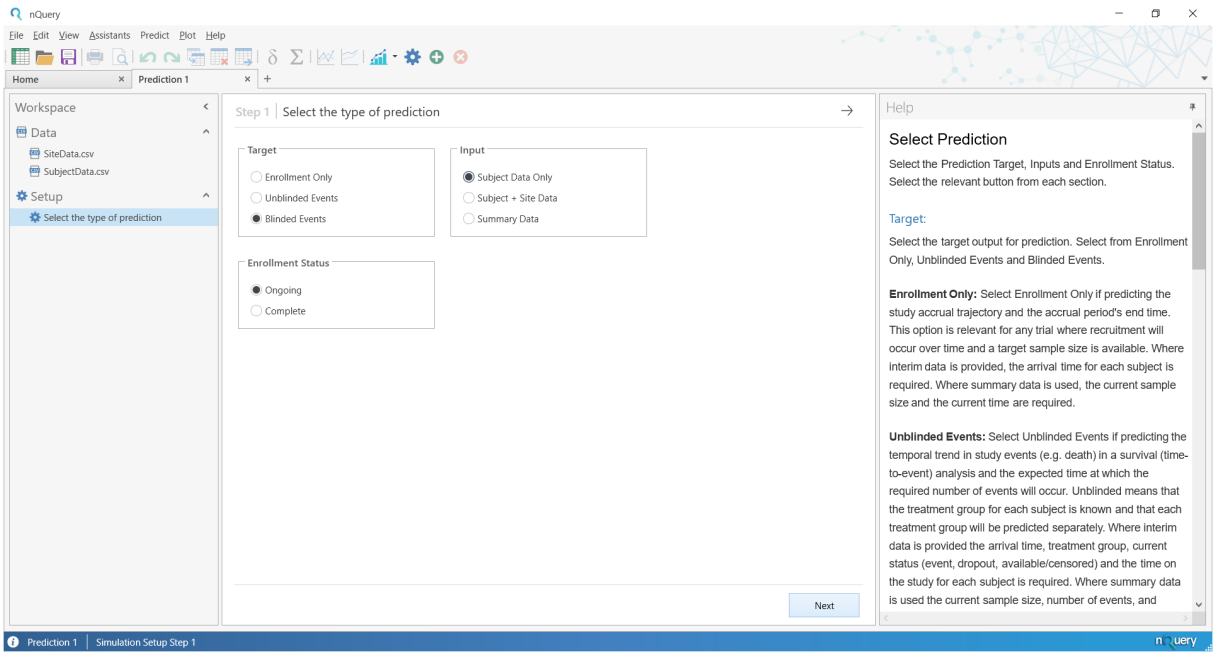


Figure 11.65: Select the Type of Prediction Setup Step for Blinded Events using Subject-level Data

The next step is the **Subject-level Data** step. The **Subject-level Data** step is a Data Field Selection step. The **Subject-level Data** is the dataset where each row corresponds to a specific subject enrolled in the study.

Data Field Selection steps are steps in which the required dataset in the current Workspace is selected and columns in the selected dataset are assigned to the required fields for that prediction problem. The options in a given Data Field Selection field are opened by selecting the button on the right of each field which is found to the right of the field name e.g. **Select Data**. Each field will have specific requirements (e.g. numeric only, two distinct values only) and nQuery Predict only displays options which are consistent with those fields.

In this prediction there are four fields which are as follows:

- Select Dataset: Select the dataset that is the Subject-level Data from the datasets in the current workspace
- Arrival Time: The arrival time column contains the length of time since the study start (Time = 0) until a subject entered the study. Each subject's Arrival Time should be greater than or equal to zero
- Status Indicator: The status (event, dropout, censored/active) for each subject. This Status Indicator column should have a minimum of one alphanumeric unique value and a maximum of three unique values. It has the following sub-fields
  - Event Status: Enter value in Status Indicator column that corresponds to subject having had an event
  - Dropout Status: Enter value in Status Indicator column that corresponds to a subject having dropped out
  - Censored Status: Enter value in Status Indicator column that corresponds to a subject having neither had the event or dropped out
- Time on Study: The length of time after Arrival Time that a subject was in the study. Must be numeric value greater than or equal to zero. The definition depends on Status Indicator (see below)

When the **Status Indicator** field is selected, the **Event Status**, **Dropout Status** and **Censored Status** rows become active. These sub-fields are used to select which values in the **Status Indicator** field correspond to each subject status of interest. The **Censored Status** is also referred to as the **Available Status** as the subject would have been administratively censored if the study ended at the **Current Time** but will be available to have the event of interest in the future during the event milestone prediction.

If the nQuery Predict default values of 1 = Event, -1 = Dropout, 0 = Censored is used in the **Status Indicator** field in the **Subject-level Data** then the **Status** sub-fields will be filled automatically with those assignments. Otherwise, manually enter values by either inputting a value directly into the field or selecting the button on the right of each **Status** sub-field and selecting from the list of unique values in the selected **Status Indicator** field. If there are less than three unique values in the **Status Indicator** field (for example if there have been no dropouts in the **Subject-Level Data** i.e. zero rows with **Dropout Status**) then the user must manually enter the value they would like to have assigned for that **Status** outcome. Note that appropriate defaults will be provided for the rate of previously unused **Status** category in subsequent steps e.g. Dropout Hazard Rate(s) = 0.

The definition of **Time on Study** will depend on the **Status Indicator** for that subject. If the **Status Indicator** is equal to **Event Status** or **Dropout Status**, the **Time on**

Study is the length of time a subject was followed for after their **Arrival Time** before they had an event/dropped out. If the **Status Indicator** is equal to **Censored Status**, the **Time on Study** is the length of time a subject was followed for after their **Arrival Time** until the **Current Time.**

For this prediction, in the **Select Dataset** field select **SubjectData.csv**. Then in the **Arrival Time** field select **Arrival**, in the **Status Indicator** field select **Current** (assign 1 to **Event Status**, -1 to **Dropout Status**, 0 to **Censored Status**) and in the **Time on Study** field select **Followup.** These selections are shown in Figure 11.66. Select the Next or → button to move to the next **Setup** step.

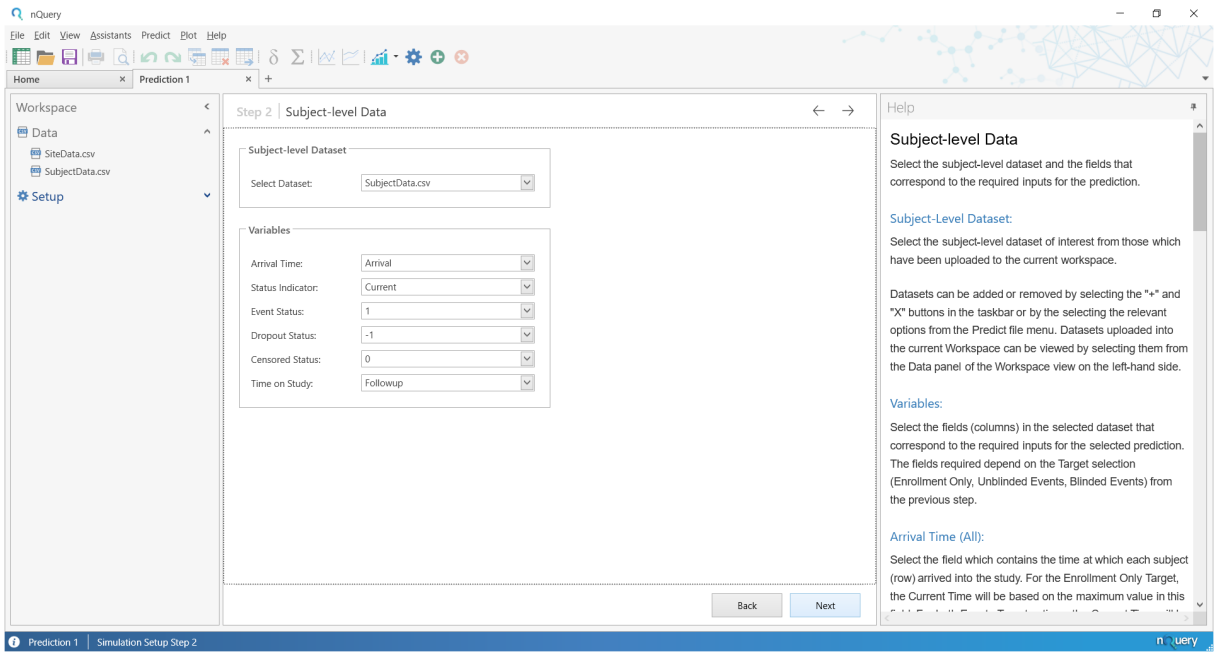


Figure 11.66: Subject-level Data Setup Step for Blinded Events Prediction using Subject-level Data

The next step is the **Accrual Options** step which specifies the **Target Sample Size, Accrual Model, Followup Option** and future **Accrual Rate**. The **Accrual Options** step, and its defaults, for this demonstration are shown in Figure 11.67.

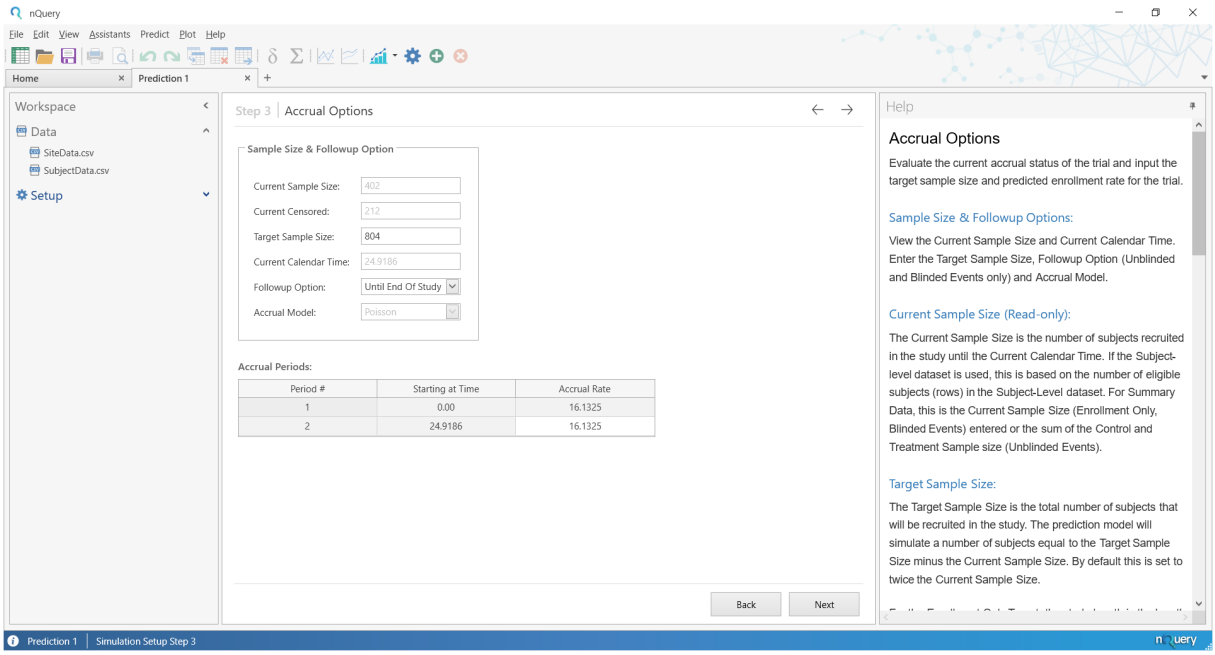


Figure 11.67: Accrual Options Setup Step for Blinded Events Prediction using Subject-level Data

The **Accrual Options** step consists of two main elements: the **Sample Size & Followup Option** input fields and the **Accrual Periods** table.

The **Sample Size & Followup Option** input fields provides information on enrollment process, censored status and current time based on the subject-level data and allows the user to edit the **Target Sample Size** and select the **Followup Option** and **Accrual Model**. The following fields are provided in this prediction:

- Current Sample Size (Read-only): Sample Size recruited into a study so far. Equals the number of rows in the Subject-level Data
- Current Censored (Read-only): The number of subjects who have not had the event or dropped out at the current time. Equals the number of subjects with the Censored Status in the Status Indicator field
- Target Sample Size (Editable): Total number of subjects that will be recruited in this study. The number of simulated subjects equals the Total Sample Size minus the Current Sample Size
- Current Time (Read-only): The length of time that has passed since the study started. Equals the maximum of the sum of the Arrival Time + Time on Study values for each subject
- Followup Option: Specifies whether subjects who do not have the event/dropout will be administratively censored at the end of the study or after a fixed follow up period
  - Followup Time (Followup Option = For Fixed Period only): Length of time a subject is followed for until administratively censored if they do not have the event/dropout
- Accrual Model (Editable): The statistical model that will be used to generate simulated enrollments

In nQuery Predict, the **Target Sample Size** defaults to twice the **Current Sample Size**, **Followup Option** is set to **Until End of Study** and the **Accrual Model** defaults to **Poisson.** In this demonstration, the **Current Sample Size** equals 402 and therefore the default **Target Sample Size** is $402\,(2) = 804$.

If **Followup Option** is set to **Until End of Study** then subjects who do not have the event or dropout will be followed until the end of the study when the **Target Number of Events** is reached, at which point they will be administratively right-censored.

If **Followup Option** is set to **For Fixed Period** then subjects who do not have the event or dropout will be followed until they have a **Time on Study** equal to the value specified in the **Followup Time** field, which appears automatically below the **Followup Option** field when **For Fixed Period** is selected, at which point a subject will be administratively right-censored. Note that for subjects whose **Followup Time** is less than length of the time a subject was on study before the study ended when the **Target Number of Events** was reached, they will be administratively censored at the study end rather than after their **Followup Time**.

The **Accrual Periods** table contains information on the **Accrual Rate** up the **Current Time** and allows the user to edit the future **Accrual Rate** used to generate enrollment simulations. The **Accrual Periods** has three columns ,with each row corresponding to a time period, with the columns defined as follows:

- Period #: A numeric ID for the current time period. Increases in increments of one for each subsequent row
- Starting at Time: The starting time for the current time period row. The first row will equal 0 (rate from study start to Current Time) and the second row will equal the Current Time
- Accrual Rate: The accrual rate is the average number of subjects recruited per unit time (months). The accrual rate in the first row will equal the accrual rate up to the Current Time

For the **Poisson Accrual Model**, the **Accrual Periods** table will consist of two time period rows. The first row will correspond to the information provided by the user regarding the study up until the **Current Time.** The second row will correspond to the inputs used to generate future enrollments. By default the **Accrual Rate** in the future second row will equal the **Accrual Rate** from the first row i.e. the accrual rate up until the **Current Time.** For the inputs used in this demonstration, this **Accrual Rate** column values in each row equal 16.13254936. The user can edit the **Accrual Rate** for generating future enrollments by editing the second cell of the **Accrual Rate** column.

For now, the default values will be used for **Target Sample Size** (804), **Followup Option** (Until End of Study) **Accrual Model** (Poisson) and **Accrual Rate** (16.13254936) as per Figure 11.67. Select the Next or $\rightarrow$ button to move to the next **Setup** step.

The next step is the **Event and Dropout Information** step which specifies the **Target Number of Events,** event model (and associated statistical parameters) and dropout model (and associated statistical parameters). The **Event and Dropout Information** step on the default **Events Model** tab is shown in Figure 11.68.

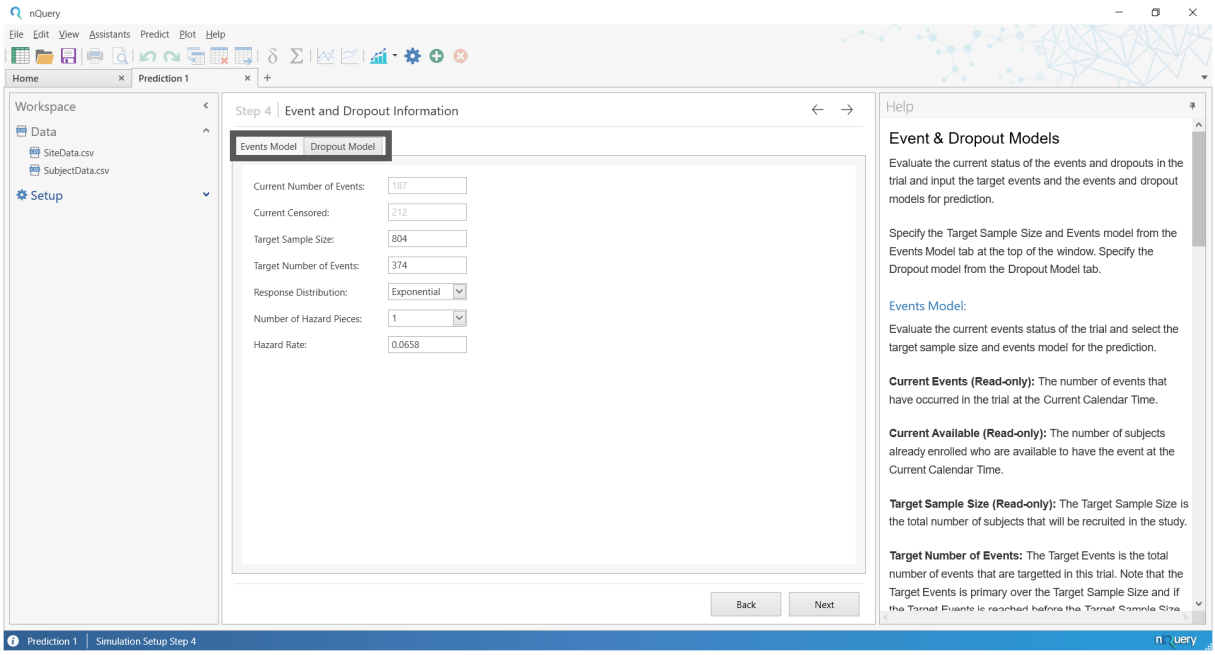


Figure 11.68: Event and Dropout Information Setup Step for Blinded Events Prediction using Subject-level Data

The **Event and Dropout Information** step consists of two tabs: the **Events Model** tab and the **Dropout Model** tab. These tabs have been highlighted in Figure 11.68 and are opened by selecting the required tab name at the top of the main window, below the step title. For **Blinded Events**, it is assumed that survival and dropout times will be simulated using a single "global" process which is specified by the user.

The **Events Model** tab provides fields which provide information on the current number of subject who have had an event, could have an event going forward and allows the input of the **Target Number of Events, Target Sample Size, Response Distribution** for the events model and additional parameters needed for that specific model. The following fields are provided in this prediction:

- Current Events (Read-only): The number of subjects who had the event of interest at the current time. Equals the number of subjects with the Event Status in the Status Indicator field
- Current Censored (Read-only): The number of subjects who have not had the event or dropped out at the current time. Equals the number of subjects with the Censored Status in the Status Indicator field
- Target Sample Size (Editable): Total number of subjects that will be recruited in this study. The number of simulated subjects equals the Total Sample Size minus the Current Sample Size
- Target Number of Events (Editable): The required number of subjects needed to have the event of interest for the study to end
- Response Distribution: The statistical model that will be used to generate survival times for subjects available to have the event
- Number of Hazard Pieces (Response Distribution = Exponential only): Number of hazard pieces used to specify the piecewise exponential model. Select value between

1 and 10

- Hazard Rate (Response Distribution = Exponential only, Number of Hazard Pieces =1, Editable): The exponential hazard rate for the constant exponential survival model specified above

In nQuery Predict, the **Target Sample Size** at this step is inherited from the prior **Accrual Options** step, the **Target Number of Events** defaults to twice the **Current Events**, the default **response Distribution** is **Exponential** with the **Number of Hazard Pieces** set to 1 and the default **Hazard Rate** set the expected event rate from the provided information (see subsubsection 11.1.2.2 for details on the survival distributions used in nQuery Predict, see section 3.5 for details on how to calculate a exponential **Hazard Rate** using a median survival or survival probability)**.**

In this demonstration, the **Current Number of Events** is 187 and therefore the default **Target Number of Events** is $187\,(2) = 374$ giving an estimated exponential **Hazard Rate** of 0.0658. Note that if the **Target Number of Events** is reached before the **Target Sample Size** has been enrolled then the it is assumed the enrollment process will stop early and the total sample size achieved may be less than the **Target Sample Size** specified.

In nQuery, there are effectively three primary survival distributions that survival times can be generated from:

- Constant Exponential (Response Distribution = Exponential, Number of Hazard Pieces =1): Input Hazard Rate
- Piecewise Exponential (Response Distribution = Exponential, Number of Hazard Pieces > 1): Input table of Starting at Time and Hazard Rate columns
- Weibull (Response Distribution = Weibull): Input Scale Parameter and Shape Parameter

Details on how survival times are generated from each of these distributions is provided in subsubsection 11.1.2.2, alongside how the default values provided in nQuery Predict are estimated from the provided information. The change in the **Events Model** tab for each of these choices is shown in Figure 11.69.

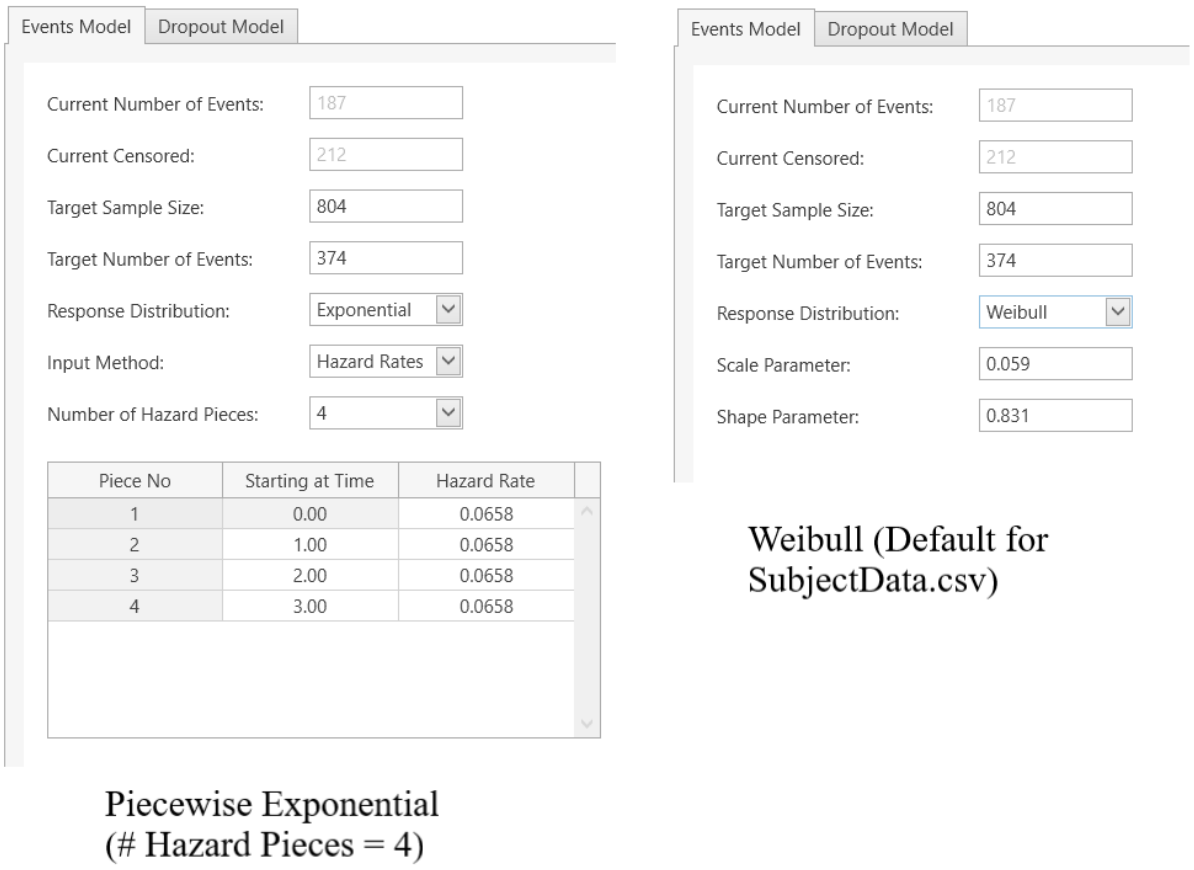


Figure 11.69: Piecewise Exponential (4 Pieces) and Weibull Defaults for Subject-Data.csv

The piecewise exponential table will have a number of rows equal to **Number of Hazard Pieces.** The **Piece No** column indicates the hazard piece number of a row. The **Starting at Time** column sets the start time for when the **Hazard Rate** value in that row takes effect. The **Hazard Rate** column sets the exponential hazard rate in effect from the start time of the current hazard piece to the start time in the next row (see section 3.5 for details on how to calculate a exponential **Hazard Rate** using a median survival or survival probability and the Compute Effect Size side table for STT3 may also be useful). By default the piecewise exponential assumes a constant exponential model **Hazard Rate** (same **Hazard Rate** as for the **Number of Hazard Pieces** = 1 case) with **Starting at Time** being values increasing by 1 up to the final row.

The Weibull distribution has two parameters: the Weibull **Scale Parameter** and Weibull **Shape Parameter**. The default for these is found by fitting the survival data from the subject-level data (see subsubsection 11.1.2.2 for details).

The **Dropout Model** tab is opened by selecting the **Dropout Model** tab name at the top of the main window. For this demonstration, the **Dropout Model** tab is shown in Figure 11.70.

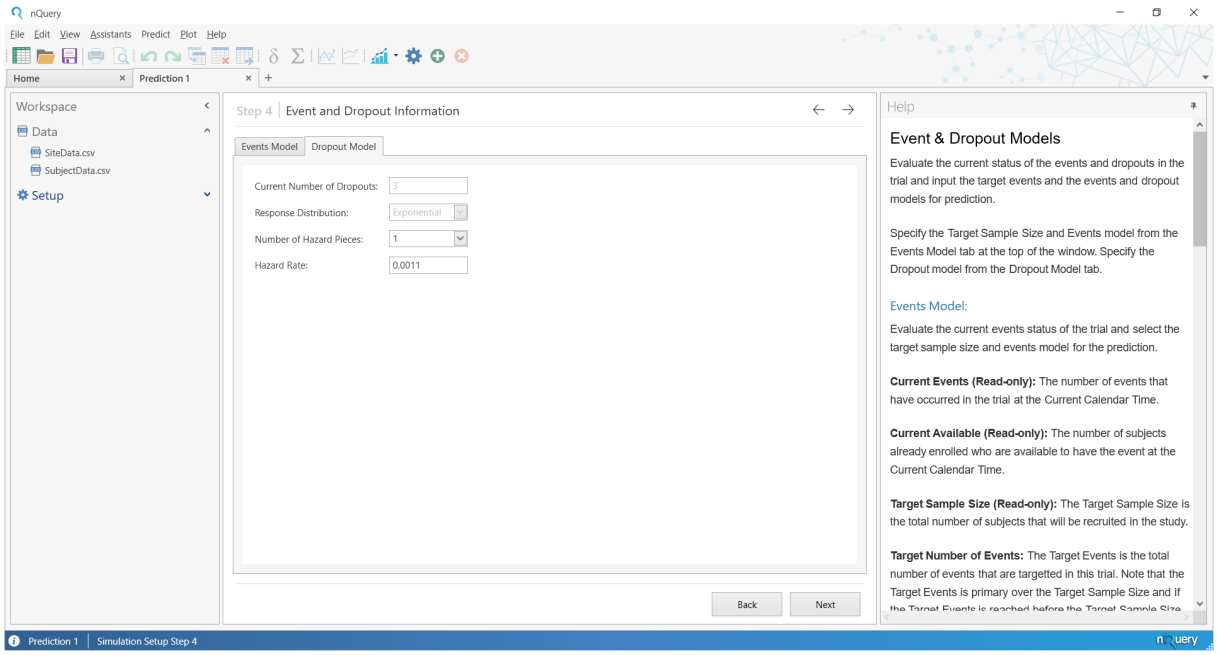


Figure 11.70: Dropout Model tab for Blinded Events with Subject-level Data

For **Dropout Model**, the **Current Number of Dropouts** (number of subjects who have dropped out up to the **Current Time**), **Response Distribution** and **Number of Hazard Pieces** are available. For dropout, the only **Response Distribution** option is **Exponential**. The inputs and defaults for dropout **Exponential Response Distribution**, for both the case where **Hazard Pieces = 1** (Constant Exponential) or **Hazard Pieces > 1** (Piecewise Exponential), are the same as from the **Events Model** described above and therefore will not be replicated here. In this demonstration, the constant exponential **Hazard Rate** for dropout calculated from the information provided equals 0.0011.

In this demonstration the default for all inputs (**Target Sample Size = 804, Target Number of Events = 374, Events Model Exponential Response Distribution (1 Hazard Piece) Hazard Rate = 0.0658, Dropout Model Exponential Response Distribution (1 Hazard Piece) Hazard Rate = 0.0011**) are used. Select the Next or → button to move to the next **Setup** step.

The final step is the **Simulation Controls** step. The **Simulation Controls** step consists of three sections: Simulation Controls, Output for All Trials and Output Options.

Simulation Controls (top-left) sets the **Number of Simulations**, **Refresh Frequency** and **Random Seed**

Output For All Trials (bottom-left) sets the Percentiles desired in the **Percentile Summary** table in the **Simulation Summary** report for key simulation outputs such as study length and sample size.

Output Options (right) selects which additional datasets the user wants in the **Tables** field of the simulation results. Additional datasets will be summary statistics for each simulation and outputs from a set number of individual of simulations.

The **Simulation Controls** step is described in detail in subsubsection 11.2.9.4. In this demonstration, the defaults will be used which corresponds to 1000 simulations with the

default percentiles (5%, 25%, 50%, 75%, 95%) and with the "Save summary statistics for every simulation run" **Output Options** table active. The **Simulation Controls** defaults for this demonstration are shown in Figure 11.71. To start the milestone prediction, Select the Run (where Next button was in previous steps) or → button.

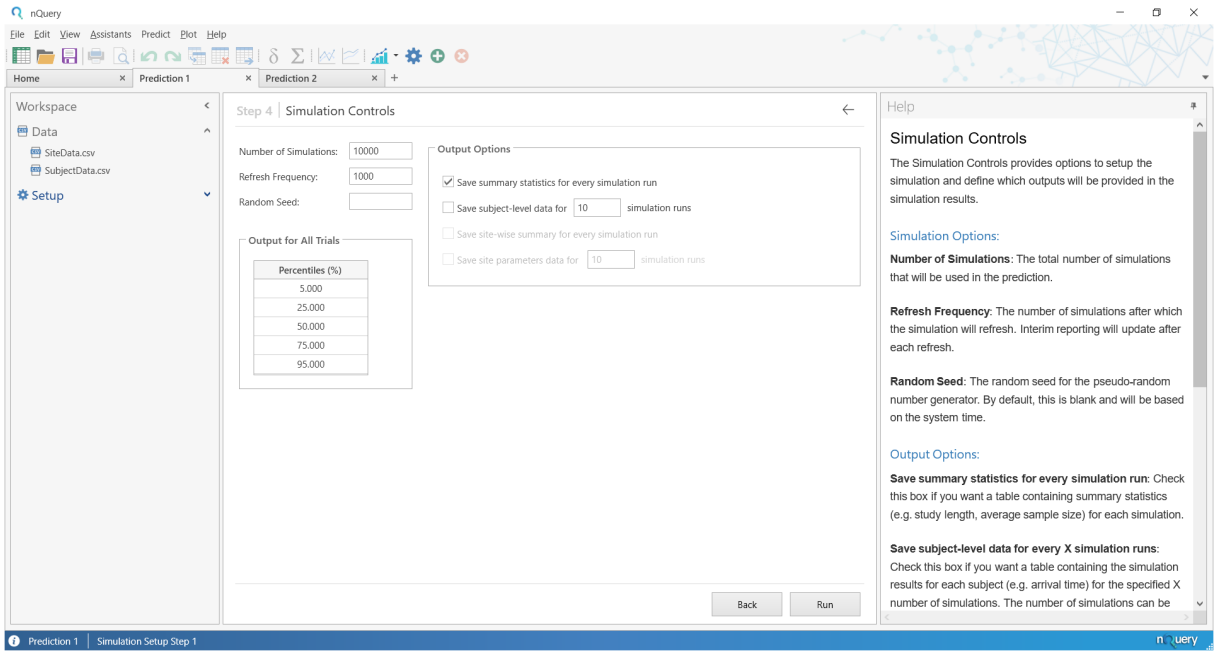


Figure 11.71: Simulation Controls Setup Step for Blinded Events Prediction using Subject-level Data

Results While a milestone prediction is being run, a **Simulation in Progress** window will be displayed. The **Simulation in Progress** window provides updated information on key simulation metrics while the simulation is ongoing. An example for this demonstration is given in Figure 11.72.

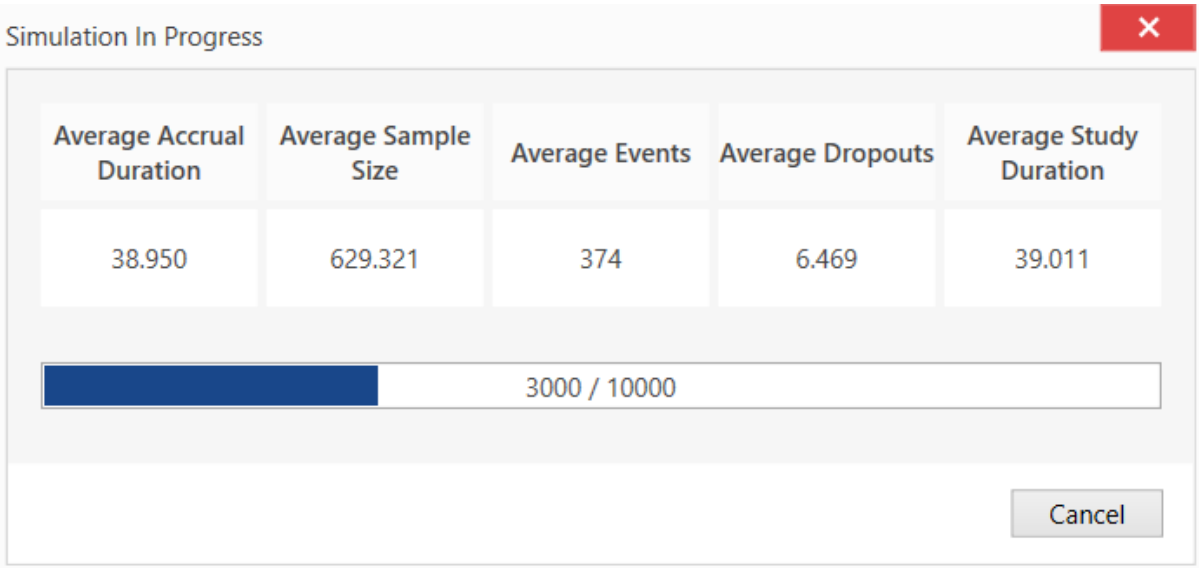


Figure 11.72: Simulation in Progress Window for Blinded Events Prediction using Subject-level Data

Once the simulation is complete, the results will automatically be added to the Workspace Navigation Bar on the left and the first element under the **Plots** header will be displayed. In this demonstration, the **Enrollment Prediction Plot** will be displayed. This is shown in Figure 11.73.

Figure 11.73: Enrollment Prediction Plot for Blinded Events Prediction using Subject-level Data

The results of a nQuery Predict milestone prediction can be divided into three categories: **Reports, Plots** and **Tables**. A high-level summary of the results in nQuery Predict is provided in subsection 11.2.8 with demonstration specific elements highlighted here.

For this demonstration the **Reports** header contains the **Simulation Summary** report, the **Plots** header contains the **Enrollment Prediction, Events Prediction** and **Dropout Prediction** plot and the **Tables** header contains the **Enrollment Prediction Table, Events Prediction Table, Dropout Prediction Table** and **Summary Statistics Per-Simulation**. To select any result element, select it from the appropriate header in the Workspace Navigation Bar on the left (see subsection 11.2.2 for details on the Navigation Bar).

The **Simulation Summary** provides a tabular summary of the inputs and outputs from the current milestone prediction simulation. The **Simulation Summary** for this demonstration is shown in Figure 11.74.

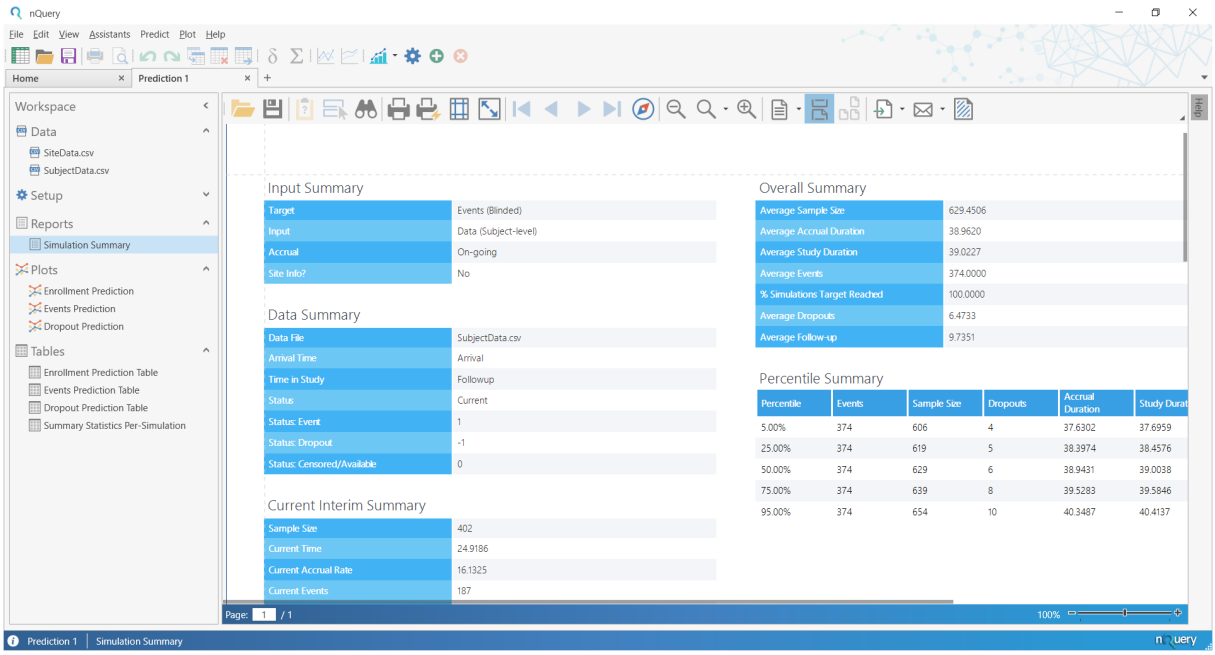


Figure 11.74: Simulation Summary Report for Blinded Events Prediction using Subject-level Data

In the **Simulation Summary** report, the left-hand column provides a summary of inputs used to generate the current simulation and the right-hand column provides the results of the current simulation. In this demonstration, we will skip the left-hand Inputs column and focus on the main results in the right-hand column and the main report options.

The results column (on the right) is shown in Figure 11.75. For this demonstration, the **Overall Summary** shows that the **Target Number of Events** of 374 was reached in every simulation with an **Average Study Duration** over all the simulations of 39.0227. The **Percentile Summary** shows that 90% of predictions had a **Study Duration** between 37.6959 (5% Percentile) and 40.4137 (95% Percentile), 50% a duration between 38.4576 (25% Percentile) and 39.5846 (75% Percentile) and a median (50% Percentile) duration of 39.0038. The **Average Dropouts** was 6.4733 (Percentiles: 4, 5, 6, 8, 10) and subjects had an **Average Followup** (until either event/dropout or until study end for censored subjects) of 9.7351.

The accrual process in this study ended early for all simulations with an **Average Sample Size** of 629.4506 (Percentiles: 606, 619, 629, 639, 654) enrolled before the **Target Number of Events** of 804 was reached. This meant the **Average Accrual Duration** of 38.9620 (Percentiles: 37.6302, 38.3974, 38.9431, 39.5283, 40.3487) is effectively equal to the **Average Study Duration** of 39.0227 with the accrual duration effectively the time of the last enrollment before study end.

Overall Summary

Average Sample Size	629.4506
Average Accrual Duration	38.9620
Average Study Duration	39.0227
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	6.4733
Average Follow-up	9.7351

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	374	606	4	37.6302	37.6959
25.00%	374	619	5	38.3974	38.4576
50.00%	374	629	6	38.9431	39.0038
75.00%	374	639	8	39.5283	39.5846
95.00%	374	654	10	40.3487	40.4137

Figure 11.75: Simulation Summary Report Results for Blinded Events Prediction

To edit the **Simulation Summary** report there a number of buttons available at the top of the report. For full detail on the **Simulation Summary** report and options to edit the report see subsubsection 11.2.8.2. However the Zoom options  , Page Layout and Setup options  and Export option  will be the more commonly used options.

The **Enrollment Prediction** plot provides a visual summary of enrollment simulation from the study start to when the **Target Sample Size** was reached in all simulations. The X-axis is **Time** (relative to study start) and the Y-axis is **Sample Size** (enrolled at Time X-axis value). When the cursor is placed over the **Enrollment Prediction** plot, information on the **Sample Size** enrolled at a given **Time** is shown as per Figure 11.76.

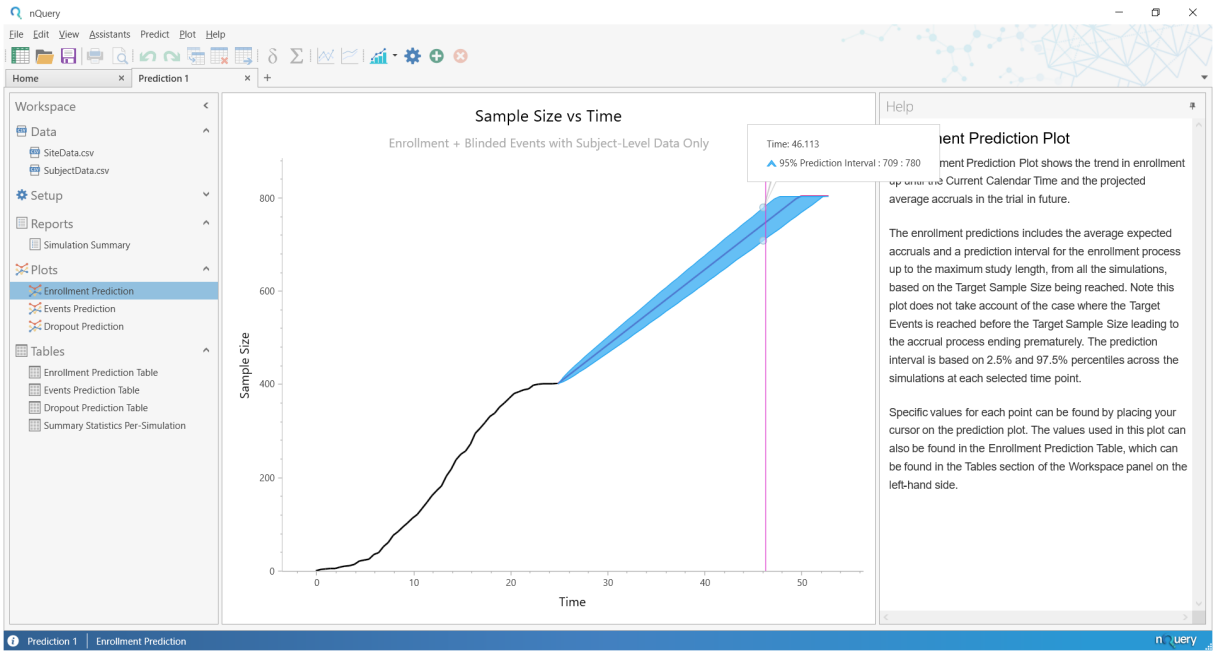


Figure 11.76: Enrollment Prediction Plot for Blinded Events Prediction using Subject-level Data

The **Enrollment Prediction** plot consists of two parts: from Time = 0 to **Current Time** and from **Current Time** to the **Maximum Time**. The first part is a black line which plots the accrual pattern from the user inputs provided. The second part is a blue conic section with a grey line where the blue conic section plots the 95% prediction interval for the **Sample Size** enrolled at a given **Time** across all simulations and the grey line is the average **Sample Size** enrolled at a given time. The 95% prediction interval indicates the 95% of predictions had a sample size that fell between the lower and upper limit at a given time.

Note that the **Enrollment Prediction** plot will show the projection for **Target Sample Size** and its associated **Accrual Duration** and therefore will usually have a different **Time** scale than the **Event Prediction** and **Dropout Prediction** plots which will be associated with the **Study Duration.** Note the **Enrollment Prediction** plot ignores the case where **Accrual Duration** is cut short due to the **Target Number of Events** being reached before the enrollment process is complete.

The **Events Prediction** plot is very similar to the **Enrollment Prediction** plot where the first part is a black line which plots the events pattern from the user inputs provided and the second part is a yellow conic section with a grey line where the yellow conic section plots the 95% prediction interval for the **Number of Events** that have occurred at a given **Time** across all simulations and the grey line is the average **Number of Events** at a given time. The 95% prediction interval indicates the 95% of predictions had a number of events that fell between the lower and upper limit at a given time. The **Events Prediction** plot for this demonstration is shown in Figure 11.77.

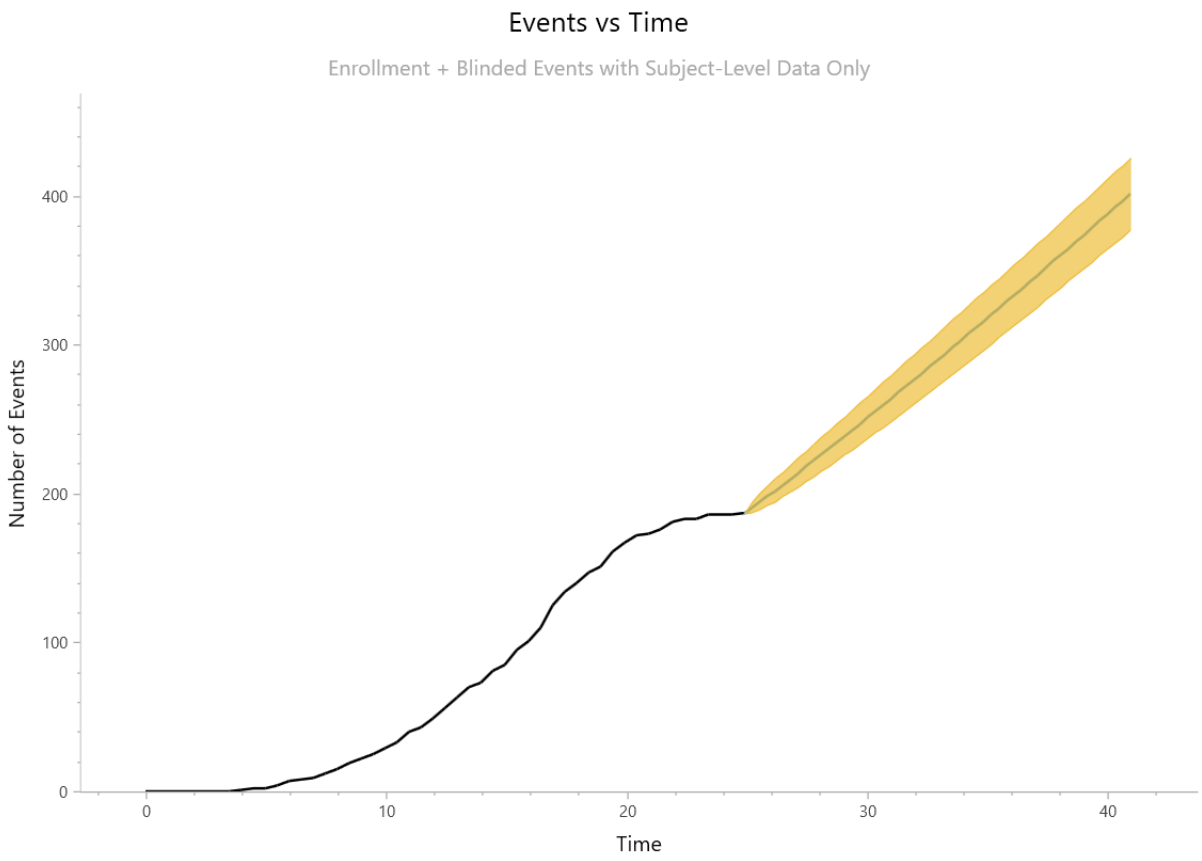


Figure 11.77: Events Prediction Plot for Blinded Events Prediction using Subject-level Data

It is important the note that these event times are when these events occurred relative to the start of the study, not how long they happened after follow up i.e. this is not a Kaplan-Meier type plot!

The **Dropout Prediction** plot works effectively the same as the **Events Prediction** plot except for the dropout process. The **Dropout Prediction** plot for this demonstration is shown in Figure 11.78.

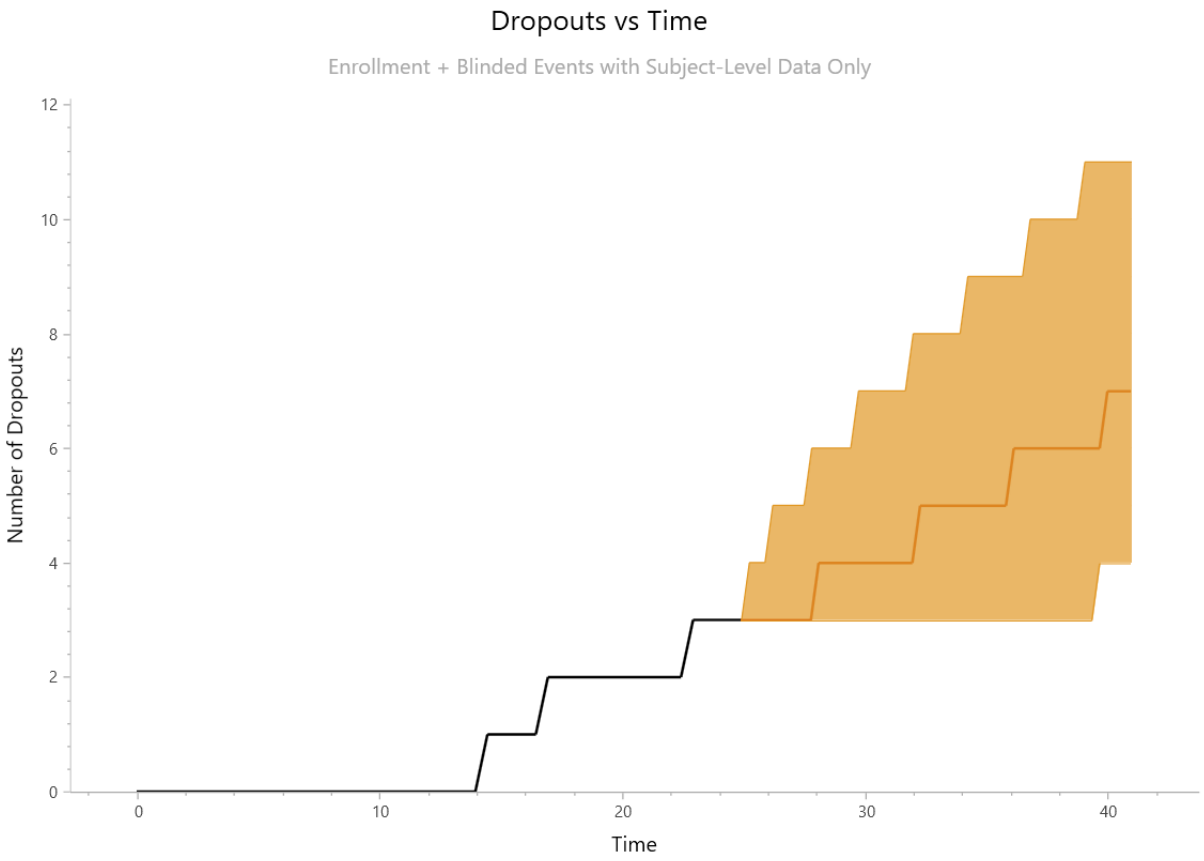


Figure 11.78: Dropout Prediction Plot for Blinded Events Prediction using Subject-level Data

The **Enrollment Prediction Table, Events Prediction Table and Dropout Prediction Tables** are the tables used to create the respective **Enrollment Prediction, Events Prediction** and **Dropout Prediction** plots, which by default all consists of ~100 rows (50 pre-simulation and 50 post-simulation). Each consists of five columns: **Time, Actual, Predicted Avg. Sample Size/Events/Dropouts, Predicted Median Sample Size/Events/Dropouts, 95% Prediction Interval LL, 95% Prediction Interval UL**. One prediction table (the **Events Prediction Table**) for this demonstration at the start of the simulated period is given in Figure 11.79.

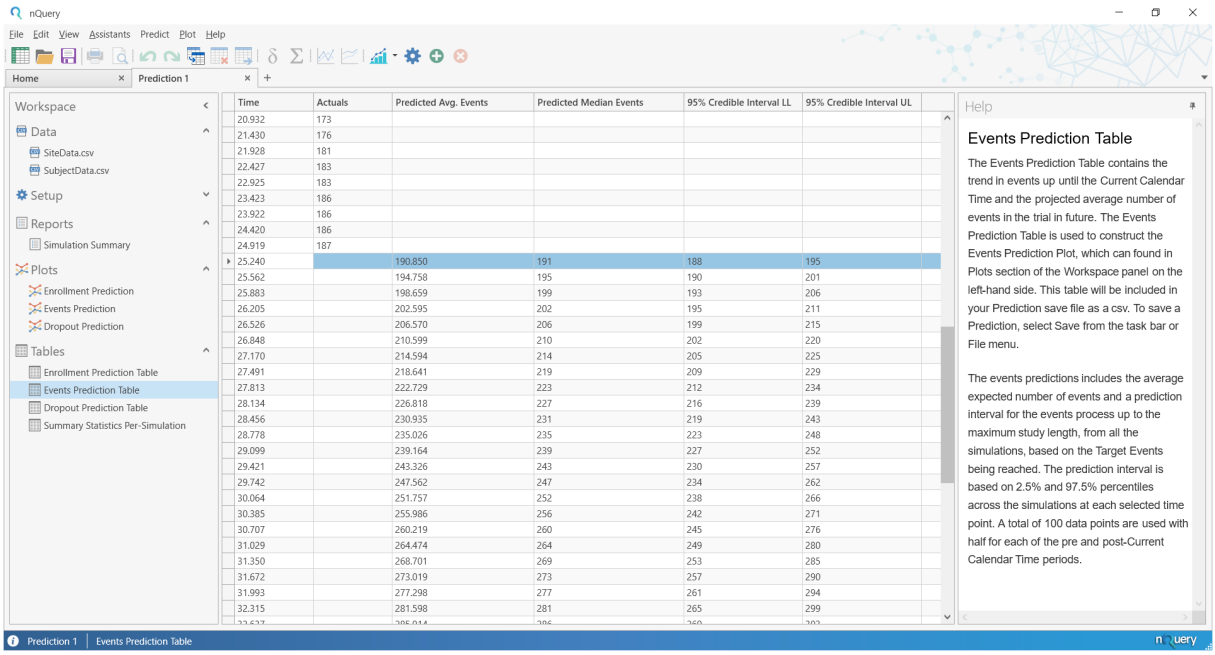


Figure 11.79: Events Prediction Table for Blinded Events Prediction using Subject-level Data

Time is the time value relative to the study start time of zero. **Actual** is the actual number of events achieved at a pre-simulation **Time** row. **Predicted Avg. Events** is the predicted average (mean) number of events at a post-simulation **Time** row. **Predicted Median Events** is the predicted median number of events at a post-simulation **Time** row. **95% Prediction Interval LL** is the lower limit for the 95% prediction interval for the number of events at a post-simulation **Time** row. **95% Prediction Interval UL** is the upper limit for the 95% prediction interval for the number of events at a post-simulation **Time** row.

Note that the **Enrollment Prediction Table** will show the projection for **Target Sample Size** and its associated **Accrual Duration** and therefore will usually have a different **Time** scale than the **Event Prediction Table** and **Dropout Prediction Table** which will be associated with the **Study Duration.** Note the **Enrollment Prediction Table** ignores the case where **Accrual Duration** is cut short due to the **Target Number of Events** being reached before the enrollment process is complete.

The **Summary Statistics Per-Simulation Table** provides the summary statistics achieved for primary outputs in each simulation. For this demonstration this includes the **Simulation ID, Current Time, Current Sample Size, Current Events, Current Dropout, Current Available, Target Sample Size, Target Events, Study End Time, Total Sample Size, Total Events, Total Dropouts, Total Censored, Accrual Duration, Accrual Duration Uncensored, Average Followup, Median Followup, Target Events Reached.**

The **Summary Statistics Per-Simulation Table** for this demonstration, focused on the simulation results, is shown in Figure 11.80.

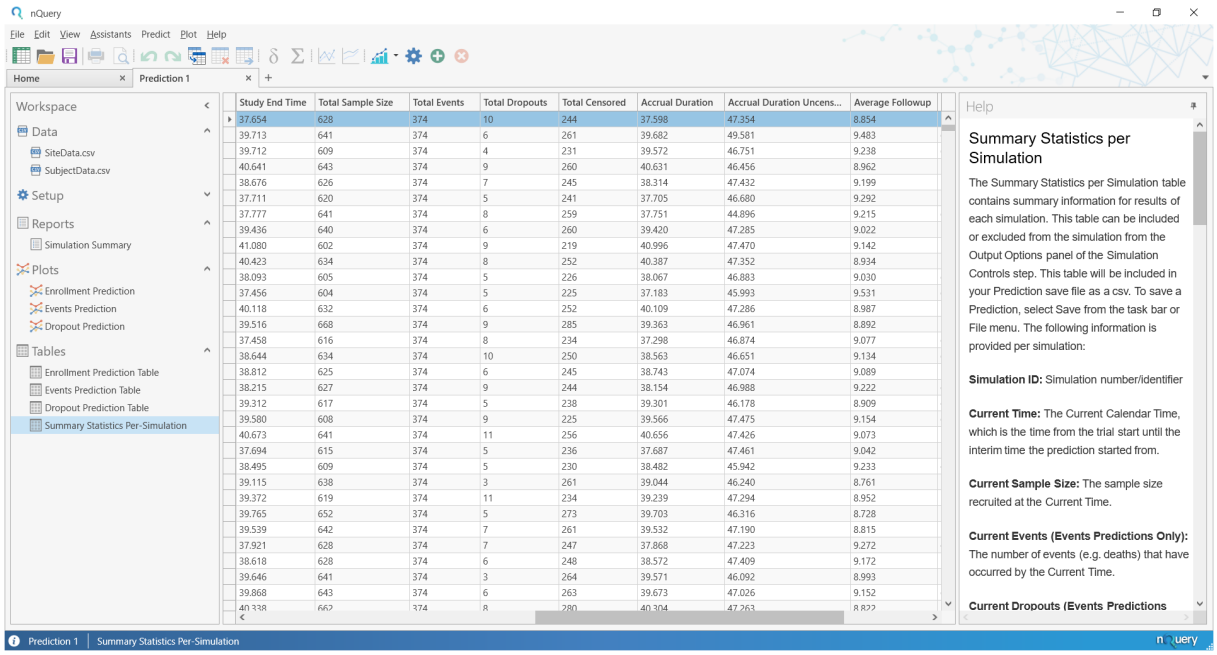


Figure 11.80: Summary Statistics Per-Simulation Table for Blinded Events Prediction using Subject-level Data

Details on each field are provided in the Help window on the right but broadly the "Current" fields described the information provided up to the **Current Time**, the "Target" fields describe the study targets and the remainder give the projection achieved for key parameters in the simulation with that **Simulation ID**.

Alternative Scenarios The demonstration has focused on the default inputs using **SubjectData.csv** up to this point. However, as noted in the data summary given in subsection 11.2.4 the study from which the example data was simulated had an original sample size target of 460 (402 enrolled in **SubjectData.csv**). Additionally, in the **Enrollment Prediction Plot** there is noticeable "kink" where the accrual rate was slowing down for the final 4-5 months before the current time and the best fitting **Weibull Shape Parameter** was equal to 0.831 which indicates some deviation from the exponential assumption of a constant hazard rate (Weibull and exponential are equivalent if **Shape Parameter = 1**)

To explore this additional information, we will investigate two additional scenarios

- Scenario A: **Target Sample Size = 460** using default **Accrual Rate**
- Scenario B: **Target Sample Size = 460** using slower "updated" **Accrual Rate** and **Weibull Response Distribution** (using nQuery Predict default fit) model
- Scenario C: **Target Sample Size = 460** using default **Accrual Rate** with **Fixed Followup** = 12 months

Scenario A The only changes required compared to the first demonstration is to change the **Target Sample Size** to 460 at the **Accrual Options** step. The simplest way to do this is to select the **Setup** header in the Workspace Navigation Bar on the left and then select the **Accrual Options** drop down option. Then edit the **Target Sample**

Size 460 in the **Current and Target Sample Sizes** section in the top-left and select the Next or → button. At the next **Simulation Controls** step, we will add a single simulation run by selecting the checkbox beside the **Save subject-level data for (x) simulation runs** and replace the default of 10 runs with 1 runs at the "(x)" spot. An edited down summary of the **Setup** changes is provided in Figure 11.81.

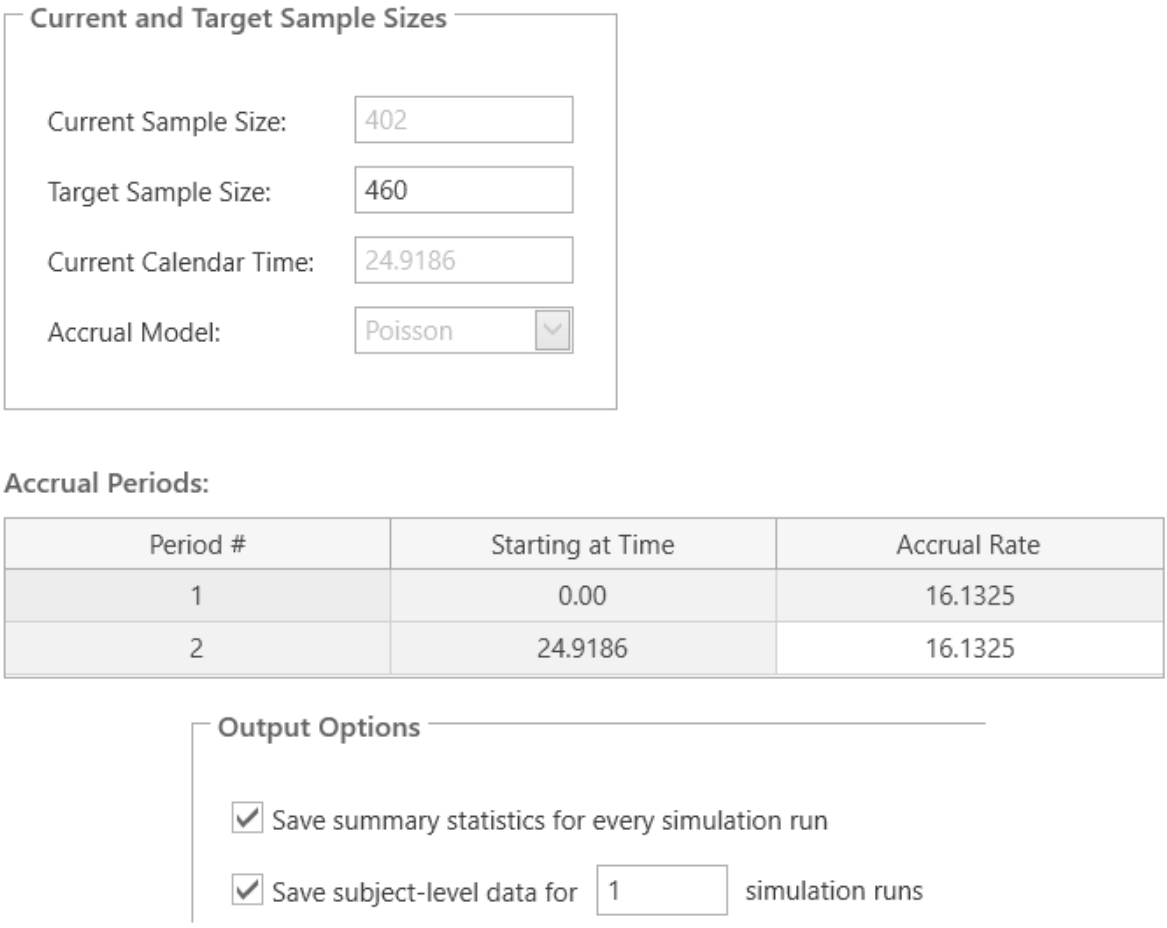


Figure 11.81: Scenario A Setup Changes for Blinded Events Prediction using Subject-level Data

To run the simulation again with the new Scenario A, select the Run/→ button. The main results of this Scenario A simulation are shown in Figure 11.82.

Overall Summary

Average Sample Size	460.0000
Average Accrual Duration	28.5145
Average Study Duration	43.4715
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	6.0007
Average Follow-up	12.3579

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	374	460	3	27.7722	41.1954
25.00%	374	460	5	28.1872	42.4874
50.00%	374	460	6	28.4944	43.4284
75.00%	374	460	7	28.8220	44.4065
95.00%	374	460	9	29.3153	45.9318

Figure 11.82: Scenario A Results for Blinded Events Prediction using Subject-level Data

For Scenario A, the **Overall Summary** shows that the **Target Number of Events** of 374 was reached in every simulation with an **Average Study Duration** over all the simulations of 43.4715. The **Percentile Summary** shows that 90% of predictions had a **Study Duration** between 41.1954 (5% Percentile) and 45.9318 (95% Percentile), 50% a duration between 42.4874 (25% Percentile) and 44.4065 (75% Percentile) and a median (50% Percentile) duration of 43.4284. The **Average Dropouts** was 6.0007 (Percentiles: 3, 5, 6, 7, 9) and subjects had an **Average Followup** (until either event/dropout or until study end for censored subjects) of 12.3579.

The original target study duration was 40 months and therefore this study is expected to end 3.5 months later than expected. There are multiple possible causes of delays in a survival trial including, but not limited to, a slower than expected accrual rate, a slower than expected event hazard rates and a higher than expected dropout (or other competing process) rate.

The **Target Sample Size** of 460 was reached in all simulations with an **Average Accrual Duration** of 28.5154 (Percentiles: 27.7722, 28.1872, 28.4944, 28.8220, 29.3153).

Given that the original target accrual period length was 30 months, this indicates that if the average accrual rate over the entire period up to the current time was being maintained that the accrual period would around 1.5 months less than expected and the accrual pattern before the current time does not indicate any significant delay in starting accrual (see Figure 11.76). Since accrual was ahead of target, this indicates the longer than

expected **Study Duration** was due to a lower than expected hazard rate since the dropout rate was quite low (6.0007 subjects dropped out on average).

In the original demonstration with a **Target Sample Size** of 804, the **Average Study Duration** was 39.0277. This would indicate a large increase in sample size would be needed to reduce the study duration sufficiently and would likely be infeasible.

The **Per-Simulation Subject-level Data Table** was also generated here and is shown for Scenario A in Figure 11.83 with the first simulated subject (and their **Arrival Time**) in the first simulation (**Simulation ID = 1**) highlighted. The tables consists of the following fields: **Simulation ID**, **Subject ID**, **Arrival Time**, **Event Time**, **Dropout Time** and **Final Status**. The order of the Subject ID is based on **Arrival Time** order.

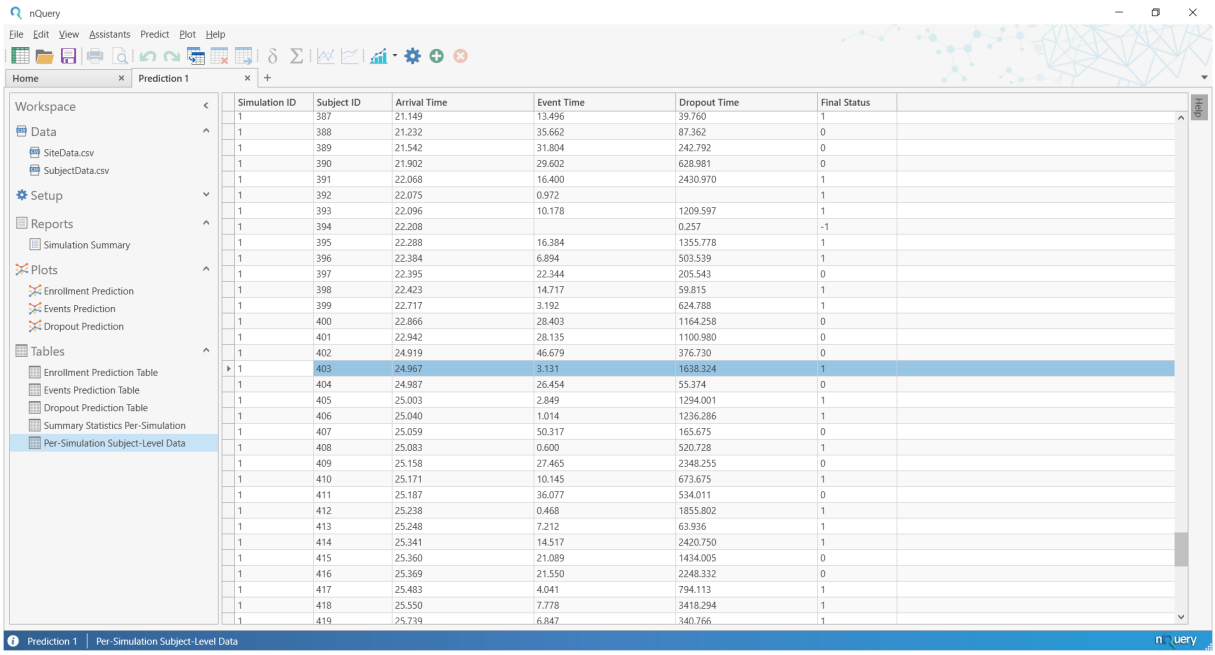


Figure 11.83: Per-Simulation Subject-level Data Table for Blinded Events Subject-level Data

Arrival Time is generated for all simulated subjects (i.e. **Subject ID > 402**). **Event Time** and **Dropout Time** are generated for all simulated subjects and all subjects which were **Censored Status** (all status values from **Status Indicator** field in **Subject-level Data Setup** step) in the subject-level data (for example **Subject ID = 402** in this example). Blank fields for **Event Time** or **Dropout Time** indicate cases where the subject already had the event/dropout and therefore the time for the other status does not exist and does not need to be simulated.

The **Final Status** is from the subject-level data for subjects with **Event Status** or **Dropout Status** and based on the **Event Time** and **Dropout Time** for simulated subjects and **Censored Status** subjects in the subject-level data. **Final Status** will equal **Event Status** if **Event Time** is less than **Dropout Time** and the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.80 for per-simulation end times). **Final Status** will equal **Dropout Status** if **Dropout Time** is less than **Event Time** and the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.80 for per-simulation end times). **Final Status** will equal **Censored Status** if **Event Time**

and **Dropout Time** are greater than the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.80 for per-simulation end times)

Scenario B Scenario A assumed the **Accrual Rate** would continue at average rate over the entirety of the period up until this simulation was made and the constant **Exponential Response Distribution** model was appropriate. However, there is evidence that in the last five months there was a significant reduction in the **Accrual Rate**, perhaps reflecting a wind down of the enrollment process and that the **Weibull Response Distribution** fit indicated some deviation from the exponential model (where Weibull **Shape Parameter = 1**).

To evaluate this scenario, note that 31 subjects where recruited after 20 months of the accrual period is passed. The remaining accrual period after 20 months to the current time equals 4.9186 (24.9816 (Current Time) - 20). This gives an average accrual rate over this period of ($31/4.9186 \approx 6.3$). This is significantly lower than the average 16.13 **Accrual Rate** over the entire period up to now. The default **Weibull** model will also be used.

To evaluate this scenario, select **Accrual Options** from under the **Setup** header in the Workspace Navigation Bar on the left then change the **Accrual Rate** in the **Period # = 2** row to 6.3 at the **Accrual Options** step by and then select the Next or → button.

At the next **Event and Dropout Information** step in the **Events Model** tab, change the **Response Distribution** field to **Weibull.** Select the Run or → button to move to the next step.

At the next **Simulation Controls** step, select the Run or → button to simulate Scenario B. The changes and results for Scenario B are summarized in Figure 11.84.

Accrual Periods:

Period #	Starting at Time	Accrual Rate
1	0.00	16.1325
2	24.9186	6.30

Events Model | Dropout Model

Current Number of Events:	187
Current Censored:	212
Target Sample Size:	460
Target Number of Events:	374
Response Distribution:	Weibull
Scale Parameter:	0.059
Shape Parameter:	0.831

Overall Summary

Average Sample Size	460.0000
Average Accrual Duration	34.1232
Average Study Duration	50.3707
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	6.8860
Average Follow-up	14.2191

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	374	460	4	32.2322	46.9750
25.00%	374	460	5	33.2865	48.8669
50.00%	374	460	7	34.0656	50.2908
75.00%	374	460	8	34.8904	51.7489
95.00%	374	460	10	36.2181	54.0922

Figure 11.84: Scenario B for Blinded Event Prediction with Subject-level Data

For Scenario B, the **Overall Summary** shows that the **Target Number of Events** of 374 was reached in every simulation with an **Average Study Duration** over all the simulations of 50.3707 (Percentiles: 46.9750, 48.8669, 50.2908, 51.7489, 54.0922). The **Average Dropouts** was 6.8860 (Percentiles: 4, 5, 7, 8, 10) and subjects had an **Average Followup** (until either event/dropout or until study end for censored subjects) of 14.2191. The original target study duration was 40 months and therefore this study is expected to end 10.4 months later than expected.

The **Target Sample Size** of 460 was reached in all simulations with an **Average Accrual Duration** of 34.1232 (Percentiles: 32.2322, 33.2865, 34.0656, 34.8904, 36.2181) which is 4.1 months longer than expected. This likely contributed to the higher duration expected compared with **Scenario A (Average Study Duration =43.4715)**. In addition, the Weibull fit **Shape Parameter** of 0.8310 indicates a lower hazard rate the longer subjects were on the study which may also have contributed to the slower event rate in a study that was well underway. Given the larger increase in the expected study length, the case for a larger change (e.g. request ad-hoc sample size increase) may be greater.

Scenario C The prior examples have assumed the study was an event-driven (i.e. variable followup) design where all subjects who have not had the event or dropped out are followed until the **Target Number of Events** is reached and then administratively censored. nQuery Predict gives the option to do a fixed followup design where subjects are instead followed for a pre-specified maximum period of time after which are administratively censored.

In Scenario C, we explore what effect setting a **Fixed Followup** of 12 months would have on the event milestone prediction compared to **Scenario A** above.

To evaluate this scenario, select **Accrual Options** from under the **Setup** header in the Workspace Navigation Bar on the left then change the **Accrual Rate** in the **Period # = 2** row back to its default of 16.1325. Then select **For Fixed Period** from the **Followup Option** dropdown and enter 12 in the new **Followup Time** field. Then select the Next or → button.

At the next **Event and Dropout Information** step in the **Events Model** tab, change the **Response Distribution** field back to **Exponential.** Select the Run or → button to move to the next step.

At the next **Simulation Controls** step, select the Run or → button to simulate Scenario C. The changes and results for Scenario C are summarized in Figure 11.85.

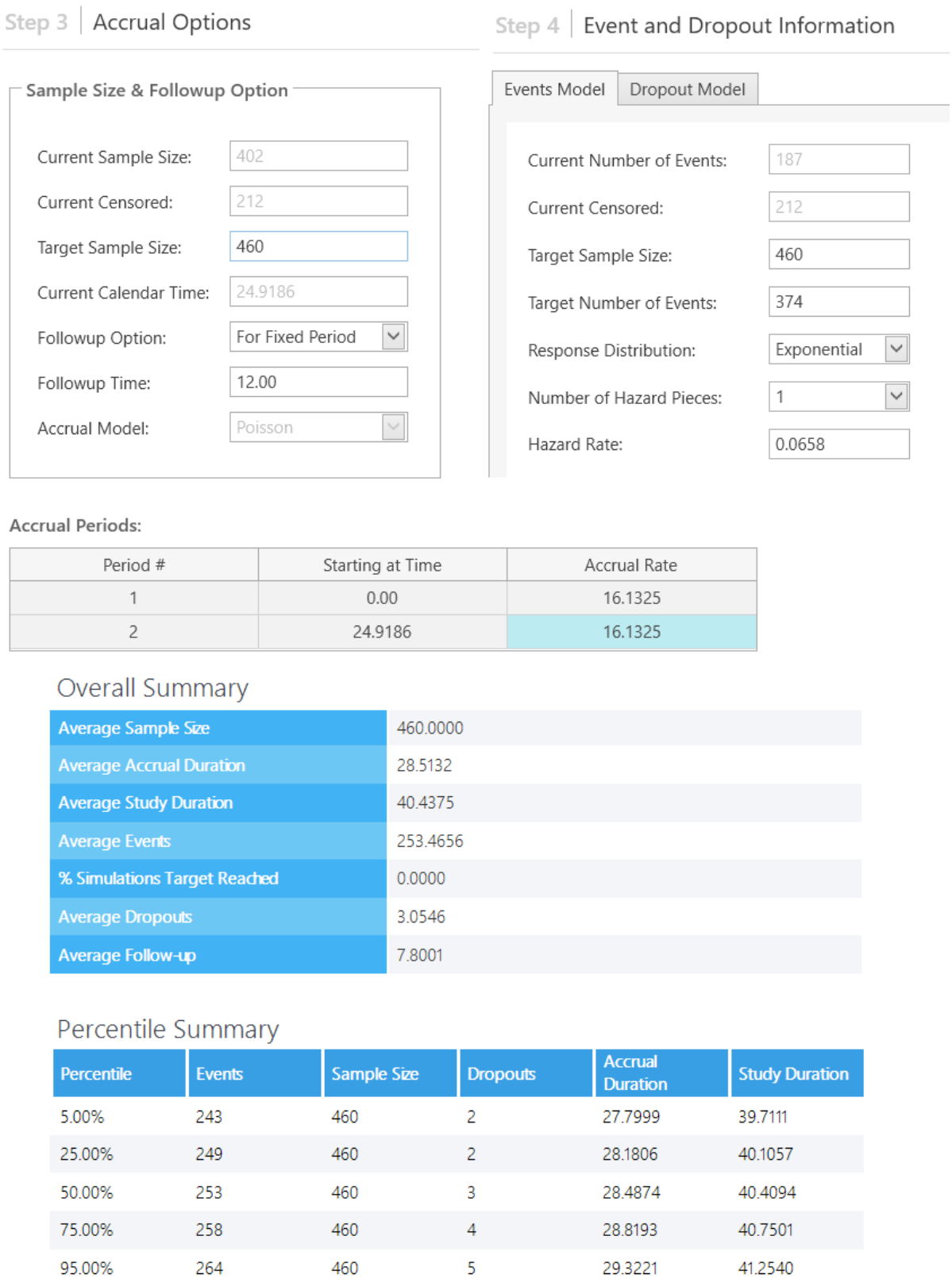


Figure 11.85: Scenario C for Blinded Event Prediction with Subject-level Data

For Scenario B, the **Overall Summary** shows that the **Target Number of Events** of 374 was not reached in any simulation with an **Average Events** of 253.4656 (Percentiles:

243, 249, 253, 258, 264) and an **Average Study Duration** over all the simulations of 40.4375 (Percentiles: 39.7111, 40.1507, 40.4094, 40.7501, 41.2540).

From this example it is obvious that the length of **Fixed Followup** would require a significantly higher **Target Sample Size** as many of the event times from the Scenario A would be greater than the 12 month cutoff used here and therefore these subjects are censored here instead of having the event of interest. This highlights the relative inefficiency of the fixed followup design and why it is generally only used over an event-driven design when there is a strong clinical reason to value that fixed followup period e.g. 12 month progression free survival (PFS).

Note that unlike in the other demonstrations, the **Study Duration** achieved here is the time at which the final subject was administratively censored due to reaching their **Fixed Followup** time (since **% Simulation Target Reached = 0**). In the other examples, the **Study Duration** was the time taken to reach the **Target Number of Events**. This definition of **Study Time** is also true for the **Fixed Followup** if **% Simulation Target Reached = 100%** (as for other demonstrations) or it can be a hybrid of these two outcomes if **% Simulation Target Reached** was between 0 and 100%.

The **Average Dropouts** was 3.0546 (Percentiles: 2, 2, 3, 4, 5) and subjects had an **Average Followup** (until either event/dropout or until study end for censored subjects) of 7.8001. The **Target Sample Size** of 460 was reached in all simulations with an **Average Accrual Duration** of 28.5132 (Percentiles: 27.9999, 28.1806, 28.4874, 28.8193, 29.3221) which replicates Scenario A.

11.2.7.2 Unblinded Events Prediction with Subject + Site Data with Enrollment Ongoing

Setup **Unblinded Events** milestone prediction using **Subject + Site-level Data** means that the prediction will project the expected length of the accrual period and study needed to achieve a specified **Target Number of Events** using subject-level and site-level data, though note the site-level data is only used for the enrollment process.

In the **Setup** for this prediction, first in the **Select the type of Prediction** step select **Unblinded Events** from the **Target** field, **Subject + Site Data** from the **Input** field and **Ongoing** from the **Enrollment Status** field.

These selections are shown in Figure 11.86. Select the Next button in the bottom-right or → button in the top-right of the Main Window to move to the next step of the prediction **Setup** stage.

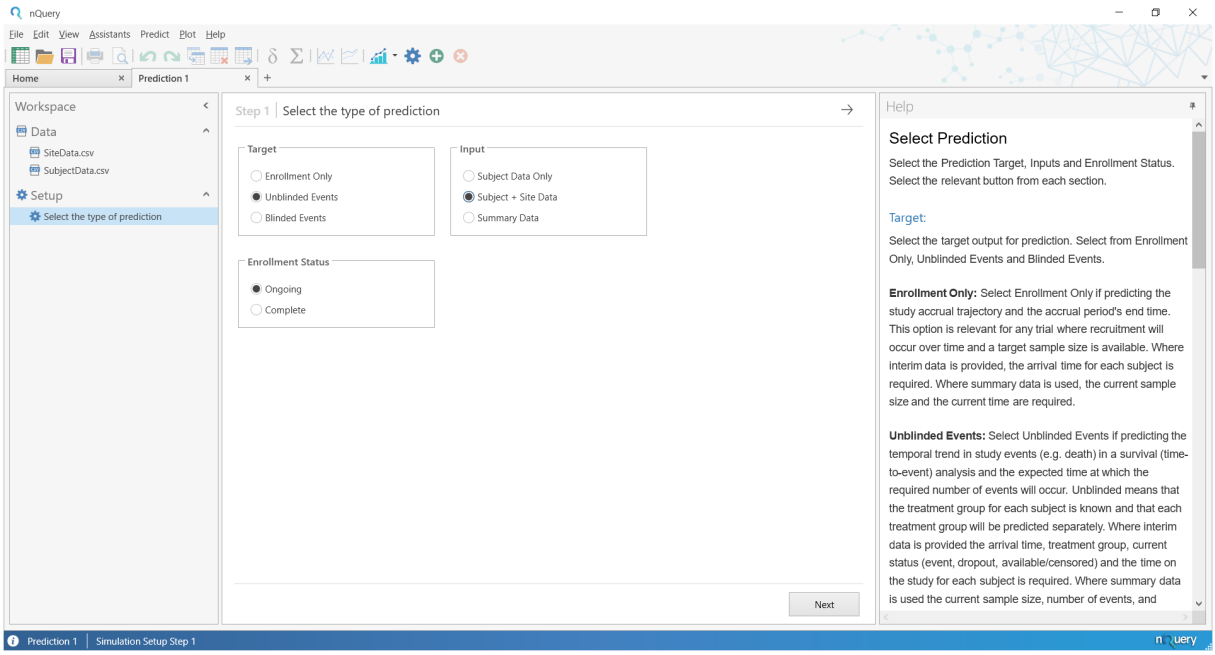


Figure 11.86: Select the Type of Prediction Setup Step for Unblinded Events using Subject + Site-level Data

The next step is the **Subject-level Data** step. The **Subject-level Data** step is a Data Field Selection step. The **Subject-level Data** is the dataset where each row corresponds to a specific subject enrolled in the study.

Data Field Selection steps are steps in which the required dataset in the current Workspace is selected and columns in the selected dataset are assigned to the required fields for that prediction problem. The options in a given Data Field Selection field are opened by selecting the button on the right of each field which is found to the right of the field name e.g. **Select Data**. Each field will have specific requirements (e.g. numeric only, two distinct values only) and nQuery Predict only displays options which are consistent with those fields.

In this prediction there are six fields which are as follows:

- Select Dataset: Select the dataset that is the Subject-level Data from the datasets in the current workspace
- Arrival Time: The arrival time column contains the length of time since the study start (Time = 0) until a subject entered the study. Each subject's Arrival Time should be greater than or equal to zero
- Treatment ID: The treatment code associated with each treatment group. The Treatment ID should have two unique values for the following two sub-fields:
  - Control Group: Treatment ID value associated with subject being assigned to control group
  - Treatment Group: Treatment ID value associated with subject being assigned to treatment group
- Status Indicator: The status (event, dropout, censored/active) for each subject. This Status Indicator column should have a minimum of one alphanumeric unique value and a maximum of three unique values. It has the following sub-fields

  - Event Status: Enter value in Status Indicator column that corresponds to subject having had an event
  - Dropout Status: Enter value in Status Indicator column that corresponds to a subject having dropped out
  - Censored Status: Enter value in Status Indicator column that corresponds to a subject having neither had the event or dropped out
- Time on Study: The length of time after Arrival Time that a subject was in the study. Must be numeric value greater than or equal to zero. The definition depends on Status Indicator (see below)
- Site ID: Site ID of site from which a subject was recruited. Site IDs here must correspond to Site ID contained in the Site-level Data

When the **Status Indicator** field is selected, the **Event Status**, **Dropout Status** and **Censored Status** rows become active. These sub-fields are used to select which values in the **Status Indicator** field correspond to each subject status of interest. The **Censored Status** is also referred to as the **Available Status** as the subject would have been administratively censored if the study ended at the **Current Time** but will be available to have the event of interest in the future during the event milestone prediction.

In the **Treatment ID** sub-fields, the lower alphanumeric input will be assigned to the **Control Group** and the other to the **Treatment Group.** To swap the sub-field values, manually enter the required value in the **Control Group** sub-field by either inputting that value directly into the field or selecting the button on the right of the sub-field and selecting from the two unique values in the selected **Treatment ID** field.

If the nQuery Predict default values of 1 = Event, -1 = Dropout, 0 = Censored is used in the **Status Indicator** field in the **Subject-level Data** then the **Status** sub-fields will be filled automatically with those assignments. Otherwise, manually enter values by either inputting a value directly into the field or selecting the button on the right of each **Status** sub-field and selecting from the list of unique values in the selected **Status Indicator** field. If there are less than three unique values in the **Status Indicator** field (for example if there have been no dropouts i.e. zero rows with **Dropout Status**) then the user must manually enter the value they would like to have assigned for that **Status** outcome. Note that appropriate defaults will be provided for the rate of previously unused **Status** category in subsequent steps e.g. Dropout Hazard Rate(s) = 0.

The definition of **Time on Study** will depend on the **Status Indicator** for that subject. If the **Status Indicator** is equal to **Event Status** or **Dropout Status**, the **Time on Study** is the length of time a subject was followed for after their **Arrival Time** before they had an event/dropped out. If the **Status Indicator** is equal to **Censored Status**, the **Time on Study** is the length of time a subject was followed for after their **Arrival Time** until the **Current Time.**

For this prediction, in the **Select Dataset** field select **SubjectData.csv**. Then in the **Arrival Time** field select **Arrival**, in the **Status Indicator** field select **Current** (assign 1 to **Event Status**, -1 to **Dropout Status**, 0 to **Censored Status**), in the **Time on Study** field select **Followup** and in the **Site ID** field select **SID.** These selections are shown in Figure 11.87. Select the Next or → button to move to the next **Setup** step.

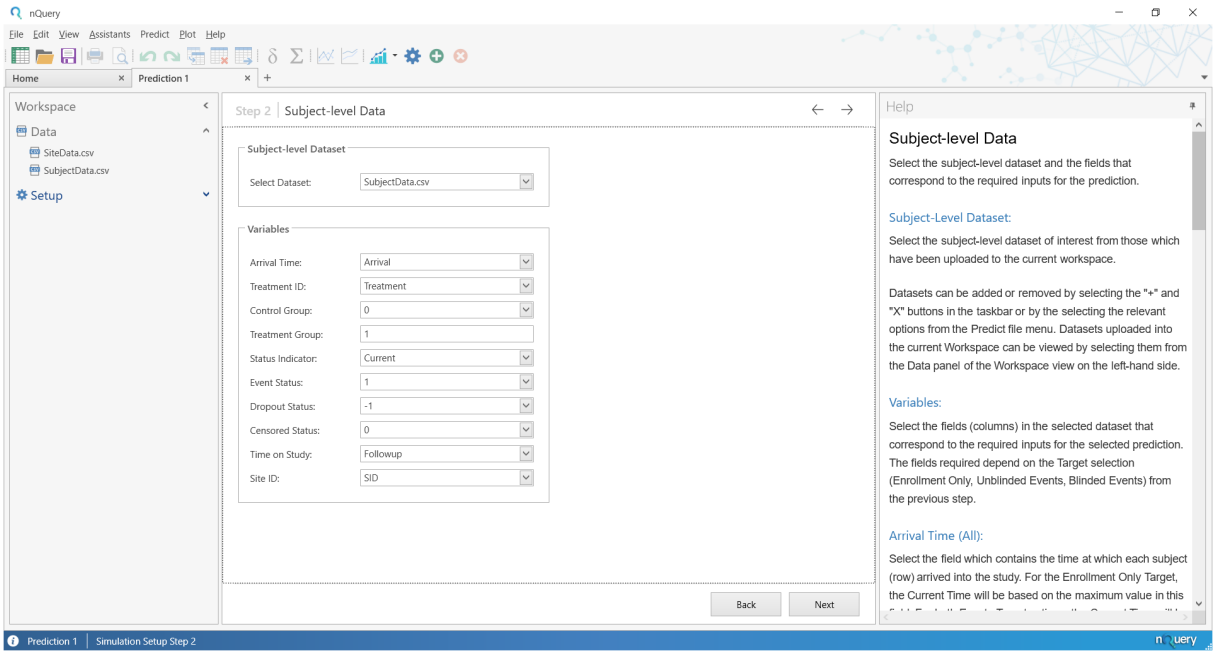


Figure 11.87: Subject-level Data Setup Step for Unblinded Events Prediction using Subject + Site-level Data

The next step is the **Site-level Data** step. The **Site-level Data** step is a Data Field Selection step as per the **Subject-level Data** step. The **Site-level Data** is the dataset where each row corresponds to a specific site.

The **Site-level Data** step fields are the same for all predictions. These fields are:

- Select Dataset: Select the dataset that is the Site-level Data from the datasets in the current workspace
- Site ID: Site ID for each site. Each row should have a distinct Site ID and Site IDs from Subject-level Data must be included in the list of Site IDs selected here
- Accrual Rate/Site: The planned accrual rate (subjects recruited per unit time) in a site. Each site's Accrual Rate/Site should be a numeric value greater than zero
- Enrollment Cap: The maximum number of subjects that can be recruited from that site. Each site's Enrollment Cap should be an integer greater than the higher of zero and the No. of Accruals (see below)
- Site Initiation Time (Opened Sites): The time at which a site was open and able to start enrolling subjects. Each site's Site Initiation Time should be a numeric value less than the Current Time
- Start Time (Unopened Sites): The start time of the window during which an unopened site could open. Optional field for unopened sites, should be numeric value greater than or equal to the Current Time
- End Time (Unopened Sites): The start time of the window during which an unopened site could open. Optional field for unopened sites, should be numeric value greater than or equal to the Start Time (Unopened Sites) for that site

For this prediction, in the **Select Dataset** field select **SiteData.csv,** in the **Site ID** field select **SID**, in the **Accrual Rate/Site** field select **Rate**, in the **Enrollment Cap** field

select **Cap**, in the **Site Initiation Time** field select **OpenTime**, in the **Start Time** field select **Start** and in the **End Time** field select **End.** These selections are shown in Figure 11.30. Select the Next or → button to move to the next **Setup** step.

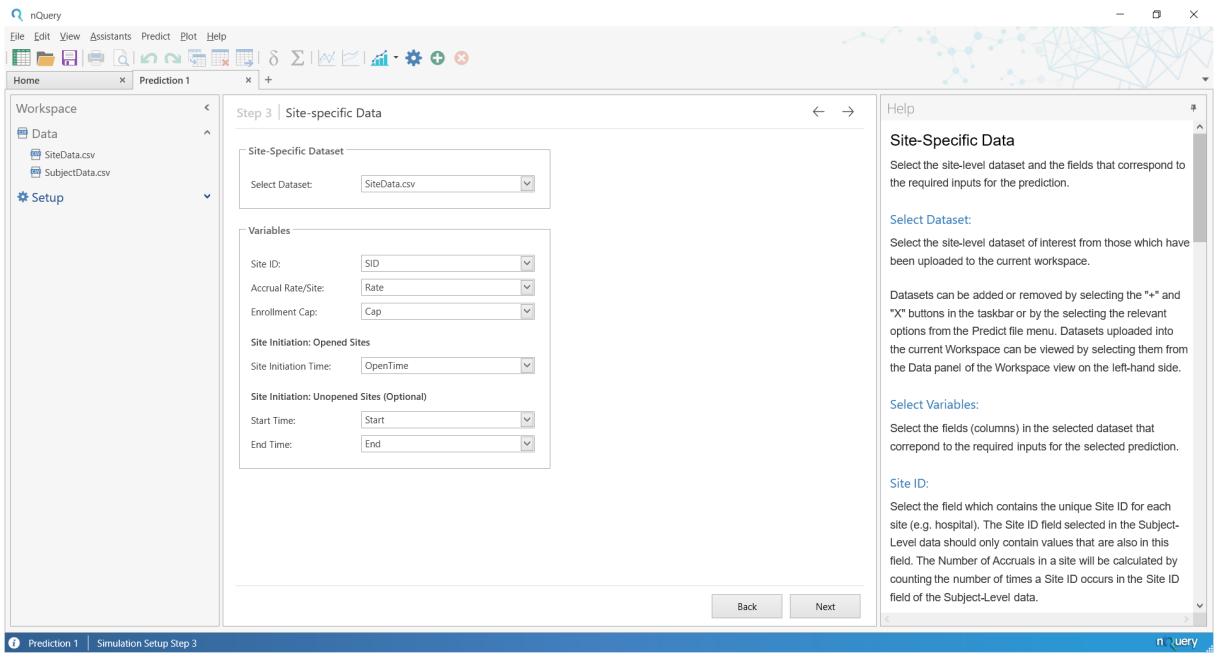


Figure 11.88: Site-level Data Setup Step

The next step is the **Accrual Options** step. When **Site-level Data** is used, the **Accrual Options** consists of two tabs: **Sample Size & Followup Options** and **Accrual Options/Site**. A given tab can be opened by selecting the grey tab name at the top of the main window, just below the **Step 4 | Accrual Options** name. These tabs are highlighted in Figure 11.89.

The **Sample Size & Followup Options** tab provides overall information about the trial up until the current time alongside the **Target Sample Size** and **Accrual Model.** The **Sample Size & Followup Options** tab for this demonstration is shown in Figure 11.89.

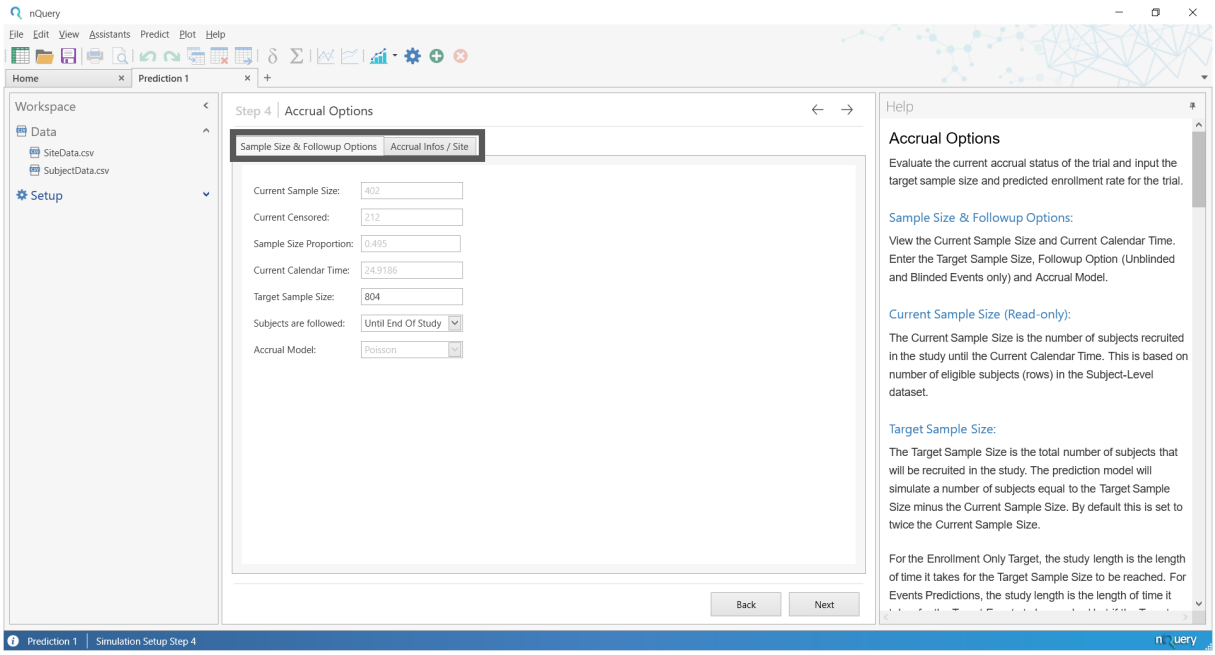


Figure 11.89: Accrual Options Step Sample Size & Followup Options tab for Site-level Data

The **Sample Size & Followup Options** fields are:

- Current Sample Size (Read-only): Sample Size recruited into a study so far. Equals the number of rows in the Subject-level Data
- Current Censored (Read-only): The number of subjects who have not had the event or dropped out at the current time. Equals the number of subjects with the Censored Status in the Status Indicator field
- Sample Size Proportion (Read-only): Proportion of subjects in the Control Group. Based on number of Control Group subjects in Treatment ID field. Controls the allocation proportion in simulated data
- Current Time (Read-only): The length of time that has passed since the study started. Equals the maximum Arrival Time value
- Target Sample Size (Editable): Total number of subjects that will be recruited in this study. The number of simulated subjects equals the Total Sample Size minus the Current Sample Size.
- Accrual Model (Editable): The statistical model that will be used to generate simulated enrollments

In nQuery Predict, the **Target Sample Size** defaults to twice the **Current Sample Size** and the **Accrual Model** defaults to **Poisson.** In this demonstration, the **Current Sample Size** equals 402 and therefore the default **Target Sample Size** is $402\,(2) = 804$.

To open the **Accrual Options/Site** tab select the tab at the top of the main window with that name. This is shown in Figure 11.90

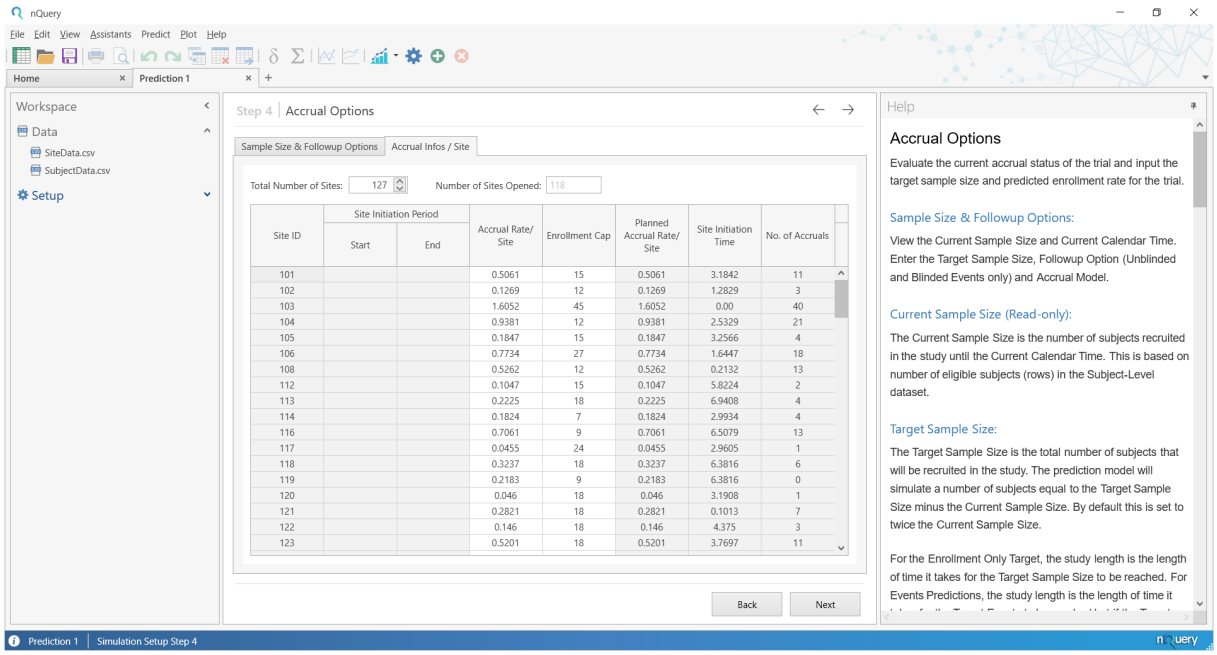


Figure 11.90: Accrual Options Step Accrual Options/Site tab for Site-level Data

The **Accrual Options/Site** tab has three main elements: the **Total Number of Sites** field, the **Number of Sites Open** field and the **Site Accrual Table**.

The **Total Number of Sites** and **Number of Sites Open** field are found at the top of tab window. The **Total Number of Sites** field sets the total number of sites that will be used to simulate subjects in this milestone prediction and by default is equal to the number of rows/sites in the **Site-level Data**.

The **Number of Sites Open** field is the number sites that are already open at the time the simulation is being performed and is the number of sites which had a **Site Initiation Time** in the site-level data. The **Total Number of Sites** must always be greater than or equal to the **Number of Sites Open**.

The **Site Accrual Table** consists of eight columns with each row corresponding to required information for each site. The columns are defined as follows:

- Site ID (Read-only for Open Sites, Editable for Unopened Sites): Site ID for a site. Taken directly from Site-level Data. All Site ID must be unique and include all Site ID in the subject-level Site ID field
- Site Initiation Period - Start Time (Editable for Unopened Sites, Numeric $\geq$ Current Time): Start time for window during which unopened site can open. Not used for open sites
- Site Initiation Period - End Time (Editable for Unopened Sites, Numeric $\geq$ Start Time): End time for window during which unopened site can open. Not used for open sites
- Accrual Rate/Site (Editable, Numeric > 0): The accrual rate (subjects recruited per unit time) that will be used to simulate subjects for that site
- Enrollment Cap (Editable, Numeric $\geq$ No. of Accruals) The maximum number of subjects that can be recruited in a site. This must be greater than the No. of Accruals in a site

- Planned Accrual Rate/Site (Read-only): The original planned accrual rate in a site. Taken from Site-level Data
- Site Initiation Time (Read-only): The site initiation time for opened sites. Taken from Site-level Data. Not used for unopened sites
- No. of Accruals (Read-only): The number of subjects that have been enrolled in an open site at the current time. Not used for unopened sites

Site ID, Site Initiation Period (Start Time, End Time), Enrollment Cap, Planned Accrual Rate/Site and **Site Initiation Time** are taken directly from the **Site-level Data**.

For sites which have already recruited subjects (i.e. **No. of Accruals** > 0), the default **Accrual Rate/Site** is calculated using the **No. of Accruals** and **Site Initiation Time** using the following relationship:

$$R = \frac{\#A}{(CT - SIT)}$$

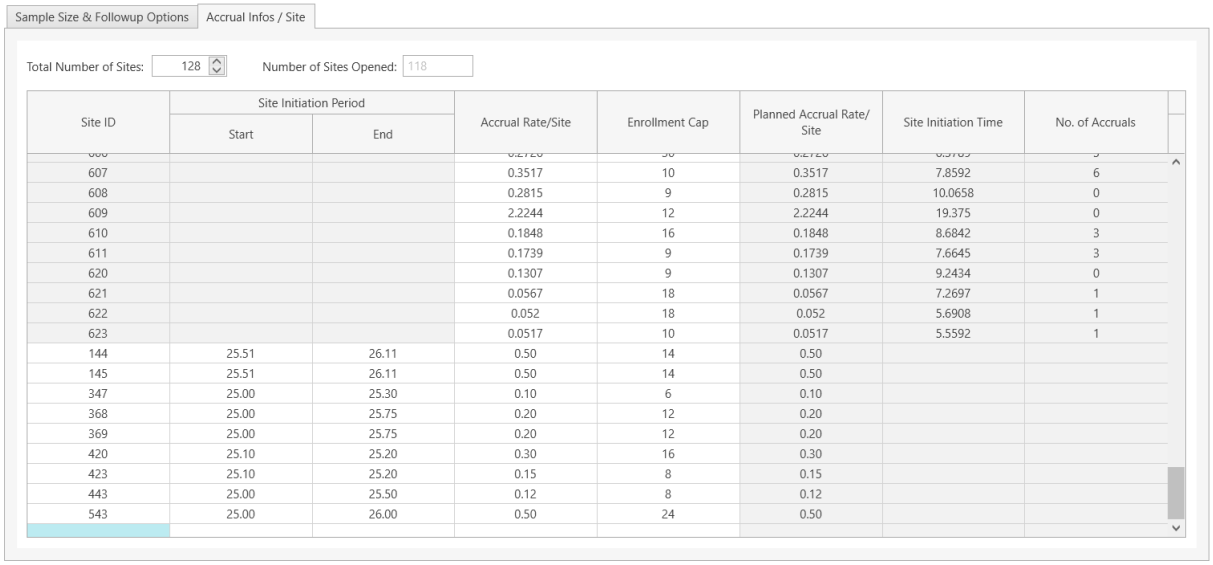
where R is the **Accrual Rate/Site**, $\#A$ is the **No. of Accruals** in a site, CT is the **Current Time** and SIT is the **Site Initiation Time** for that site.

For sites which are unopened sites or which have not recruited a subject (i.e. **No. of Accruals** $= 0$), the **Planned Accrual Rate/Site** from the **Site-level Data's Accrual Rate** field is used.

The **No. of Accruals** is calculated by counting the number of times each **Site ID** value occurred in the **Subject-level Data's Site ID** column.

As referenced above, the inputs for the **Site Accrual Table** for each site depend on whether a site is open or unopened. Unopened sites are automatically placed at the bottom of the **Site Accrual Table**.

The user can also add additional sites (rows) by increasing the **Total Number of Sites** field above the original value derived from the number of rows in the **Site-level Data**. This will add a blank row at the bottom of the **Site Accrual Table**. Note **Setup** cannot continue until all new rows are filled appropriately. An example of **Site Accrual Table** with the unopened sites from the **SiteLevel.csv** data alongside one blank new site by increasing **Total Number of Sites** to 128 is provided in Figure 11.91.



Site ID	Site Initiation Period		Accrual Rate/Site	Enrollment Cap	Planned Accrual Rate/ Site	Site Initiation Time	No. of Accruals
	Start	End					
607			0.3517	10	0.3517	7.8592	6
608			0.2815	9	0.2815	10.0658	0
609			2.2244	12	2.2244	19.375	0
610			0.1848	16	0.1848	8.6842	3
611			0.1739	9	0.1739	7.6645	3
620			0.1307	9	0.1307	9.2434	0
621			0.0567	18	0.0567	7.2697	1
622			0.052	18	0.052	5.6908	1
623			0.0517	10	0.0517	5.5592	1
144	25.51	26.11	0.50	14	0.50		
145	25.51	26.11	0.50	14	0.50		
347	25.00	25.30	0.10	6	0.10		
368	25.00	25.75	0.20	12	0.20		
369	25.00	25.75	0.20	12	0.20		
420	25.10	25.20	0.30	16	0.30		
423	25.10	25.20	0.15	8	0.15		
443	25.00	25.50	0.12	8	0.12		
543	25.00	26.00	0.50	24	0.50		

Figure 11.91: Unopened and New Sites in Site Accrual Table

For this demonstration, assume the **Total Number of Sites** is reset to its default of 127. Select the Next or → button to move to the next **Setup** step.

The next step is the **Event and Dropout Information** step which specifies the **Target Number of Events,** event model (and associated statistical parameters) and dropout model (and associated statistical parameters). The **Event and Dropout Information** step on the default **Events Model** tab is shown in Figure 11.92.

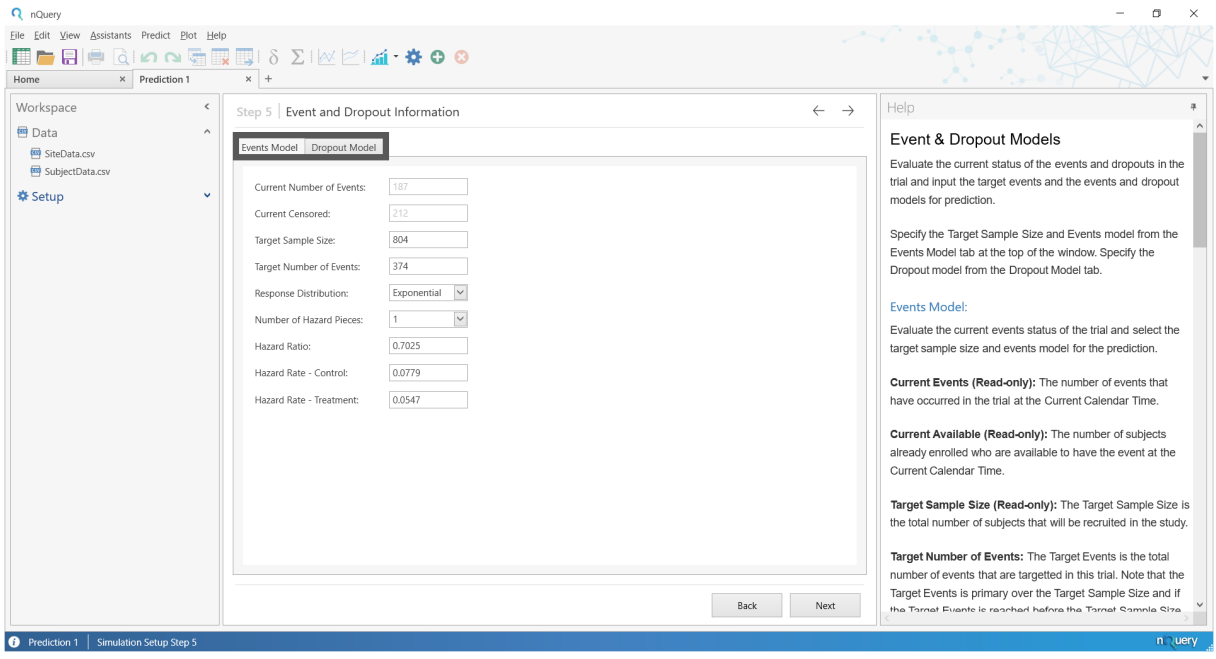


Figure 11.92: Event and Dropout Information Setup Step for Unblinded Events Prediction using Subject + Site-level Data

The **Event and Dropout Information** step consists of two tabs: the **Events Model** tab and the **Dropout Model** tab. These tabs have been highlighted in Figure 11.92 and

are opened by selecting the required tab name at the top of the main window, below the step title. For **Unblinded Events**, it is assumed that survival and dropout times will be simulated individually for each treatment group using their own user specified model.

The **Events Model** tab provides fields which provide information on the current number of subject who have had an event, could have an event going forward and allows the input of the **Target Number of Events, Target Sample Size, Response Distribution** for the events model and additional parameters needed for that specific model. The following fields are provided in this prediction:

- Current Events (Read-only): The number of subjects who had the event of interest at the current time. Equals the number of subjects with the Event Status in the Status Indicator field
- Current Censored (Read-only): The number of subjects who have not had the event or dropped out at the current time. Equals the number of subjects with the Censored Status in the Status Indicator field
- Target Sample Size (Editable): Total number of subjects that will be recruited in this study. The number of simulated subjects equals the Total Sample Size minus the Current Sample Size.
- Target Number of Events (Editable): The required number of subjects needed to have the event of interest for the study to end
- Response Distribution: The statistical model that will be used to generate survival times for subjects available to have the event
- Number of Hazard Pieces (Response Distribution = Exponential only): Number of hazard pieces used to specify the piecewise exponential model. Select value between 1 and 10
- Hazard Ratio (Response Distribution = Exponential only, Number of Hazard Pieces =1, Editable): The hazard ratio between the Treatment and Control Hazard Rates
- Hazard Rate - Control (Response Distribution = Exponential only, Number of Hazard Pieces =1, Editable): The control group's exponential hazard rate for the constant exponential survival model specified above
- Hazard Rate - Treatment (Response Distribution = Exponential only, Number of Hazard Pieces =1, Editable): The treatment group's exponential hazard rate for the constant exponential survival model specified above

In nQuery Predict, the **Target Sample Size** at this step is inherited from the prior **Accrual Options** step, the **Target Number of Events** defaults to twice the **Current Events**, the default **Response Distribution** is **Exponential** with the **Number of Hazard Pieces** set to 1 and the default **Hazard Ratio** and **Hazard Rate - Control/Treatment** set using the provided information (see subsubsection 11.1.2.2 for details on the survival distributions used in nQuery Predict, see section 3.5 for details on how to calculate a exponential **Hazard Rate** using a median survival or survival probability). When one of the **Hazard Ratio, Hazard Rate - Control** and **Hazard Rate - Treatment** is changed (both for **Number of Hazard Pieces = 1** and **>1** cases, for latter see below) one of the other parameters will be auto-calculated to ensure consistency (**Hazard Rate - Treatment** changes if **Hazard Ratio** or **Hazard Rate - Control** edited, **Hazard Rate - Control** changes if **Hazard Rate - Treatment** edited).

In this demonstration, the **Current Number of Events** is 187 and therefore the default **Target Number of Events** is $187\,(2) = 374$ giving an estimated exponential **Hazard Ratio** of 0.7025, **Hazard Rate - Control** of 0.0779 and **Hazard Rate - Treatment** of 0.0547. Note that if the **Target Number of Events** is reached before the **Target Sample Size** has been enrolled then the it is assumed the enrollment process will stop early and the total sample size achieved may be less than the **Target Sample Size** specified.

In nQuery, there are effectively three primary survival distributions that survival times can be generated from:

- Constant Exponential (Response Distribution = Exponential, Number of Hazard Pieces =1): Input Hazard Rate
- Piecewise Exponential (Response Distribution = Exponential, Number of Hazard Pieces > 1): Input table of Starting at Time and Hazard Rate columns
- Weibull (Response Distribution = Weibull): Input Scale Parameter and Shape Parameter

Details on how survival times are generated from each of these distributions is provided in subsubsection 11.1.2.2, alongside how the default values provided in nQuery Predict are estimated from the provided information. The change in the **Events Model** tab for each of these choices is shown in Figure 11.93.

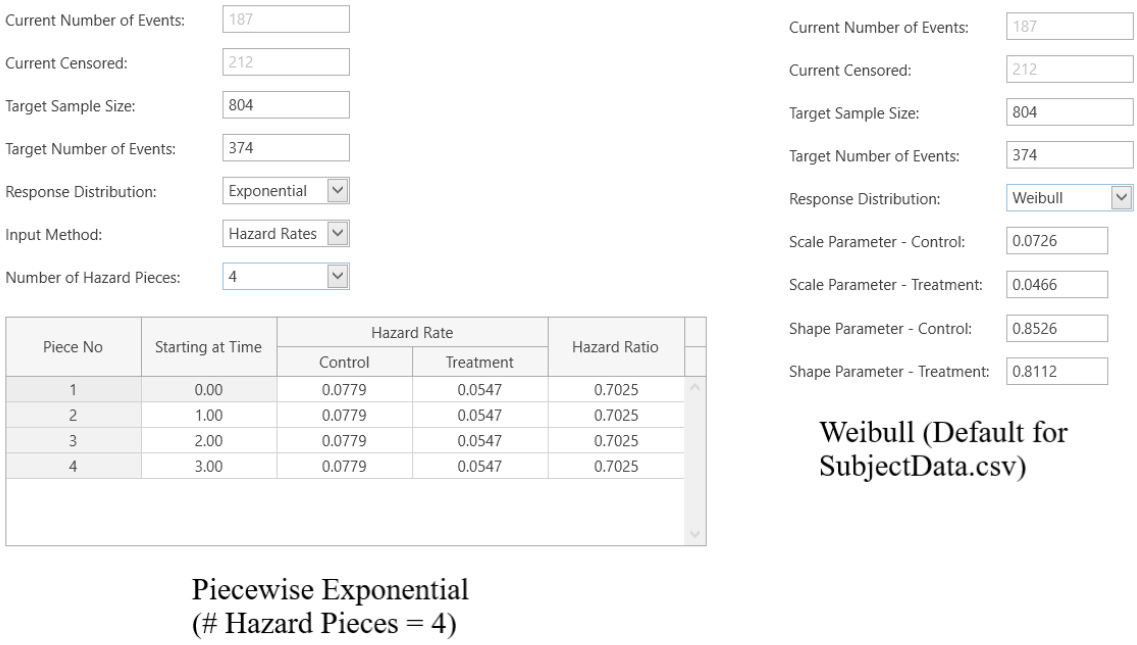


Figure 11.93: Piecewise Exponential (4 Pieces) and Weibull Defaults for SubjectData.csv

The piecewise exponential table will have a number of rows equal to **Number of Hazard Pieces.** The **Piece No** column indicates the hazard piece number of a row. The **Starting at Time** column sets the start time for when the **Hazard Rate** value in that row takes effect. The **Hazard Rate** columns sets the exponential hazard rate for the **Control** group and **Treatment** group in effect from the start time of the current hazard piece to

the start time in the next row. The **Hazard Ratio** row is also available for each period and changing either **Hazard Rate** or the **Hazard Ratio** will automatically update a cell in that row to ensure consistency as for the **Number of Hazard Pieces = 1** case.

See section 3.5 for details on how to calculate a exponential **Hazard Rate** using a median survival or survival probability and the Compute Effect Size side table for STT3 may also be useful. By default the piecewise exponential assumes constant control and treatment exponential hazard rates (same **Hazard Rate** as for the **Number of Hazard Pieces = 1** case) with **Starting at Time** being values increasing by 1 up to the final row.

The Weibull distribution has four parameters: the Weibull **Scale Parameter - Control,** Weibull **Shape Parameter - Treatment**, the Weibull **Shape Parameter - Control** and Weibull **Shape Parameter - Treatment**. **Control/Treatment** indicates the treatment group the Weibull parameter is associated with. The default for these is found by fitting the survival data from the subject-level data (see subsubsection 11.1.2.2 for details).

The **Dropout Model** tab is opened by selecting the **Dropout Model** tab name at the top of the main window. For this demonstration, the **Dropout Model** tab is shown in Figure 11.94.

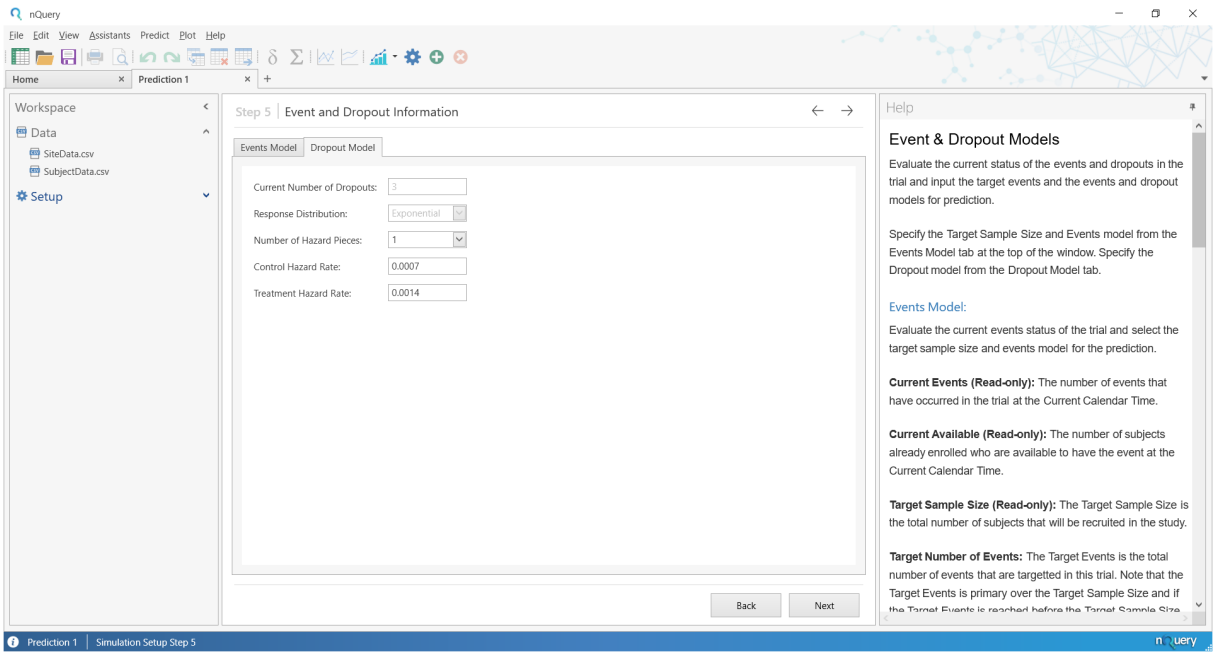


Figure 11.94: Dropout Model tab for Unblinded Events with Subject + Site-level Data

For **Dropout Model**, the **Current Number of Dropouts** (number of subjects who have dropped out up to the **Current Time**), **Response Distribution** and **Number of Hazard Pieces** are available. For dropout, the only **Response Distribution** option is **Exponential**. The inputs and defaults for dropout **Exponential Response Distribution**, for both the case where **Hazard Pieces = 1** (Constant Exponential) or **Hazard Pieces > 1** (Piecewise Exponential), are the same as from the **Events Model** described above (with the exception of removing the **Hazard Ratio** field) and therefore will not be replicated here. In this demonstration, the constant exponential **Control Hazard Rate**

and **Treatment Hazard Rate** for dropout calculated from the information provided equals 0.0007 and 0.0014 respectively.

In this demonstration the default for all inputs (**Target Sample Size = 804, Target Number of Events = 374, Events Model Exponential Control Hazard Rate = 0.0779, Events Model Exponential Treatment Hazard Rate = 0.0547, Dropout Model Exponential Control Hazard Rate = 0.0007, Dropout Model Exponential Treatment Hazard Rate = 0.0014**) are used. Select the Next or → button to move to the next **Setup** step.

The final step is the **Simulation Controls** step. The **Simulation Controls** step consists of three sections: Simulation Controls, Output for All Trials and Output Options.

Simulation Controls (top-left) sets the **Number of Simulations**, **Refresh Frequency** and **Random Seed**

Output For All Trials (bottom-left) sets the Percentiles desired in the **Percentile Summary** table in the **Simulation Summary** report for key simulation outputs such as study length and sample size.

Output Options (right) selects which additional datasets the user wants in the **Tables** field of the simulation results. Additional datasets will be summary statistics for each simulation and outputs from a set number of individual of simulations.

The **Simulation Controls** step is described in detail in subsubsection 11.2.9.4. In this demonstration, the defaults will be used which corresponds to 1000 simulations with the default percentiles (5%, 25%, 50%, 75%, 95%) and with the "Save summary statistics for every simulation run" **Output Options** table active. The **Simulation Controls** defaults for this demonstration are shown in Figure 11.95. To start the milestone prediction, Select the Run (where Next button was in previous steps) or → button.

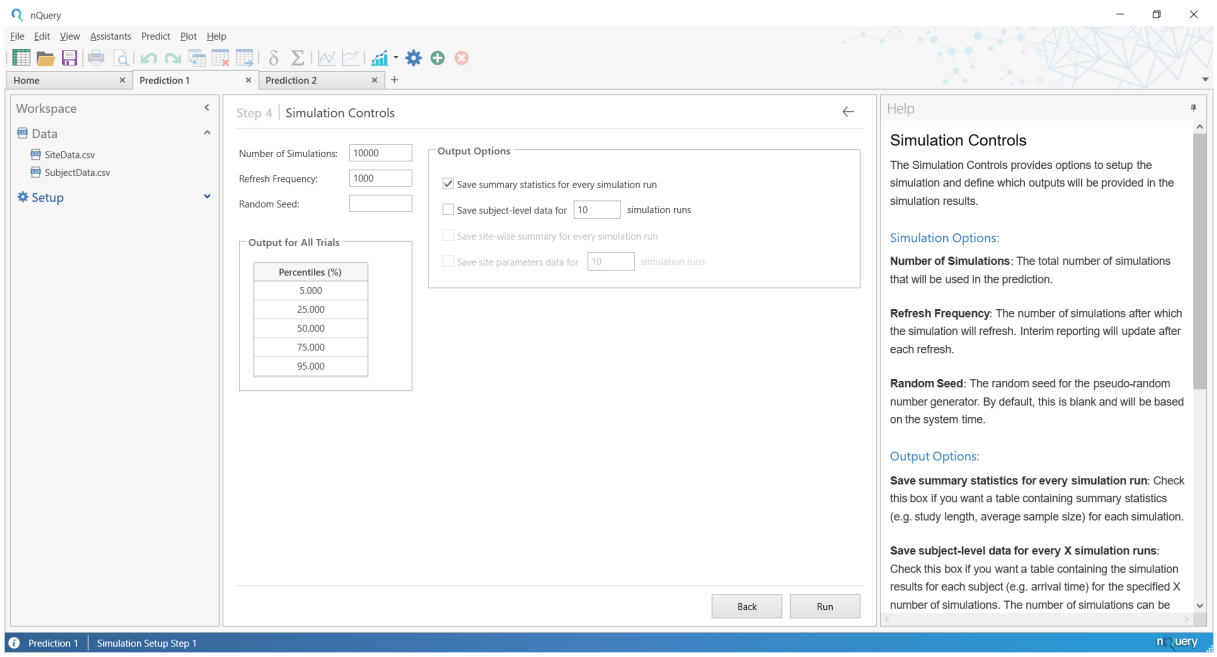


Figure 11.95: Simulation Controls Setup Step for Unblinded Events Prediction using Subject + Site-level Data

Results While a milestone prediction is being run, a **Simulation in Progress** window will be displayed. The **Simulation in Progress** window provides updated information on key simulation metrics while the simulation is ongoing. An example for this demonstration is given in Figure 11.96.

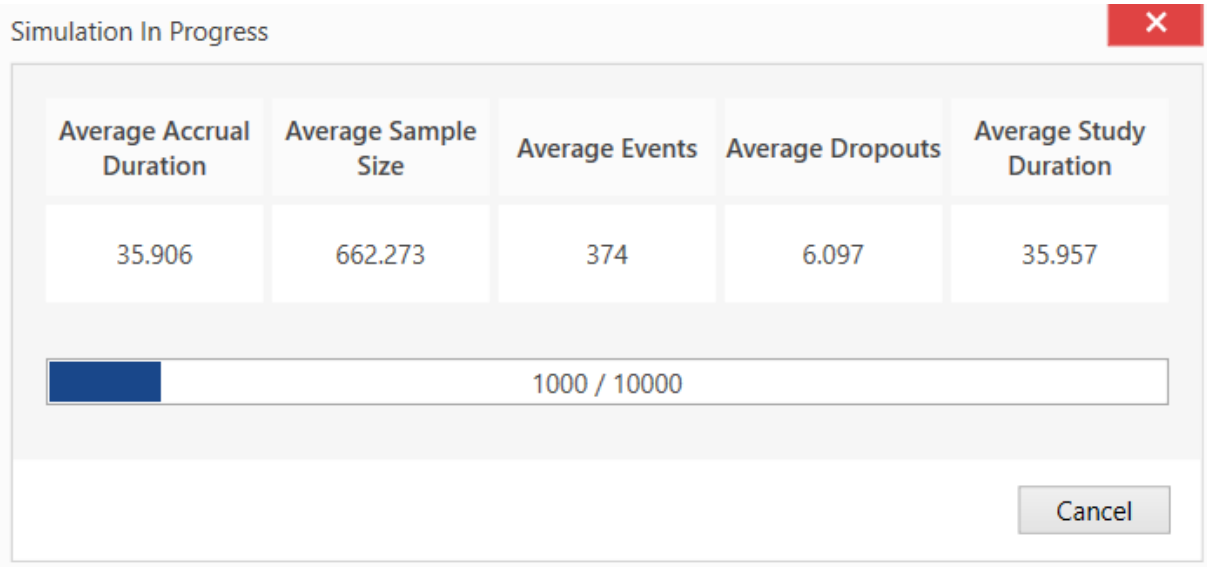


Figure 11.96: Simulation in Progress Window for Unblinded Events Prediction using Subject + Site-level Data

Once the simulation is complete, the results will automatically be added to the Workspace Navigation Bar on the left and the first element under the **Plots** header will be displayed. In this demonstration, the **Enrollment Prediction Plot** will be displayed. This is shown in Figure 11.97.

Figure 11.97: Enrollment Prediction Plot for Unblinded Events Prediction using Subject + Site-level Data

The results of a nQuery Predict milestone prediction can be divided into three categories: **Reports, Plots** and **Tables**. A high-level summary of the results in nQuery Predict is provided in subsection 11.2.8 with demonstration specific elements highlighted here.

For this demonstration the **Reports** header contains the **Simulation Summary** report, the **Plots** header contains the **Enrollment Prediction, Events Prediction** and **Dropout Prediction** plot and the **Tables** header contains the **Enrollment Prediction Table, Events Prediction Table, Dropout Prediction Table** and **Summary Statistics Per-Simulation**. To select any result element, select it from the appropriate header in the Workspace Navigation Bar on the left (see subsection 11.2.2 for details on the Navigation Bar).

The **Simulation Summary** provides a tabular summary of the inputs and outputs from the current milestone prediction simulation. The **Simulation Summary** for this demonstration is shown in Figure 11.98.

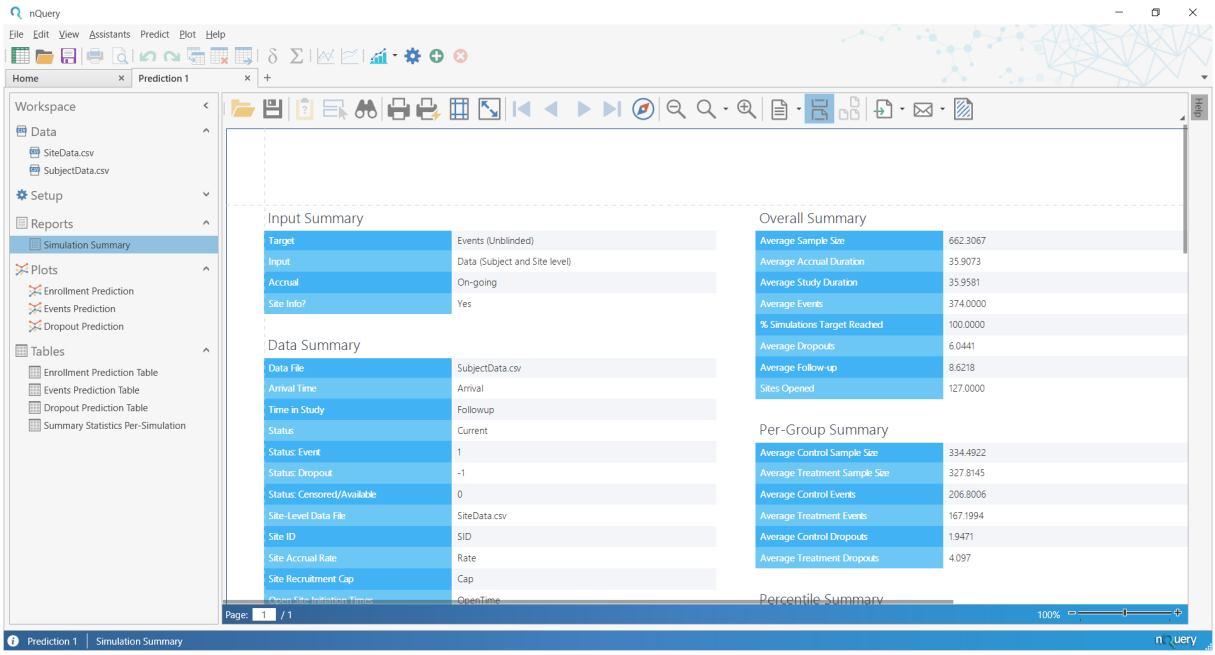


Figure 11.98: Simulation Summary Report for Unblinded Events Prediction using Subject + Site-level Data

In the **Simulation Summary** report, the left-hand column provides a summary of inputs used to generate the current simulation and the right-hand column provides the results of the current simulation. In this demonstration, we will skip the left-hand Inputs column and focus on the main results in the right-hand column and the main report options.

The results column (on the right) is shown in Figure 11.99. For this demonstration, the **Overall Summary** shows that the **Target Number of Events** of 374 was reached in every simulation with an **Average Study Duration** over all the simulations of 35.9581. The **Percentile Summary** shows that 90% of predictions had a **Study Duration** between 34.9694 (5% Percentile) and 36.9366 (95% Percentile), 50% a duration between 35.4936 (25% Percentile) and 36.3094 (75% Percentile) and a median (50% Percentile) duration of 35.8942 The **Average Dropouts** was 6.0441 (Percentiles: 4, 5, 6, 7, 9) and subjects had an **Average Followup** (until either event/dropout or until study end for censored subjects) of 8.6218.

The accrual process in this study ended early for all simulations with an **Average Sample Size** of 662.3067 (Percentiles: 638, 652, 662, 672, 687) enrolled before the **Target Number of Events** of 804 was reached. This meant the **Average Accrual Duration** of 38.9620 (Percentiles: 34.9164, 35.4936, 35.8942, 36.3094, 36.9366) is effectively equal to the **Average Study Duration** of 35.9073 with the accrual duration effectively the time of the last enrollment before study end.

For **Unblinded Events,** a **Per-Group Summary** which provides the average sample size, events and dropouts for each group. The **Control Group** had an **Average Sample Size** 334.4922, **Average Events** of 206.8006 and **Dropouts** of 4.097. The **Treatment Group** had an **Average Sample Size** 327.8145, **Average Events** of 167.1994 and **Dropouts** of 4.097.

Overall Summary

Average Sample Size	662.3067
Average Accrual Duration	35.9073
Average Study Duration	35.9581
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	6.0441
Average Follow-up	8.6218
Sites Opened	127.0000

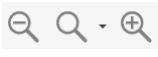
Per-Group Summary

Average Control Sample Size	334.4922
Average Treatment Sample Size	327.8145
Average Control Events	206.8006
Average Treatment Events	167.1994
Average Control Dropouts	1.9471
Average Treatment Dropouts	4.097

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration	Sites Opened
5.00%	374	638	4	34.9164	34.9694	127
25.00%	374	652	5	35.4936	35.5429	127
50.00%	374	662	6	35.8942	35.9449	127
75.00%	374	672	7	36.3094	36.3630	127
95.00%	374	687	9	36.9366	36.9843	127

Figure 11.99: Simulation Summary Report Results for Unblinded Events Prediction

To edit the **Simulation Summary report there a** number of buttons available at the top of the report. For full detail on the **Simulation Summary** report and options to edit the report see subsubsection 11.2.8.2. However the Zoom options  ,

Page Layout and Setup options  and Export option  will be the more commonly used options.

The **Enrollment Prediction** plot provides a visual summary of enrollment simulation from the study start to when the **Target Sample Size** was reached in all simulations. The X-axis is **Time** (relative to study start) and the Y-axis is **Sample Size** (enrolled at Time X-axis value). When the cursor is placed over the **Enrollment Prediction** plot, information on the **Sample Size** enrolled at a given **Time** is shown as per Figure 11.100.

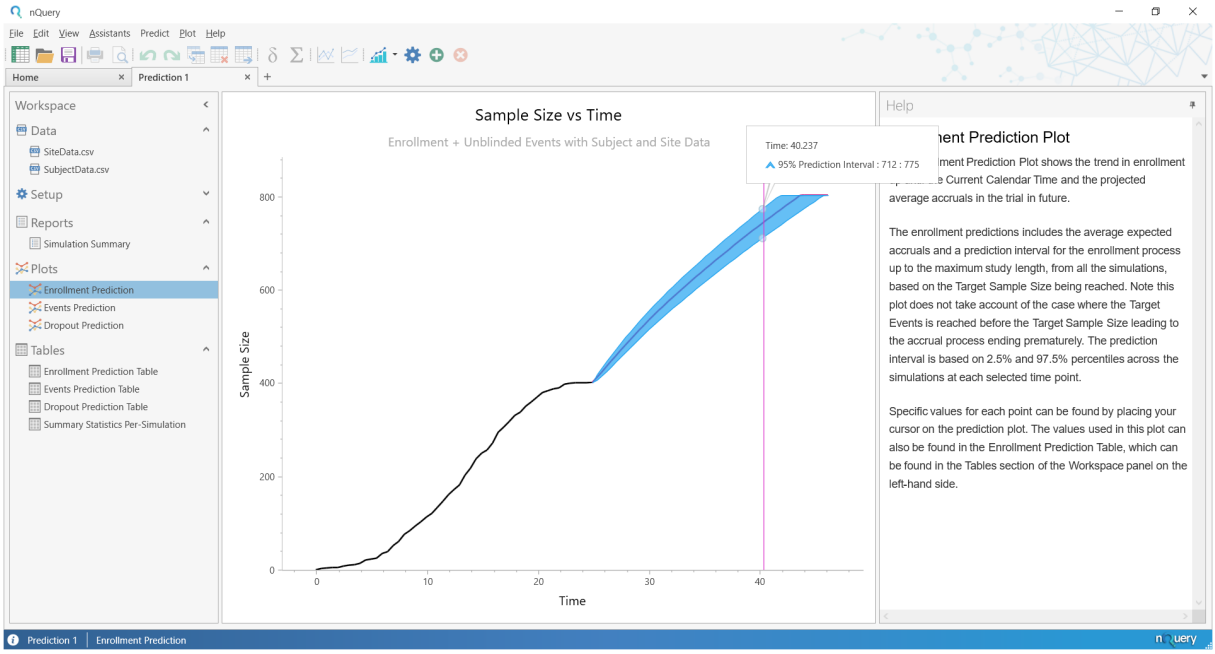


Figure 11.100: Enrollment Prediction Plot for Unblinded Events Prediction using Subject + Site-level Data

The **Enrollment Prediction** plot consists of two parts: from Time = 0 to **Current Time** and from **Current Time** to the **Maximum Time**. The first part is a black line which plots the accrual pattern from the user inputs provided. The second part is a blue conic section with a grey line where the blue conic section plots the 95% prediction interval for the **Sample Size** enrolled at a given **Time** across all simulations and the grey line is the average **Sample Size** enrolled at a given time. The 95% prediction interval indicates the 95% of predictions had a sample size that fell between the lower and upper limit at a given time.

Note that the **Enrollment Prediction** plot will show the projection for **Target Sample Size** and its associated **Accrual Duration** and therefore will usually have a different **Time** scale than the **Event Prediction** and **Dropout Prediction** plots which will be associated with the **Study Duration.** Note the **Enrollment Prediction** plot ignores the case where **Accrual Duration** is cut short due to the **Target Number of Events** being reached before the enrollment process is complete.

The **Events Prediction** plot is very similar to the **Enrollment Prediction** plot where the first part is a black line which plots the events pattern from the user inputs provided and the second part is a yellow conic section with a grey line where the yellow conic section plots the 95% prediction interval for the **Number of Events** that have occurred

at a given **Time** across all simulations and the grey line is the average **Number of Events** at a given time. The 95% prediction interval indicates the 95% of predictions had a number of events that fell between the lower and upper limit at a given time. The **Events Prediction** plot for this demonstration is shown in Figure 11.101.

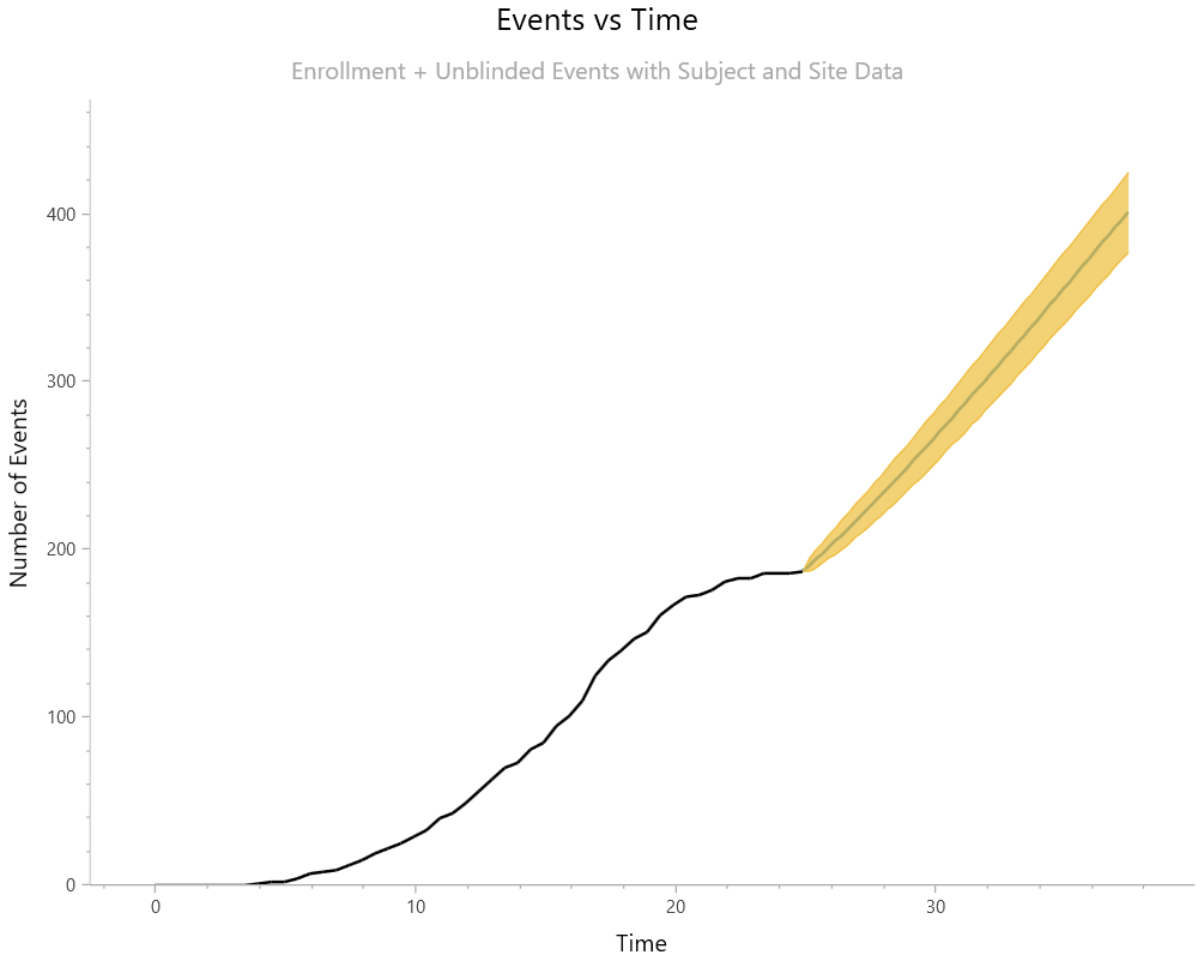


Figure 11.101: Events Prediction Plot for Unblinded Events Prediction using Subject + Site-level Data

It is important the note that these event times are when these events occurred relative to the start of the study, not how long they happened after follow up i.e. this is not a Kaplan-Meier type plot!

The **Dropout Prediction** plot works effectively the same as the **Events Prediction** plot except for the dropout process. The **Dropout Prediction** plot for this demonstration is shown in Figure 11.102.

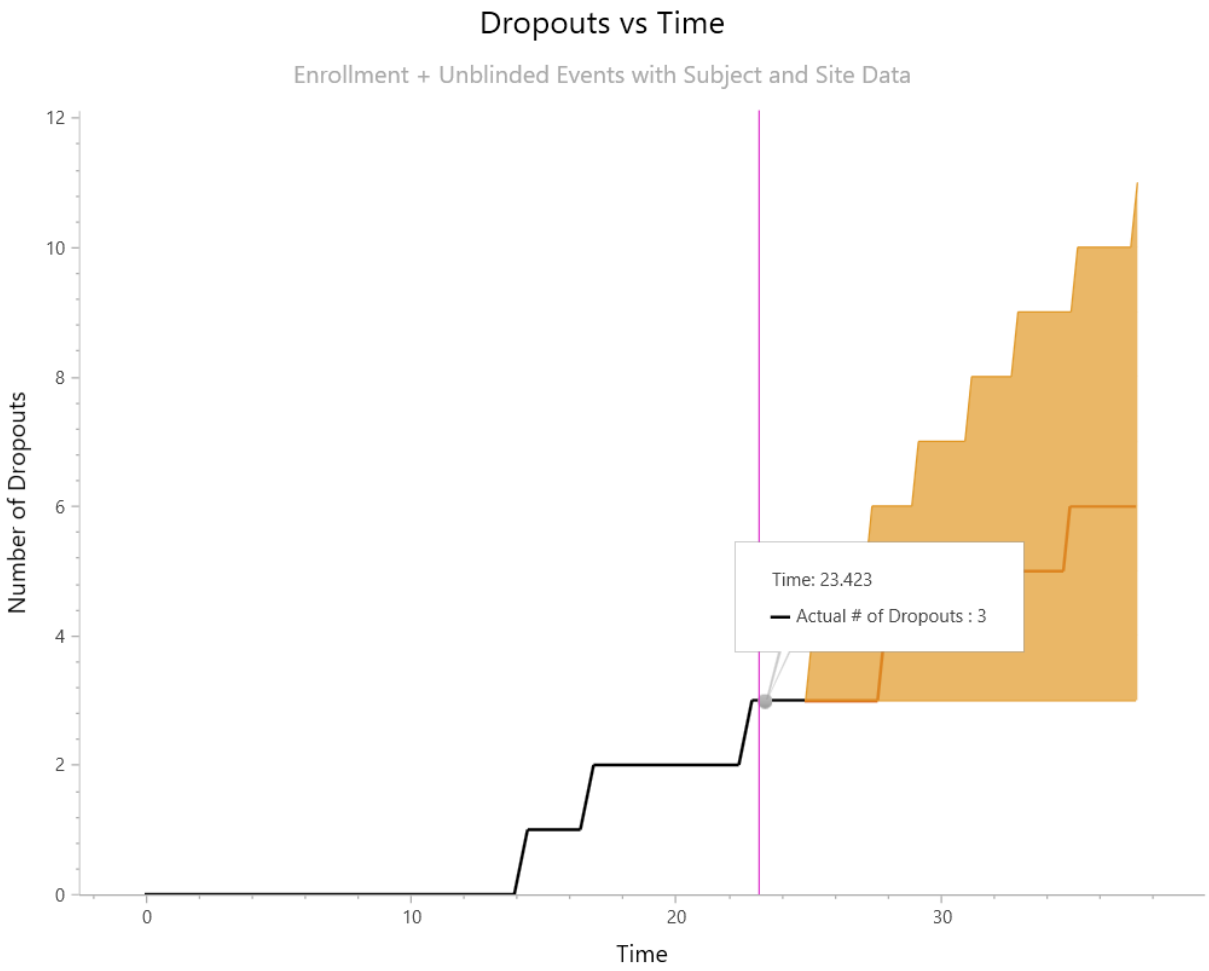


Figure 11.102: Dropout Prediction Plot for Unblinded Events Prediction using Subject + Site-level Data

The **Enrollment Prediction Table, Events Prediction Table and Dropout Prediction Tables** are the tables used to create the respective **Enrollment Prediction, Events Prediction** and **Dropout Prediction** plots, which by default all consists of ~100 rows (50 pre-simulation and 50 post-simulation). Each consists of five columns: **Time, Actual, Predicted Avg. Sample Size/Events/Dropouts, Predicted Median Sample Size/Events/Dropouts, 95% Prediction Interval LL, 95% Prediction Interval UL**. One prediction table (the **Events Prediction Table**) for this demonstration at the start of the simulated period is given in Figure 11.103.

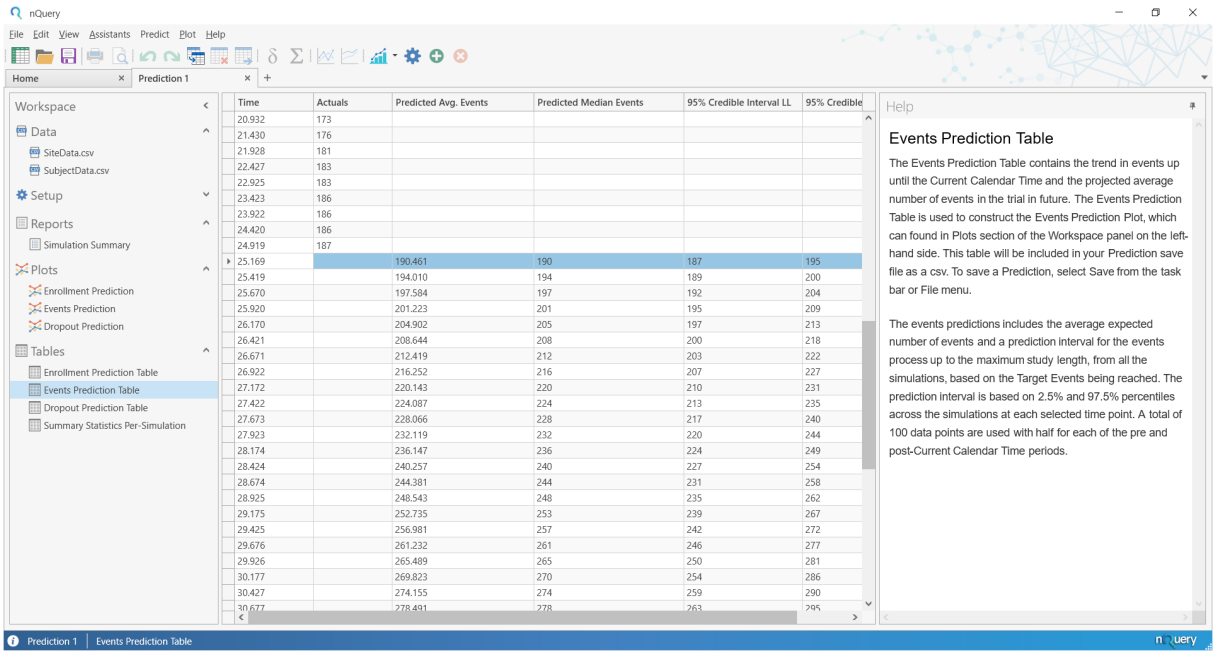


Figure 11.103: Events Prediction Table for Unblinded Events Prediction using Subject + Site-level Data

Time is the time value relative to the study start time of zero. **Actual** is the actual number of events achieved at a pre-simulation **Time** row. **Predicted Avg. Events** is the predicted average (mean) number of events at a post-simulation **Time** row. **Predicted Median Events** is the predicted median number of events at a post-simulation **Time** row. **95% Prediction Interval LL** is the lower limit for the 95% prediction interval for the number of events at a post-simulation **Time** row. **95% Prediction Interval UL** is the upper limit for the 95% prediction interval for the number of events at a post-simulation **Time** row.

Note that the **Enrollment Prediction Table** will show the projection for **Target Sample Size** and its associated **Accrual Duration** and therefore will usually have a different **Time** scale than the **Event Prediction Table** and **Dropout Prediction Table** which will be associated with the **Study Duration.** Note the **Enrollment Prediction Table** ignores the case where **Accrual Duration** is cut short due to the **Target Number of Events** being reached before the enrollment process is complete.

The **Summary Statistics Per-Simulation Table** provides the summary statistics achieved for primary outputs in each simulation. For this demonstration this includes the **Simulation ID, Current Time, Current Sample Size, Current Events, Current Dropout, Current Available, Target Sample Size, Target Events, Study End Time, Total Sample Size, Total Events, Total Dropouts, Total Censored, Control Sample Size, Control Events, Control Dropouts, Treatment Sample Size, Treatment Events, Treatment Dropouts, Accrual Duration, Accrual Duration Uncensored, Average Followup, Median Followup, Target Events Reached.**

The **Summary Statistics Per-Simulation Table** for this demonstration, focused on the per-group simulation results, is shown in Figure 11.104.

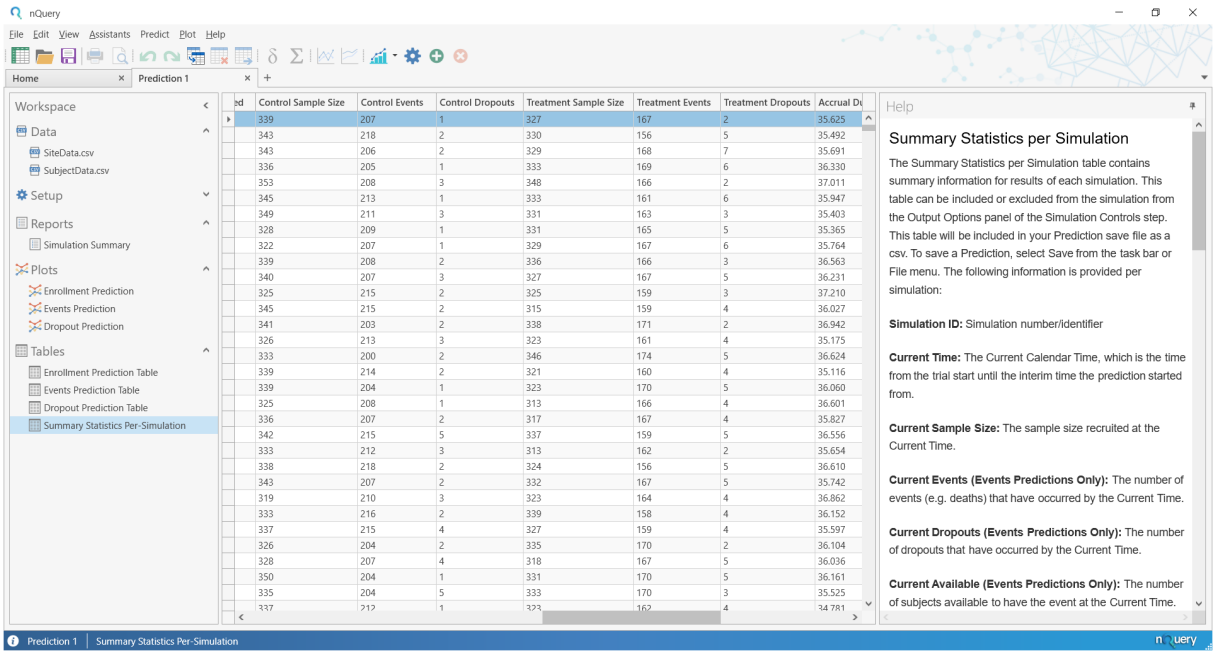


Figure 11.104: Summary Statistics Per-Simulation Table for Unblinded Events Prediction using Subject + Site-level Data

Details on each field are provided in the Help window on the right but broadly the "Current" fields described the information provided up to the **Current Time**, the "Target" fields describe the study targets, the "Total" fields (and final Accrual, Followup and Target Event Reached columns) give the projection achieved for key parameters in total, the "Control" fields give the key results in the **Control Group** and the "Treatment" fields give the results in the **Treatment Group.**

Alternative Scenarios The demonstration has focused on the default inputs using **SubjectData.csv** up to this point. However, as noted in the data summary given in subsection 11.2.4 the study from which the example data was simulated had an original sample size target of 460 (402 enrolled in **SubjectData.csv**).

However, note that the percentage of the **Target Sample Size** enrolled $(100(402/406) = 87.5)$ at the **Current Time** of 24.9186 months is higher than the percentage of the targetted accrual period length (30 months) used so far $(100\,(24.9186/30) = 83.1\%)$. Based on this, it could be decided to discontinue the opening of new sites and to close the "worst" performing site in terms of recruitment. Additionally, there is some evidence of deviations from the constant exponential model and the more flexible nQuery Predict default Weibull model is used.

To explore this additional information, we will investigate two additional scenarios

- Scenario A: **Target Sample Size = 460** using defaults for each site
- Scenario B: **Target Sample Size = 460** with no unopened sites added, "worst" site closed and **Weibull** model

Scenario A The change required compared to the first demonstration is to change the **Target Sample Size** to 460 in the **Sample Size & Followup Options** tab of the

Accrual Options step. The simplest way to do this is to select the **Setup** header in the Workspace Navigation Bar on the left and then select the **Accrual Options** drop down option. Then edit the **Target Sample Size** 460 in the **Sample Size & Followup Options tab** in the top-left and select the Next or → button.

At the **Simulation Controls** step, we will add the three additional tables under the **Output Options** field by selecting the checkbox beside each. We will replace the default of 10 with 1 (at "(x)" spot) for **Save subject-level data for (x) simulation runs** and **Save site parameters data for (x) simulation runs**. An edited down summary of the **Setup** changes is provided in Figure 11.105.

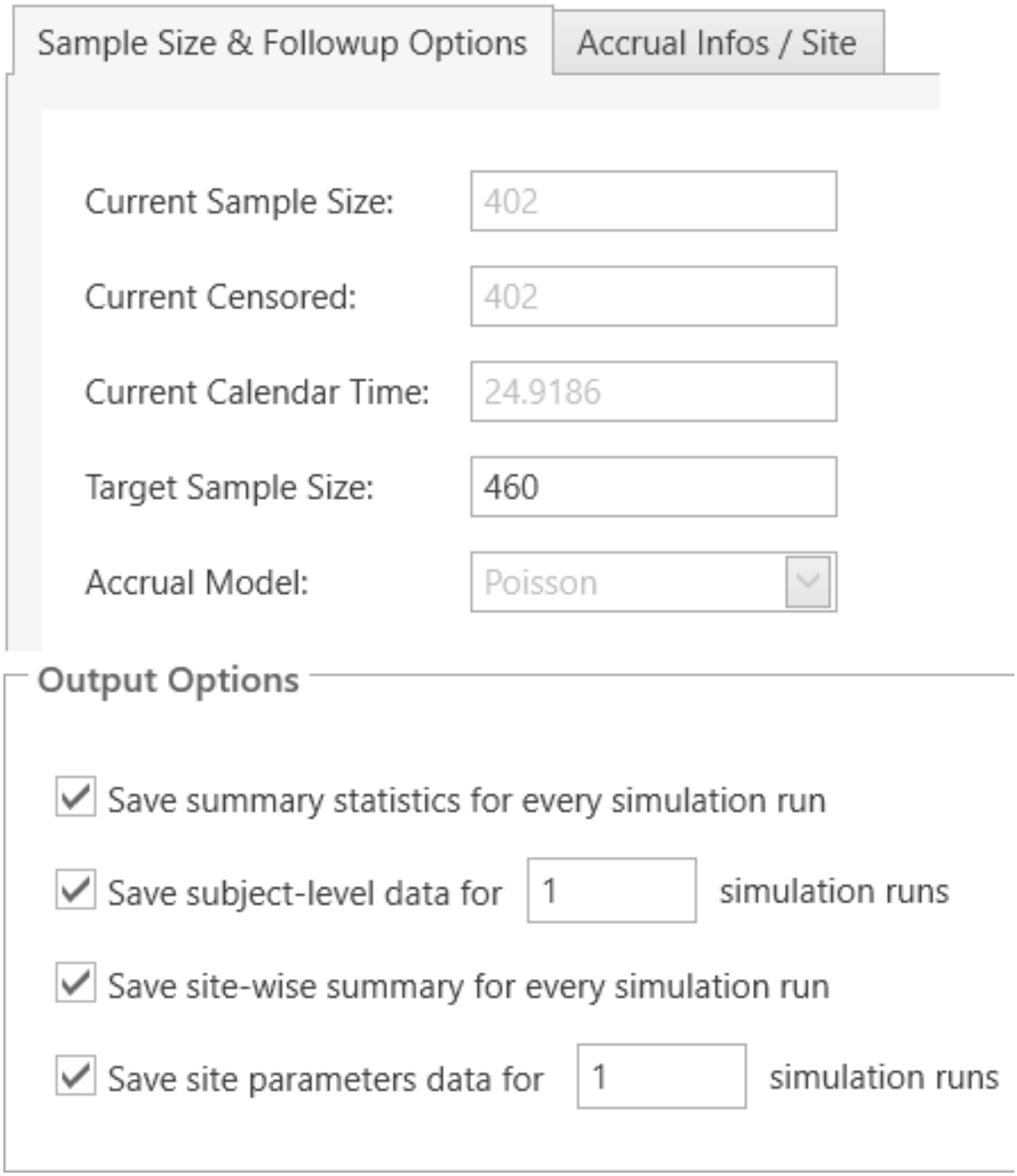


Figure 11.105: Scenario A Setup Changes for Unblinded Events Prediction using Subject + Site-level Data

To run the simulation again with the new Scenario A, select the Run/$^{\rightarrow}$ button. The main results of this Scenario A simulation are shown in Figure 11.106.

Overall Summary

Average Sample Size	460.0000
Average Accrual Duration	27.0596
Average Study Duration	43.7440
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	6.1895
Average Follow-up	12.4849
Sites Opened	127.0000

Per-Group Summary

Average Control Sample Size	232
Average Treatment Sample Size	228
Average Control Events	201.1749
Average Treatment Events	172.8251
Average Control Dropouts	1.9175
Average Treatment Dropouts	4.272

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration	Sites Opened
5.00%	374	460	4	26.6271	41.3850	127
25.00%	374	460	5	26.8709	42.7187	127
50.00%	374	460	6	27.0490	43.6915	127
75.00%	374	460	7	27.2382	44.7063	127
95.00%	374	460	9	27.5262	46.2982	127

Figure 11.106: Scenario A Results for Unblinded Events Prediction using Subject + Site-level Data

For Scenario A, the **Overall Summary** shows that the **Target Number of Events** of 374 was reached in every simulation with an **Average Study Duration** over all the simulations of 43.7440. The **Percentile Summary** shows that 90% of predictions had a **Study Duration** between 41.3850 (5% Percentile) and 46.2982 (95% Percentile), 50% a duration between 42.7187 (25% Percentile) and 44.7063 (75% Percentile) and a median (50% Percentile) duration of 43.9615. The **Target Sample Size** of 460 was reached in all simulations with an **Average Accrual Duration** of 27.0596.

With an expected **Study Duration** of 40 months, this indicates the study is currently

behind schedule by around 3.7 months. However, the enrollment process is expected to be completed after 27.0596 months which is around 3 months earlier than the expected 30 months accrual. This implies the most likely reason for the delay is a lower than expected event hazard rate and this is consistent with a 1-2 month increase in median survival compared to the sample size determination used during the trial's design (see Figure 11.168).

The **Per-Simulation Subject-level Data Table** was also generated here and is shown for Scenario A in Figure 11.107 with the first simulated subject in the first simulation (**Simulation ID = 1**) highlighted. The tables consists of the following fields: **Simulation ID, Subject ID, Arrival Time, Event Time, Dropout Time, Final Status, Site ID, Group**. Note that the order of the Subject ID is based on **Arrival Time** order.

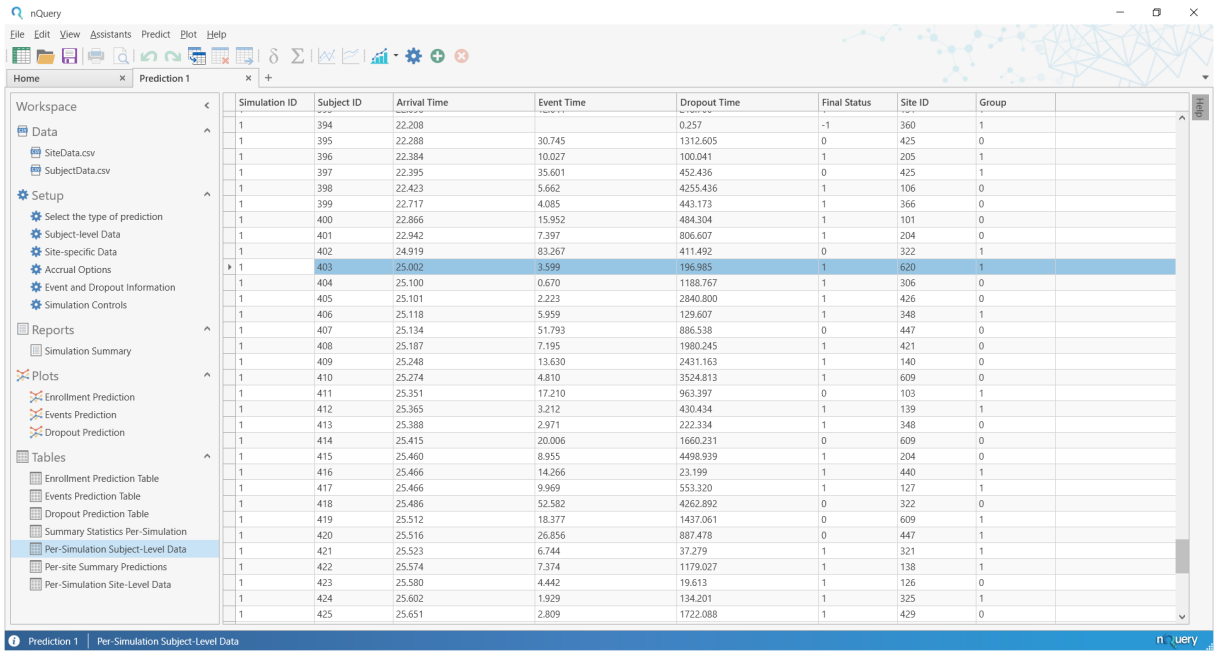


Figure 11.107: Per-Simulation Subject-level Data Table for Subject + Site-level Data

Arrival Time is generated for all simulated subjects (i.e. **Subject ID > 402**). **Event Time** and **Dropout Time** are generated for all simulated subjects and all subjects which were **Censored Status** (all status values from **Status Indicator** field in **Subject-level Data Setup** step) in the subject-level data (for example **Subject ID = 402** in this example). **Site ID** and treatment **Group** are also generated for all simulated subjects. Blank fields for **Event Time** or **Dropout Time** indicate cases where the subject already had the event/dropout and therefore the time for the other status does not exist and does not need to be simulated.

The **Final Status** is from the subject-level data for subjects with **Event Status** or **Dropout Status** and based on the **Event Time** and **Dropout Time** for simulated subjects and **Censored Status** subjects in the subject-level data. **Final Status** will equal **Event Status** if **Event Time** is less than **Dropout Time** and the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.80 for per-simulation end times). **Final Status** will equal **Dropout Status** if **Dropout Time** is less than **Event Time** and the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.80 for

per-simulation end times). **Final Status** will equal **Censored Status** if **Event Time** and **Dropout Time** are greater than the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.80 for per-simulation end times)

The **Per-Site Summary Predictions Table** was also generated here and is shown for Scenario A in Figure 11.108. The **Per-Site Summary Predictions Table** contains the following columns:

- Site ID: Site ID for a site
- Avg. Accrual: The average number of subjects enrolled from this site across all simulations
- Avg. Max Time: The average time of the final enrollment in a site
- Avg. Start Time: The average site initiation time for a site. This is from the Site-level Data for open sites and generated randomly for unopened sites
- Avg. Duration: The average length of time a site was open and enrolling subjects
- Avg. Rate: The average accrual rate for a site during the period it was open
- Times Open: The number of simulations in which the site opened before enrollment was complete

Note that **Times Opens** will equals the number of simulations except for unopened sites with any generated start times higher than a given simulation's **Accrual Duration**.

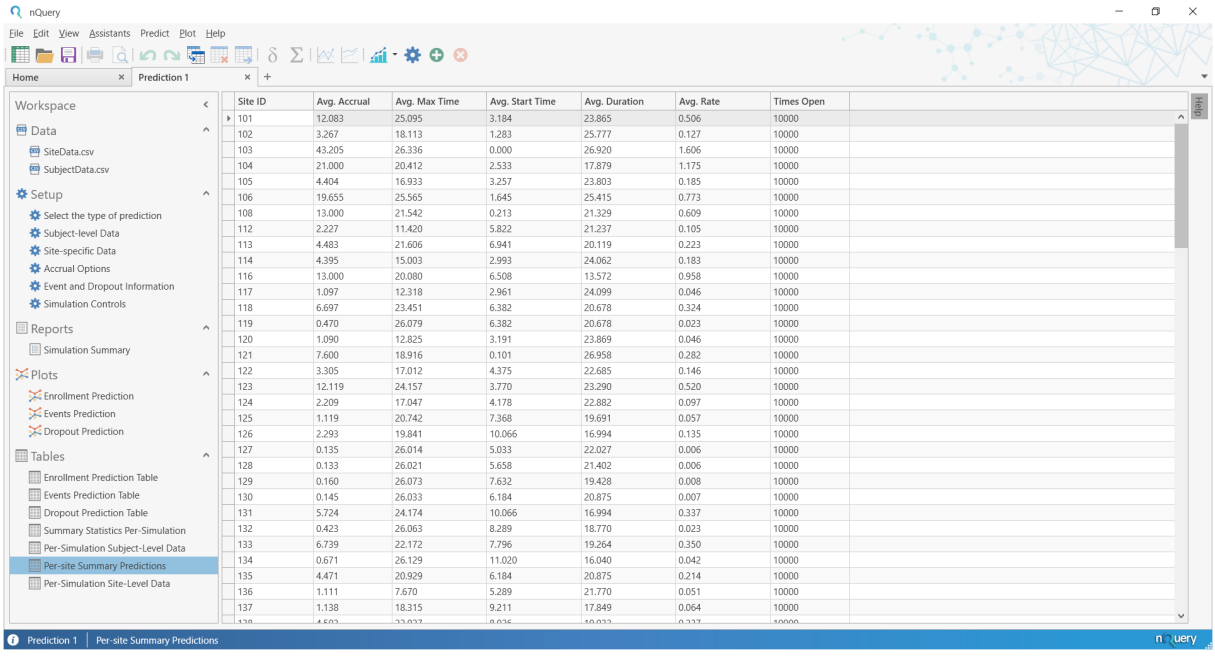


Figure 11.108: Per-Site Summary Predictions for Scenario A

The **Per-Simulation Site-level Data Table** was also generated here and is shown for Scenario A in Figure 11.109. The **Per-Simulation Site-level Data Table** contains the following columns:

- Simulation ID: The simulation number
- Site ID: Site ID for a site

- Site Activation Time: Time after study start when site become open to enroll subjects. Taken from Site-level Data for open sites, generated for unopened sites
- True Enrollment Rate: The user specified enrollment rate for a site
- Accruals: Total number of subjects enrolled from a site in a simulation
- Observed Enrollment Rate: The actual enrollment rate (subjects enrolled per unit time) achieved in a site in a simulation
- Final Enrollment Time: Time of the final enrollment in a site in a simulation
- Enrollment Duration: The length of time a site was open in a simulation
- Site Open: Indicator of whether site opened in a simulation. Tick = Open, X = Did not open

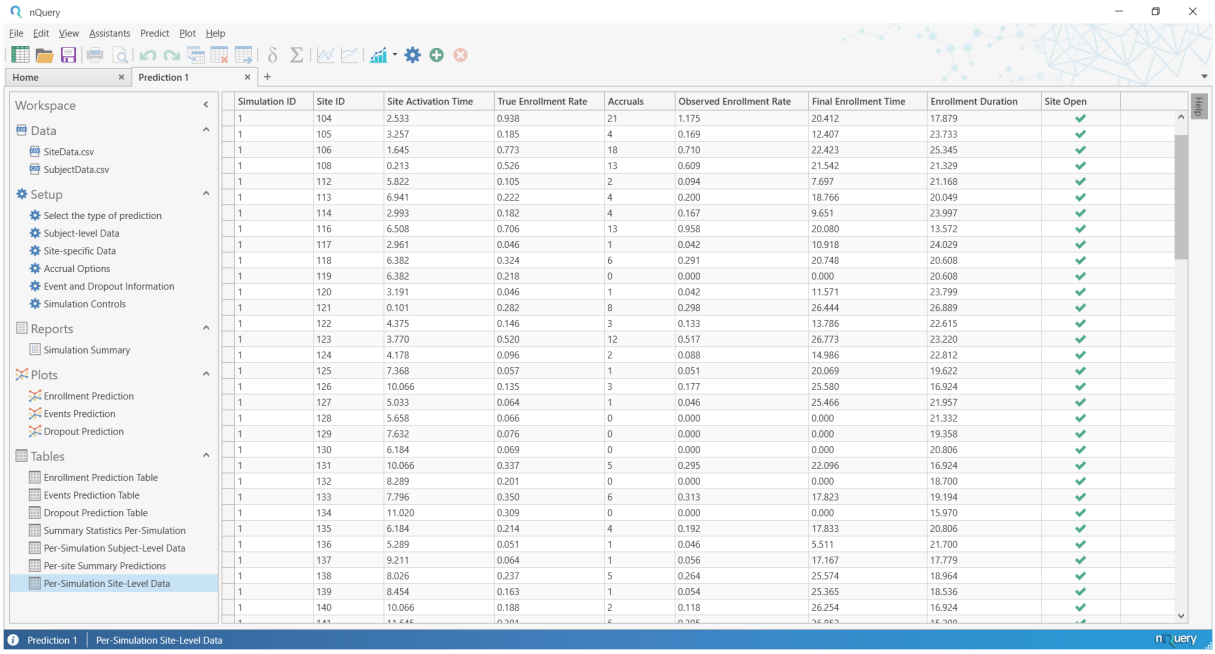


Figure 11.109: Per-Simulation Site-level Data Table for Scenario A

Scenario B Scenario A assumed that an additional 9 sites would open after the **Current Time**, as per the original study plan. Given that the enrollment is ahead of schedule in Scenario A, it was decided to remove all unopened sites from the study plan and that the site with the lowest enrollment rate up to the **Current Time** will be closed.

To evaluate this scenario, select **Accrual Options** from under the **Setup** header in the Workspace Navigation Bar. In **Accrual Options**, open the **Accrual Infos/Sites** tab. Change the **Total Number of Sites** to 118 (equal to the **Number of Sites Opened**). The site with the lowest accrual rate was Site 117. To close this site, set the **Enrollment Cap** equal to 1 (i.e. the current **No. of Accruals**) in the **Site ID = 117** row.

The updated **Accrual Infos/Sites** tab for Scenario B is shown in Figure 11.110.

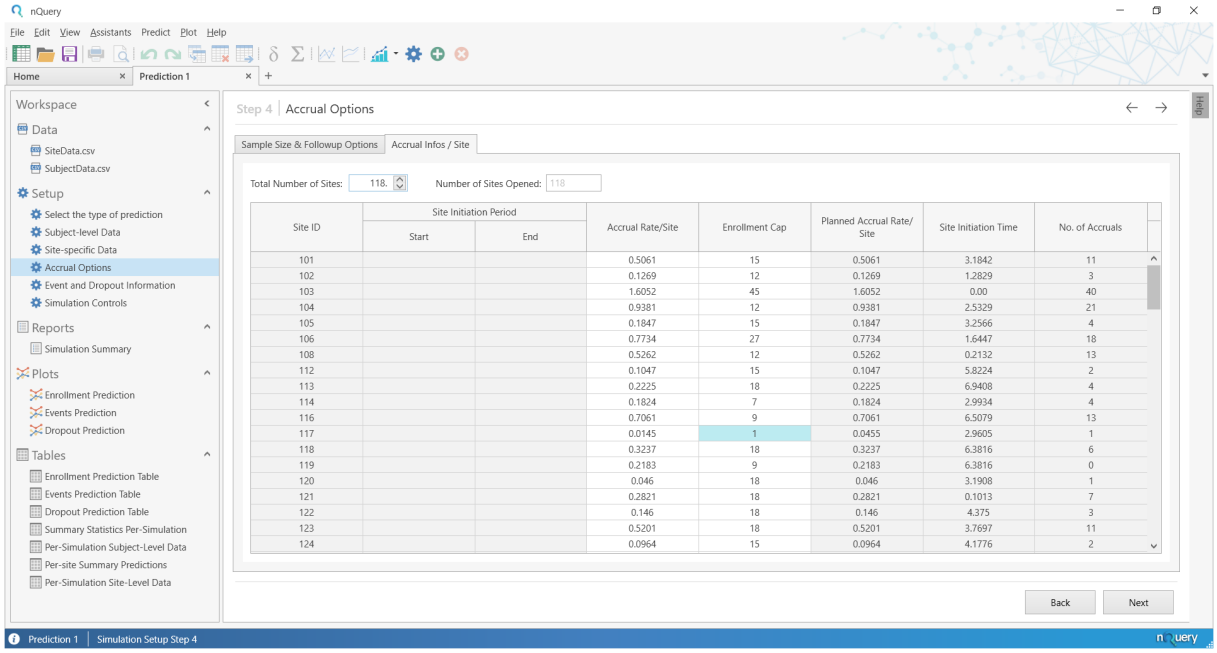


Figure 11.110: Scenario B Accrual Infos/Sites Tab

Next or → button. At the next **Simulation Controls** step, select the Run or → button to simulate Scenario B. The results for Scenario B are summarized in Figure 11.111.

Overall Summary

Average Sample Size	460.0000
Average Accrual Duration	27.2258
Average Study Duration	43.7791
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	6.1701
Average Follow-up	12.4911
Sites Opened	118.0000

Per-Group Summary

Average Control Sample Size	232
Average Treatment Sample Size	228
Average Control Events	201.1793
Average Treatment Events	172.8207
Average Control Dropouts	1.9108
Average Treatment Dropouts	4.2593

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration	Sites Opened
5.00%	374	460	4	26.7442	41.4105	118
25.00%	374	460	5	27.0171	42.7222	118
50.00%	374	460	6	27.2126	43.7471	118
75.00%	374	460	7	27.4201	44.7514	118
95.00%	374	460	9	27.7463	46.2956	118

Figure 11.111: Scenario B for Enrollment Prediction with Subject + Site-level Data

For Scenario B, the **Overall Summary** shows that the **Target Sample Size** of 460 was reached in every simulation with an **Average Accrual Duration** over all the simulations of 27.2258 with the **Percentile Summary** showing that 95% of predictions had a **Study Duration** between 26.7442 and 27.7463, 50% a duration between 27.0171 and 27.4201 with a median duration of 27.2126 with 118 **Sites Opened** in all cases as expected. This was approximately a 0.16 months increase compared to **Scenario A** which is, as expected, a minimal change due to choosing to not open any additional sites and closing Site 117. The **Average Study Duration** of 43.7991 was also a minimal increase over **Scenario A's** 43.7440.

11.2.7.3 Blinded Events Prediction with Subject Data Only with Enrollment Complete

Setup **Blinded Events** milestone prediction using **Subject-level Data Only** means that the prediction will project the expected length of study needed to achieve a specified **Target Number of Events** using subject-level interim data alone. In this demonstration, the enrollment process is assumed to be complete and therefore the total sample size available will equal the number of rows in **SubjectData.csv**, which is 402.

In the **Setup** for this prediction, first in the **Select the type of Prediction** step select **Blinded Events** from the **Target** field, **Subject Data Only** from the **Input** field and **Complete** from the **Enrollment Status** field.

These selections are shown in Figure 11.112. Select the Next button in the bottom-right or → button in the top-right of the Main Window to move to the next step of the prediction **Setup** stage.

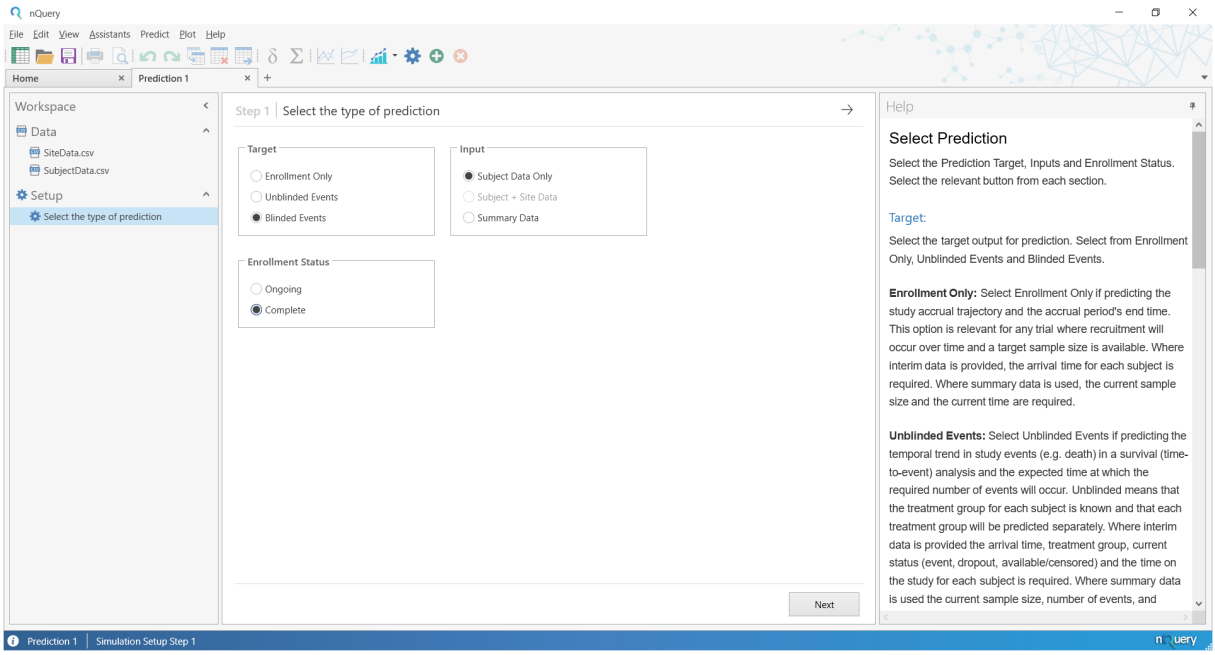


Figure 11.112: Select the Type of Prediction Setup Step for Blinded Events when Enrollment Complete

The next step is the **Subject-level Data** step. The **Subject-level Data** step is a Data Field Selection step. The **Subject-level Data** is the dataset where each row corresponds to a specific subject enrolled in the study.

Data Field Selection steps are steps in which the required dataset in the current Workspace is selected and columns in the selected dataset are assigned to the required fields for that prediction problem. The options in a given Data Field Selection field are opened by selecting the ▽ button on the right of each field which is found to the right of the field name e.g. **Select Data**. Each field will have specific requirements (e.g. numeric only, two distinct values only) and nQuery Predict only displays options which are consistent with those fields.

In this prediction there are two fields which are as follows:

- Select Dataset: Select the dataset that is the Subject-level Data from the datasets in the current workspace
- Arrival Time: The arrival time column contains the length of time since the study start (Time = 0) until a subject entered the study. Each subject's Arrival Time should be greater than or equal to zero
- Status Indicator: The status (event, dropout, censored/active) for each subject. This Status Indicator column should have a minimum of one alphanumeric unique value and a maximum of three unique values. It has the following sub-fields
  - Event Status: Enter value in Status Indicator column that corresponds to subject having had an event
  - Dropout Status: Enter value in Status Indicator column that corresponds to a subject having dropped out
  - Censored Status: Enter value in Status Indicator column that corresponds to a subject having neither had the event or dropped out
- Time on Study: The length of time after Arrival Time that a subject was in the study. Must be numeric value greater than or equal to zero. The definition depends on Status Indicator (see below)

When the **Status Indicator** field is selected, the **Event Status**, **Dropout Status** and **Censored Status** rows become active. These sub-fields are used to select which values in the **Status Indicator** field correspond to each subject status of interest. The **Censored Status** is also referred to as the **Available Status** as the subject would have been administratively censored if the study ended at the **Current Time** but will be available to have the event of interest in the future during the event milestone prediction.

If the nQuery Predict default values of 1 = Event, -1 = Dropout, 0 = Censored is used in the **Status Indicator** field in the **Subject-level Data** then the **Status** sub-fields will be filled automatically with those assignments. Otherwise, manually enter values by either inputting a value directly into the field or selecting the ▽ button on the right of each **Status** sub-field and selecting from the list of unique values in the selected **Status Indicator** field. If there are less than three unique values in the **Status Indicator** field (for example if there have been no dropouts i.e. zero rows with **Dropout Status**) then the user must manually enter the value they would like to have assigned for that **Status** outcome. Note that appropriate defaults will be provided for the rate of previously unused **Status** category in subsequent steps e.g. Dropout Hazard Rate(s) = 0.

The definition of **Time on Study** will depend on the **Status Indicator** for that subject. If the **Status Indicator** is equal to **Event Status** or **Dropout Status**, the **Time on Study** is the length of time a subject was followed for after their **Arrival Time** before they had an event/dropped out. If the **Status Indicator** is equal to **Censored Status**, the **Time on Study** is the length of time a subject was followed for after their **Arrival Time** until the **Current Time.**

For this prediction, in the **Select Dataset** field select **SubjectData.csv**. Then in the **Arrival Time** field select **Arrival**, in the **Status Indicator** field select **Current** (assign 1 to **Event Status**, -1 to **Dropout Status**, 0 to **Censored Status**) and in the **Time on Study** field select **Followup.** These selections are shown in Figure 11.113. Select the Next or → button to move to the next **Setup** step.

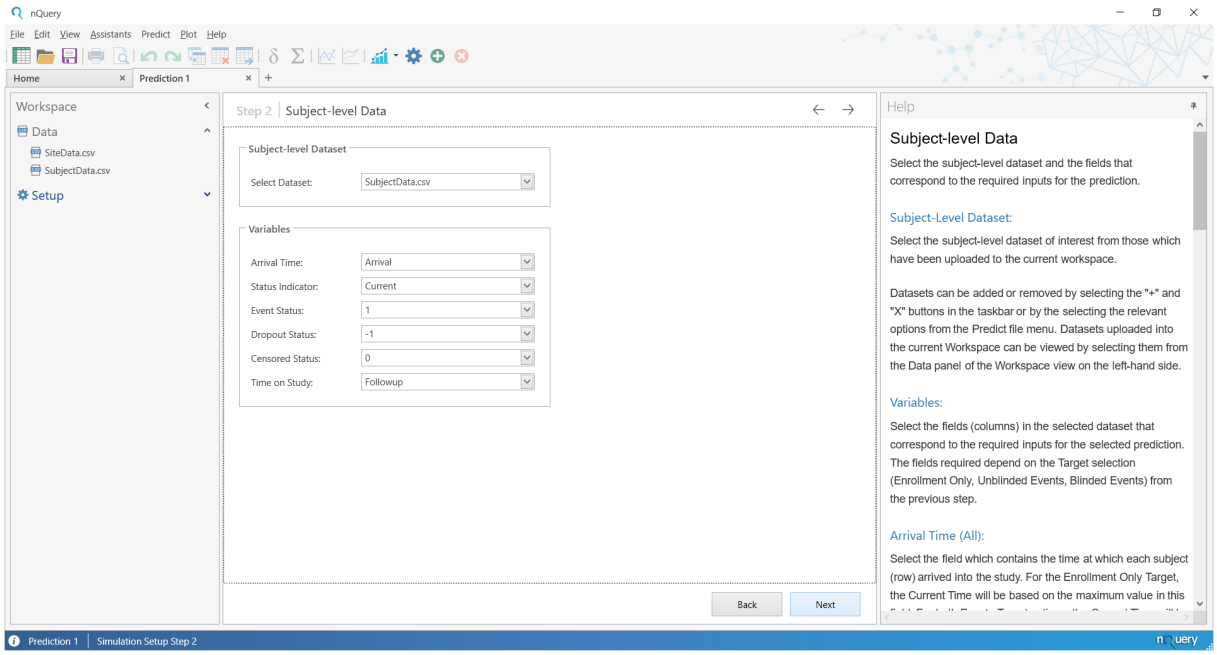


Figure 11.113: Subject-level Data Setup Step for Blinded Events when Enrollment Complete

The next step is the **Accrual Options** step which specifies the **Target Sample Size** and **Followup Option**. The **Accrual Options** step, and its defaults, for this demonstration are shown in Figure 11.114.

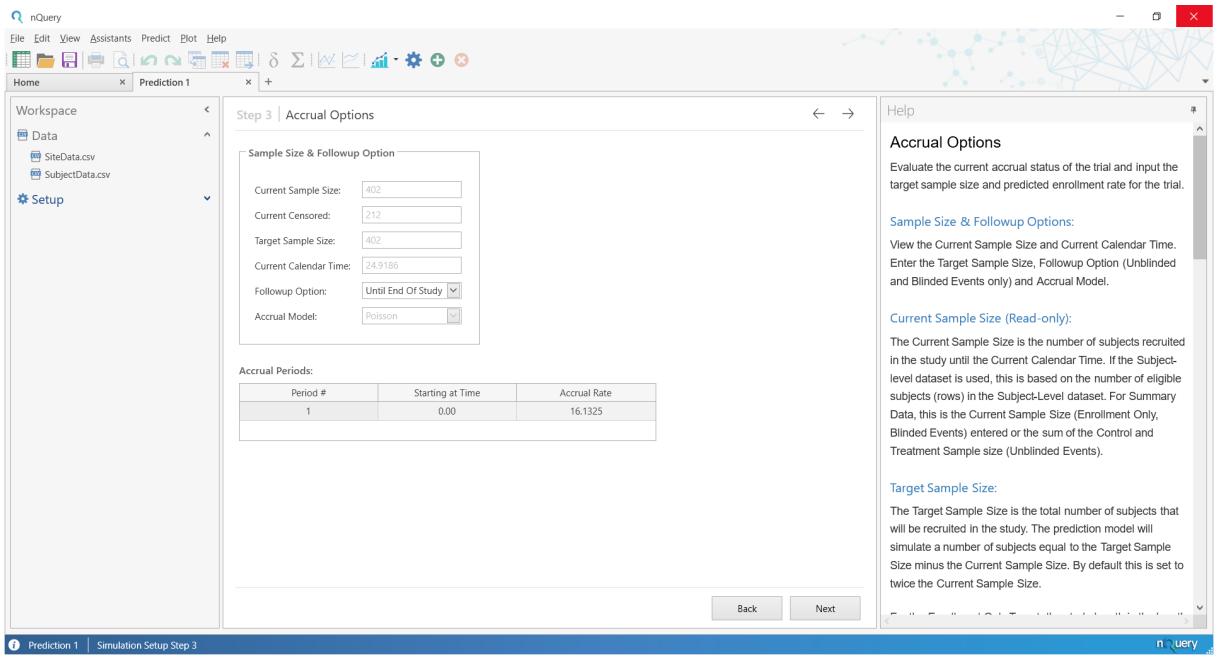


Figure 11.114: Accrual Options Setup Step for Blinded Events Prediction when Enrollment Complete

The **Accrual Options** step consists of two main elements: the **Sample Size & Followup** input fields and the **Accrual Periods** table.

The **Sample Size & Followup** input fields provides information on enrollment process, censored status and current time based on the subject-level data and allows the user to edit the **Target Sample Size** and select the **Followup Option** and **Accrual Model**. The following fields are provided in this prediction:

- Current Sample Size (Read-only): Sample Size recruited into a study so far. Equals the number of rows in the Subject-level Data. When Enrollment Status = Complete, Current and Target Sample Size are the same
- Current Censored (Read-only): The number of subjects who have not had the event or dropped out at the current time. Equals the number of subjects with the Censored Status in the Status Indicator field
- Target Sample Size (Read-only): Total number of subjects that will be recruited in this study. When Enrollment Status = Complete, Current and Target Sample Size are the same
- Current Time (Read-only): The length of time that has passed since the study started. Equals the maximum of the sum of the Arrival Time + Time on Study values for each subject
- Followup Option: Specifies whether subjects who do not have the event/dropout will be administratively censored at the end of the study or after a fixed follow up period
  - Followup Time (Followup Option = For Fixed Period only): Length of time a subject is followed for until administratively censored if they do not have the event/dropout
- Accrual Model (Read-only): The statistical model that will be used to generate simulated enrollments

When **Enrollment Status = Complete**, the **Accrual Options** step is available to see information on ernollment up to the **Current Time** but is not used to set the **Target Sample Size** (see read-only and equal to **Current Sample Size**) and therefore the **Accrual Model** is not needed.

The only editable option is **Followup Option** which by default is set to **Until End of Study**.

If **Followup Option** is set to **Until End of Study** then subjects who do not have the event or dropout will be followed until the end of the study when the **Target Events** is reached, at which point they will be administratively right-censored.

If **Followup Option** is set to **For Fixed Period** then subjects who do not have the event or dropout will be followed until they have a **Time on Study** equal to the value specified in the **Followup Time** field, which appears automatically below the **Followup Option** field when **For Fixed Period** is selected, at which point a subject will be administratively right-censored. Note that for subjects whose **Followup Time** is less than length of the time a subject was on study before the study ended when the **Target Events** was reached, they will be administratively censored at the study end rather than after their **Followup Time**.

The **Accrual Periods** table contains information on the **Accrual Rate** up the **Current Time.** When **Enrollment Status = Complete**, the **Accrual Periods** table will

consist of one row which will contain zero in the **Starting at Time** column and the accrual rate from the information provided in the **Accrual Rate** column.

In this demonstration, the default **Followup Option** = **Until End of Study** is used as per Figure 11.114. Select the Next or → button to move to the next **Setup** step.

The next step is the **Event and Dropout Information** step which specifies the **Target Number of Events,** event model (and associated statistical parameters) and dropout model (and associated statistical parameters). The **Event and Dropout Information** step on the default **Events Model** tab is shown in Figure 11.115.

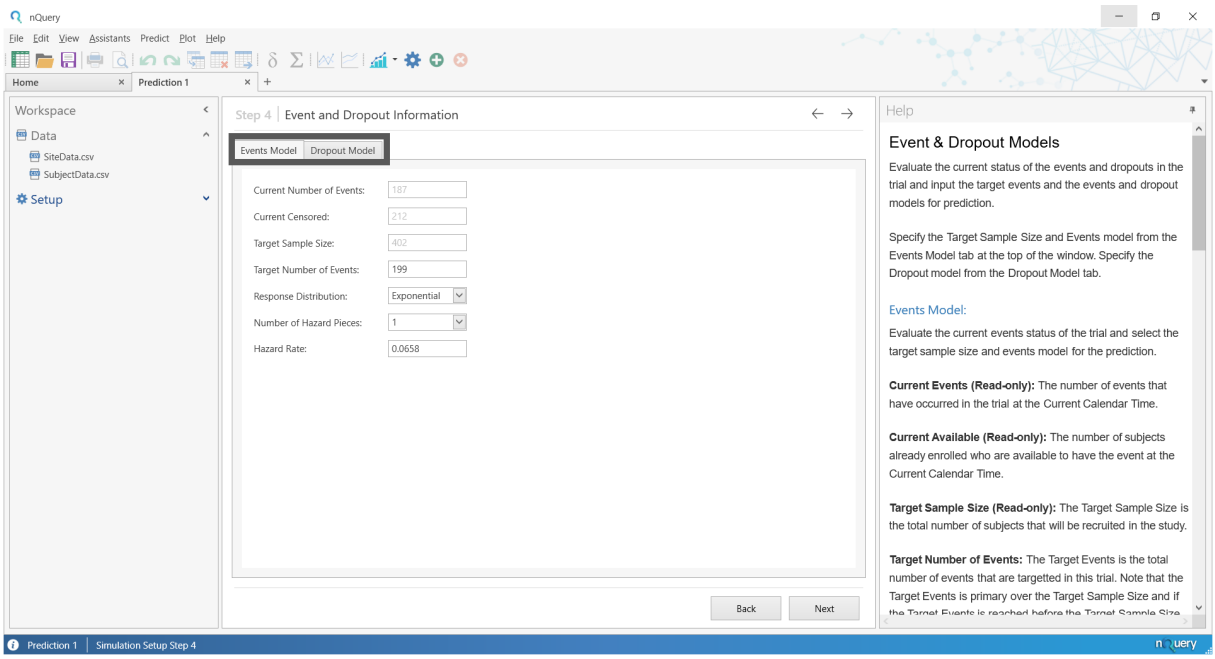


Figure 11.115: Event and Dropout Information Setup Step for Blinded Events Prediction when Enrollment Complete

The **Event and Dropout Information** step consists of two tabs: the **Events Model** tab and the **Dropout Model** tab. These tabs have been highlighted in Figure 11.115 and are opened by selecting the required tab name at the top of the main window, below the step title. For **Blinded Events**, it is assumed that survival and dropout times will be simulated using a single "global" process which is specified by the user.

The **Events Model** tab provides fields which provide information on the current number of subject who have had an event, could have an event going forward and allows the input of the **Target Number of Events** and **Response Distribution** for the events model and additional parameters needed for that specific model. The following fields are provided in this prediction:

- Current Events (Read-only): The number of subjects who had the event of interest at the current time. Equals the number of subjects with the Event Status in the Status Indicator field
- Current Censored (Read-only): The number of subjects who have not had the event or dropped out at the current time. Equals the number of subjects with the Censored Status in the Status Indicator field

- Target Sample Size (Read-only): Total number of subjects that will be recruited in this study. When Enrollment Status = Complete, this is the Current Sample Size
- Target Number of Events (Editable): The required number of subjects needed to have the event of interest for the study to end
- Response Distribution: The statistical model that will be used to generate survival times for subjects available to have the event
- Number of Hazard Pieces (Response Distribution = Exponential only): Number of hazard pieces used to specify the piecewise exponential model. Select value between 1 and 10
- Hazard Rate (Response Distribution = Exponential only, Number of Hazard Pieces =1, Editable): The exponential hazard rate for the constant exponential survival model specified above

In nQuery Predict, the default **Response Distribution** is **Exponential** with the **Number of Hazard Pieces** set to 1 and the default **Hazard Rate** set the expected event rate from the provided information (see subsubsection 11.1.2.2 for details on the survival distributions used in nQuery Predict, see section 3.5 for details on how to calculate a exponential **Hazard Rate** using a median survival or survival probability)**.** The **Target Number of Events** for this example is 199 and the default estimated exponential **Hazard Rate** is 0.0658.

In nQuery, there are effectively three primary survival distributions that survival times can be generated from:

- Constant Exponential (Response Distribution = Exponential, Number of Hazard Pieces =1): Input Hazard Rate
- Piecewise Exponential (Response Distribution = Exponential, Number of Hazard Pieces > 1): Input table of Starting at Time and Hazard Rate columns
- Weibull (Response Distribution = Weibull): Input Scale Parameter and Shape Parameter

Details on how survival times are generated from each of these distributions is provided in subsubsection 11.1.2.2, alongside how the default values provided in nQuery Predict are estimated from the provided information. The change in the **Events Model** tab for each of these choices is shown in Figure 11.116.

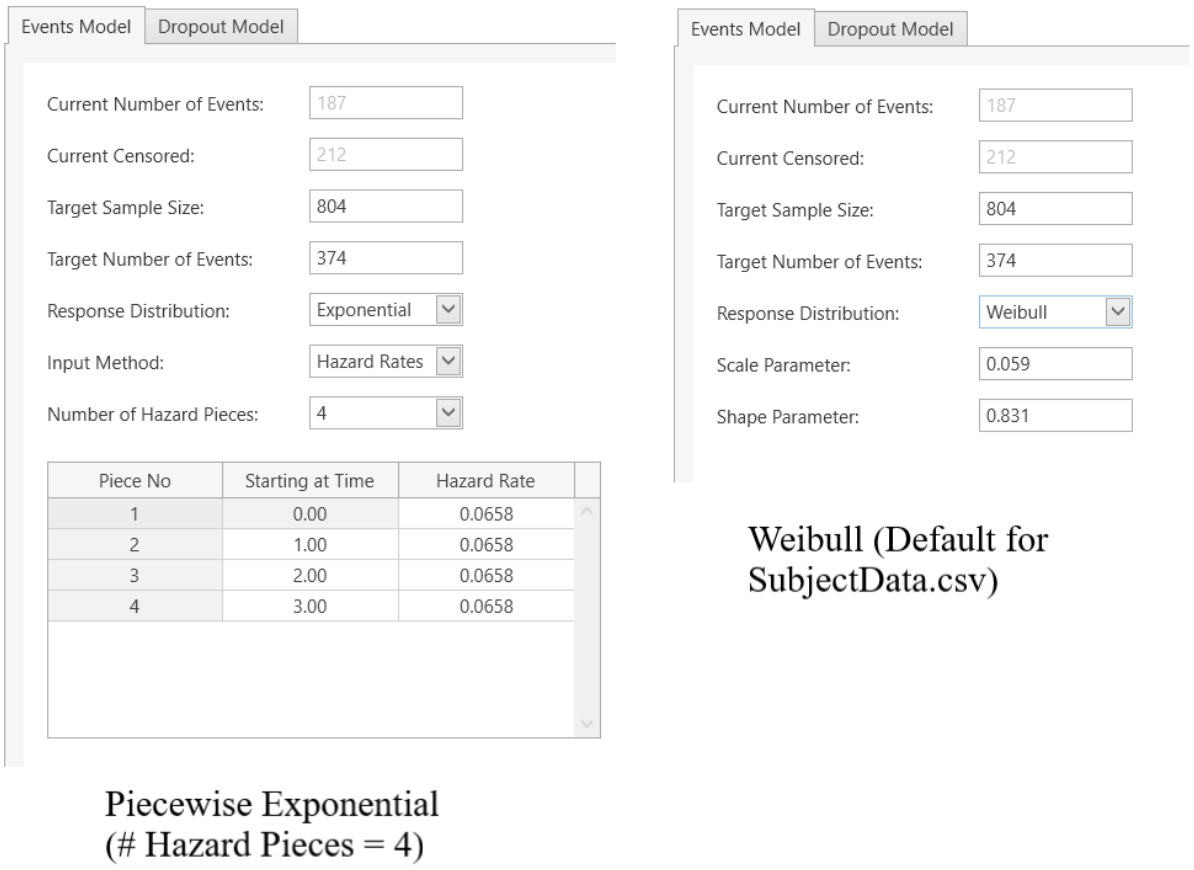


Figure 11.116: Piecewise Exponential (4 Pieces) and Weibull Defaults for Subject-Data.csv

The piecewise exponential table will have a number of rows equal to **Number of Hazard Pieces.** The **Piece No** column indicates the hazard piece number of a row. The **Starting at Time** column sets the start time for when the **Hazard Rate** value in that row takes effect. The **Hazard Rate** column sets the exponential hazard rate in effect from the start time of the current hazard piece to the start time in the next row (see section 3.5 for details on how to calculate a exponential **Hazard Rate** using a median survival or survival probability and the Compute Effect Size side table for STT3 may also be useful). By default the piecewise exponential assumes a constant exponential model **Hazard Rate** (same **Hazard Rate** as for the **Number of Hazard Pieces** = 1 case) with **Starting at Time** being values increasing by 1 up to the final row.

The Weibull distribution has two parameters: the Weibull **Scale Parameter** and Weibull **Shape Parameter**. The default for these is found by fitting the survival data from the subject-level data (see subsubsection 11.1.2.2 for details).

The **Dropout Model** tab is opened by selecting the **Dropout Model** tab name at the top of the main window. For this demonstration, the **Dropout Model** tab is shown in Figure 11.117.

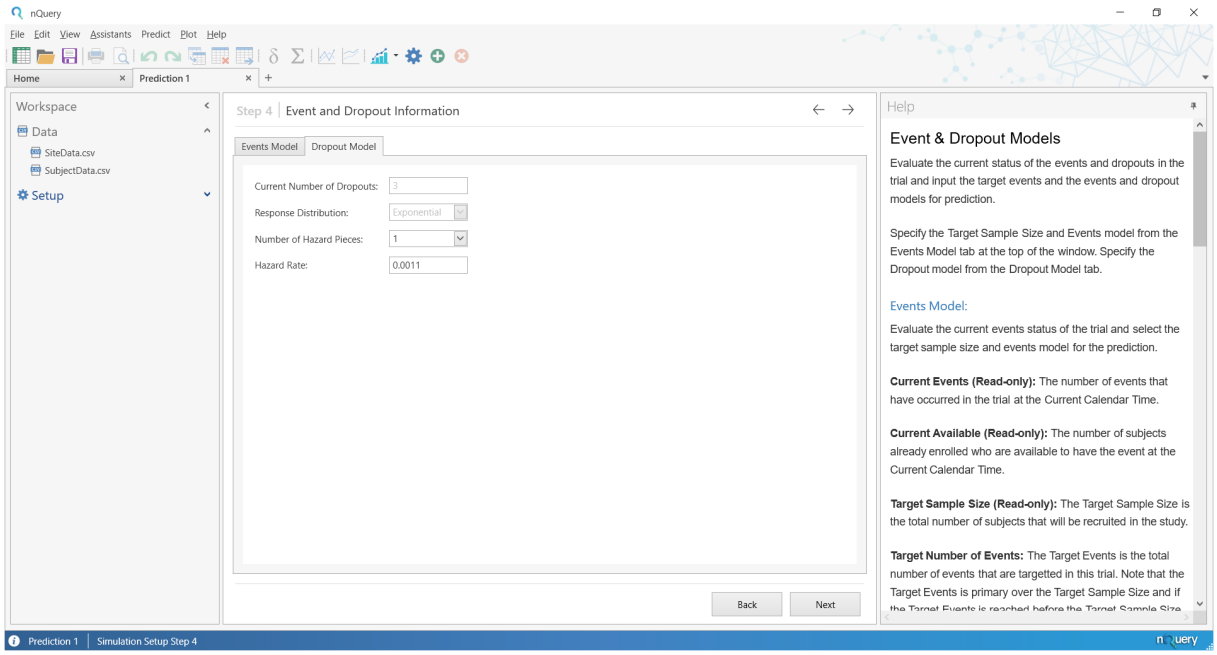


Figure 11.117: Dropout Model tab for Blinded Events with Subject-level Data

For **Dropout Model**, the **Current Number of Dropouts** (number of subjects who have dropped out up to the **Current Time**), **Response Distribution** and **Number of Hazard Pieces** are available. For dropout, the only **Response Distribution** option is **Exponential**. The inputs and defaults for dropout **Exponential Response Distribution**, for both the case where **Hazard Pieces = 1** (Constant Exponential) or **Hazard Pieces > 1** (Piecewise Exponential), are the same as from the **Events Model** described above and therefore will not be replicated here. In this demonstration, the constant exponential **Hazard Rate** for dropout calculated from the information provided equals 0.0011.

In this demonstration the default for all inputs (**Current/Target Sample Size = 402, Target Number of Events = 199, Events Model Exponential Response Distribution (1 Hazard Piece) Hazard Rate = 0.0658, Dropout Model Exponential Response Distribution (1 Hazard Piece) Hazard Rate = 0.0011**) are used. Select the Next or → button to move to the next **Setup** step.

The final step is the **Simulation Controls** step. The **Simulation Controls** step consists of three sections: Simulation Controls, Output for All Trials and Output Options.

Simulation Controls (top-left) sets the **Number of Simulations**, **Refresh Frequency** and **Random Seed**

Output For All Trials (bottom-left) sets the Percentiles desired in the **Percentile Summary** table in the **Simulation Summary** report for key simulation outputs such as study length and sample size.

Output Options (right) selects which additional datasets the user wants in the **Tables** field of the simulation results. Additional datasets will be summary statistics for each simulation and outputs from a set number of individual of simulations.

The **Simulation Controls** step is described in detail in subsubsection 11.2.9.4. In this demonstration, the defaults will be used which corresponds to 1000 simulations with the

default percentiles (5%, 25%, 50%, 75%, 95%) and with the "Save summary statistics for every simulation run" **Output Options** table active. The **Simulation Controls** defaults for this demonstration are shown in Figure 11.118. To start the milestone prediction, Select the Run (where Next button was in previous steps) or → button.

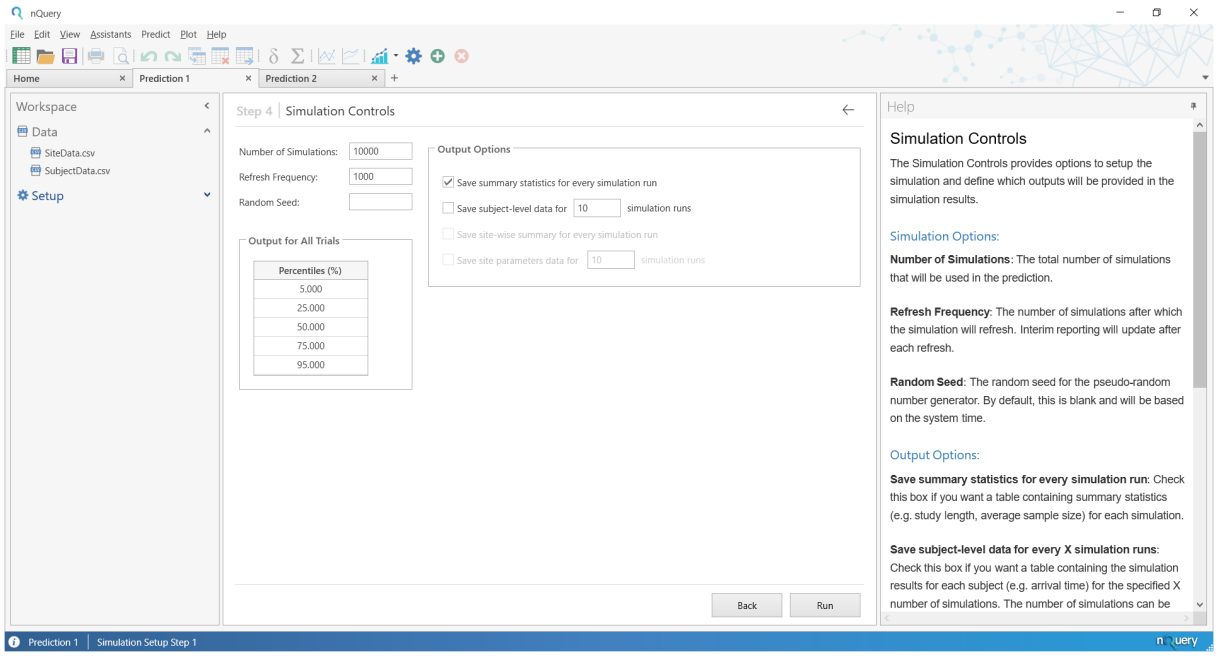


Figure 11.118: Simulation Controls Setup Step for Blinded Events Prediction when Enrollment Complete

Results While a milestone prediction is being run, a **Simulation in Progress** window will be displayed. The **Simulation in Progress** window provides updated information on key simulation metrics while the simulation is ongoing. An example for this demonstration is given in Figure 11.119.

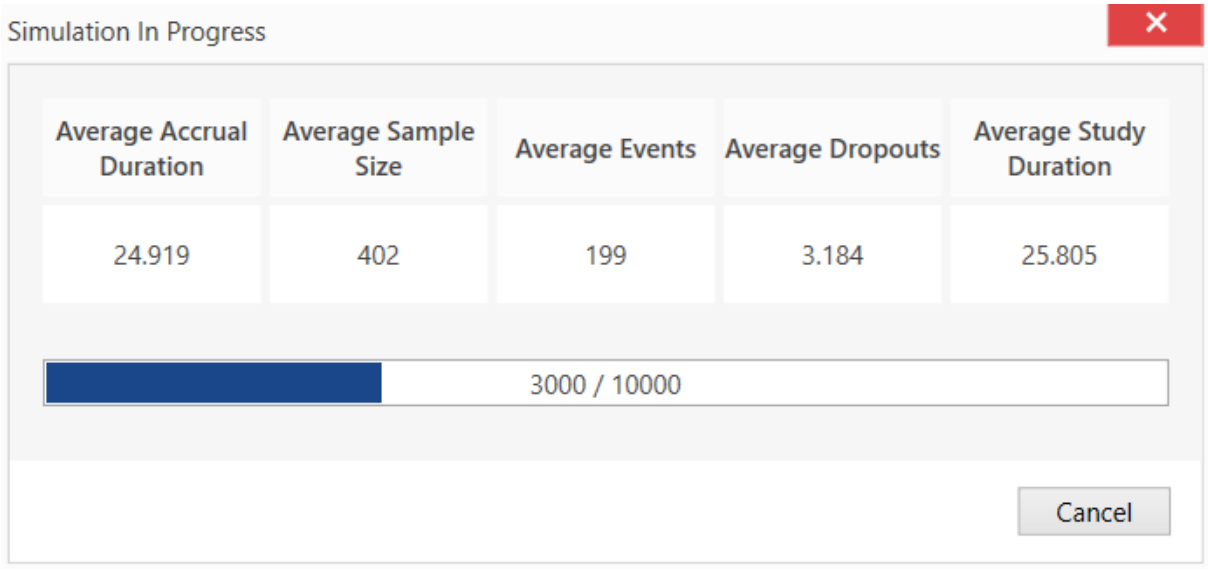


Figure 11.119: Simulation in Progress Window for Blinded Events Prediction when Enrollment Complete

Once the simulation is complete, the results will automatically be added to the Workspace Navigation Bar on the left and the first element under the **Plots** header will be displayed. In this demonstration, the **Enrollment Prediction Plot** will be displayed. This is shown in Figure 11.120.

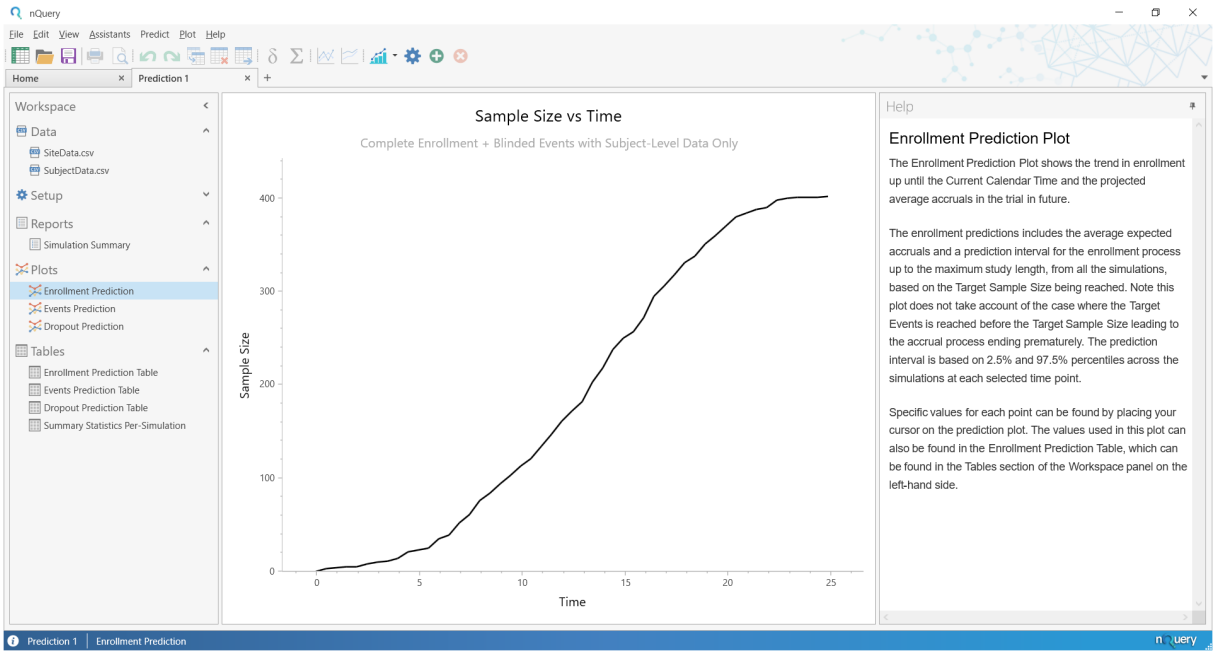


Figure 11.120: Enrollment Prediction Plot for Blinded Events Prediction when Enrollment Complete

The results of a nQuery Predict milestone prediction can be divided into three categories: **Reports, Plots** and **Tables**. A high-level summary of the results in nQuery Predict is provided in subsection 11.2.8 with demonstration specific elements highlighted here.

For this demonstration the **Reports** header contains the **Simulation Summary** report, the **Plots** header contains the **Enrollment Prediction, Events Prediction** and **Dropout Prediction** plot and the **Tables** header contains the **Enrollment Prediction Table, Events Prediction Table, Dropout Prediction Table** and **Summary Statistics Per-Simulation**. To select any result element, select it from the appropriate header in the Workspace Navigation Bar on the left (see subsection 11.2.2 for details on the Navigation Bar).

The **Simulation Summary** provides a tabular summary of the inputs and outputs from the current milestone prediction simulation. The **Simulation Summary** for this demonstration is shown in Figure 11.121.

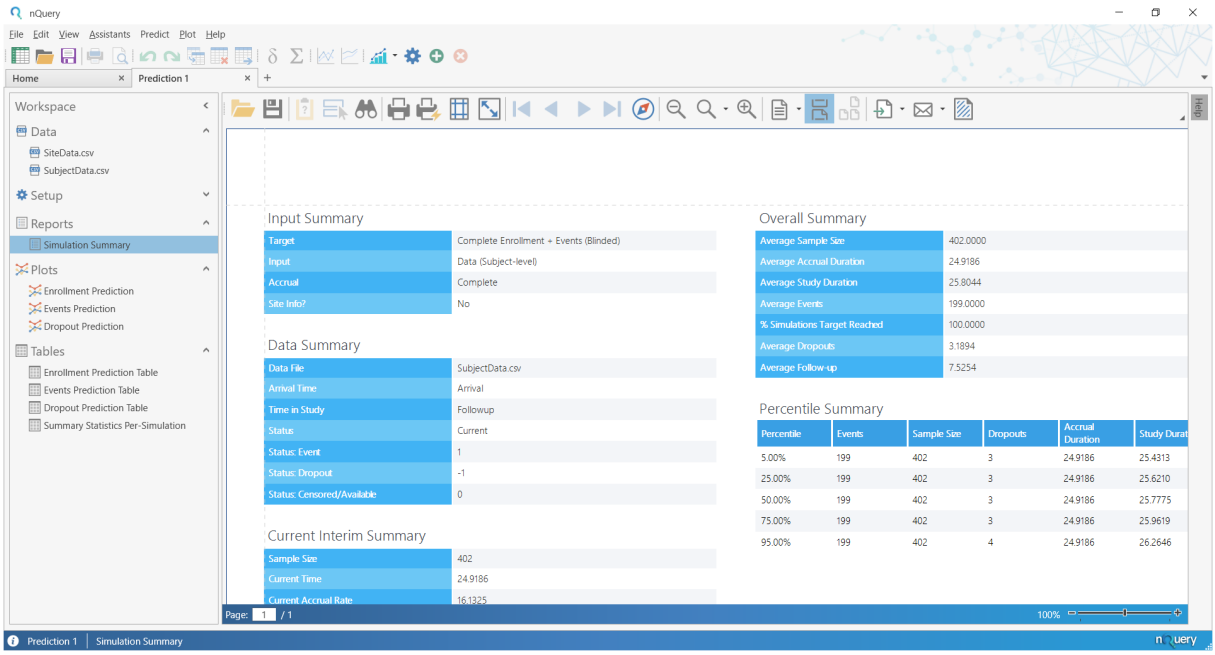


Figure 11.121: Simulation Summary Report for Blinded Events Prediction when Enrollment Complete

In the **Simulation Summary** report, the left-hand column provides a summary of inputs used to generate the current simulation and the right-hand column provides the results of the current simulation. In this demonstration, we will skip the left-hand Inputs column and focus on the main results in the right-hand column and the main report options.

The results column (on the right) is shown in Figure 11.122. For this demonstration, the **Overall Summary** shows that the **Target Number of Events** of 199 was reached in every simulation with an **Average Study Duration** over all the simulations of 25.8044. The **Percentile Summary** shows that 90% of predictions had a **Study Duration** between 25.4313 (5% Percentile) and 26.2646 (95% Percentile), 50% a duration between 25.6210 (25% Percentile) and 25.9619 (75% Percentile) and a median (50% Percentile) duration of 25.7775. The **Average Dropouts** was 3.1894 (Percentiles:3, 3, 3, 3, 4) and subjects had an **Average Followup** (until either event/dropout or until study end for censored subjects) of 7.5254. As enrollment was complete, the **Accrual Duration** and **Sample Size** are constant.

Overall Summary

Average Sample Size	402.0000
Average Accrual Duration	24.9186
Average Study Duration	25.8044
Average Events	199.0000
% Simulations Target Reached	100.0000
Average Dropouts	3.1894
Average Follow-up	7.5254

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	199	402	3	24.9186	25.4313
25.00%	199	402	3	24.9186	25.6210
50.00%	199	402	3	24.9186	25.7775
75.00%	199	402	3	24.9186	25.9619
95.00%	199	402	4	24.9186	26.2646

Figure 11.122: Simulation Summary Report Results for Blinded Events Prediction when Enrollment Complete

To edit the **Simulation Summary report there a** number of buttons available at the top of the report. For full detail on the **Simulation Summary** report and options to edit the report see subsubsection 11.2.8.2. However the Zoom options  , Page Layout and Setup options  and Export option  will be the more commonly used options.

The **Enrollment Prediction** plot provides a visual summary of enrollment. The X-axis is **Time** (relative to study start) and the Y-axis is **Sample Size** (enrolled at Time X-axis value). When the cursor is placed over the **Enrollment Prediction** plot, information on the **Sample Size** enrolled at a given **Time** is shown as per Figure 11.123.

Figure 11.123: Enrollment Prediction Plot for Blinded Events Prediction when Enrollment Complete

The **Enrollment Prediction** plot when **Enrollment Status = Complete** will show the accrual pattern up to the **Current Time**, with the sample size at a given prior time given by placing the cursor over the plot. Note this means a different **Time** scale than the **Event Prediction** and **Dropout Prediction** plots which will be associated with the **Study Duration.**

The **Events Prediction** plot consists of two parts: from Time = 0 to **Current Time** and from **Current Time** to the **Maximum Time**. The first part is a black line which plots the accrual pattern from the user inputs provided. The second part is a yellow conic section with a grey line where the yellow conic section plots the 95% prediction interval for the **Events** achieved at a given **Time** across all simulations and the grey line is the average **Events** at a given time. The 95% prediction interval indicates the 95% of predictions had a number of events that fell between the lower and upper limit at a given time. The **Events Prediction** plot for this demonstration is shown in Figure 11.124.

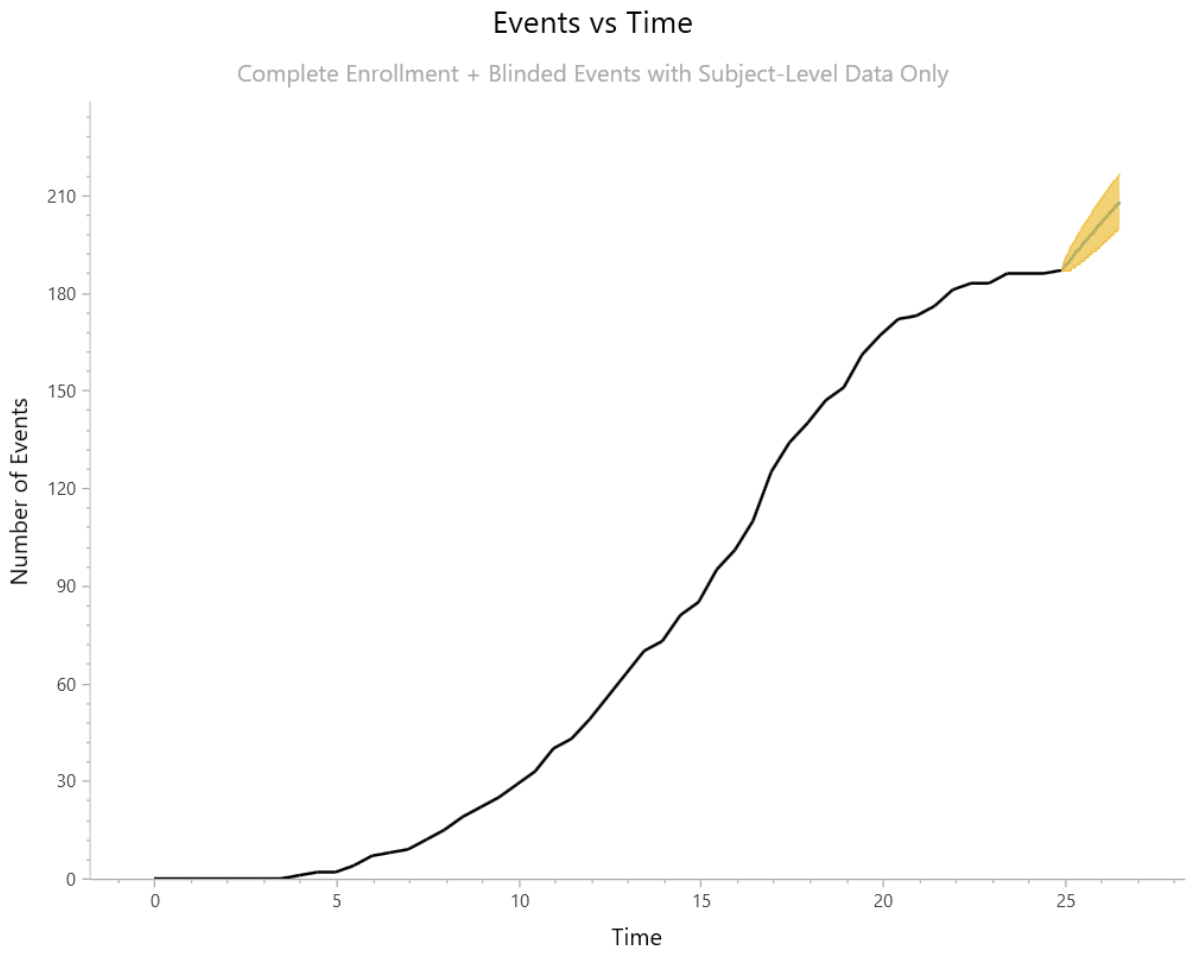


Figure 11.124: Events Prediction Plot for Blinded Events Prediction when Enrollment Complete

It is important the note that these event times are when these events occurred relative to the start of the study, not how long they happened after follow up i.e. this is not a Kaplan-Meier type plot!

The **Dropout Prediction** plot works effectively the same as the **Events Prediction** plot except for the dropout process. The **Dropout Prediction** plot for this demonstration is shown in Figure 11.125.

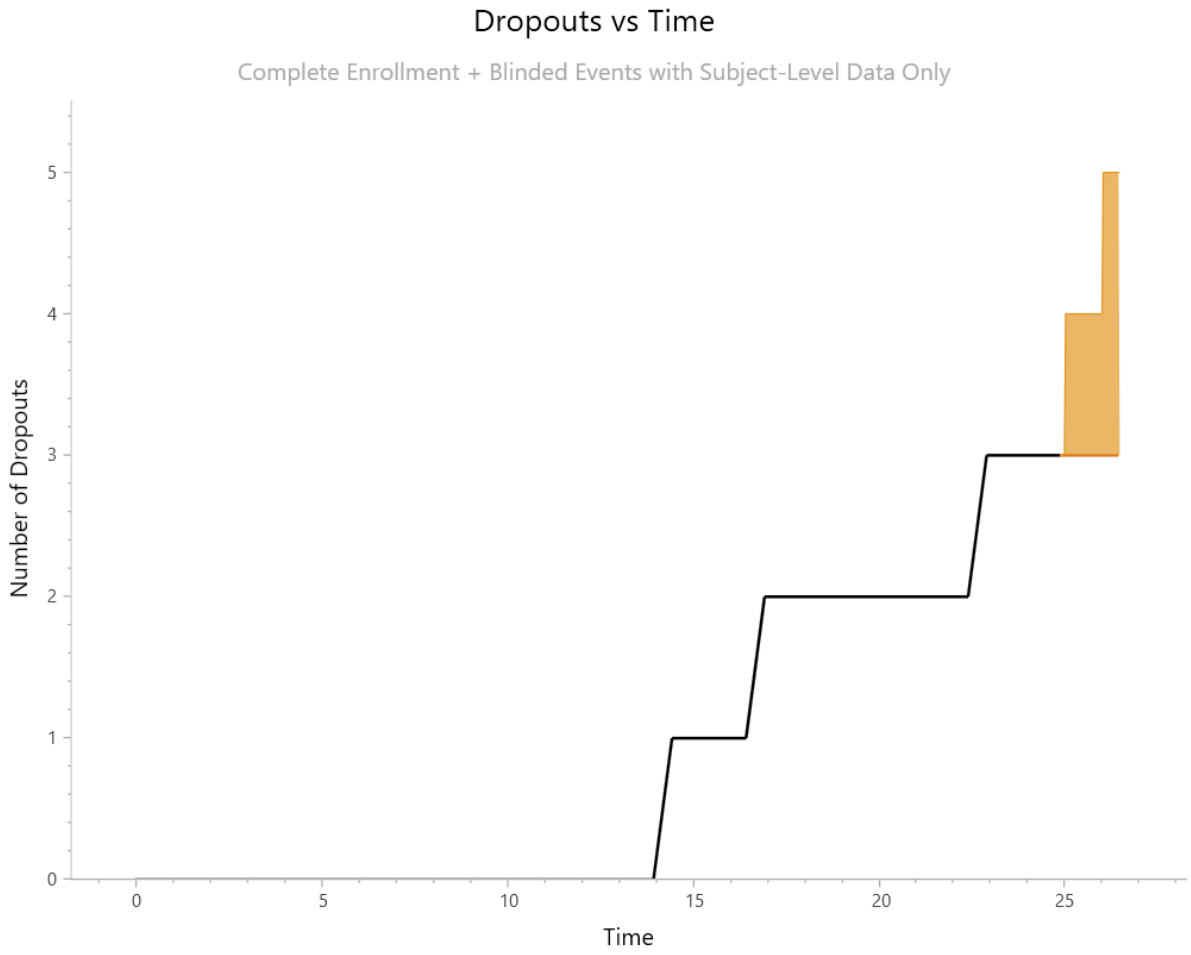


Figure 11.125: Dropout Prediction Plot for Blinded Events Prediction when Enrollment Complete

The **Enrollment Prediction Table, Events Prediction Table and Dropout Prediction Tables** are the tables used to create the respective **Enrollment Prediction, Events Prediction** and **Dropout Prediction** plots, which by default all consists of ~100 rows (50 pre-simulation and 50 post-simulation). Each consists of five columns: **Time, Actual, Predicted Avg. Sample Size/Events/Dropouts, Predicted Median Sample Size/Events/Dropouts, 95% Prediction Interval LL, 95% Prediction Interval UL**. One prediction table (the **Events Prediction Table**) for this demonstration at the start of the simulated period is given in Figure 11.126.

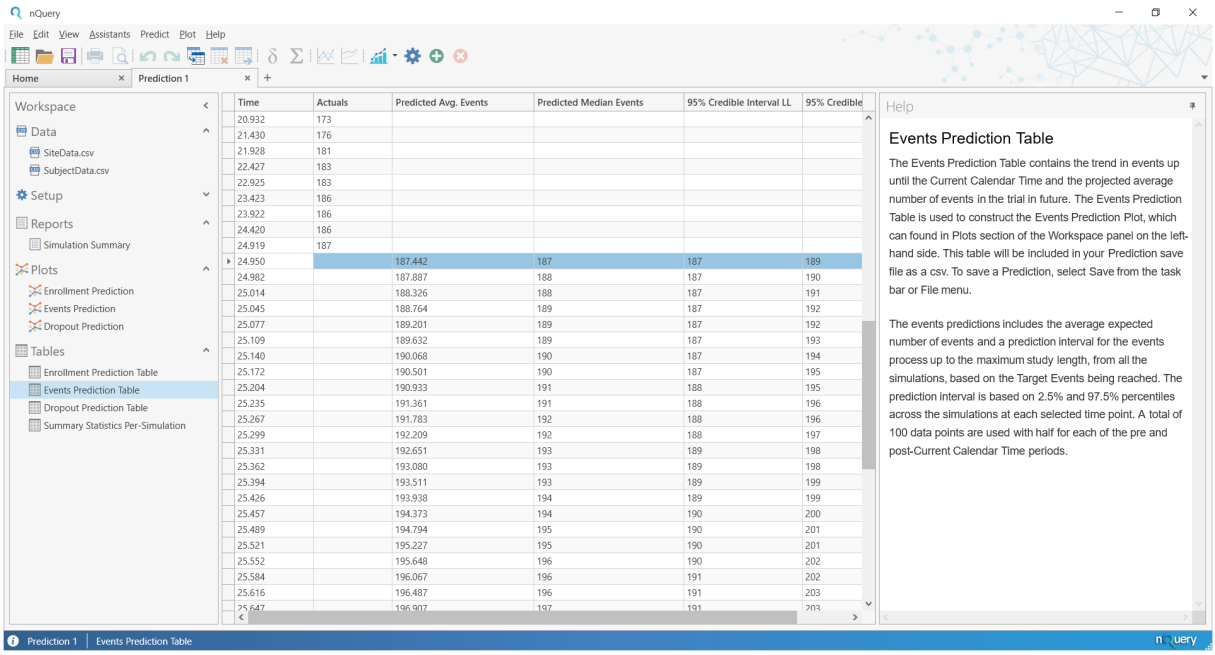


Figure 11.126: Events Prediction Table for Blinded Events Prediction when Enrollment Complete

Time is the time value relative to the study start time of zero. **Actual** is the actual number of events achieved at a pre-simulation **Time** row. **Predicted Avg. Events** is the predicted average (mean) number of events at a post-simulation **Time** row. **Predicted Median Events** is the predicted median number of events at a post-simulation **Time** row. **95% Prediction Interval LL** is the lower limit for the 95% prediction interval for the number of events at a post-simulation **Time** row. **95% Prediction Interval UL** is the upper limit for the 95% prediction interval for the number of events at a post-simulation **Time** row.

The **Summary Statistics Per-Simulation Table** provides the summary statistics achieved for primary outputs in each simulation. For this demonstration this includes the **Simulation ID, Current Time, Current Sample Size, Current Events, Current Dropout, Current Available, Target Sample Size, Target Events, Study End Time, Total Sample Size, Total Events, Total Dropouts, Total Censored, Accrual Duration, Accrual Duration Uncensored, Average Followup, Median Followup, Target Events Reached.**

The **Summary Statistics Per-Simulation Table** for this demonstration, focused on the simulation results, is shown in Figure 11.127.

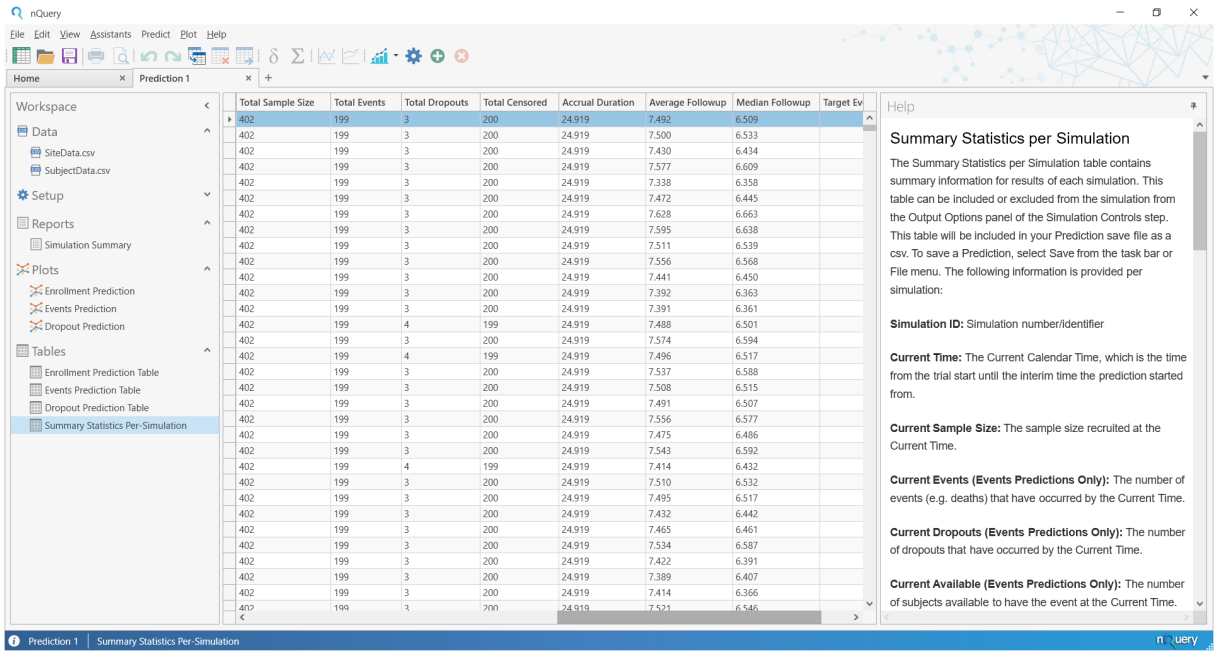


Figure 11.127: Summary Statistics Per-Simulation Table for Blinded Events Prediction when Enrollment Complete

Details on each field are provided in the Help window on the right but broadly the "Current" fields described the information provided up to the **Current Time**, the "Target" fields describe the study targets and the remainder give the projection achieved for key parameters in the simulation with that **Simulation ID**.

Alternative Scenarios The demonstration has focused on the default inputs using **SubjectData.csv** up to this point. However, as noted in the data summary given in subsection 11.2.4 the study from which the example data was simulated had an original sample size target of 460 (402 enrolled in **SubjectData.csv**) and target number of events of 374. Given that **Enrollment Status = Complete** in this demonstration, the following scenarios will evaluate the outcome if the **Target Number of Events** is set to its original value of 374. A piecewise exponential model will also be investigated.

To explore this additional information, we will investigate two additional scenarios

- Scenario A: **Target Number of Events = 374** using all other defaults from above
- Scenario B: **Target Number of Events = 374** using Piecewise Exponential **Response Distribution** (i.e. Exponential with **Number of Hazard Pieces > 1**)

Scenario A The only changes required compared to the first demonstration is to change the **Target Number of Events** to 374 in the **Events Model** tab at the **Event and Dropout Information** step. The simplest way to do this is to select the **Setup** header in the Workspace Navigation Bar on the left and then select the **Event and Dropout Information** drop down option. Then edit the **Target Number of Events** to 374 and select the Next or → button. At the next **Simulation Controls** step, we will add a single simulation run by selecting the checkbox beside the **Save subject-level**

data for (x) simulation runs and replace the default of 10 runs with 1 runs at the "(x)" spot. An edited down summary of the **Setup** changes is provided in Figure 11.128.

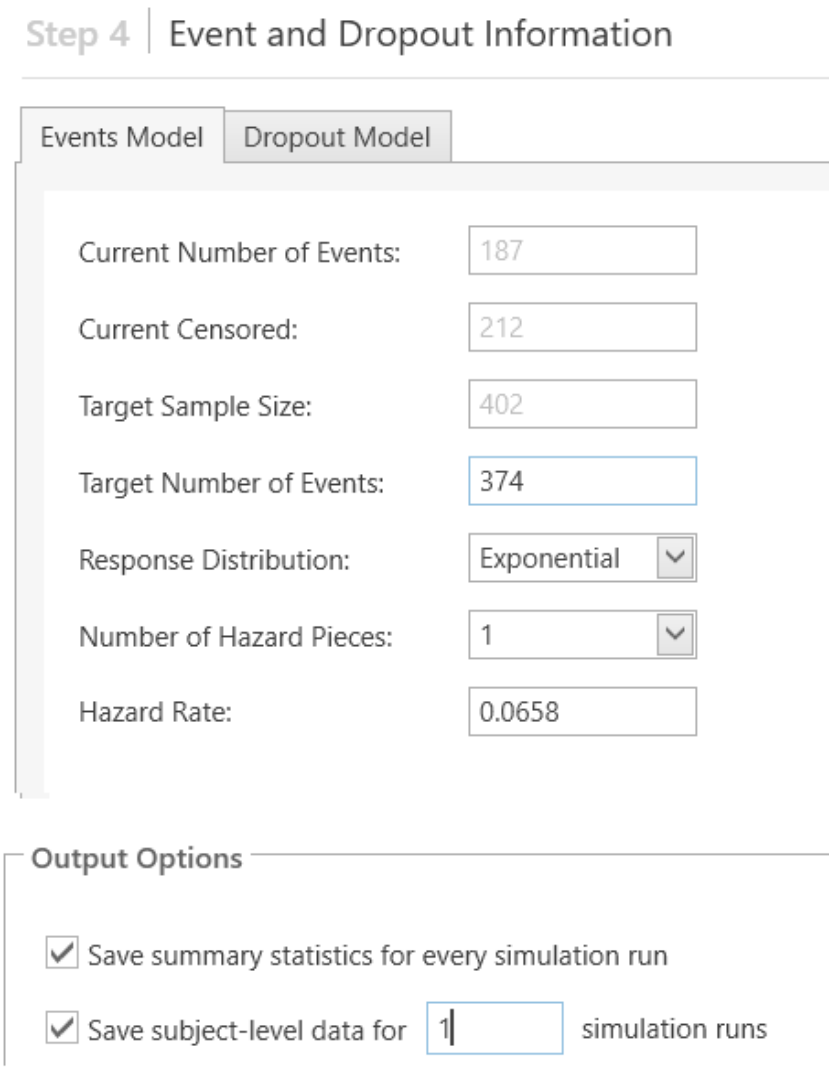


Figure 11.128: Scenario A Setup Changes for Blinded Events Prediction when Enrollment Complete

To run the simulation again with the new Scenario A, select the Run/$^{\rightarrow}$ button. The main results of this Scenario A simulation are shown in Figure 11.129.

Overall Summary

Average Sample Size	402.0000
Average Accrual Duration	24.9186
Average Study Duration	58.5459
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	6.0327
Average Follow-up	14.1409

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	374	402	4	24.9186	53.5240
25.00%	374	402	5	24.9186	56.2714
50.00%	374	402	6	24.9186	58.3829
75.00%	374	402	7	24.9186	60.6105
95.00%	374	402	9	24.9186	64.1180

Figure 11.129: Scenario A Results for Blinded Events Prediction when Enrollment Complete

For Scenario A, the **Overall Summary** shows that the **Target Number of Events** of 374 was reached in every simulation with an **Average Study Duration** over all the simulations of 58.5459. The **Percentile Summary** shows that 90% of predictions had a **Study Duration** between 53.5240 (5% Percentile) and 64.1180 (95% Percentile), 50% a duration between 56.2714 (25% Percentile) and 60.6150 (75% Percentile) and a median (50% Percentile) duration of 58.3829. The **Average Dropouts** was 6.0327 (Percentiles: 4, 5, 6, 7, 9) and subjects had an **Average Followup** (until either event/dropout or until study end for censored subjects) of 14.1409.

The original target study duration was 40 months and therefore this study is expected to end 18.5 months later than expected. As expected, stopping the enrollment process prematurely causes a significant delay compared to the original plan and the expected duration based on **SubjectData.csv** if the original **Target Sample Size** of 460 had been recruited (see Scenario A for subsubsection 11.2.1.1)

The **Per-Simulation Subject-level Data Table** was also generated here and is shown for Scenario A in Figure 11.130 with the first simulation (**Simulation ID = 1**). The tables consists of the following fields: **Simulation ID**, **Subject ID**, **Arrival Time**, **Event Time**, **Dropout Time** and **Final Status**. The order of the Subject ID is based on **Arrival Time** order.

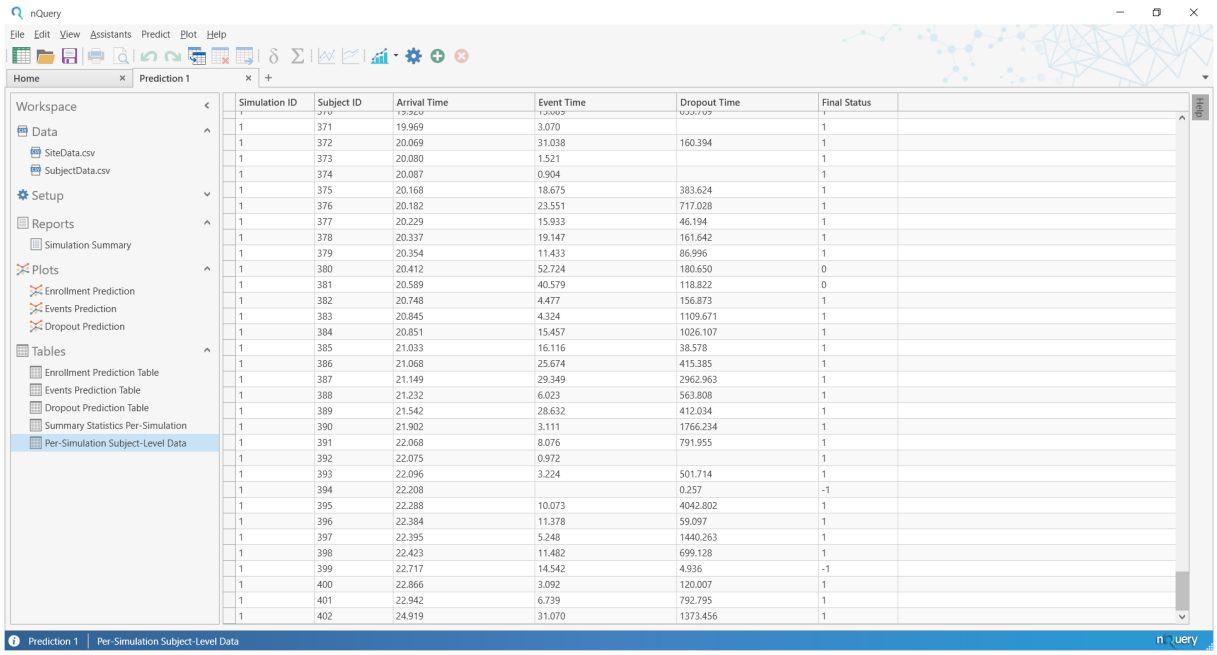


Figure 11.130: Per-Simulation Subject-level Data Table for Blinded Events when Enrollment Complete

Event Time and **Dropout Time** are generated for all subjects which were **Censored Status** (all status values from **Status Indicator** field in **Subject-level Data Setup** step) in the subject-level data (for example **Subject ID = 402** in this example). Blank fields for **Event Time** or **Dropout Time** indicate cases where the subject already had the event/dropout and therefore the time for the other status does not exist and does not need to be simulated.

The **Final Status** is from the subject-level data for subjects with **Event Status** or **Dropout Status** and based on the **Event Time** and **Dropout Time** for simulated subjects and **Censored Status** subjects in the subject-level data. **Final Status** will equal **Event Status** if **Event Time** is less than **Dropout Time** and the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.127 for per-simulation end times). **Final Status** will equal **Dropout Status** if **Dropout Time** is less than **Event Time** and the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.127 for per-simulation end times). **Final Status** will equal **Censored Status** if **Event Time** and **Dropout Time** are greater than the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.127 for per-simulation end times)

Scenario B Scenario A assumed an **Exponential Response Distribution** which had a constant hazard rate (i.e. **Number of Hazard Pieces = 1**). However, a piecewise **Exponential** model can also be used where the hazard rate changes over time. There are methods available for the automatic fitting of piecewise exponential curves [Fang and Su, 2011] but here a simple case where the hazard rate halves after 5 months of follow up is used.

To evaluate this scenario, from the **Setup** header in the Workspace Navigation Bar on the left select the **Event and Dropout Information** drop down option. Set the **Response**

Distribution to **Exponential** and the **Number of Hazard Pieces** to 3. The piecewise exponential model for this case will equal the following:

Piece #	Starting at Time	Hazard Rate
1	0	0.065789598
2	5	0.032894799

Table 11.1: Piecewise Exponential Fit for Scenario B

In nQuery Predict, this will be as per Figure 11.131.

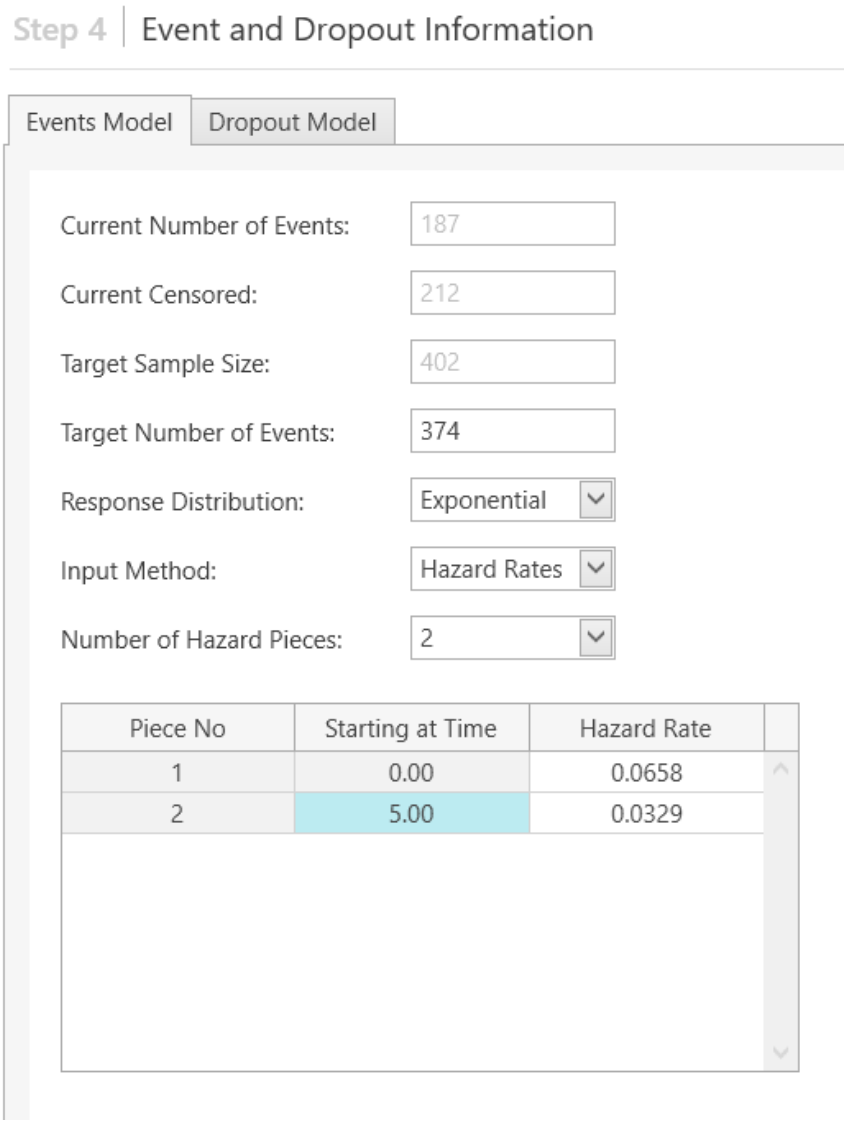


Figure 11.131: Scenario B for Blinded Event Prediction when Enrollment Complete

Select the Run or → button to move to the next step. At the next **Simulation Controls** step, select the Run or → button to simulate Scenario B. The changes and results for Scenario B are summarized in

Overall Summary

Average Sample Size	402.0000
Average Accrual Duration	24.9186
Average Study Duration	89.1947
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	8.0357
Average Follow-up	18.9834

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	374	402	5	24.9186	78.2691
25.00%	374	402	6	24.9186	84.1662
50.00%	374	402	8	24.9186	88.8058
75.00%	374	402	9	24.9186	93.6197
95.00%	374	402	12	24.9186	101.4556

Figure 11.132: Results for Scenario B for Blinded Event Prediction when Enrollment Complete

For Scenario B, the **Overall Summary** shows that the **Target Number of Events** of 374 was reached in every simulation with an **Average Study Duration** over all the simulations of 89.1947 (Percentiles: 78.2691, 84.1662, 88.8058. 93.6197, 101.4556). The **Average Dropouts** was 8.0357 (Percentiles: 5, 6, 8, 9, 12) and subjects had an **Average Followup** (until either event/dropout or until study end for censored subjects) of 18.9834. This gives an increase of around 32 months over the constant exponential case which shows that the study length is sensitive to the assumed survival model.

11.2.7.4 Unblinded Events Prediction with Summary Data with Enrollment Ongoing

Setup **Unblinded Events** milestone prediction using **Summary Data** means that the prediction will project the expected length of study needed to achieve a specified **Target Number of Events** using summary data fixed parameters from each treatment group.

In the **Setup** for this prediction, first in the **Select the type of Prediction** step select **Unblinded Events** from the **Target** field, **Summary Data** from the **Input** field and **Ongoing** from the **Enrollment Status** field.

These selections are shown in Figure 11.133. Select the Next button in the bottom-right or → button in the top-right of the Main Window to move to the next step of the prediction **Setup** stage.

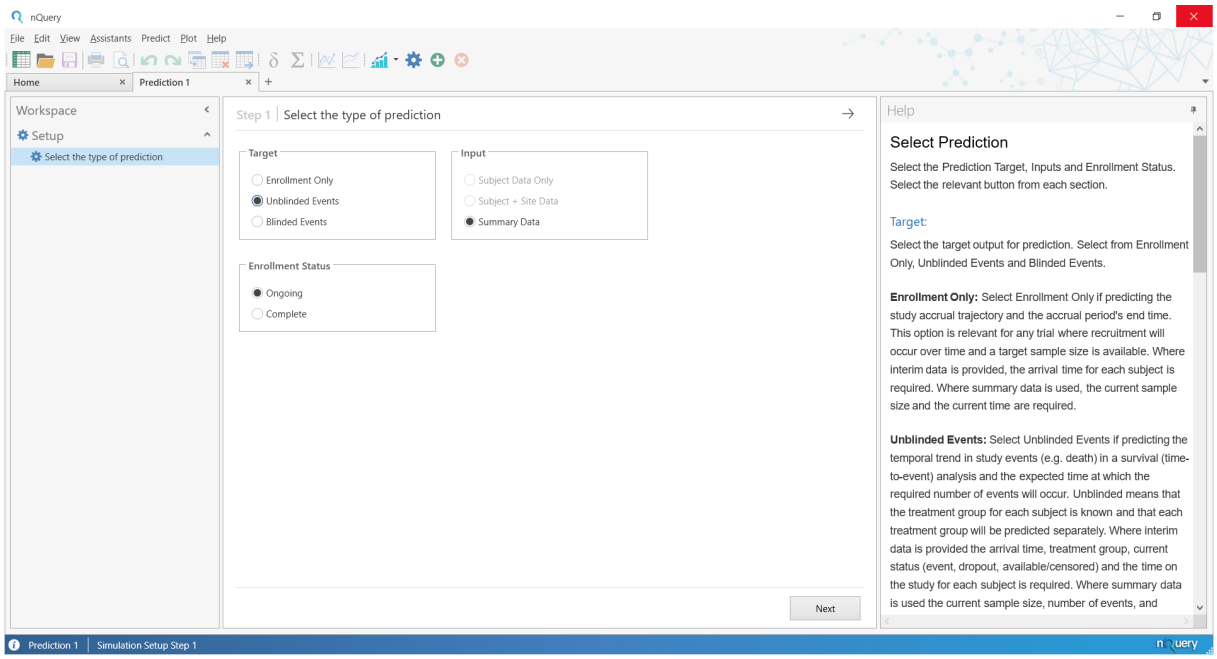


Figure 11.133: Select the Type of Prediction Setup Step for Unblinded Events using Summary Data

The next step is the **Fixed Parameters** step. For this demonstration, there is a **Sample Sizes, Events & Dropouts** section which contains nine fields which are as follows:

- Current Sample Size (Control): The sample size enrolled into the control group at the Current Time
- Current Sample Size (Treatment): The sample size enrolled into the treatment group at the Current Time
- Current No. of Events (Control): The number of events that have occurred in the control group at the Current Time
- Current No. of Events (Treatment): The number of events that have occurred in the treatment group at the Current Time
- Current No. of Dropouts (Control): The number of dropouts that have occurred in the control group at the Current Time
- Current No. of Dropouts (Treatment): The number of dropouts that have occurred in the treatment group at the Current Time
- Current No. Censored (Control) (Read-only): The subjects censored (not had event or dropout) in the control group if the study ended at the Current Time
- Current No. Censored (Treatment) (Read-only): The subjects censored (not had event or dropout) in the treatment group if the study ended at the Current Time
- Current Time: The length of time the study has been on-going since the study began

For this demonstration, inputs are selected which mirror those from Scenario A of the **Unblinded Events Prediction with Subject + Site Data with Enrollment Ongoing (subsubsection 11.2.7.2)** example using **SubjectData.csv.**

Based on **SubjectData.csv,** the fixed parameters for this example give a **Current Sample Size (Control)** of 203, **Current Sample Size (Treatment)** of 199, **Current No. of Events (Control)** of 106, **Current No. of Events (Treatment)** of 81, **Current No. of Dropouts (Control)** of 1, **Current No. of Dropouts (Treatment)** of 2 and a **Current Time** of 24.9186. The **Current No. Censored (Control)** is automatically calculated as 96 and the **Current No. Censored (Treatment)** is automatically calculated as 116.

The **Fixed Parameters** step with these values inputted is shown in Figure 11.134. After all fields all filled, select the Next or → button to move to the next **Setup** step.

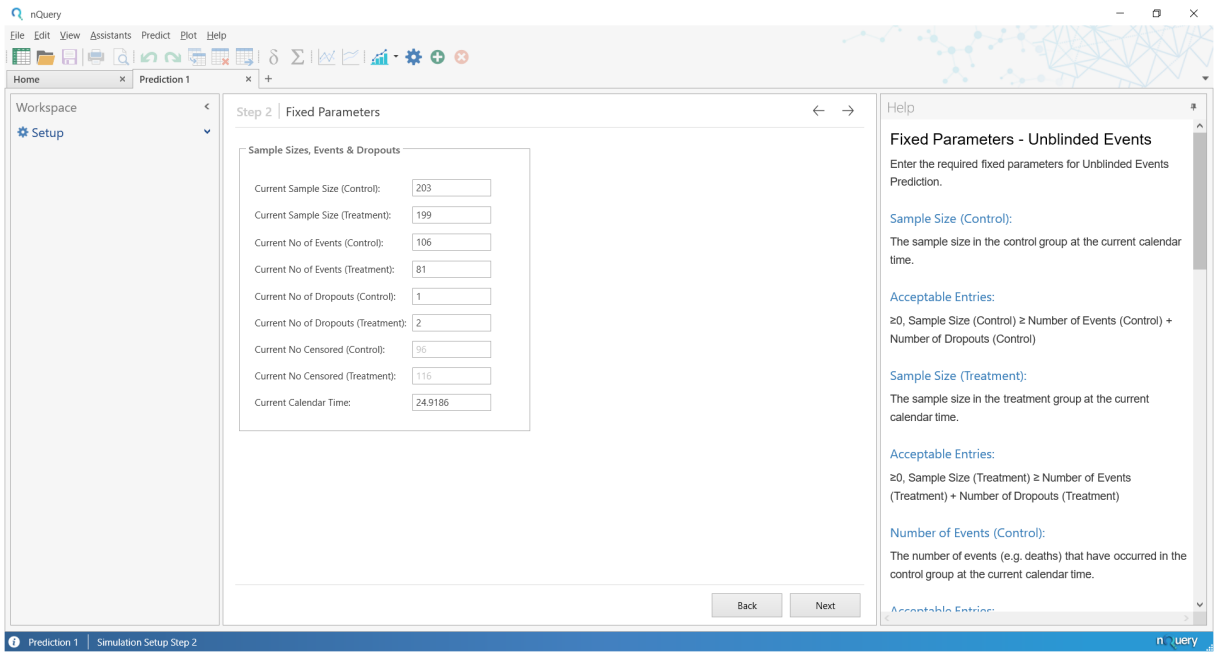


Figure 11.134: Fixed Parameters Setup Step for Unblinded Events using Summary Data

The next step is the **Accrual Options** step which specifies the **Target Sample Size**. The **Accrual Options** step, and its defaults, for this demonstration are shown in Figure 11.135.

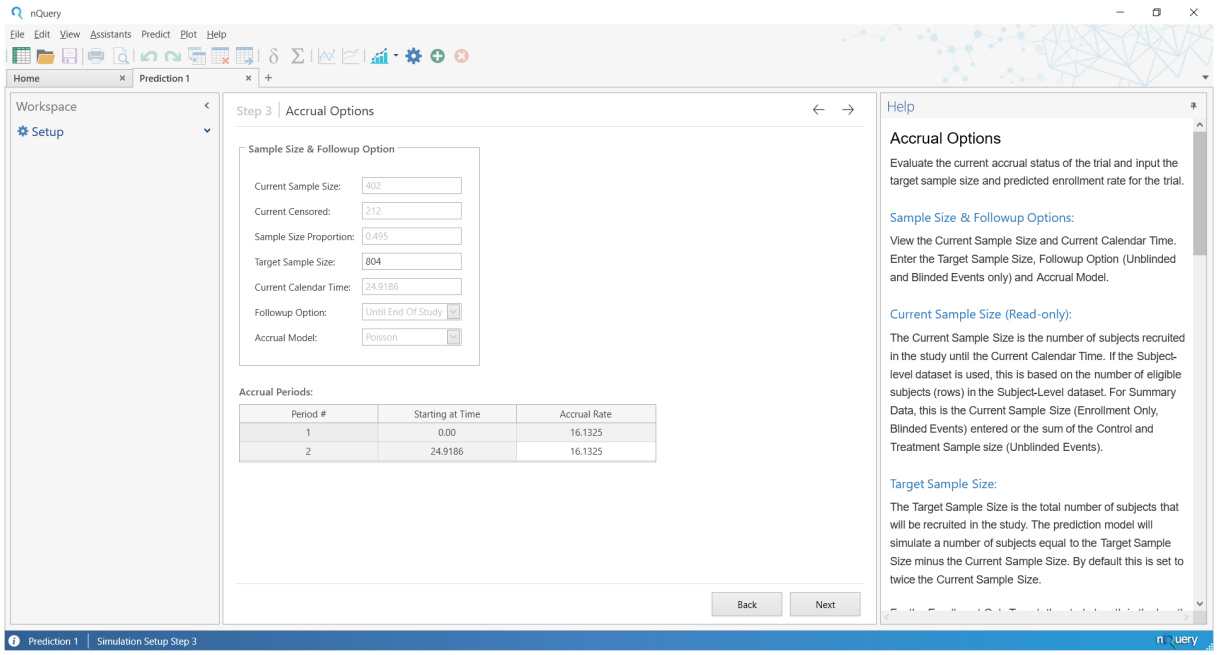


Figure 11.135: Accrual Options Setup Step Defaults for Unblinded Events Prediction using Summary Data

The **Accrual Options** step consists of two main elements: the **Sample Size & Followup** input fields and the **Accrual Periods** table.

The **Sample Size & Followup** input fields provides information on enrollment process, censored status and current time based on the subject-level data and allows the user to edit the **Target Sample Size** and select the **Followup Option** and **Accrual Model**. The following fields are provided in this prediction:

- Current Sample Size (Read-only): Sample Size recruited into a study so far. Equals the number of rows in the Subject-level Data
- Current Censored (Read-only): The number of subjects who have not had the event or dropped out at the current time. Equals the number of subjects with the Censored Status in the Status Indicator field
- Sample Size Proportion (Read-only): Proportion of subjects in the Control Group. Based on number of Control Group subjects in Treatment ID field. Controls the allocation proportion in simulated data
- Target Sample Size (Editable): Total number of subjects that will be recruited in this study
- Current Time (Read-only): The length of time that has passed since the study started. Equals the maximum of the sum of the Arrival Time + Time on Study values for each subject
- Followup Option (Read-only): Specifies whether subjects who do not have the event/dropout will be administratively censored at the end of the study or after a fixed follow up period. For Summary Data, this is set to Until End of Study
- Accrual Model (Editable): The statistical model that will be used to generate simulated enrollments

In nQuery Predict, the **Target Sample Size** defaults to twice the **Current Sample Size** and the **Accrual Model** defaults to **Poisson.** In this demonstration, the **Current Sample Size** equals 402 and therefore the default **Target Sample Size** is 402 (2) = 804. However, in this demonstration the **Target Sample Size** is set to 460.

When **Input = Summary Data,** the **Followup Option** must be set to **Until End of Study.**

The **Accrual Periods** table contains information on the **Accrual Rate** up the **Current Time** and allows the user to edit the future **Accrual Rate** used to generate enrollment simulations. The **Accrual Periods** has three columns ,with each row corresponding to a time period, with the columns defined as follows:

- Period #: A numeric ID for the current time period. Increases in increments of one for each subsequent row
- Starting at Time: The starting time for the current time period row. The first row will equal 0 (rate from study start to Current Time) and the second row will equal the Current Time
- Accrual Rate: The accrual rate is the average number of subjects recruited per unit time (months). The accrual rate in the first row will equal the accrual rate up to the Current Time.

For the **Poisson Accrual Model**, the **Accrual Periods** table will consist of two time period rows. The first row will correspond to the information provided by the user regarding the study up until the **Current Time.** The second row will correspond to the inputs used to generate future enrollments. By default the **Accrual Rate** in the future second row will equal the **Accrual Rate** from the first row i.e. the accrual rate up until the **Current Time.** For the inputs used in this demonstration, this **Accrual Rate** column values in each row equal 16.13254936. The user can edit the **Accrual Rate** for generating future enrollments by editing the second cell of the **Accrual Rate** column.

In this demonstration, **Target Sample Size** = 460 and **Accrual Rate** =16.13254936 as per Figure 11.136. Select the Next or → button to move to the next **Setup** step.

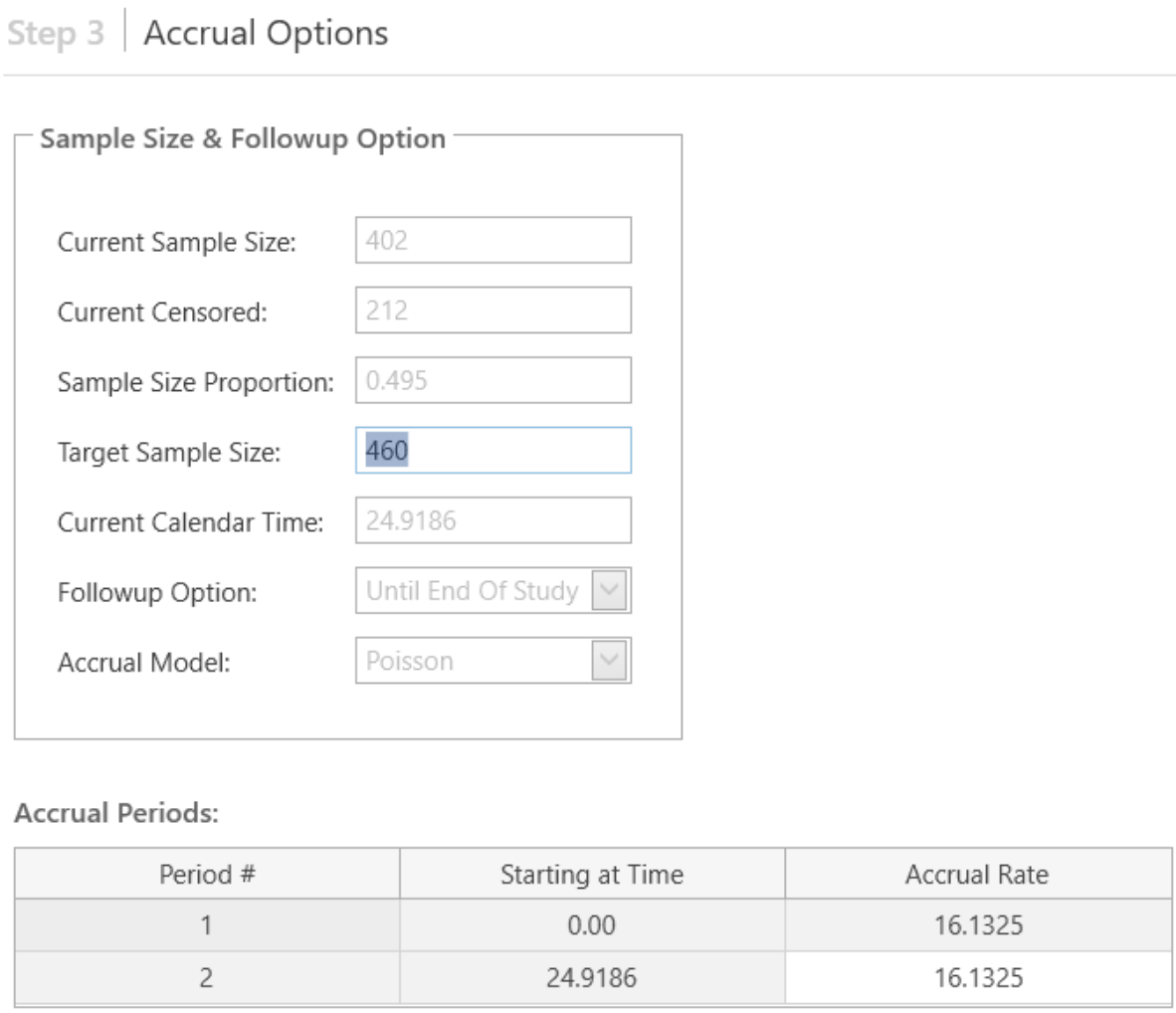


Figure 11.136: Accrual Options Setup Step Final Inputs for Unblinded Events Prediction using Summary Data

The next step is the **Event and Dropout Information** step which specifies the **Target Number of Events,** event model (and associated statistical parameters) and dropout model (and associated statistical parameters). The **Event and Dropout Information** step on the default **Events Model** tab is shown in Figure 11.137.

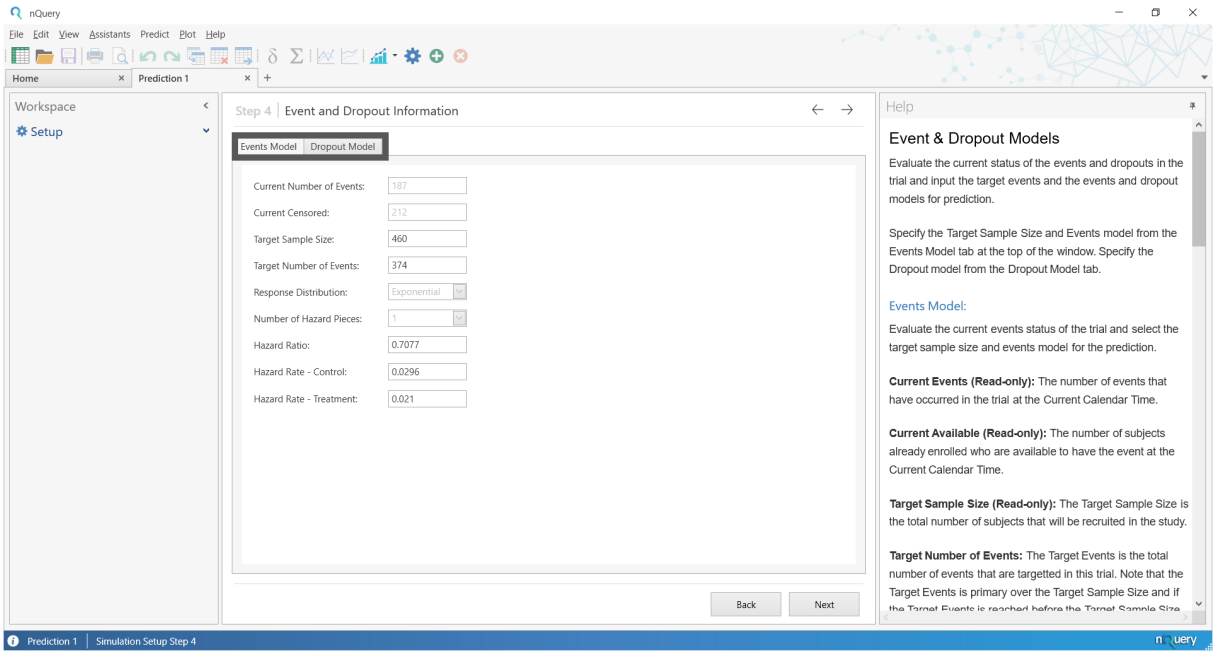


Figure 11.137: Event and Dropout Information Setup Step for Unblinded Events Prediction using Summary Data

The **Event and Dropout Information** step consists of two tabs: the **Events Model** tab and the **Dropout Model** tab. These tabs have been highlighted in Figure 11.137 and are opened by selecting the required tab name at the top of the main window, below the step title. For **Unblinded Events**, it is assumed that survival and dropout times will be simulated individually for each treatment group using their own user specified model.

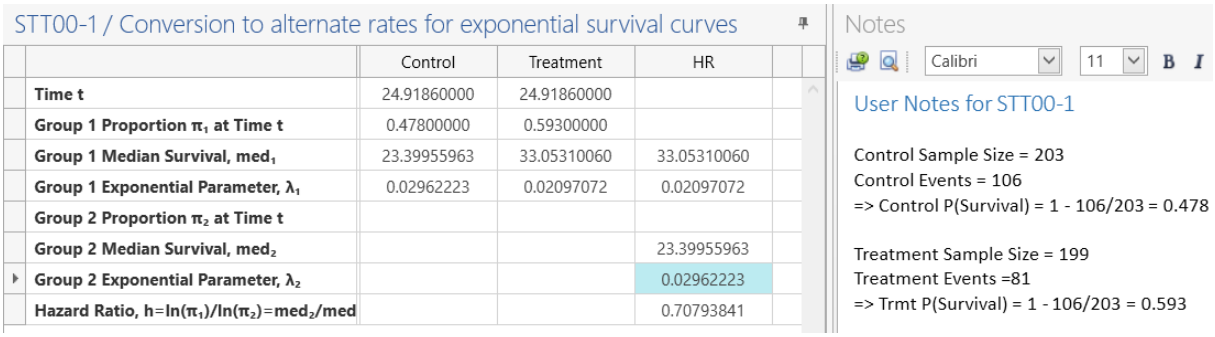
The **Events Model** tab provides fields which provide information on the current number of subject who have had an event, could have an event going forward and allows the input of the **Target Number of Events** and **Response Distribution** for the events model and additional parameters needed for that specific model. The following fields are provided in this prediction:

- Current Events (Read-only): The number of subjects who had the event of interest at the current time. Equals the number of subjects with the Event Status in the Status Indicator field
- Current Censored (Read-only): The number of subjects who have not had the event or dropped out at the current time. Equals the number of subjects with the Censored Status in the Status Indicator field
- Target Sample Size (Read-only): Total number of subjects that will be recruited in this study
- Target Number of Events (Editable): The required number of subjects needed to have the event of interest for the study to end
- Response Distribution: The statistical model that will be used to generate survival times for subjects available to have the event
- Number of Hazard Pieces (Response Distribution = Exponential only): Number of hazard pieces used to specify the piecewise exponential model. Set to 1 for Input = Summary Data

- Hazard Ratio (Response Distribution = Exponential only, Number of Hazard Pieces =1, Editable): The hazard ratio between the Treatment and Control Hazard Rates
- Hazard Rate - Control (Response Distribution = Exponential only, Number of Hazard Pieces =1, Editable): The control group's exponential hazard rate for the constant exponential survival model specified above
- Hazard Rate - Treatment (Response Distribution = Exponential only, Number of Hazard Pieces =1, Editable): The treatment group's exponential hazard rate for the constant exponential survival model specified above

When **Input = Summary Data**, the only **Response Distribution** is **Exponential** (**Number of Hazard Pieces** = 1) and the default **Hazard Rates** set at the expected event rate for each group from the provided **Fixed Parameters**.

In nQuery Predict when **Input = Summary Data**, the default **Hazard Rates** are calculated based on the assumption that all recruitment in a group occurred at the start of the trial and using the implied survival rate from the **Current Sample Size** (N) and **Current No. of Events** (E) i.e. 1 - E/N. The **Survival Parameter Converter** tool from the Assistants menu can be used to show this as per Figure 11.138.



	Control	Treatment	HR
Time t	24.91860000	24.91860000	
Group 1 Proportion π_1 at Time t	0.47800000	0.59300000	
Group 1 Median Survival, med_1	23.39955963	33.05310060	33.05310060
Group 1 Exponential Parameter, λ_1	0.02962223	0.02097072	0.02097072
Group 2 Proportion π_2 at Time t			
Group 2 Median Survival, med_2			23.39955963
Group 2 Exponential Parameter, λ_2			0.02962223
Hazard Ratio, $h=\ln(\pi_1)/\ln(\pi_2)=med_2/med$			0.70793841

Figure 11.138: Default Hazard Rate Calculation using Summary Data

The constant **Exponential** model (i.e. **Number of Hazards Pieces = 1**) is the only model provided as the other (conditional) models available in nQuery Predict rely on subject-level survival times being available, which are obviously not available for hypothetical subjects assumed to have had the event using fixed parameters inputs.

The default **Target Number of Events** is double the **Current Events**, which for this example is 374, with default estimated exponential **Hazard Rate - Control** of 0.0296, **Hazard Rate - Treatment** of 0.021 (**Hazard Ratio = 0.7077**).

The **Dropout Model** tab is opened by selecting the **Dropout Model** tab name at the top of the main window. For this demonstration, the **Dropout Model** tab is shown in Figure 11.139.

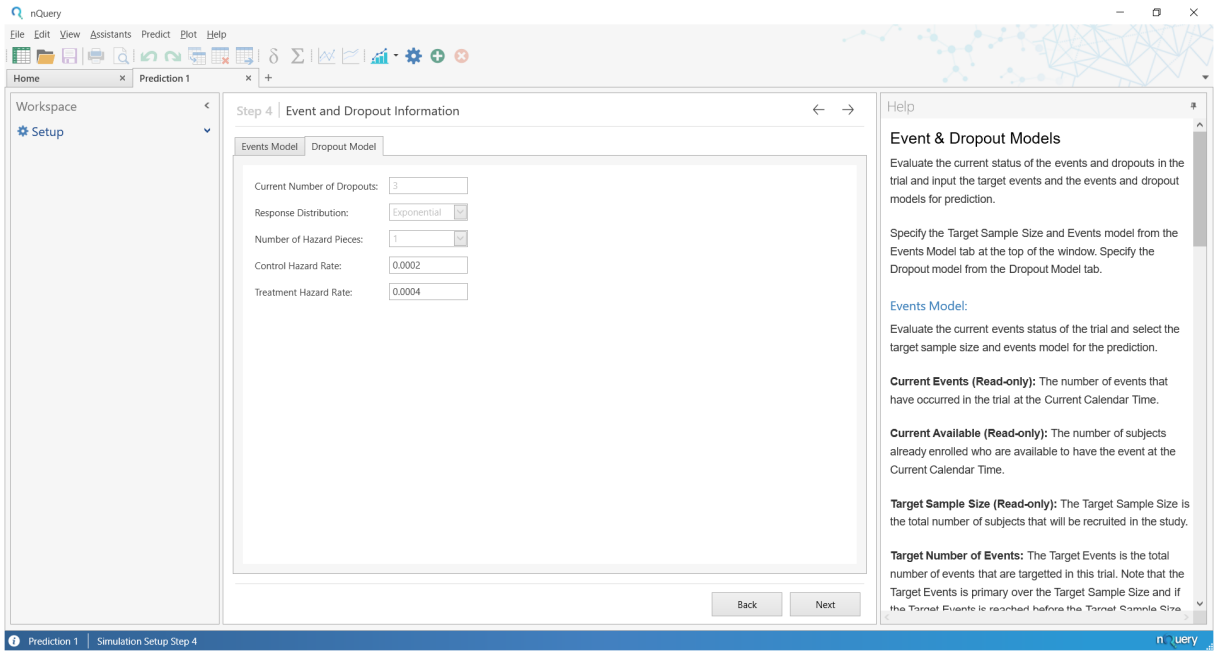


Figure 11.139: Dropout Model tab for Unblinded Events using Summary Data

For **Dropout Model**, the **Current Number of Dropouts** (number of subjects who have dropped out up to the **Current Time**), **Response Distribution** (**Number of Hazard Pieces** must equal 1 as per **Event Model** tab). For dropout, the only **Response Distribution** option is **Exponential**. The inputs and defaults for dropout **Exponential Response Distribution** are the same as from the **Events Model** described above and therefore will not be replicated here. In this demonstration, the constant exponential **Hazard Rate - Control** and **Hazard Rate - Treatment** for dropout calculated from the information provided equal 0.0002 and 0.0004 respectively. Select the Next or → button to move to the next **Setup** step.

The final step is the **Simulation Controls** step. The **Simulation Controls** step consists of three sections: Simulation Controls, Output for All Trials and Output Options.

Simulation Controls (top-left) sets the **Number of Simulations**, **Refresh Frequency** and **Random Seed**

Output For All Trials (bottom-left) sets the Percentiles desired in the **Percentile Summary** table in the **Simulation Summary** report for key simulation outputs such as study length and sample size.

Output Options (right) selects which additional datasets the user wants in the **Tables** field of the simulation results. Additional datasets will be summary statistics for each simulation and outputs from a set number of individual of simulations.

The **Simulation Controls** step is described in detail in subsubsection 11.2.9.4. In this demonstration, the defaults will be used which corresponds to 1000 simulations with the default percentiles (5%, 25%, 50%, 75%, 95%) and with the "Save summary statistics for every simulation run" **Output Options** table active. The **Simulation Controls** defaults for this demonstration are shown in Figure 11.140. To start the milestone prediction, Select the Run (where Next button was in previous steps) or → button.

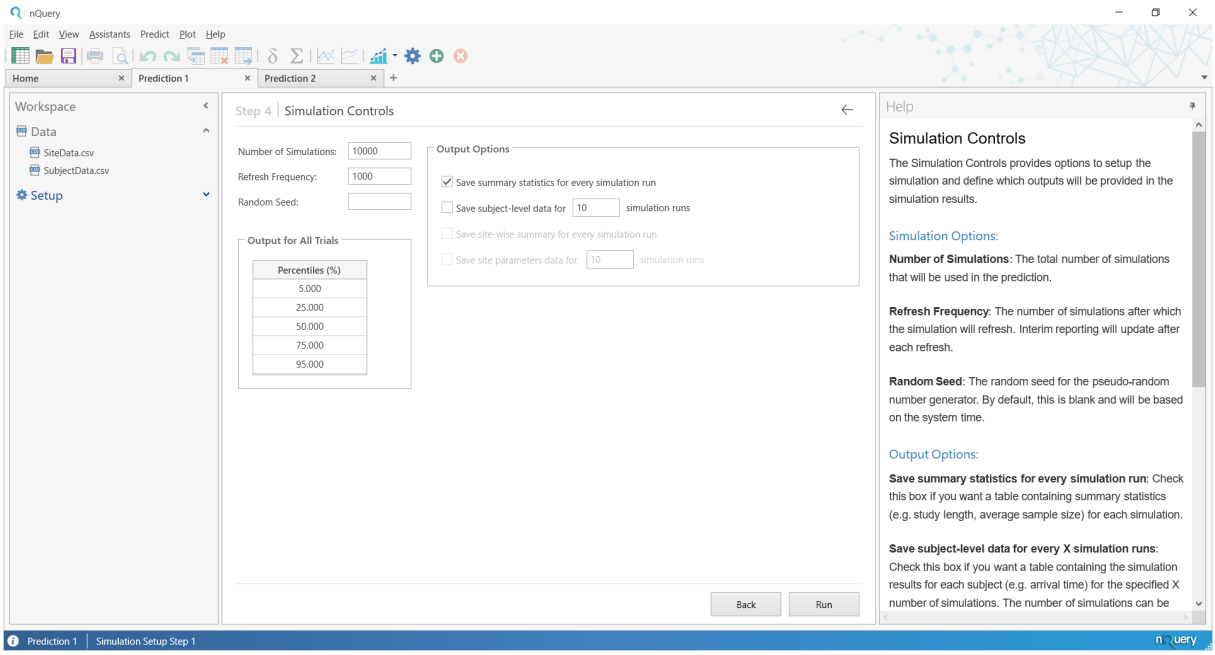


Figure 11.140: Simulation Controls Setup Step for Unblinded Events Prediction using Summary Data

Results While a milestone prediction is being run, a **Simulation in Progress** window will be displayed. The **Simulation in Progress** window provides updated information on key simulation metrics while the simulation is ongoing. An example for this demonstration is given in Figure 11.141.

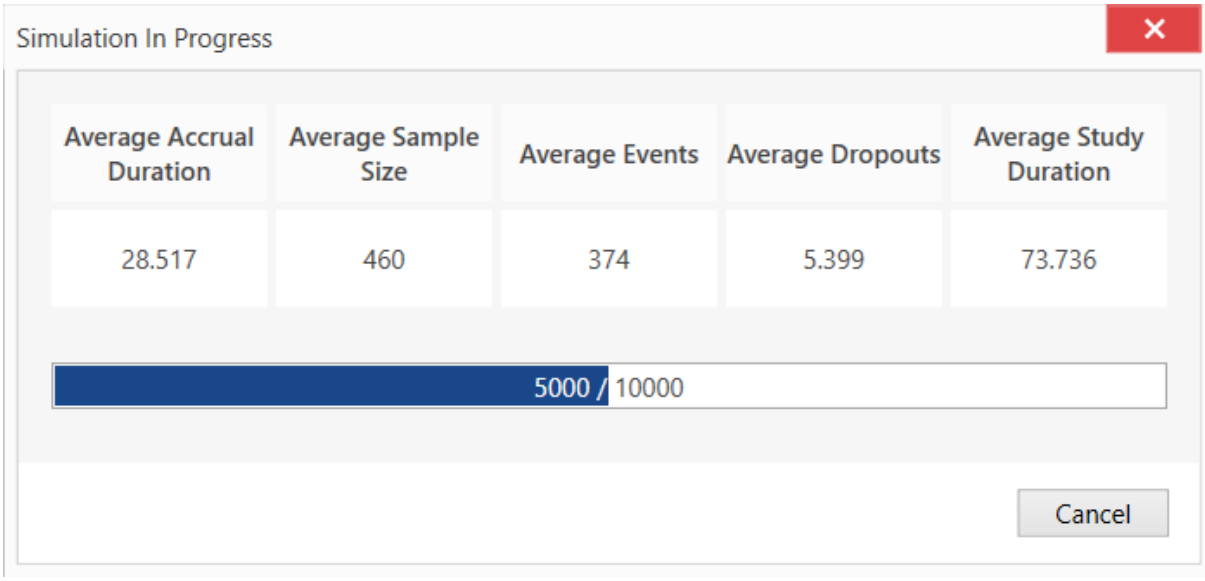


Figure 11.141: Simulation in Progress Window for Unblinded Events Prediction using Summary Data

Once the simulation is complete, the results will automatically be added to the Workspace Navigation Bar on the left and the first element under the **Plots** header will be displayed.

In this demonstration, the **Enrollment Prediction Plot** will be displayed. This is shown in Figure 11.142.

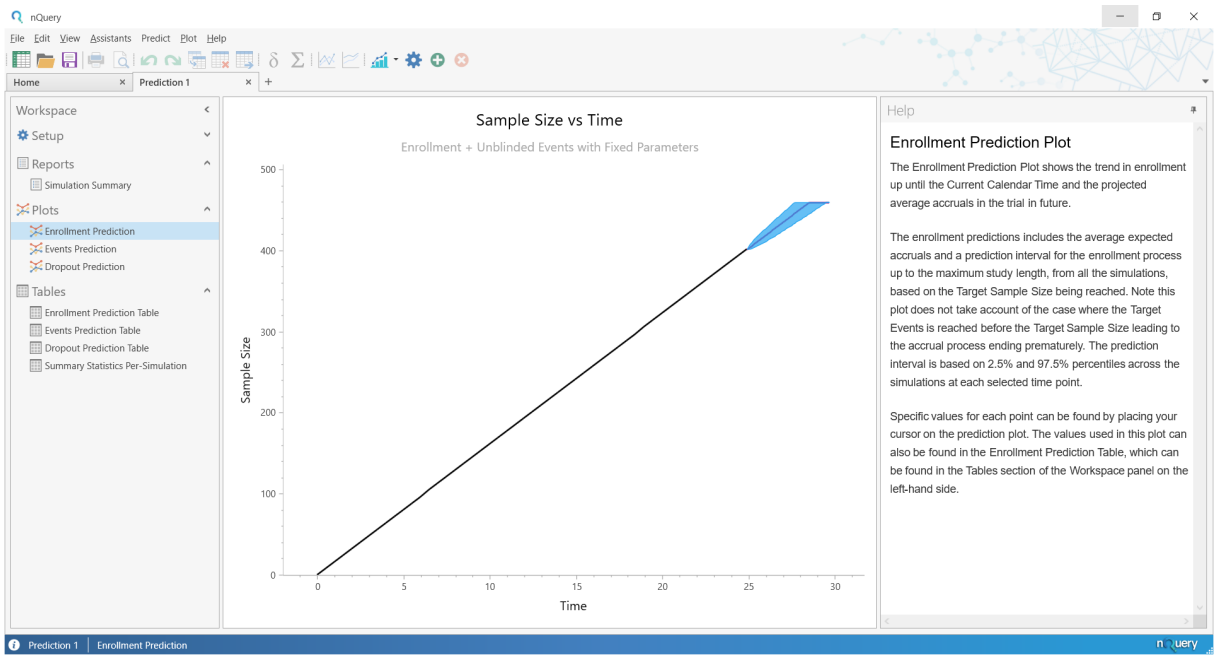


Figure 11.142: Enrollment Prediction Plot for Unblinded Events Prediction using Summary Data

The results of a nQuery Predict milestone prediction can be divided into three categories: **Reports, Plots** and **Tables**. A high-level summary of the results in nQuery Predict is provided in subsection 11.2.8 with demonstration specific elements highlighted here.

For this demonstration the **Reports** header contains the **Simulation Summary** report, the **Plots** header contains the **Enrollment Prediction, Events Prediction** and **Dropout Prediction** plot and the **Tables** header contains the **Enrollment Prediction Table, Events Prediction Table, Dropout Prediction Table** and **Summary Statistics Per-Simulation**. To select any result element, select it from the appropriate header in the Workspace Navigation Bar on the left (see subsection 11.2.2 for details on the Navigation Bar).

The **Simulation Summary** provides a tabular summary of the inputs and outputs from the current milestone prediction simulation. The **Simulation Summary** for this demonstration is shown in Figure 11.143.

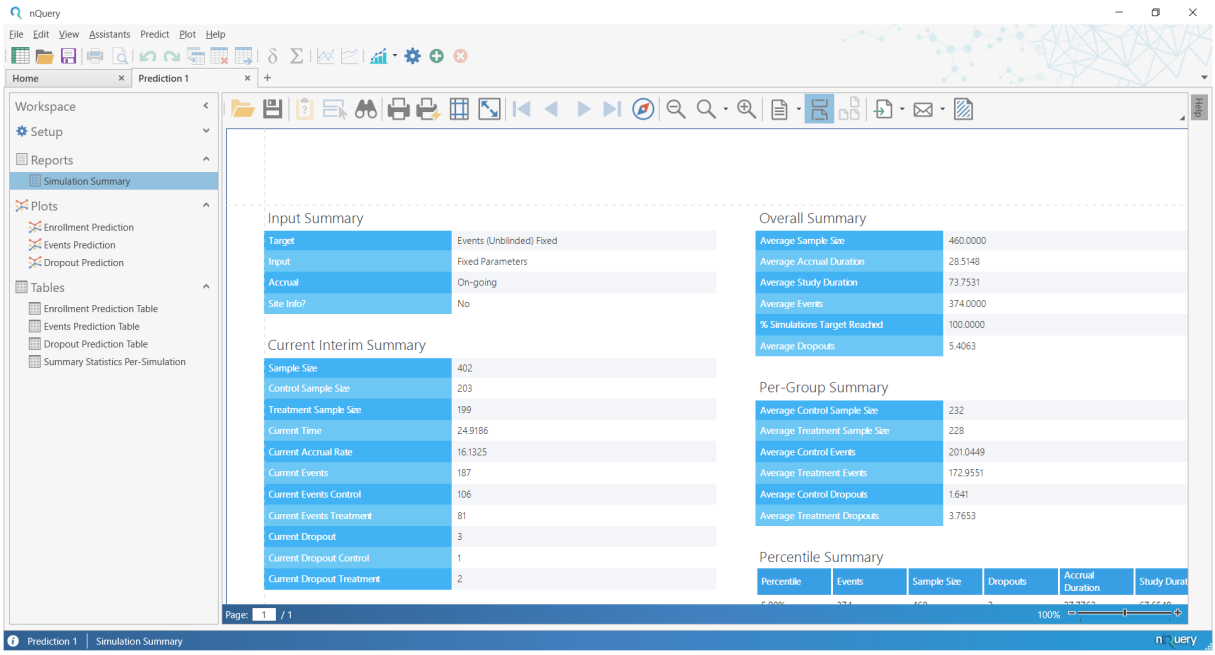


Figure 11.143: Simulation Summary Report for Unblinded Events Prediction using Summary Data

In the **Simulation Summary** report, the left-hand column provides a summary of inputs used to generate the current simulation and the right-hand column provides the results of the current simulation. In this demonstration, we will skip the left-hand Inputs column and focus on the main results in the right-hand column and the main report options.

The results column (on the right) is shown in Figure 11.144. For this demonstration, the **Overall Summary** shows that the **Target Number of Events** of 374 was reached in every simulation with an **Average Study Duration** over all the simulations of 73.7531. The **Percentile Summary** shows that 90% of predictions had a **Study Duration** between 67.6548 (5% Percentile) and 80.2711 (95% Percentile), 50% a duration between 71.1336 (25% Percentile) and 76.2677 (75% Percentile) and a median (50% Percentile) duration of 73.6307.

The **Average Dropouts** was 5.4063 (Percentiles: 3, 4, 5, 6, 8) and subjects had an **Average Followup** (until either event/dropout or until study end for censored subjects) of 5.4063. For the enrollment process, the **Average Accrual Duration** was 28.5148 (Percentiles: 27.7762, 28.1781, 28.4940, 28.8244, 29.3288) with the **Target Sample Size** of 460 reached in all simulations. The **Control Group** had a **Average Sample Size** 232, **Average Events** of 201.0449 and **Dropouts** of 1.641. The **Treatment Group** had a **Average Sample Size** 228, **Average Events** of 172.9551 and **Dropouts** of 3.7653.

Overall Summary

Average Sample Size	460.0000
Average Accrual Duration	28.5148
Average Study Duration	73.7531
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	5.4063

Per-Group Summary

Average Control Sample Size	232
Average Treatment Sample Size	228
Average Control Events	201.0449
Average Treatment Events	172.9551
Average Control Dropouts	1.641
Average Treatment Dropouts	3.7653

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	374	460	3	27.7762	67.6548
25.00%	374	460	4	28.1781	71.1336
50.00%	374	460	5	28.4940	73.6307
75.00%	374	460	6	28.8244	76.2677
95.00%	374	460	8	29.3288	80.2711

Figure 11.144: Simulation Summary Report Results for Unblinded Events Prediction using Summary Data

To edit the **Simulation Summary report there a** number of buttons available at the top of the report. For full detail on the **Simulation Summary** report and options to edit the report see subsubsection 11.2.8.2. However the Zoom options  , Page Layout and Setup options  and Export option  will be the more commonly used options.

The **Enrollment Prediction** plot provides a visual summary of enrollment. The X-axis is **Time** (relative to study start) and the Y-axis is **Sample Size** (enrolled at Time X-axis

value). When the cursor is placed over the **Enrollment Prediction** plot, information on the **Sample Size** enrolled at a given **Time** is shown as per Figure 11.145.

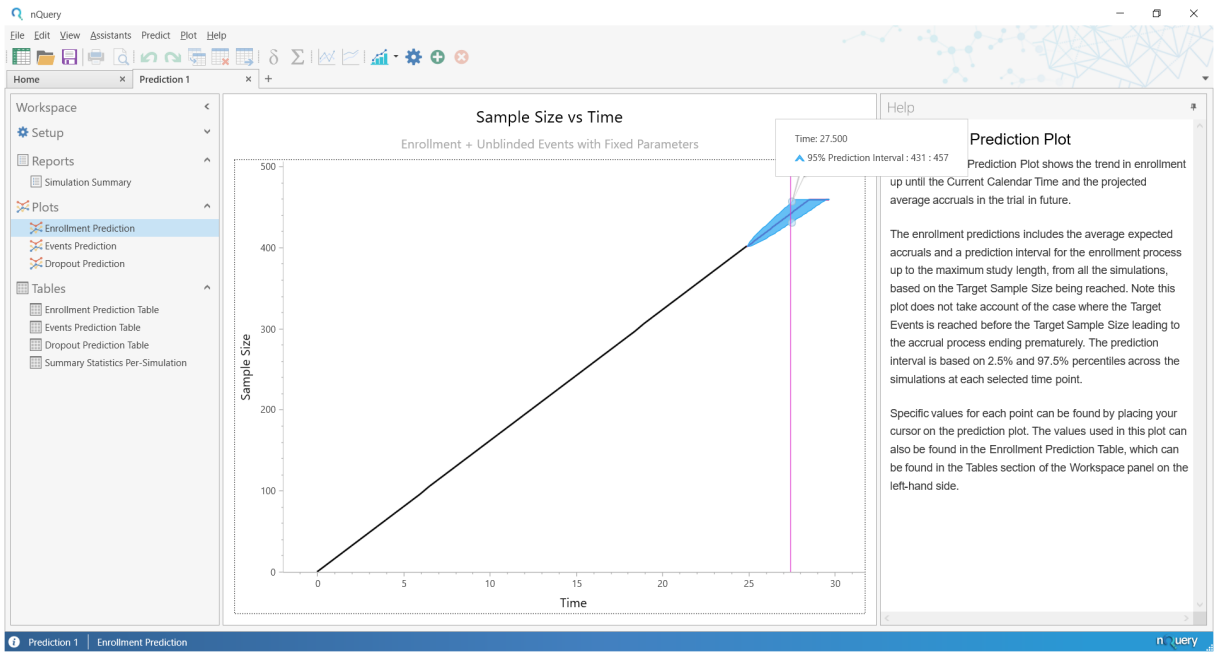


Figure 11.145: Enrollment Prediction Plot for Unblinded Events Prediction using Summary Data

The **Enrollment Prediction** plot when **Input = Summary Data** will assume a uniform (linear) accrual pattern up to the **Current Time**, with the assumed sample size at a given prior time given by placing the cursor over the plot. After the **Current Time,** a blue conic section with a grey line where the blue conic section plots the 95% prediction interval for the **Events** achieved at a given **Time** across all simulations and the grey line is the average **Sample Size** enrolled at a given time. Note the **Enrollment Prediction** plot **Time** scale will be related to the **Accrual Duration** rather than the **Event Prediction** and **Dropout Prediction** plots which will be associated with the **Study Duration.**

The **Events Prediction** plot consists of two parts: from Time = 0 to **Current Time** and from **Current Time** to the **Maximum Time**. The first part is a black line which plots the events pattern from the user inputs provided, which for **Input = Summary Data** will be a linear constant event rate. The second part is a yellow conic section with a grey line where the yellow conic section plots the 95% prediction interval for the **Events** achieved at a given **Time** across all simulations and the grey line is the average **Events** at a given time. The 95% prediction interval indicates the 95% of predictions had a number of events that fell between the lower and upper limit at a given time. The **Events Prediction** plot for this demonstration is shown in Figure 11.146.

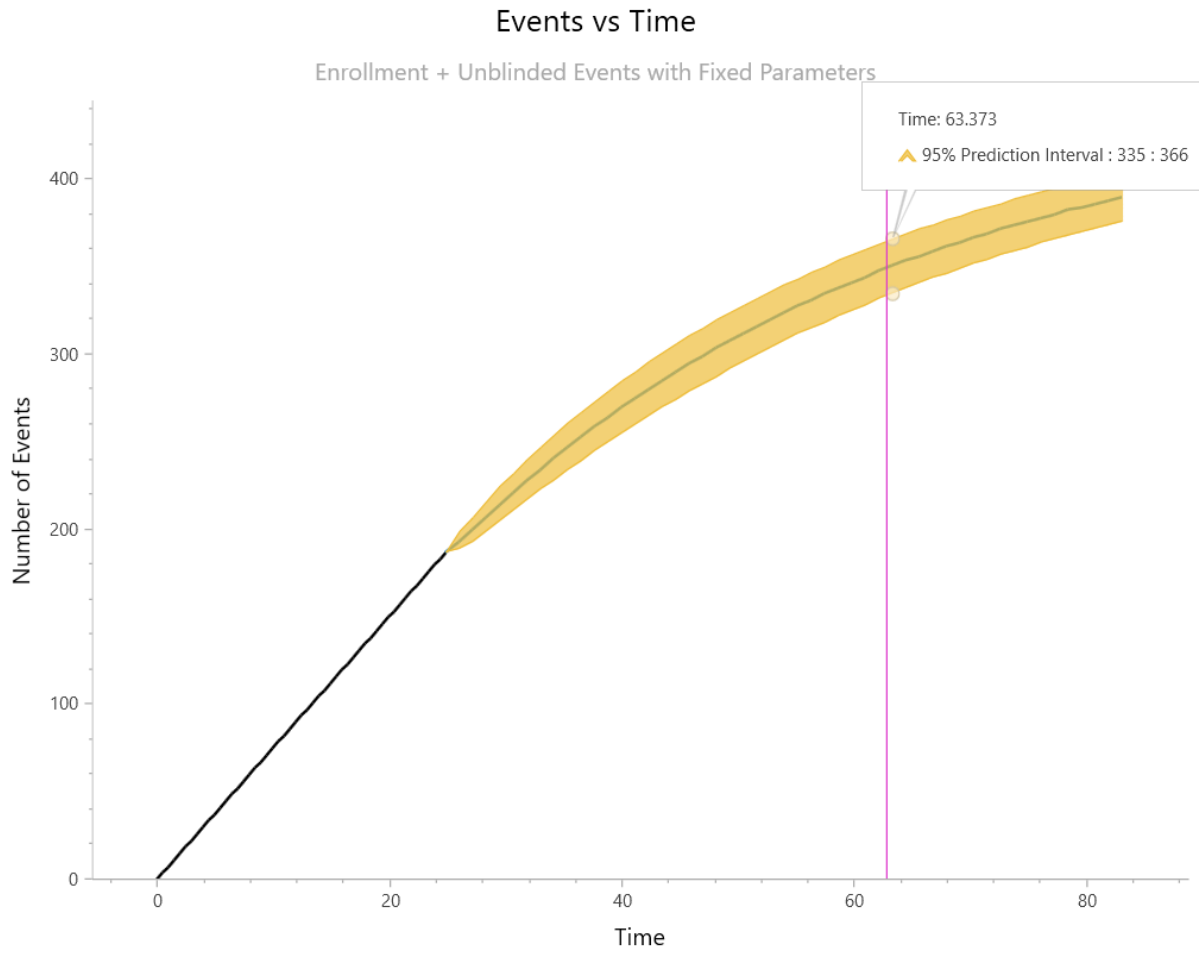


Figure 11.146: Events Prediction Plot for Unblinded Events Prediction using Summary Data

The **Dropout Prediction** plot works effectively the same as the **Events Prediction** plot except for the dropout process. The **Dropout Prediction** plot for this demonstration is shown in Figure 11.147.

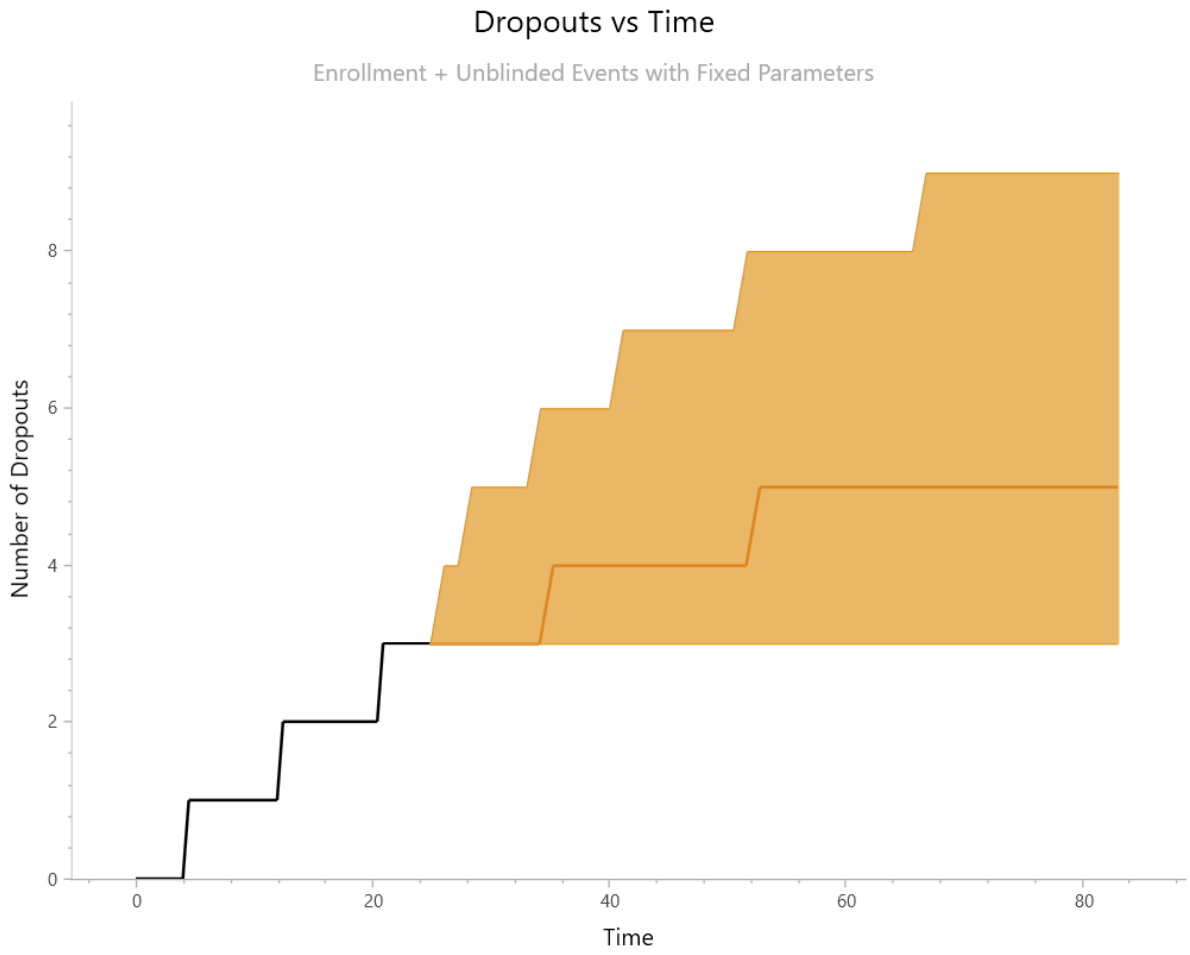


Figure 11.147: Dropout Prediction Plot for Unblinded Events Prediction using Summary Data

The **Enrollment Prediction Table, Events Prediction Table and Dropout Prediction Tables** are the tables used to create the respective **Enrollment Prediction, Events Prediction** and **Dropout Prediction** plots, which by default all consists of ~100 rows (50 pre-simulation and 50 post-simulation). Each consists of five columns: **Time, Actual, Predicted Avg. Sample Size/Events/Dropouts, Predicted Median Sample Size/Events/Dropouts, 95% Prediction Interval LL, 95% Prediction Interval UL**. One prediction table (the **Events Prediction Table**) for this demonstration at the start of the simulated period is given in Figure 11.148.

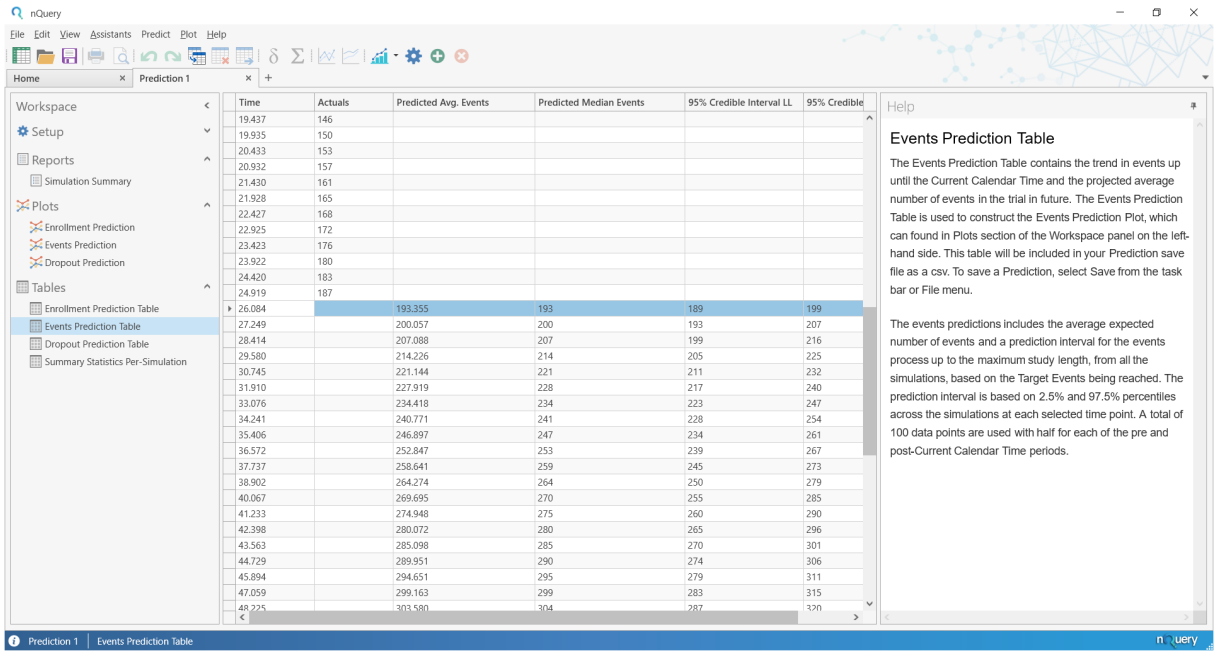


Figure 11.148: Events Prediction Table for Unblinded Events Prediction using Summary Data

Time is the time value relative to the study start time of zero. **Actual** is the actual number of events achieved at a pre-simulation **Time** row. **Predicted Avg. Events** is the predicted average (mean) number of events at a post-simulation **Time** row. **Predicted Median Events** is the predicted median number of events at a post-simulation **Time** row. **95% Prediction Interval LL** is the lower limit for the 95% prediction interval for the number of events at a post-simulation **Time** row. **95% Prediction Interval UL** is the upper limit for the 95% prediction interval for the number of events at a post-simulation **Time** row.

The **Summary Statistics Per-Simulation Table** provides the summary statistics achieved for primary outputs in each simulation. For this demonstration this includes the **Simulation ID, Current Time, Current Sample Size, Current Events, Current Dropout, Current Available, Target Sample Size, Target Events, Study End Time, Total Sample Size, Total Events, Total Dropouts, Total Censored, Control Sample Size, Control Events, Control Dropouts, Treatment Sample Size, Treatment Events, Treatment Dropouts, Accrual Duration, Accrual Duration Uncensored, Average Followup, Median Followup, Target Events Reached.**

The **Summary Statistics Per-Simulation Table** for this demonstration, focused on the simulation results, is shown in Figure 11.149.

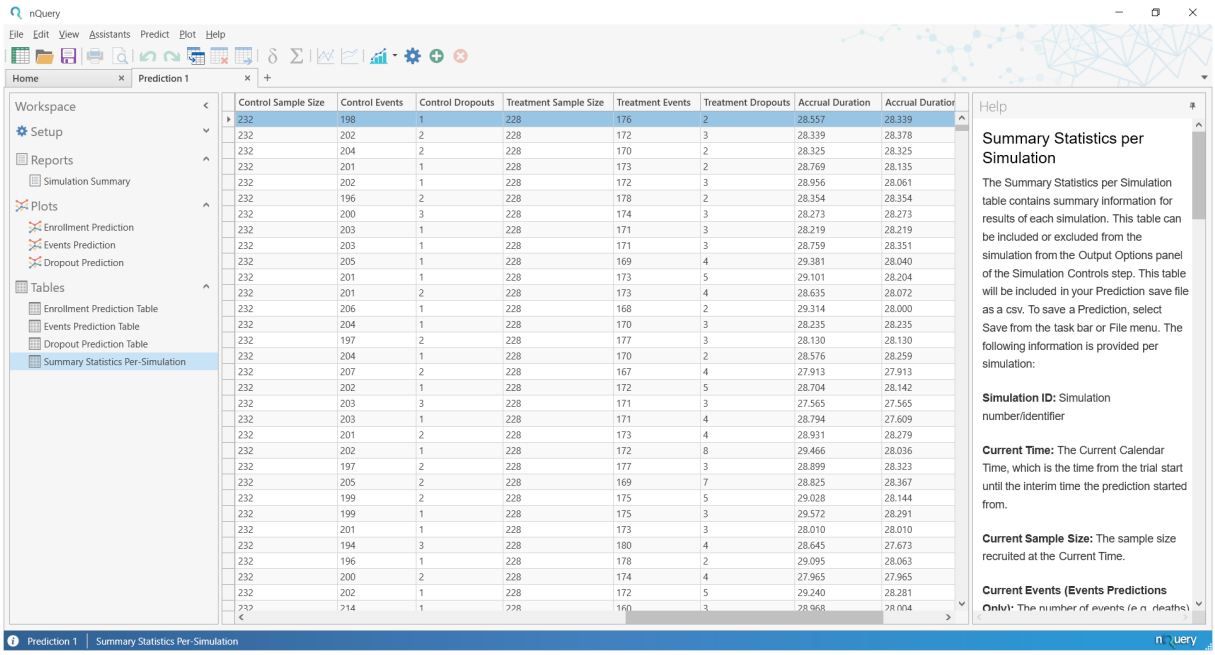


Figure 11.149: Summary Statistics Per-Simulation Table for Unblinded Events Prediction using Summary Data

Details on each field are provided in the Help window on the right but broadly the "Current" fields described the information provided up to the **Current Time**, the "Target" fields describe the study targets, the "Total" fields (and final Accrual, Followup and Target Event Reached columns) give the projection achieved for key parameters in total, the "Control" fields give the key results in the **Control Group** and the "Control" fields give the results in the **Treatment Group.**

Alternative Scenarios The demonstration used inputs based on **SubjectData.csv** and its original design. However, the "real" prediction using **Target = Unblinded Events** with **SubjectData.csv** (subsubsection 11.2.7.2) gave significantly different estimates for event and dropout hazard rates. As noted above, when **Input = Summary Data** the default hazard rates are based on all subjects being recruited at the start of the study but this is effectively a lower bound for hazard rate where every subject's maximum potential follow up time was at its highest possible value.

- Scenario A: **Hazard Rates** set to "true" values based on **SubjectData.csv**

Scenario A For **Scenario A**, the **Event Rates** and **Hazard Rates** will be replaced with the values derived from the demonstration using **SubjectData.csv** (see subsubsection 11.2.7.2). The defaults based on **SubjectData.csv** for the **Event Model Hazard Rates** are 0.0779 and 0.0547 in the **Control** and **Treatment Group** respectively. The default **Control** and **Treatment Group** dropout hazard rates are 0.0007 and 0.0014.

To make the required changes, edit the **Hazard Rate - Control** field to 0.0779 and **Hazard Rate - Treatment** to 0.0547 in the **Events Model** tab at the **Event and Dropout Information** step. The simplest way to do this is to select the **Setup** header

in the Workspace Navigation Bar on the left and then select the **Event and Dropout Information** drop down option.

Then select the **Dropout Model** tab and edit **Hazard Rate - Control** field to 0.0007 and **Hazard Rate - Treatment** to 0.0014. Then select the Next or → button.

At the next **Simulation Controls** step, we will add a single simulation run by selecting the checkbox beside the **Save subject-level data for (x) simulation runs** and replace the default of 10 runs with 1 runs at the "(x)" spot. An edited down summary of the **Setup** changes is provided in Figure 11.150.

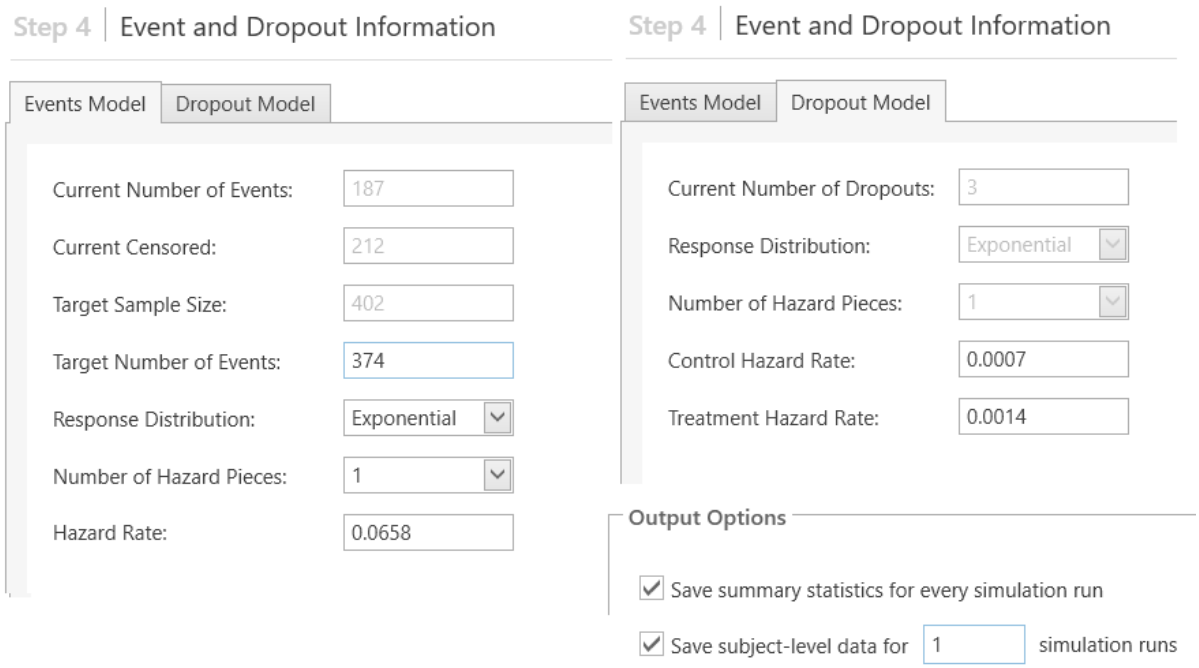


Figure 11.150: Scenario A Setup Changes for Unblinded Events Prediction using Summary Data

To run the simulation again with the new Scenario A, select the Run/→ button. The main results of this Scenario A simulation are shown in Figure 11.151.

Overall Summary

Average Sample Size	460.0000
Average Accrual Duration	28.5066
Average Study Duration	43.9197
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	6.1932

Per-Group Summary

Average Control Sample Size	232
Average Treatment Sample Size	228
Average Control Events	201.16
Average Treatment Events	172.84
Average Control Dropouts	1.8957
Average Treatment Dropouts	4.2975

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	374	460	4	27.7784	41.5365
25.00%	374	460	5	28.1814	42.9178
50.00%	374	460	6	28.4869	43.8695
75.00%	374	460	7	28.8076	44.8857
95.00%	374	460	9	29.2999	46.4096

Figure 11.151: Scenario A Results for Unblinded Events Prediction using Summary Data

For Scenario A, the **Overall Summary** shows that the **Target Number of Events** of 374 was reached in every simulation with an **Average Study Duration** over all the simulations of 43.9197. The **Percentile Summary** shows that 90% of predictions had a **Study Duration** between 41.5365 (5% Percentile) and 46.4096 (95% Percentile), 50% a duration between 42.9178 (25% Percentile) and 44.8857 (75% Percentile) and a median (50% Percentile) duration of 43.8695. The **Average Dropouts** was 6.1932 (Percentiles: 4, 5, 6, 7, 9) and subjects had an **Average Followup** (until either event/dropout or until study end for censored subjects) of 6.1932.

The original target study duration was 40 months and therefore this study is expected to end 3.9 months later than expected. However, this is significantly lower than the **Average**

Study Duration of 73.7531 found above using the "worst case" **Summary Data** default and is effectively the same as the results generated using the actual **SubjectData.csv** (see subsubsection 11.2.7.2 Scenario A for example).

The enrollment process led to the **Target Sample Size** of 460 being achieved in all cases with an **Average Accrual Duration** of 28.5066 (Percentiles: 27.7784, 28.1814, 28.4869, 28.8076, 29.2999) which is effectively the same as before.

The per-group estimates were broadly the same as expected as the hazard ratio was effectively the same for **Scenario A** and the above example. The **Control Group** had a **Average Sample Size** 232, **Average Events** of 201.16 and **Dropouts** of 1.8957. The **Treatment Group** had a **Average Sample Size** 228, **Average Events** of 172.84 and **Dropouts** of 4.2975.

For "better" **Hazard Rate** estimates in the absence of real data, the user may wish to simulate an artificial dataset(s) using pre-trial assumptions (see subsubsection 11.2.7.5 for example) and use this artificial data (by selecting **Save subject-level data for (x) simulation runs** at the **Simulation Controls** step and using the **Per-Simulation Subject-level Data Table**, see below) as an input to a **Input = Subject Data Only** simulation to generate "new" defaults at the **Event & Dropout Information** step.

The **Per-Simulation Subject-level Data Table** was also generated here and is shown for Scenario A in Figure 11.152 with the first simulation (**Simulation ID = 1**). The tables consists of the following fields: **Simulation ID**, **Subject ID**, **Arrival Time**, **Event Time**, **Dropout Time, Final Status** and **Group.** The order of the Subject ID is based on **Arrival Time** order.

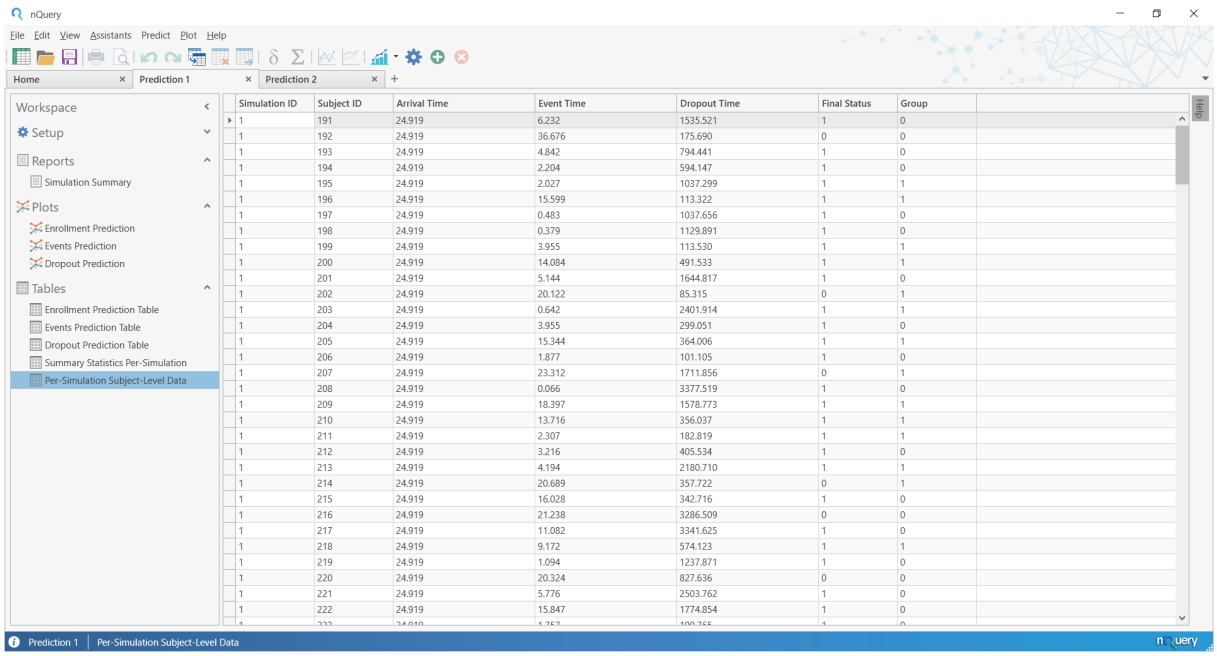


Figure 11.152: Per-Simulation Subject-level Data Table for Unblinded Events using Summary Data

When **Input = Summary Data**, **Event Time** and **Dropout Time** are generated for all subjects. This set of subjects includes the **No. of Censored** subjects at the **Current Time** from the **Fixed Parameters** step and the new subjects simulated after

the **Current Time**. For **Censored Subject**, the **Arrival Time** is set to the **Current Time** (since no information exists for an actual **Arrival Time**). New subjects have an **Arrival Time** generated after the **Current Time** as per the normal. Note that the implied subjects who had **Event/Dropout** before the **Current Time** based on the **Fixed Parameters** are not simulated and therefore are not shown here.

Final Status will equal **Dropout Status** if **Dropout Time** is less than **Event Time** and the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.167 for per-simulation end times). **Final Status** will equal **Censored Status** if **Event Time** and **Dropout Time** are greater than the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.167 for per-simulation end times).

11.2.7.5 Blinded Events Prediction with Summary Data Pre-Trial

Setup **Blinded Events** milestone prediction using **Summary Data** means that the prediction will project the expected length of study needed to achieve a specified **Target Number of Events** using summary data fixed parameters for the whole study as per-group parameters are unknown. In this demonstration, the **Fixed Parameters** are based on pre-trial estimates rather than estimates from an on-going trial.

In the **Setup** for this prediction, first in the **Select the type of Prediction** step select **Blinded Events** from the **Target** field, **Summary Data** from the **Input** field and **Ongoing** from the **Enrollment Status** field.

These selections are shown in Figure 11.153. Select the Next button in the bottom-right or → button in the top-right of the Main Window to move to the next step of the prediction **Setup** stage.

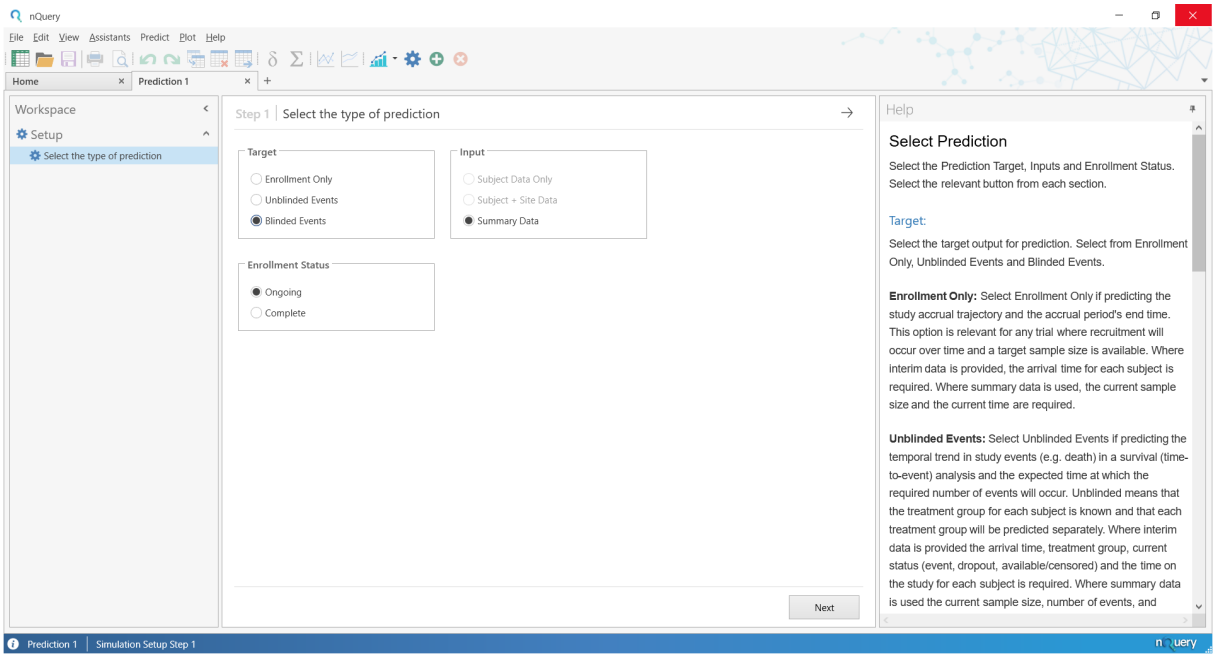


Figure 11.153: Select the Type of Prediction Setup Step for Blinded Events Pre-Trial

The next step is the **Fixed Parameters** step. For this demonstration, there is a **Sample Sizes, Events & Dropouts** section which contains five fields which are as follows:

- Current Sample Size: The total sample size enrolled at the Current Time
- Current No. of Events: The total number of events at the Current Time
- Current No. of Dropouts: The total number of dropouts that have occurred at the Current Time
- Current No. Censored (Read-only): The subjects censored (not had event or dropout) if the study ended at the Current Time
- Current Time: The length of time the study has been on-going since the study began

For this demonstration, it assumed the prediction is being made pre-trial. To make a pre-trial prediction set all of the fields above equal to zero as per Figure 11.154. After all fields all filled, select the Next or → button to move to the next **Setup** step.

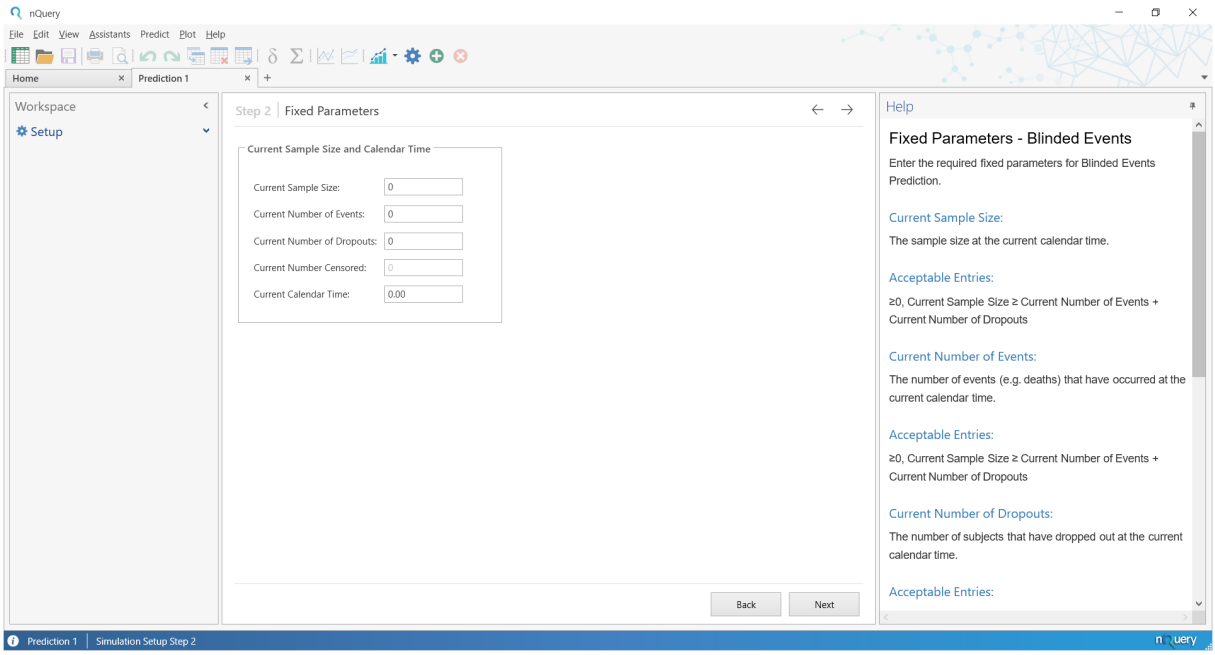


Figure 11.154: Fixed Parameters Setup Step for Blinded Events Pre-Trial

The next step is the **Accrual Options** step which specifies the **Target Sample Size**. The **Accrual Options** step, and its defaults, for this demonstration are shown in Figure 11.155.

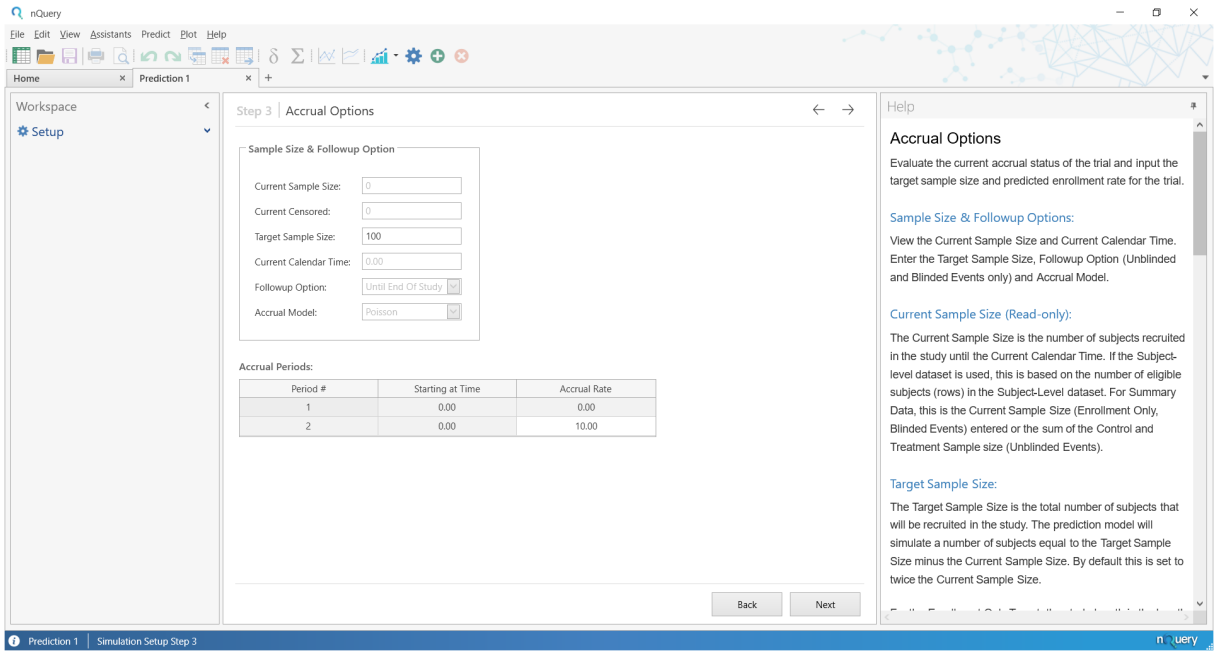


Figure 11.155: Accrual Options Setup Step Defaults for Blinded Events Pre-Trial

The **Accrual Options** step consists of two main elements: the **Sample Size & Followup** input fields and the **Accrual Periods** table.

The **Sample Size & Followup** input fields provides information on enrollment process, censored status and current time based on the subject-level data and allows the user to edit the **Target Sample Size** and select the **Followup Option** and **Accrual Model**. The following fields are provided in this prediction:

- Current Sample Size (Read-only): Sample Size recruited into a study so far
- Current Censored (Read-only): The number of subjects who have not had the event or dropped out at the current time. Equals the number of subjects with the Censored Status in the Status Indicator field
- Sample Size Proportion (Read-only): Proportion of subjects in the Control Group. Based on number of Control Group subjects in Treatment ID field. Controls the allocation proportion in simulated data
- Target Sample Size (Editable): Total number of subjects that will be recruited in this study
- Current Time (Read-only): The length of time that has passed since the study started. Equals the maximum of the sum of the Arrival Time + Time on Study values for each subject
- Followup Option (Read-only): Specifies whether subjects who do not have the event/dropout will be administratively censored at the end of the study or after a fixed follow up period. For Summary Data, this is set to Until End of Study
- Accrual Model (Editable): The statistical model that will be used to generate simulated enrollments

When **Input = Summary Data** and a **Pre-Trial** prediction is being conducted, nQuery Predict defaults to a **Target Sample Size** of 100 and a **Poisson Accrual Model**.

When **Input = Summary Data,** the **Followup Option** must be set to **Until End of Study.**

The **Accrual Periods** table contains information on the **Accrual Rate** up the **Current Time** and allows the user to edit the future **Accrual Rate** used to generate enrollment simulations. The **Accrual Periods** has three columns ,with each row corresponding to a time period, with the columns defined as follows:

- Period #: A numeric ID for the current time period. Increases in increments of one for each subsequent row
- Starting at Time: The starting time for the current time period row. The first row will equal 0 (rate from study start to Current Time) and the second row will equal 0 for pre-trial prediction
- Accrual Rate: The accrual rate is the average number of subjects recruited per unit time (months). The accrual rate in the first row will equal the accrual rate up to the Current Time.

For the **Poisson Accrual Model**, the **Accrual Periods** table will consist of two time period rows. For pre-trial prediction, the first row will just indicate that no information has been provided since **Starting at Time** equals zero for both rows. The second row will correspond to the inputs used to generate future enrollments. By default the **Accrual Rate** for **Pre-Trial** prediction in the future second row will equal 10. The user can edit the **Accrual Rate** for generating future enrollments by editing the second cell of the **Accrual Rate** column. Select the Next or → button to move to the next **Setup** step.

The next step is the **Event and Dropout Information** step which specifies the **Target Number of Events,** event model (and associated statistical parameters) and dropout model (and associated statistical parameters). The **Event and Dropout Information** step on the default **Events Model** tab is shown in Figure 11.156.

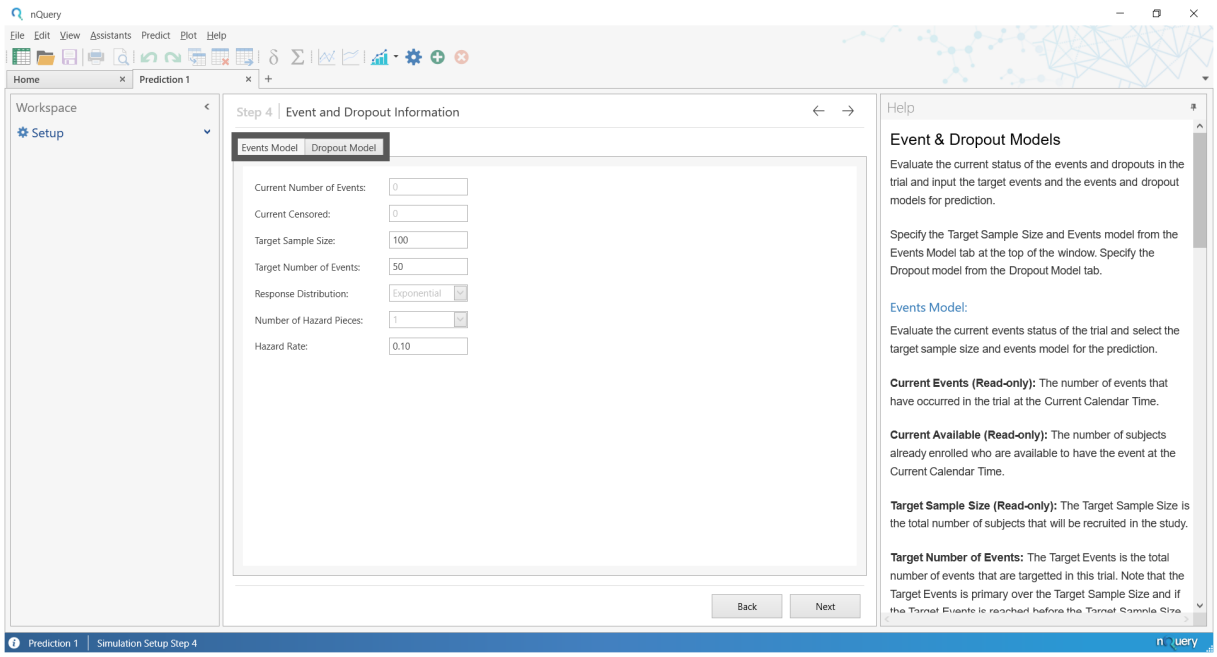


Figure 11.156: Event and Dropout Information Setup Step for Blinded Events Pre-Trial

The **Event and Dropout Information** step consists of two tabs: the **Events Model** tab and the **Dropout Model** tab. These tabs have been highlighted in Figure 11.156 and are opened by selecting the required tab name at the top of the main window, below the step title. For **Blinded Events**, it is assumed that survival and dropout times will be simulated using a single "global" process which is specified by the user.

The **Events Model** tab provides fields which provide information on the current number of subject who have had an event, could have an event going forward and allows the input of the **Target Number of Events** and **Response Distribution** for the events model and additional parameters needed for that specific model. The following fields are provided in this prediction:

- Current Events (Read-only): The number of subjects who had the event of interest at the current time. Equals the number of subjects with the Event Status in the Status Indicator field
- Current Censored (Read-only): The number of subjects who have not had the event or dropped out at the current time. Equals the number of subjects with the Censored Status in the Status Indicator field
- Target Sample Size (Editable): Total number of subjects that will be recruited in this study
- Target Number of Events: The required number of subjects needed to have the event of interest for the study to end
- Response Distribution: The statistical model that will be used to generate survival times for subjects available to have the event
- Number of Hazard Pieces (Response Distribution = Exponential only): Number of hazard pieces used to specify the piecewise exponential model. Select value between 1 and 10
- Hazard Rate (Response Distribution = Exponential only, Number of Hazard Pieces =1, Editable): The exponential hazard rate for the constant exponential survival model specified above

When **Input = Summary Data** pre-trial the only **Response Distribution** is **Exponential** (**Number of Hazard Pieces** = 1) and the default **Hazard Rate** equals 0.1 with a default **Target Number of Events** of 50.

The **Dropout Model** tab is opened by selecting the **Dropout Model** tab name at the top of the main window. For this demonstration, the **Dropout Model** tab is shown in Figure 11.157.

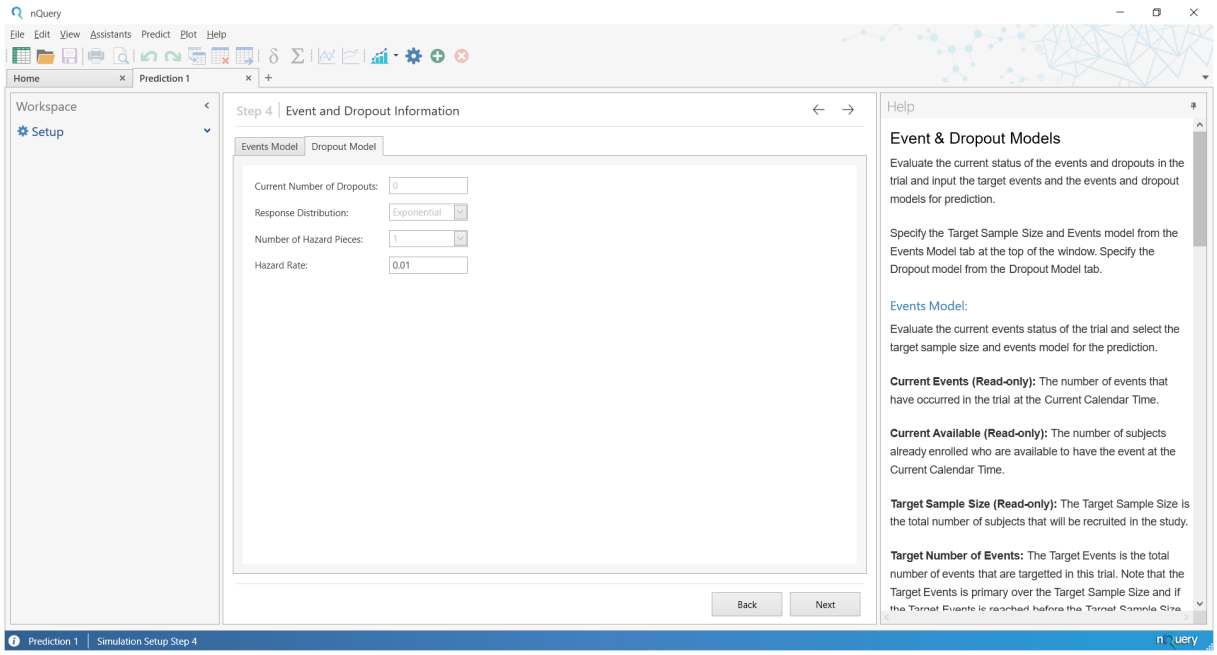


Figure 11.157: Dropout Model tab for Blinded Events Pre-Trial

For dropout, the only **Response Distribution** option is exponential with one hazard piece with a **Hazard Rate** equal to 0.01. The inputs for dropout **Exponential Response Distribution** are the same as from the **Events Model** described above and therefore will not be replicated here. Select the Next or → button to move to the next **Setup** step.

The final step is the **Simulation Controls** step. The **Simulation Controls** step consists of three sections: Simulation Controls, Output for All Trials and Output Options.

Simulation Controls (top-left) sets the **Number of Simulations**, **Refresh Frequency** and **Random Seed**

Output For All Trials (bottom-left) sets the Percentiles desired in the **Percentile Summary** table in the **Simulation Summary** report for key simulation outputs such as study length and sample size.

Output Options (right) selects which additional datasets the user wants in the **Tables** field of the simulation results. Additional datasets will be summary statistics for each simulation and outputs from a set number of individual of simulations.

The **Simulation Controls** step is described in detail in subsubsection 11.2.9.4. In this demonstration, the defaults will be used which corresponds to 1000 simulations with the default percentiles (5%, 25%, 50%, 75%, 95%) and with the "Save summary statistics for every simulation run" **Output Options** table active. The **Simulation Controls** defaults for this demonstration are shown in Figure 11.158. To start the milestone prediction, Select the Run (where Next button was in previous steps) or → button.

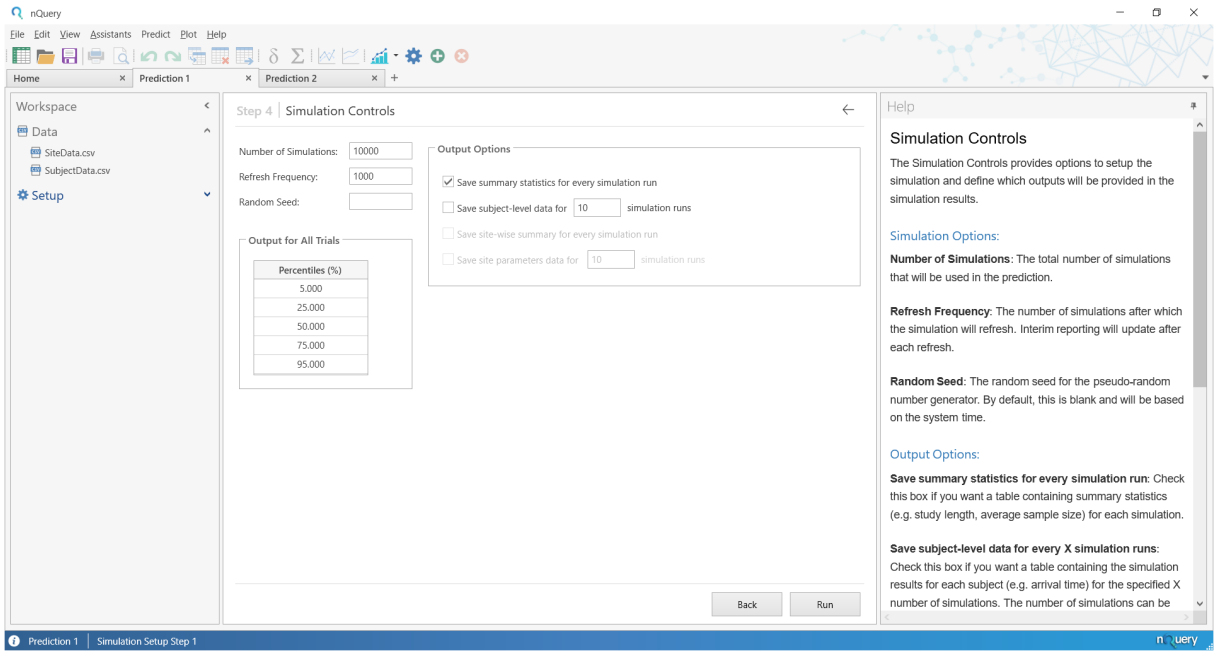


Figure 11.158: Simulation Controls Setup Step for Blinded Events Pre-Trial

Results While a milestone prediction is being run, a **Simulation in Progress** window will be displayed. The **Simulation in Progress** window provides updated information on key simulation metrics while the simulation is ongoing. An example for this demonstration is given in Figure 11.159.

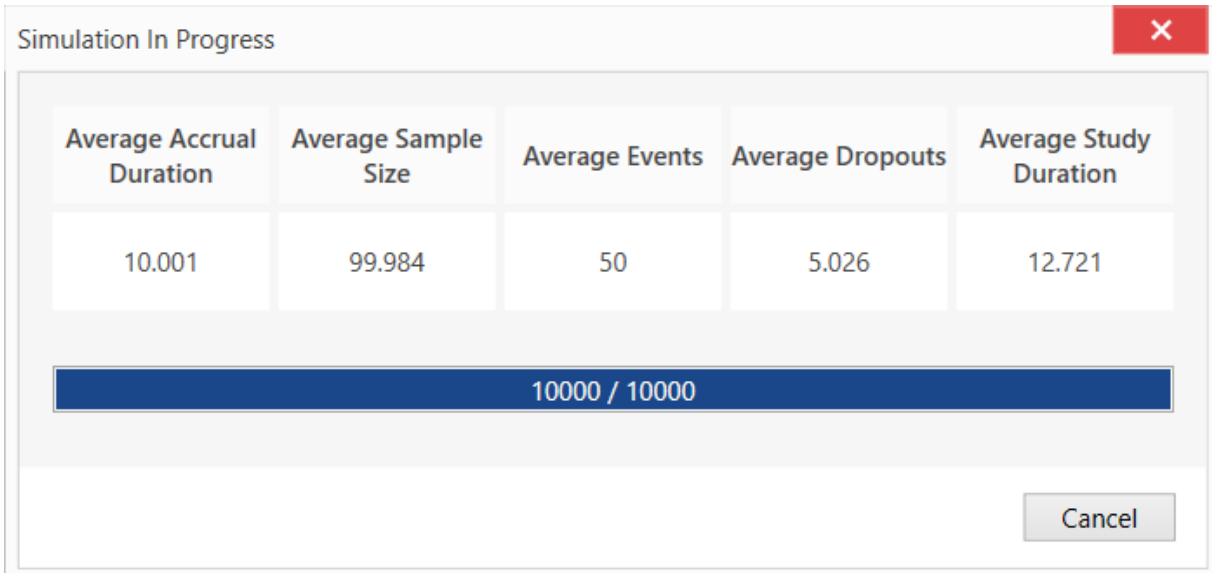


Figure 11.159: Simulation in Progress Window for Blinded Events Pre-Trial

Once the simulation is complete, the results will automatically be added to the Workspace Navigation Bar on the left and the first element under the **Plots** header will be displayed. In this demonstration, the **Enrollment Prediction Plot** will be displayed. This is shown in Figure 11.160.

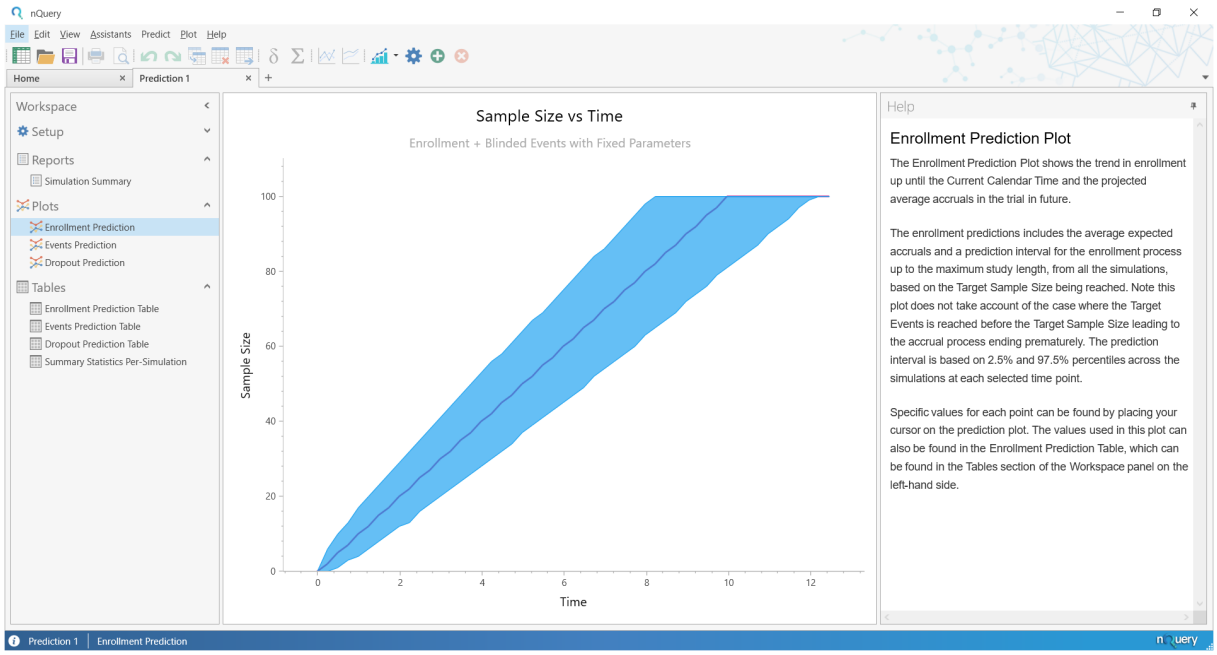


Figure 11.160: Enrollment Prediction Plot for Blinded Events Pre-Trial

The results of a nQuery Predict milestone prediction can be divided into three categories: **Reports, Plots** and **Tables**. A high-level summary of the results in nQuery Predict is provided in subsection 11.2.8 with demonstration specific elements highlighted here.

For this demonstration the **Reports** header contains the **Simulation Summary** report, the **Plots** header contains the **Enrollment Prediction, Events Prediction** and **Dropout Prediction** plot and the **Tables** header contains the **Enrollment Prediction Table, Events Prediction Table, Dropout Prediction Table** and **Summary Statistics Per-Simulation**. To select any result element, select it from the appropriate header in the Workspace Navigation Bar on the left (see subsection 11.2.2 for details on the Navigation Bar).

The **Simulation Summary** provides a tabular summary of the inputs and outputs from the current milestone prediction simulation. The **Simulation Summary** for this demonstration is shown in Figure 11.161.

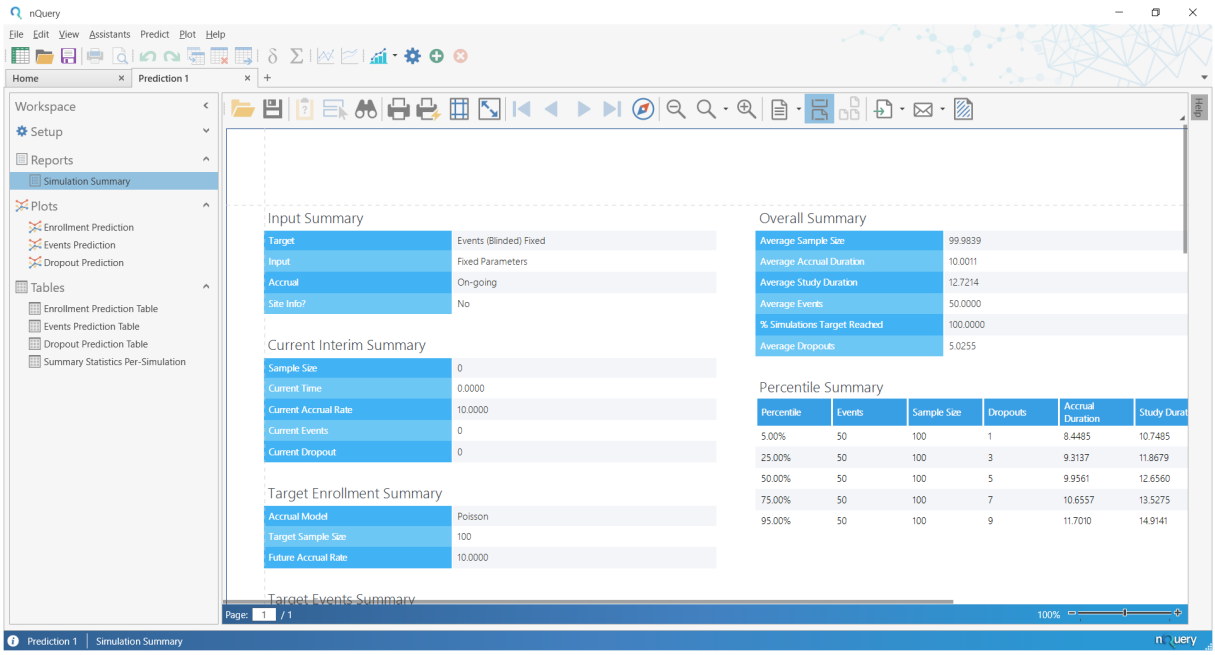


Figure 11.161: Simulation Summary Report for Blinded Events Pre-Trial

In the **Simulation Summary** report, the left-hand column provides a summary of inputs used to generate the current simulation and the right-hand column provides the results of the current simulation. In this demonstration, we will skip the left-hand Inputs column and focus on the main results in the right-hand column and the main report options.

The results column (on the right) is shown in Figure 11.162. For this demonstration, the **Overall Summary** shows that the **Target Number of Events** of 50 was reached in every simulation with an **Average Study Duration** over all the simulations of 12.7214. The **Percentile Summary** shows that 90% of predictions had a **Study Duration** between 10.7485 (5% Percentile) and 14.9141 (95% Percentile), 50% a duration between 11.8679 (25% Percentile) and 13.5275 (75% Percentile) and a median (50% Percentile) duration of 12.656.

The **Average Dropouts** was 5.0255 (Percentiles: 1, 3, 5, 7, 9) and subjects had an **Average Followup** (until either event/dropout or until study end for censored subjects) of 5.0255. For the enrollment process, the **Average Accrual Duration** was 10.0011 (Percentiles: 8.4485, 9.3137, 9.9561, 10.6557, 11.7010) with the **Target Sample Size** of 100 reached in all simulations.

Overall Summary

Average Sample Size	99.9839
Average Accrual Duration	10.0011
Average Study Duration	12.7214
Average Events	50.0000
% Simulations Target Reached	100.0000
Average Dropouts	5.0255

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	50	100	1	8.4485	10.7485
25.00%	50	100	3	9.3137	11.8679
50.00%	50	100	5	9.9561	12.6560
75.00%	50	100	7	10.6557	13.5275
95.00%	50	100	9	11.7010	14.9141

Figure 11.162: Simulation Summary Report Results for Blinded Events Pre-Trial

To edit the **Simulation Summary report there a** number of buttons available at the top of the report. For full detail on the **Simulation Summary** report and options to edit the report see subsubsection 11.2.8.2. However the Zoom options  , Page Layout and Setup options  and Export option  will be the more commonly used options.

The **Enrollment Prediction** plot provides a visual summary of enrollment. The X-axis is **Time** (relative to study start) and the Y-axis is **Sample Size** (enrolled at Time X-axis value). When the cursor is placed over the **Enrollment Prediction** plot, information on the **Sample Size** enrolled at a given **Time** is shown as per Figure 11.163.

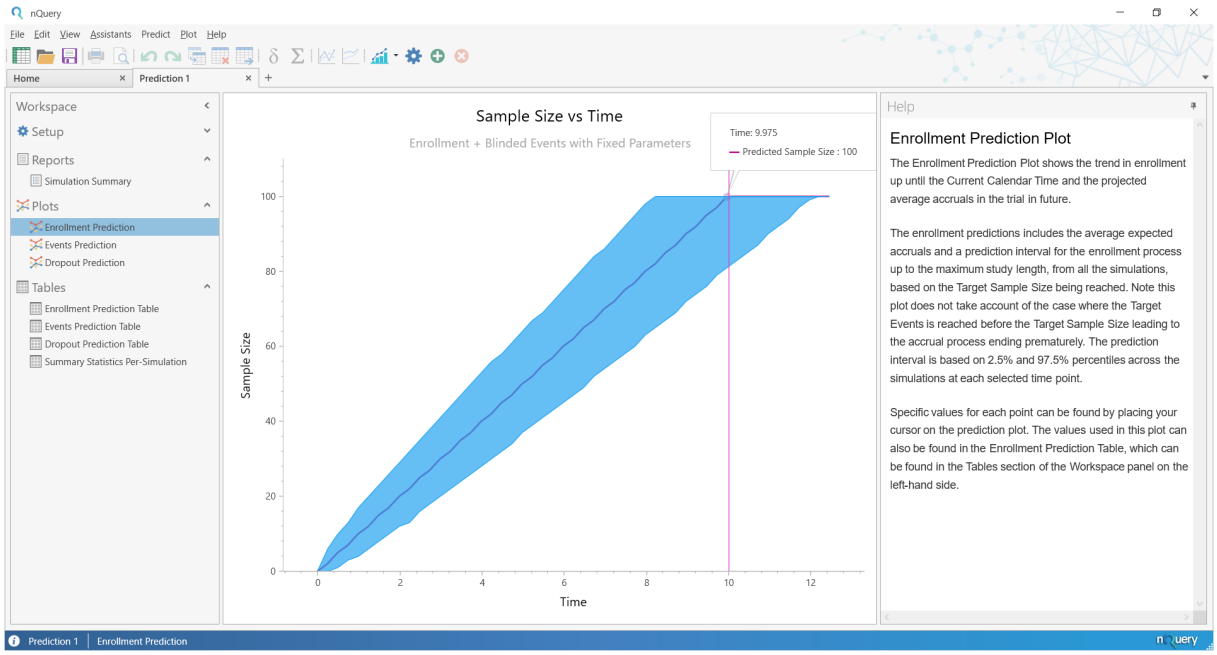


Figure 11.163: Enrollment Prediction Plot for Blinded Events Pre-Trial

The **Enrollment Prediction** plot for pre-trial prediction will have a blue conic section with a grey line where the blue conic section plots the 95% prediction interval for the **Sample Size** achieved at a given **Time** across all simulations and the grey line is the average **Sample Size** enrolled at a given time. The 95% prediction interval indicates the 95% of predictions had a sample size that fell between the lower and upper limit at a given time. Note the **Enrollment Prediction** plot **Time** scale will be related to the **Accrual Duration** rather than the **Event Prediction** and **Dropout Prediction** plots which will be associated with the **Study Duration.**

The **Event Prediction** plot for pre-trial prediction will have a yellow conic section with a grey line where the yellow conic section plots the 95% prediction interval for the **Events** achieved at a given **Time** across all simulations and the grey line is the average **Events** enrolled at a given time. The 95% prediction interval indicates the 95% of predictions had an event that fell between the lower and upper limit at a given time. The **Events Prediction** plot for this demonstration is shown in Figure 11.164.

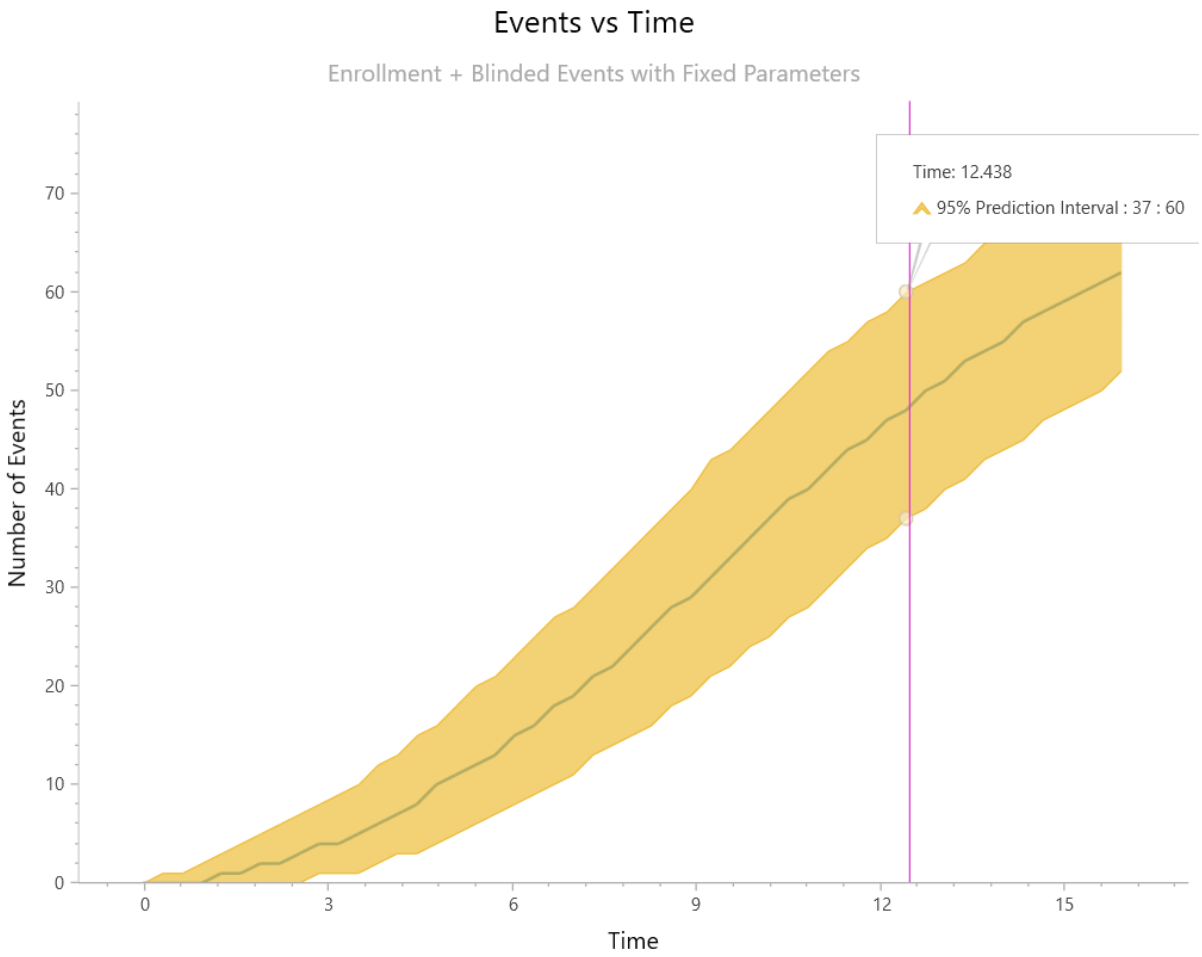


Figure 11.164: Events Prediction Plot for Blinded Events Pre-Trial

The **Dropout Prediction** plot works effectively the same as the **Events Prediction** plot except for the dropout process. The **Dropout Prediction** plot for this demonstration is shown in Figure 11.165.

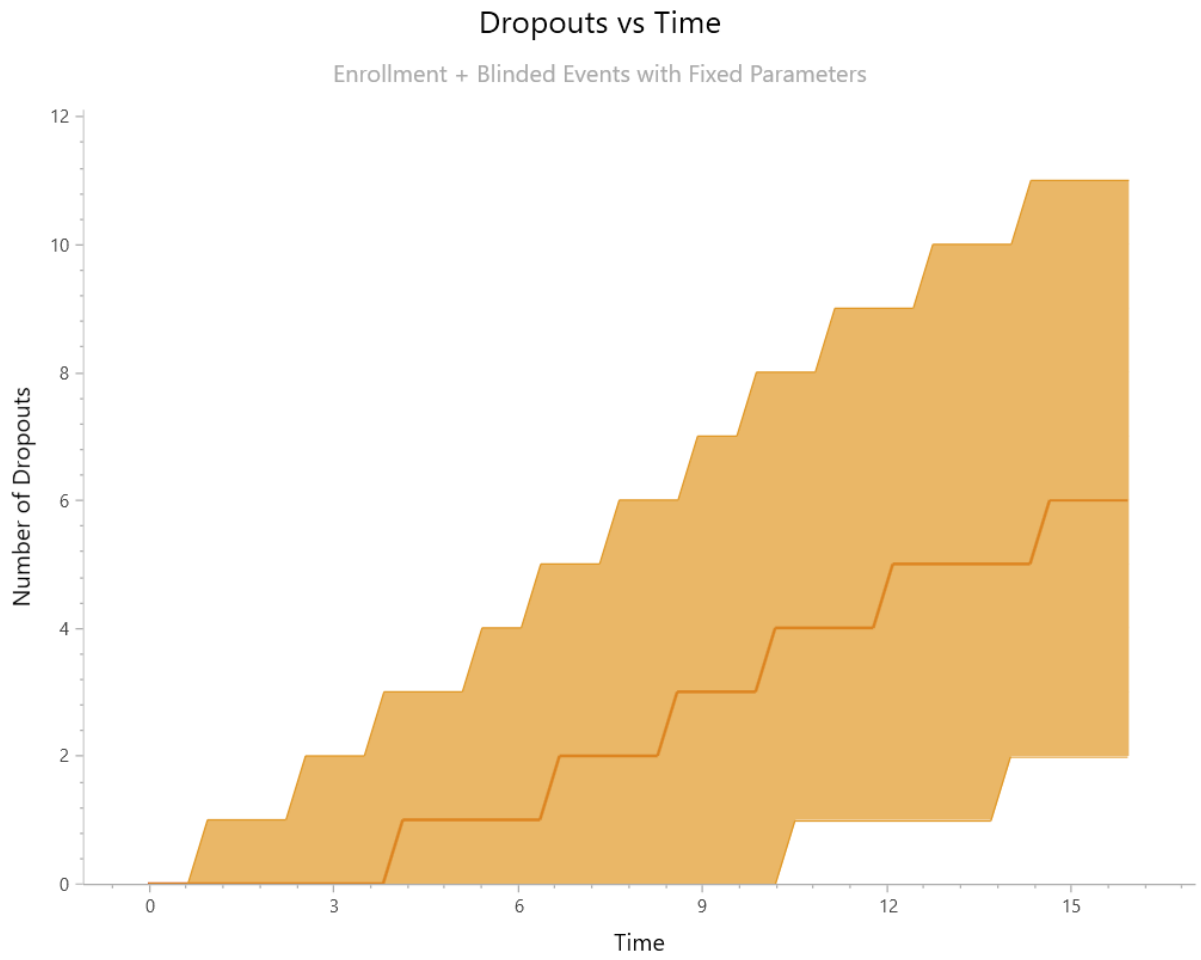
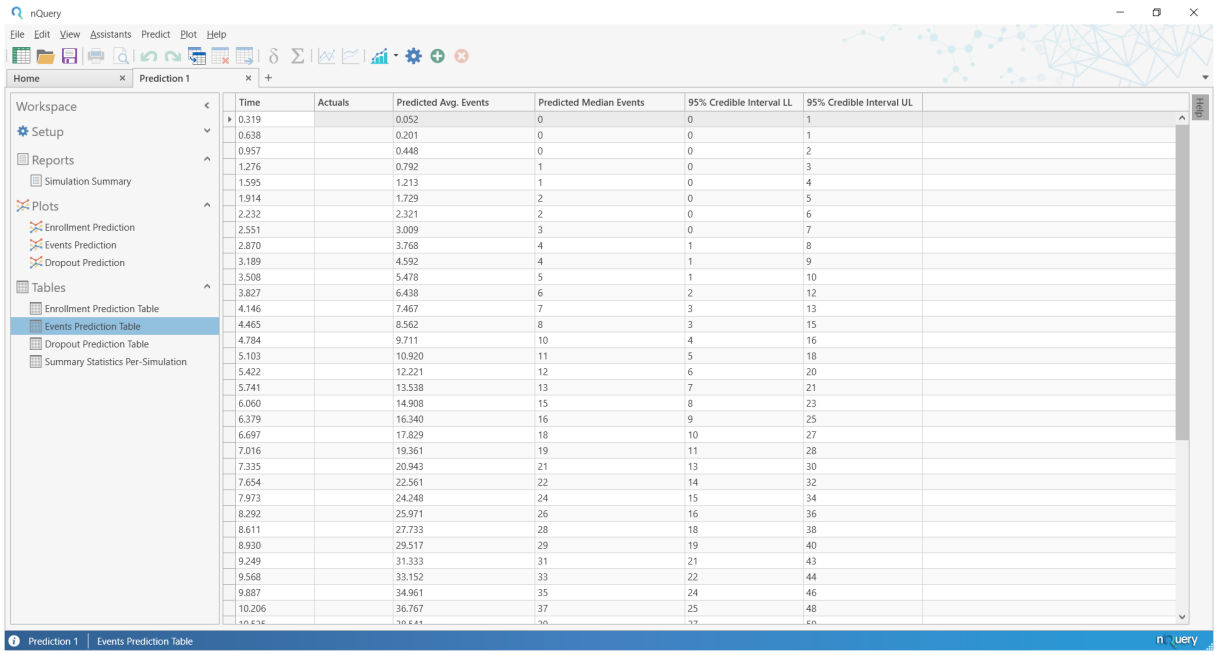


Figure 11.165: Dropout Prediction Plot for Blinded Events Pre-Trial

The **Enrollment Prediction Table, Events Prediction Table and Dropout Prediction Tables** are the tables used to create the respective **Enrollment Prediction, Events Prediction** and **Dropout Prediction** plots, which by default all consists of ~100 rows (50 pre-simulation and 50 post-simulation). Each consists of five columns: **Time, Actual, Predicted Avg. Sample Size/Events/Dropouts, Predicted Median Sample Size/Events/Dropouts, 95% Prediction Interval LL, 95% Prediction Interval UL**. One prediction table (the **Events Prediction Table**) for this demonstration at the start is given in Figure 11.166.



Time	Actuals	Predicted Avg. Events	Predicted Median Events	95% Credible Interval LL	95% Credible Interval UL
0.319		0.052	0	0	1
0.638		0.201	0	0	1
0.957		0.448	0	0	2
1.276		0.792	1	0	3
1.595		1.213	1	0	4
1.914		1.729	2	0	5
2.232		2.321	2	0	6
2.551		3.009	3	0	7
2.870		3.768	4	1	8
3.189		4.592	4	1	9
3.508		5.478	5	1	10
3.827		6.438	6	2	12
4.146		7.467	7	3	13
4.465		8.562	8	3	15
4.784		9.711	10	4	16
5.103		10.920	11	5	18
5.422		12.221	12	6	20
5.741		13.538	13	7	21
6.060		14.908	15	8	23
6.379		16.340	16	9	25
6.697		17.829	18	10	27
7.016		19.361	19	11	28
7.335		20.943	21	13	30
7.654		22.561	22	14	32
7.973		24.248	24	15	34
8.292		25.971	26	16	36
8.611		27.733	28	18	38
8.930		29.517	29	19	40
9.249		31.333	31	21	43
9.568		33.152	33	22	44
9.887		34.961	35	24	46
10.206		36.767	37	25	48

Figure 11.166: Events Prediction Table for Blinded Events Pre-Trial

Time is the time value relative to the study start time of zero. **Actual** is the actual number of events achieved at a pre-simulation **Time** row but will be empty for pre-trial prediction. **Predicted Avg. Events** is the predicted average (mean) number of events at a post-simulation **Time** row. **Predicted Median Events** is the predicted median number of events at a post-simulation **Time** row. **95% Prediction Interval LL** is the lower limit for the 95% prediction interval for the number of events at a post-simulation **Time** row. **95% Prediction Interval UL** is the upper limit for the 95% prediction interval for the number of events at a post-simulation **Time** row.

The **Summary Statistics Per-Simulation Table** provides the summary statistics achieved for primary outputs in each simulation. For this demonstration this includes the **Simulation ID, Current Time, Current Sample Size, Current Events, Current Dropout, Current Available, Target Sample Size, Target Events, Study End Time, Total Sample Size, Total Events, Total Dropouts, Total Censored, Accrual Duration, Accrual Duration Uncensored, Average Followup, Median Followup, Target Events Reached.**

The **Summary Statistics Per-Simulation Table** for this demonstration, focused on the simulation results, is shown in Figure 11.167.

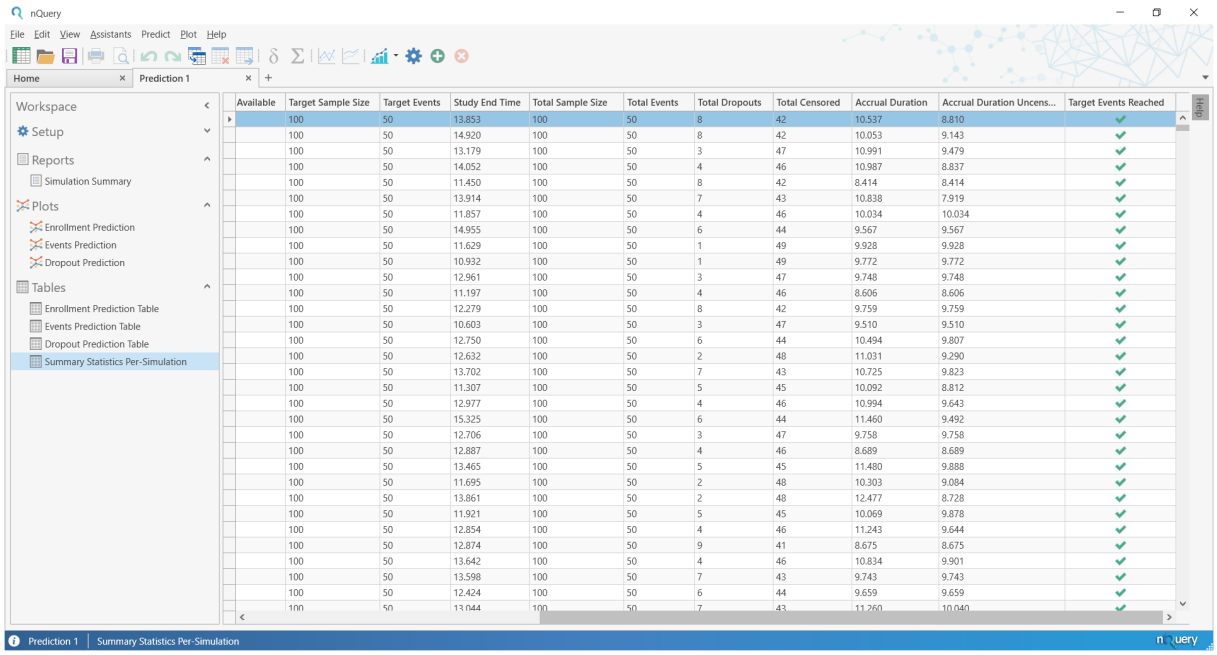


Figure 11.167: Summary Statistics Per-Simulation Table for Blinded Events Pre-Trial

Details on each field are provided in the Help window on the right but broadly the "Current" fields described the information provided up to the **Current Time**, the "Target" fields describe the study targets and the "Total" fields (and final Accrual, Followup and Target Event Reached columns) give the projection achieved for key parameters in total.

Alternative Scenarios The prior demonstration used the default values for pre-trial prediction. In the following scenarios, pre-trial prediction will be created for original study design from which the **SubjectData.csv** interim results were generated.

The original study plan assumed a **Target Number of Events** of 374, **Target Sample Size** of 460, **Accrual Period** of 30 and **Study Duration** of 40. The sample size determination (0.025 1-sided significance level for 90% power) assumed a **Hazard Ratio** of ~0.715, **Hazard Rate - Control** of ~0.091 (median survival time of ~10.7 months) and zero dropout. A replication of this sample size calculation in STT2 is provided in Figure 11.168.

STT2-2 / Two Sample Log-Rank Test of Exponential Survival with Exponential Dropout

	1	2	3	4
Test Significance Level, α	0.02500000			
1 or 2 Sided Test?	1	2	2	2
Length of Accrual Period, a	30.00000000			
Maximum Length of Followup, f	40.00000000			
Common Exponential Dropout Rate, d	0.00000000			
Group 1 Exponential Parameter, λ_1	0.06500000			
Group 2 Exponential Parameter, λ_2	0.09090000			
Hazard Ratio, $h=\lambda_1/\lambda_2$	0.71507151			
Power (%)	90			
Sample Size per Group, n	**230**			
Total number of events required, E	374			

Figure 11.168: Original Sample Size Determination for Example Study

- Scenario A: Unblinded Pre-trial Prediction using original study plan
- Scenario B: Unblinded Events Pre-Trial Prediction using Study Plan with updated hazard rate based on **SubjectData.csv**

Scenario A For **Scenario A**, create a new empty prediction workspace (subsection 11.2.1). Select **Target = Unblinded Events**, **Input = Summary Data** and **Enrollment Status = Complete** at the **Select the Type of Prediction** step. Then select the Next or → button.

At the **Fixed Parameters** step, enter zero into all fields. Then select the Next or → button.

At the **Accrual Options** step, enter a **Target Sample Size** of 460 and an **Accrual Rate** of 15.3333 (460/30) in the second row of the **Accrual Periods** table. Then select the Next or → button.

At the **Event & Dropout Information** step, in the **Events Model** tab input 374 in the **Target Sample Size** field, 0.715 in the **Hazard Ratio** field and 0.091 in the **Hazard Rate - Control** field giving an automatically calculated value for **Hazard Rate - Treatment** of 0.0651. In the **Dropout Model** tab, enter zero for both **Hazard Rate** fields. Then select the Next or → button.

At the next **Simulation Controls** step, we will add a single simulation run by selecting the checkbox beside the **Save subject-level data for (x) simulation runs** and replace the default of 10 runs with 1 runs at the "(x)" spot. An edited down summary of the **Setup** changes is provided in Figure 11.169.

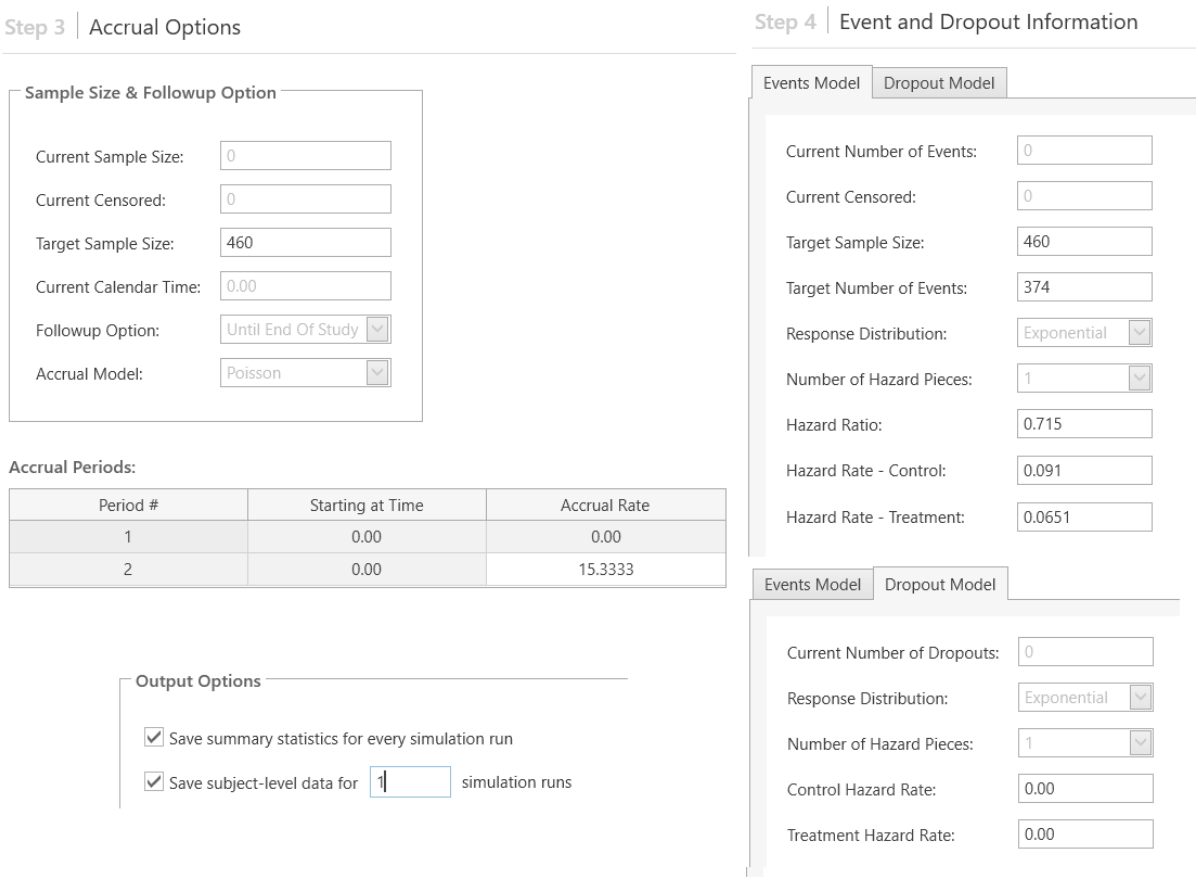


Figure 11.169: Scenario A Setup Changes for Unblinded Events Prediction Pre-Trial

To run the simulation again with the new Scenario A, select the Run/$^{\rightarrow}$ button. The main results of this Scenario A simulation are shown in Figure 11.170.

Overall Summary

Average Sample Size	460.0000
Average Accrual Duration	30.0179
Average Study Duration	39.7490
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	0.0000

Per-Group Summary

Average Control Sample Size	230
Average Treatment Sample Size	230
Average Control Events	197.5927
Average Treatment Events	176.4073
Average Control Dropouts	0
Average Treatment Dropouts	0

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	374	460	0	27.7927	37.2135
25.00%	374	460	0	29.0644	38.6711
50.00%	374	460	0	29.9905	39.7116
75.00%	374	460	0	30.9549	40.7874
95.00%	374	460	0	32.3704	42.3793

Figure 11.170: Scenario A Results for Unblinded Events Prediction Pre-Trial

For Scenario A, the **Overall Summary** shows that the **Target Number of Events** of 374 was reached in every simulation with an **Average Study Duration** over all the simulations of 39.7490. The **Percentile Summary** shows that 90% of predictions had a **Study Duration** between 37.2135 (5% Percentile) and 42.3793 (95% Percentile), 50% a duration between 38.6711 (25% Percentile) and 40.7874 (75% Percentile) and a median (50% Percentile) duration of 39.7116.

As expected, the **Average Study Duration** is very close to the pre-trial target of 40 months.

The enrollment process led to the **Target Sample Size** of 460 being achieved in all cases with an **Average Accrual Duration** of 30.0179 (Percentiles: 27.7927, 29.0644, 29.9905, 30.9549, 32.3704) which is effectively the same as the target accrual period of

30. This verifies that this prediction based on the original study plan and sample size determination is consistent with that plan.

The **Per-Simulation Subject-level Data Table** was also generated here and is shown for Scenario A in Figure 11.171 with the first simulation (**Simulation ID = 1**). The tables consists of the following fields: **Simulation ID**, **Subject ID**, **Arrival Time**, **Event Time**, **Dropout Time, Final Status** and **Group.** The order of the Subject ID is based on **Arrival Time** order.

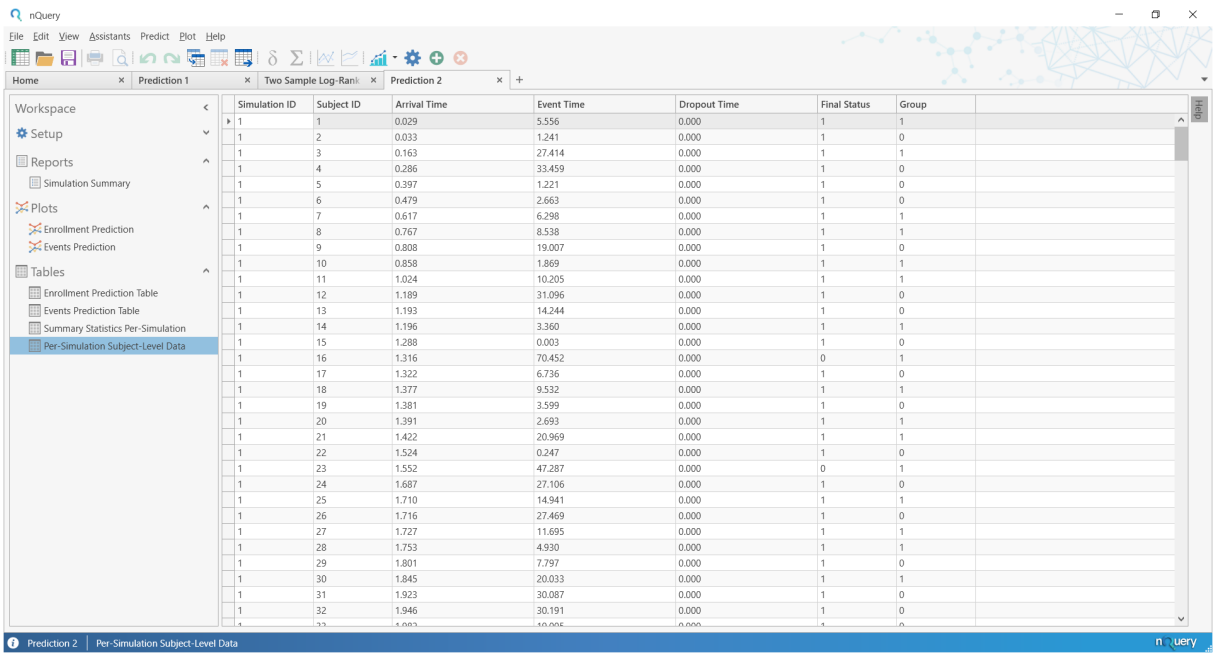


Figure 11.171: Per-Simulation Subject-level Data Table for Unblinded Events Pre-Trial

For **Pre-Trial** prediction, **Event Time** and **Dropout Time** are generated for all subjects. **Final Status** will equal **Dropout Status** if **Dropout Time** is less than **Event Time** and the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.167 for per-simulation end times). **Final Status** will equal **Censored Status** if **Event Time** and **Dropout Time** are greater than the **Study End Time** (i.e. study duration) for that simulation (see Figure 11.167 for per-simulation end times)

Scenario B Scenario B will be the same as Scenario A expect with the **Event Model** tab at the **Event & Dropout Information** step edited to have exponential hazard rates equal to those default values found using the **SubjectData.csv** (see subsubsection 11.2.7.2 for example).

To evaluate this scenario, select **Event & Dropout Information** from the Navigation Bar from the **Setup** heading on the left. On the **Events Model** tab. Then input the **SubjectData.csv** default estimates for the **Hazard Ratio** (0.7025, compared to pre-trial 0.715) and **Hazard Rate - Control** (0.0779, compared to pre-trial 0.091). **Hazard Rate - Treatment** will automatically update to the correct value of 0.0547. Then select the Next or $\rightarrow$ button at this step and the **Simulation Controls** step. A summary of the changes compared to Scenario A is provided in Figure 11.172.

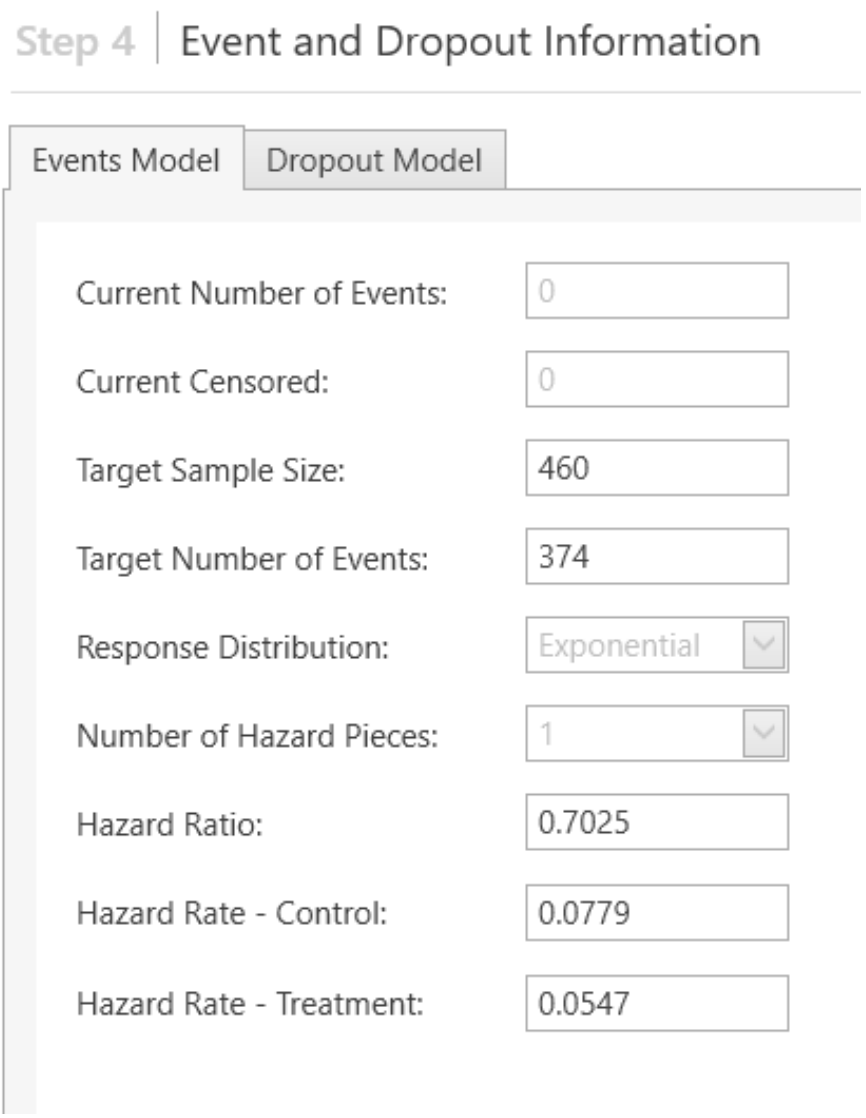


Figure 11.172: Scenario B Inputs for Unblinded Events Pre-Trial

The main results for Scenario B are shown in Figure 11.173.

Overall Summary

Average Sample Size	460.0000
Average Accrual Duration	30.0078
Average Study Duration	43.3128
Average Events	374.0000
% Simulations Target Reached	100.0000
Average Dropouts	0.0000

Per-Group Summary

Average Control Sample Size	230
Average Treatment Sample Size	230
Average Control Events	198.4642
Average Treatment Events	175.5358
Average Control Dropouts	0
Average Treatment Dropouts	0

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	374	460	0	27.7144	40.4476
25.00%	374	460	0	29.0696	42.1066
50.00%	374	460	0	30.0010	43.2917
75.00%	374	460	0	30.9451	44.4537
95.00%	374	460	0	32.2997	46.2845

Figure 11.173: Scenario B Results for Unblinded Events Prediction Pre-Trial

For Scenario B, the **Overall Summary** shows that the **Target Number of Events** of 374 was reached in every simulation with an **Average Study Duration** over all the simulations of 43.3128. The **Percentile Summary** shows that 90% of predictions had a **Study Duration** between 40.4476 (5% Percentile) and 46.2845 (95% Percentile), 50% a duration between 42.1066 (25% Percentile) and 44.4537 (75% Percentile) and a median (50% Percentile) duration of 43.2917.

With the lower "actual" rates taken from **SubjectData.csv**, the study is expected to around 3.3 months longer than the original plan of 40 months. However, the lower hazard ratio implies the power would be slightly higher than expected pre-trial all else being equal since it is further from the null hazard ratio of 1.

The enrollment process led to the **Target Sample Size** of 460 being achieved in all cases

with an **Average Accrual Duration** of 30.0078 (Percentiles: 27.7927, 29.0644, 29.9905, 30.9549, 32.3704) which is effectively the same as the target accrual period of 30 as per Scenario B.

11.2.8 Results Output Summary

11.2.8.1 Plots

nQuery Predict provides a number of plots to better explore the results of a milestone prediction. These plots are interactive and editable by the user to maximise the value of these tools. Note that all plots can be saved and edited, see subsubsection 11.2.9.2 for details. To open a given plot, select the required plot from under the **Plots** header in the Workspace Navigation Bar on the left-hand side of the nQuery Predict workspace after a prediction has been completed.

nQuery Predict provides three main plots in the results output. These are:

- Enrollment Prediction Plot (All Cases)
- Events Prediction Plot (Target = Unblinded Events or Blinded Events)
- Dropout Prediction Plot (Target = Unblinded Events or Blinded Events + Current Dropout or Dropout Hazard Rate(s) > 0)

The Enrollment Prediction, Events Prediction and Dropout Prediction plots are all self-similar. Multiple examples of each these plots is provided in the demonstrations above (Enrollment Demonstrations: subsection 11.2.6, Events Prediction: subsection 11.2.7). This section will provide a description of each plot and the tools available to explore and edit these plots.

Enrollment Prediction Plot The Enrollment Prediction Plot provides a visual summary of the actual and predicted accrual pattern using a cumulative frequency line graph. An example of an nQuery Prediction workspace with the Enrollment Prediction plot displayed is provided in Figure 11.174.

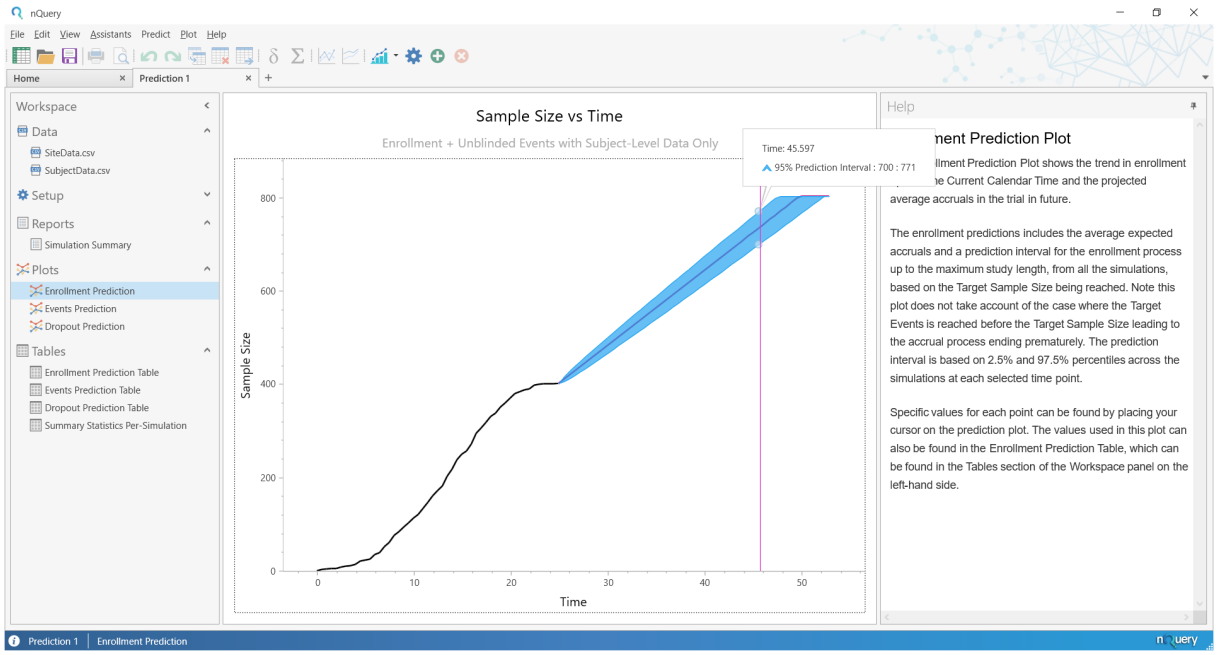


Figure 11.174: Enrollment Prediction Plot Example

In the Enrollment Prediction (Sample Size vs Time) plot, the X-axis is **Time** and the Y-axis is **Sample Size**. **Time** is the length of time after study start (**Time = 0**) at which the Y-axis is being evaluated. **Sample Size** is the actual/predicted cumulative number of subjects enrolled at a given value of **Time**. The X-axis length will be related to the **Accrual Duration** (i.e. length of time over which subjected were being enrolled to reach the **Target Sample Size**) over all simulations. The Y-axis height will be related to the **Target Sample Size** specified for that prediction.

In the majority of cases (exceptions discussed below), the Enrollment Prediction plot will consist of two parts:

1. The actual accrual pattern up to the **Current Time**
2. The predicted accrual pattern from the **Current Time** up to the maximum projected **Accrual Duration**

The actual accrual pattern provides a visual summary of when subjects entered the study. The actual accrual pattern will be represented by a solid black line. If the user places the cursor over the plot over this part of the line, a pop-up will be shown on the plot with following text:

Time: A

Actual Sample Size: B

where A and B are the actual values at the currently highlighted **Time** value.

If **Subject-level Data** has been provided, the actual pattern will be based on the **Arrival Time** column values. If **Summary Data** is used, a linear projection is used from zero to the **Current Sample Size**. If conducting a pre-trial prediction, there will be no actual accrual pattern to show. The plot subtitle will display the input used for the current plot.

The predicted accrual pattern provides a visual summary of the projected number of subjects enrolled at a given future **Time** value after the **Current Time**. The predicted

Average Sample Size at a given **Time** is represented by a grey line. This grey line is surrounded by a blue area which represents the 95% Prediction Interval for the **Sample Size** at a given time. If the user places the cursor over the plot over the grey part of the line, a pop-up will be shown on the plot with the following text:

Time : A

Predicted Sample Size: B

where A and B are the actual values at the currently highlighted **Time** value.

If the user places the cursor over the blue prediction interval section, a pop-up will be shown on the plot with the following text:

Time = A

95% Prediction Interval: B:C

where A is the **Time** and B:C is the range of the 95% Prediction Interval at the currently highlighted **Time** value. This is shown in Figure 11.174.

Note that this prediction interval section is not shown if **Enrollment Status = Complete** and only the actual accrual pattern up to the **Current Time** is shown. See subsubsection 11.2.7.3 for an example of this.

Note that where the enrollment process is stopped early due the **Target Number of Events** being reached before the **Target Sample Size**, the **Enrollment Prediction Plot** will still include the projection for the original **Target Sample Size** despite the **Simulation Summary Report** showing the sample size at the time the **Target Number of Events** was achieved instead.

Note that values used in this plot can be inspected in the **Enrollment Prediction Table.** See subsubsection 11.2.8.3 for details. This plot can also be edited and saved, see subsubsection 11.2.9.2 for details.

Event Prediction Plot The Event Prediction Plot provides a visual summary of the actual and predicted event pattern using a cumulative frequency line graph. An example of an nQuery Prediction workspace with the Event Prediction plot displayed is provided in Figure 11.175.

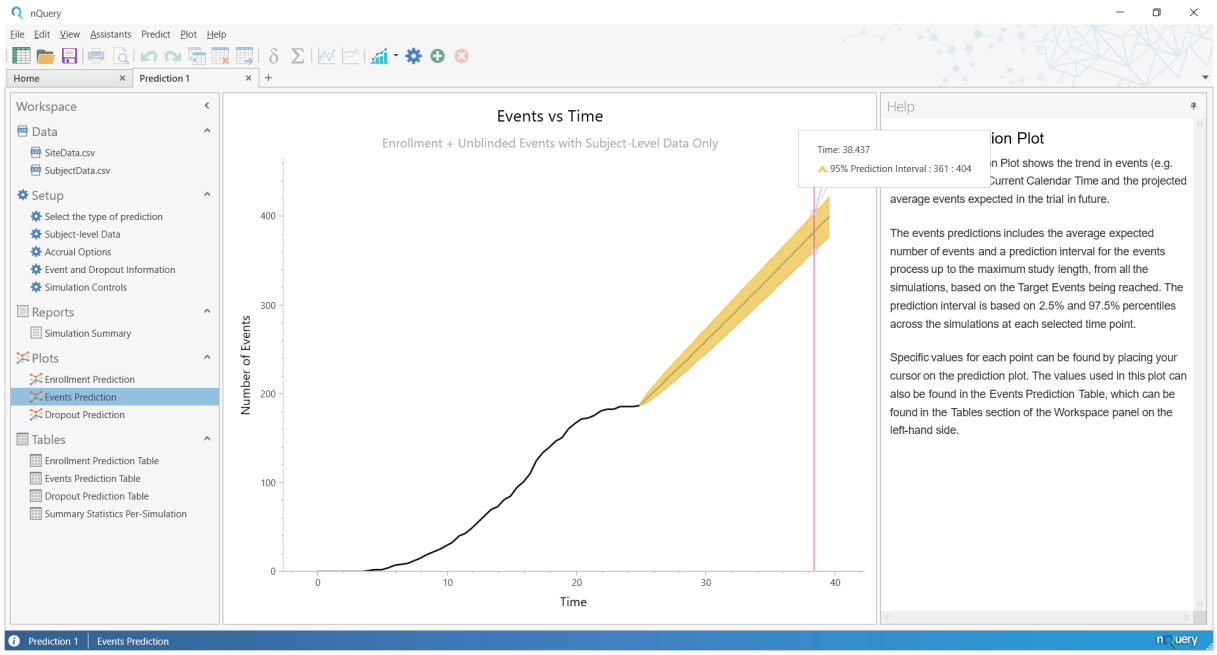


Figure 11.175: Event Prediction Plot Example

In the Event Prediction (Events vs Time) plot, the X-axis is **Time** and the Y-axis is **Number of Events**. **Time** is the length of time after study start (**Time = 0**) at which the Y-axis is being evaluated. **Number of Events** is the actual/predicted cumulative number of subjects who have had the event of interest at a given value of **Time**. The X-axis length will be related to the **Study Duration** (i.e. length of time for the **Target Number of Events** to occur) over all simulations. The Y-axis height will be related to the **Target Number of Events** specified for that prediction.

Note that the time of events represented here is when these events occurred relative to the study start (**Time = 0**) NOT when these events occurred relative to subject entry (i.e. follow up time). Therefore, this plot should not be confused with a Kaplan-Meier type plot.

In the majority of cases (exceptions discussed below), the Events Prediction plot will consist of two parts:

1. The actual event pattern up to the **Current Time**
2. The predicted event pattern from the **Current Time** up to the maximum projected **Study Duration**

The actual event pattern provides a visual summary of when subjects had the event. The actual event pattern will be represented by a solid black line. If the user places the cursor over the plot over this part of the line, a pop-up will be shown on the plot with following text:

Time: A

Actual # of Events: B

where A and B are the actual values at the currently highlighted **Time** value.

If **Subject-level Data** has been provided, the event pattern will be based on the sum of the **Arrival Time** and **Time on Study** column values (i.e. length of time after

study start at which event occurred) for subjects who had **Status Indicator = Event Status**. If **Summary Data** is used, a linear projection is used from zero to the **Current Number of Events**. If conducting a pre-trial prediction, there will be no actual event pattern to show. The plot subtitle will display the input used for the current plot.

The predicted event pattern provides a visual summary of the projected number of subjects who will have had the event of interest at a given future **Time** value after the **Current Time**. The predicted **Average Number of Events** at a given **Time** is represented by a grey line. This grey line is surrounded by a yellow area which represents the 95% Prediction Interval for the **Number of Events** at a given time. If the user places the cursor over the plot over the grey part of the line, a pop-up will be shown on the plot with the following text:

Time : A

Predicted # of Events: B

where A and B are the actual values at the currently highlighted **Time** value.

If the user places the cursor over the yellow prediction interval section, a pop-up will be shown on the plot with the following text:

Time = A

95% Prediction Interval: B:C

where A is the **Time** and B:C is the range of the 95% Prediction Interval at the currently highlighted **Time** value. This is shown in Figure 11.175.

Note that values used in this plot can be inspected in the **Events Prediction Table.** See subsubsection 11.2.8.3 for details. This plot can also be edited and saved (subsubsection 11.2.9.2).

Dropout Prediction Plot The Dropout Prediction Plot provides a visual summary of the actual and predicted dropout pattern using a cumulative frequency line graph. An example of an nQuery Prediction workspace with the Dropout Prediction plot displayed is provided in Figure 11.176.

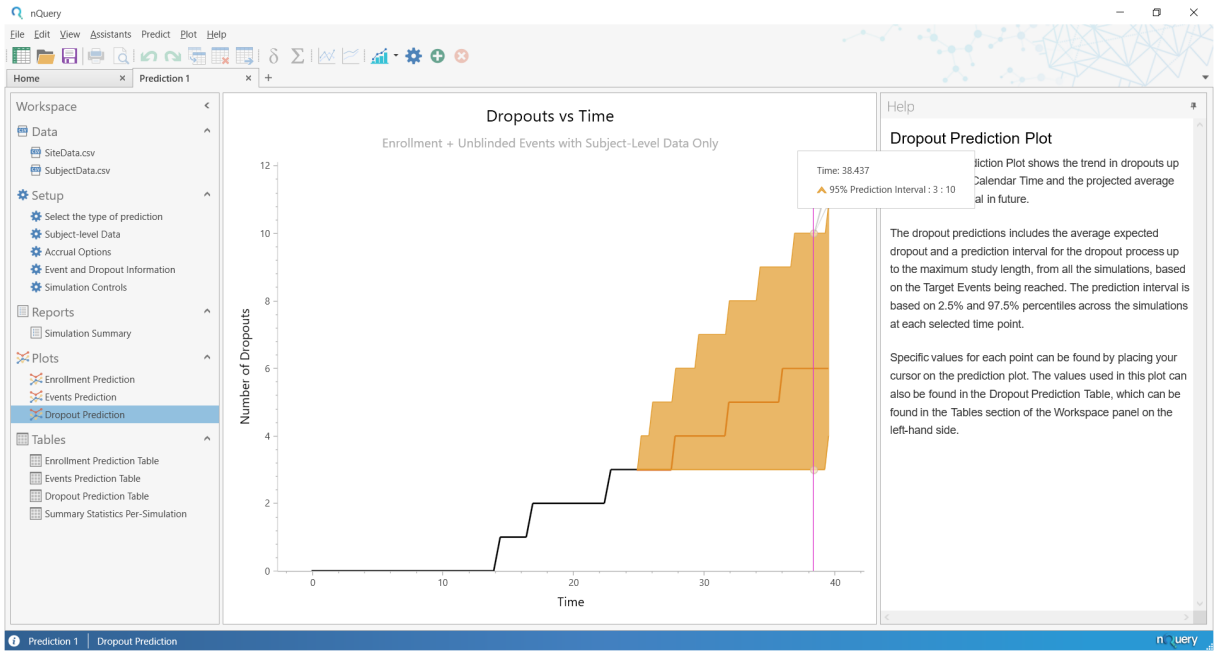


Figure 11.176: Dropout Prediction Plot Example

In the Event Prediction (Dropouts vs Time) plot, the X-axis is **Time** and the Y-axis is **Number of Dropouts**. **Time** is the length of time after study start (**Time = 0**) at which the Y-axis is being evaluated. **Number of Dropouts** is the actual/predicted cumulative number of subjects who have dropped out at a given value of **Time**. The X-axis length will be related to the **Study Duration** (i.e. length of time for the **Target Number of Events** to occur) over all simulations. The Y-axis height will be related to the upper 95% Prediction Interval Limit value for the projected **Number of Dropouts** at study end.

In the majority of cases (exceptions discussed below), the Dropout Prediction plot will consist of two parts:

1. The actual dropout pattern up to the **Current Time**
2. The predicted dropout pattern from the **Current Time** up to the maximum projected **Study Duration**

The actual dropout pattern provides a visual summary of when subjects have dropped out. The actual dropout pattern will be represented by a solid black line. If the user places the cursor over the plot over this part of the line, a pop-up will be shown on the plot with following text:

Time: A

Actual # of Dropouts: B

where A and B are the actual values at the currently highlighted **Time** value.

If **Subject-level Data** has been provided, the dropout pattern will be based on the sum of the **Arrival Time** and **Time on Study** column values (i.e. length of time after study start at which dropout occurred) for subjects who had **Status Indicator = Dropout Status**. If **Summary Data** is used, a linear projection is used from zero to the **Current Number of Dropouts**. If conducting a pre-trial prediction, there will be

no actual dropout pattern to show. The plot subtitle will display the input used for the current plot.

The predicted dropout pattern provides a visual summary of the projected number of subjects who will have dropped out at a given future **Time** value after the **Current Time**. The predicted **Average Number of Dropouts** at a given **Time** is represented by a grey line. This grey line is surrounded by an orange area which represents the 95% Prediction Interval for the **Number of Dropouts** at a given time. If the user places the cursor over the plot over the grey part of the line, a pop-up will be shown on the plot with the following text:

Time : A

Predicted # of Dropouts: B

where A and B are the actual values at the currently highlighted **Time** value.

If the user places the cursor over the orange prediction interval section, a pop-up will be shown on the plot with the following text:

Time = A

95% Prediction Interval: B:C

where A is the **Time** and B:C is the range of the 95% Prediction Interval at the currently highlighted **Time** value. This is shown in Figure 11.176.

Note that values used in this plot can be inspected in the **Dropout Prediction Table.** See subsubsection 11.2.8.3 for details. This plot can also be edited and saved (subsubsection 11.2.9.2).

Note that the **Dropout Prediction** plot and table will not be generated if there are no dropouts in the study. This will occur if up to the **Current Time** no dropouts occur (i.e. no values with **Dropout Status** in **Status Indicator** column if **Subject-level Data** used or **Number of Dropout** field(s) set to zero if **Summary Data** used) **AND** the **Hazard Rate**(s) in the **Dropout Model** tab of the **Event & Dropout Information** step are set to zero.

11.2.8.2 Reports

nQuery Predict provides reports to explore the inputs used to generate a prediction and results of the current predictions. Reports are editable by the user to maximise the functionality of the report. To open a given report, select the required report from under the **Reports** header in the Workspace Navigation Bar on the left-hand side of the nQuery Predict workspace after a prediction has been completed.

nQuery Predict provides one main report in the results output This is the:

- Simulation Summary (All Cases)

Multiple examples the **Simulation Summary** report are provided in the demonstrations above (Enrollment Demonstrations: subsection 11.2.6, Events Prediction: subsection 11.2.7). This section will provide a description of the report and the tools available to explore and edit this report.

The **Simulation Summary** report can be split into the two parts:

1. Inputs (Left-Hand Column)

2. Results (Right-Hand Column)

The **Inputs** column gives a summary of all the inputs used in the **Setup** phase to generate the current prediction. The **Results** column on the right gives a summary of the results of the current prediction. An example **Simulation Summary Report** displayed in an nQuery Predict workspace is shown in

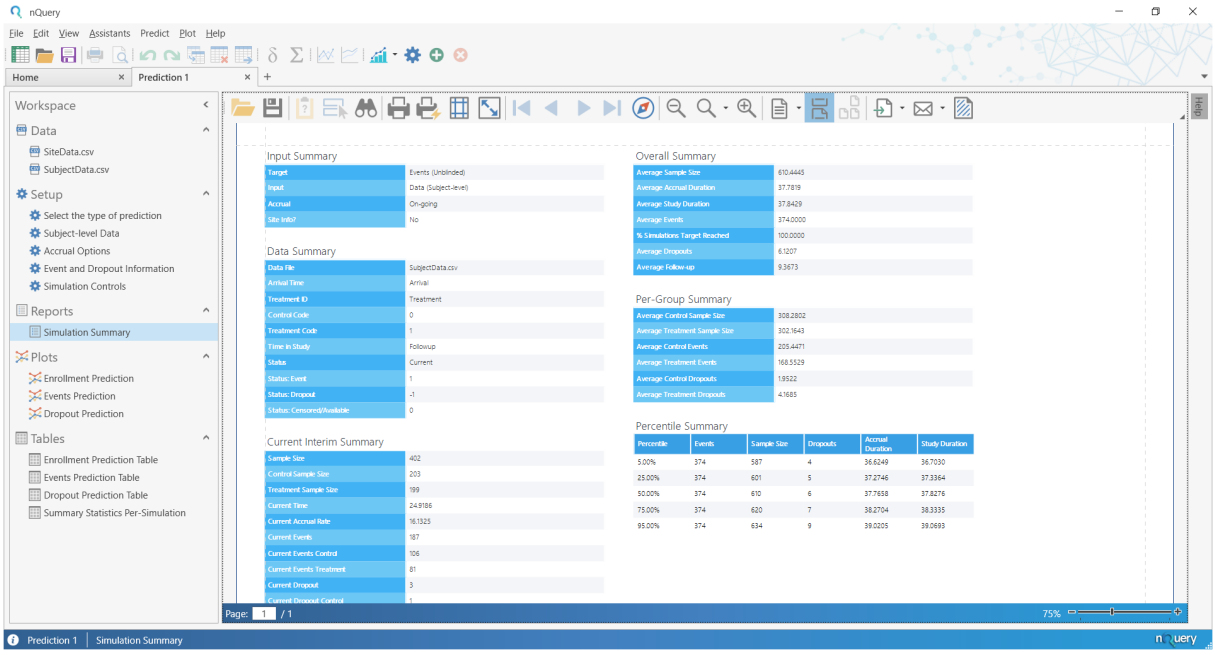


Figure 11.177: Simulation Summary Report Example

Each column is made of multiple sections which contain specific information on the setup (e.g. **Input Summary**) or results (e.g. **Overall Summary**). The sections provided in each column will sometimes change depending on the inputs provided during the **Setup** stage of the current prediction. A summary of the **Inputs** and **Results** sections follows.

Inputs The **Inputs** sections shown and the information shown in a given section will change to reflect the inputs provided by the user during the **Setup** stage. The following **Input** sections (alongside their **Select the type of Prediction** step condition of appearance if any) are as follows (in order of appearance within the **Simulation Summary Report**):

- Input Summary (All Predictions)
- Data Summary (Input = Subject Data Only, Subject + Site Data)
- Current Interim Summary (All Predictions)
- Current Site Summary (Input = Subject + Site Data)
- Target Enrollment Summary (Enrollment Status = Ongoing)
- Target Events Summary (Target = Unblinded Events, Blinded Events)
- Dropouts Summary (Target = Unblinded Events, Blinded Events + Dropouts > 0 for all simulations)

- Simulation Summary (All Predictions)

The **Input Summary** section is shown for all predictions and provides a high-level summary of the target prediction and its inputs. The **Input Summary** provides a summary of the **Target** (Enrollment Only, Events (Unblinded), Events(Blinded)), **Input** (Subject Data Only, Subject + Site Data, Summary Data), **Accrual** status (Ongoing, Complete) and if site-level data was used (**Site Info?** Yes/No). The **Target** field will also include additional information if Enrollment is complete (**Complete Enrollment**) or summary data was used (**Fixed**). Examples of **Input Summary** sections are provided in Figure 11.178.

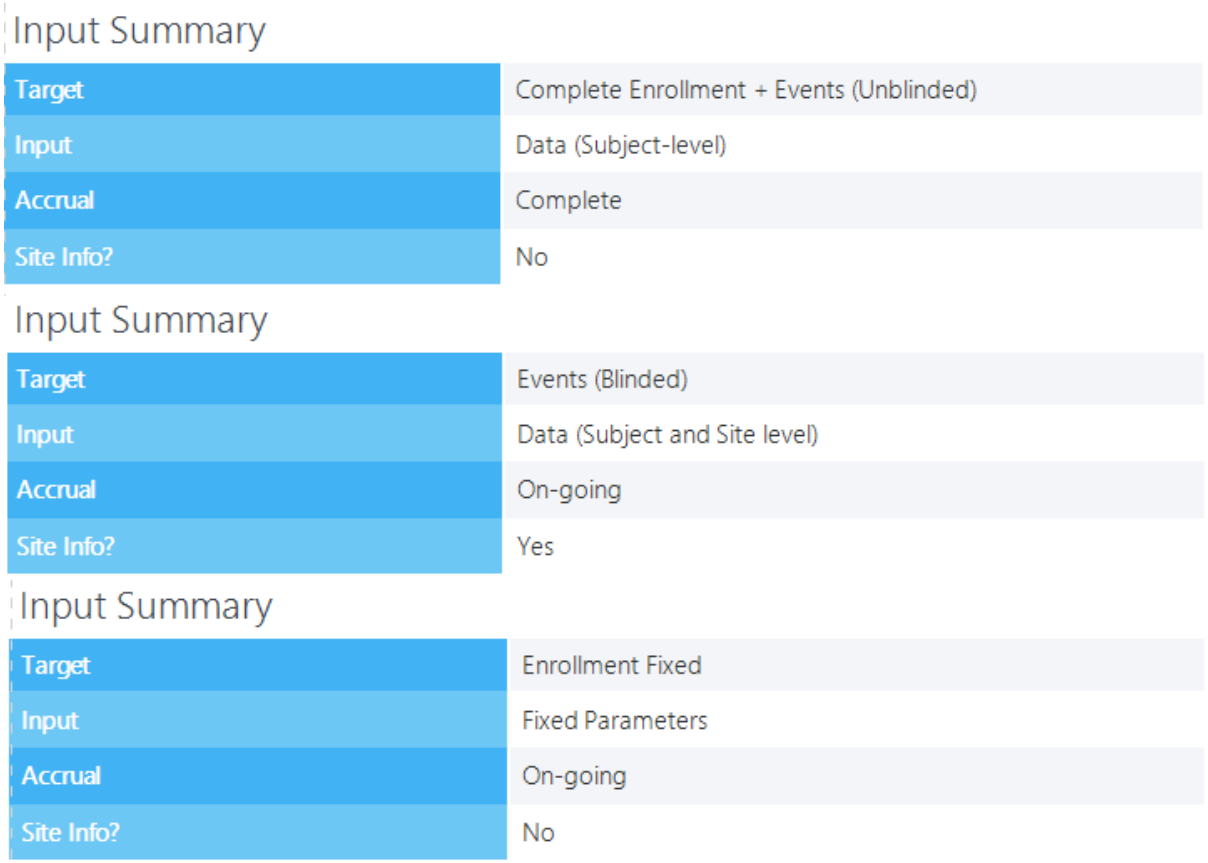


Figure 11.178: Input Summary Section Examples

The **Data Summary** section is shown only for predictions which used **Subject Data Only** or **Subject + Site Data** as an **Input** and provides a summary of which datasets were used and the columns in the selected subject and site data (if used) which were assigned to the required fields for the current prediction. These fields will correspond the choices made at the **Subject-level Data** and **Site-level Data** steps of the **Setup** stage (see Enrollment Demonstrations: subsection 11.2.6, Events Prediction: subsection 11.2.7). Examples of **Data Summary** sections are provided in Figure 11.179.

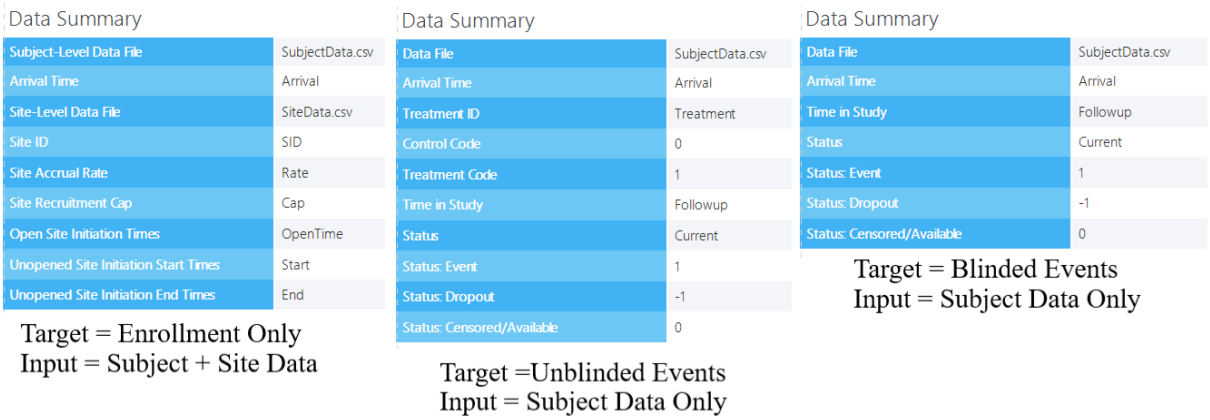


Figure 11.179: Data Summary Section Examples

The **Current Interim Summary** section is shown for all prediction and provides a summary of study up to the **Current Time** either based on the **Subject-level Data** provided (**Input = Subject Data Only** or **Subject + Site Data**) or the **Fixed Parameters** provided if **Input = Summary Data**. Note this is referred to as the **Current Status Summary** for **Target = Enrollment** only but its purpose is the same. These fields provide a summary of the current study time, sample size, events, dropouts and follow-up from the subject-level data or summary data. Per-Group summaries are also provided for the **Unblinded Events Target** (see Enrollment Demonstrations: subsection 11.2.6, Events Prediction: subsection 11.2.7). Examples of **Current Interim Summary** sections are provided in Figure 11.180.

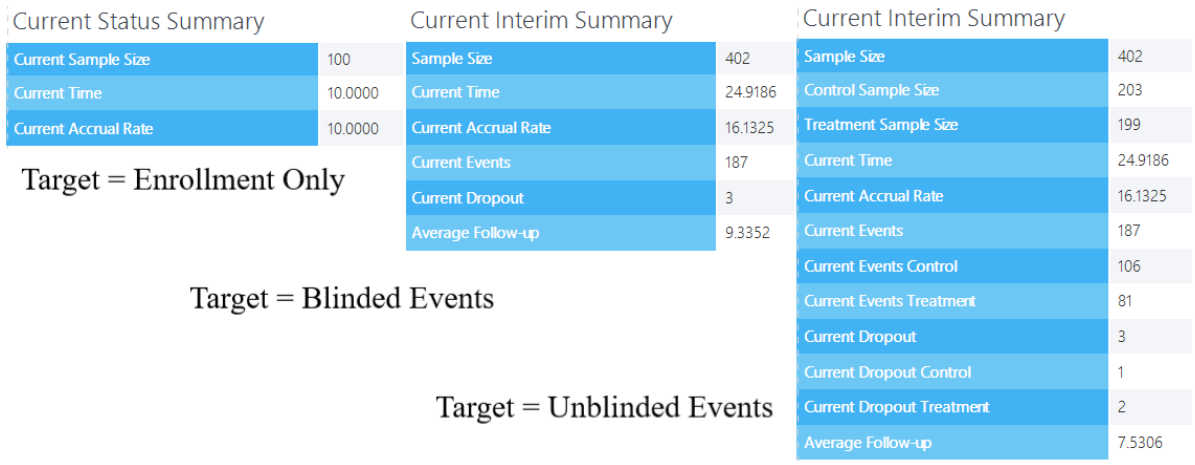


Figure 11.180: Current Interim Summary Section Examples

The **Current Site Summary** section is shown for predictions with **Input = Subject + Site Data** and provides a summary of site status at the **Current Time**. It consists of two fields: **Sites Open** and **Sites Available**. These correspond to the number of sites currently open (i.e. have a **Site Initiation Time** value for that subject) or are available to open after the **Current Time** (i.e. do not have **Site Initiation Time** value for that subject). An example of a **Current Site Summary** section is provided in Figure 11.181.

Figure 11.181: Current Site Summary Section Example

The **Target Enrollment Summary** section is shown for when **Enrollment Status = Ongoing** and provides a summary of the **Target Sample Size**, **Accrual** (i.e. Enrollment) **Model** and required parameters for generating enrollments using the selected **Accrual Model**. For example, for the **Poisson Accrual Model**, a **Future Accrual Rate** field is provided to correspond to the bottom-right cell of the **Accrual Periods** table at the **Accrual Options** step (see Enrollment Demonstrations: subsection 11.2.6, Events Prediction: subsection 11.2.7). Note that if **Input = Subject + Site Data**, this will not include the required parameters with input parameters viewable from the **Accrual Infos/Site** tab at the **Accrual Options** step of **Setup**. An example of the **Target Enrollment Summary** section is provided in Figure 11.182.

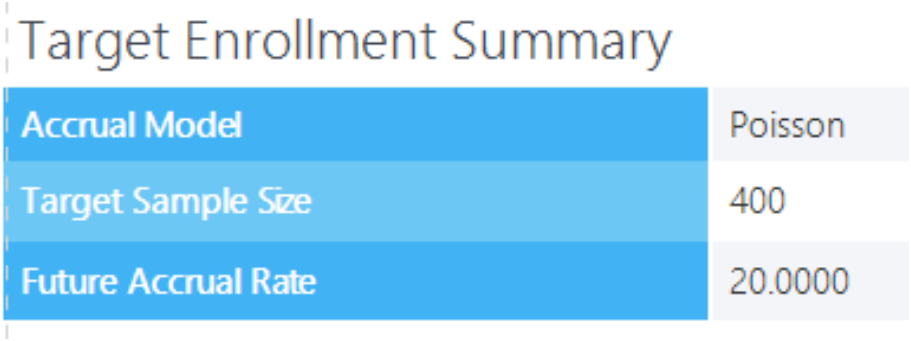


Figure 11.182: Target Enrollment Summary Section Example

The **Target Events Summary** section is shown for predictions with **Target = Unblinded Events** or **Blinded Events** and provides a summary of the (Number of) **Target Events**, **Events Model** and required parameters for generating event times using the selected **Events Model**. The **Events Model** and its parameters will depend on the choices made in the **Events Model** tab of the **Event & Dropout Information** step of **Setup** (see Events Prediction Demonstrations: subsection 11.2.7).

Note that for the case where **Response Distribution = Exponential** and **Number of Hazard Pieces > 1** in the **Events Model** tab a **Piecewise Exponential Summary** table is provided at the bottom of the **Results** column on the right. Examples of **Target Events Summary** sections are provided in Figure 11.183.

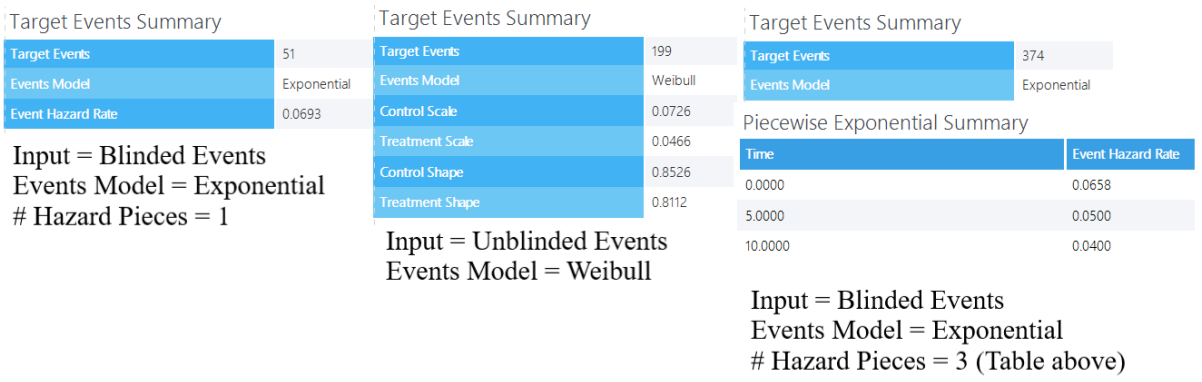


Figure 11.183: Target Events Summary Section Examples

The **Dropouts Summary** section is shown for predictions with **Target = Unblinded Events** or **Blinded Events** and provides a summary of the **Dropout Model** and required parameters for generating dropout times using the selected **Dropout Model**. The **Dropout Model** and its parameters will depend on the choices made in the **Dropouts Model** tab of the **Event & Dropout Information** step of **Setup** (see Events Prediction Demonstrations: subsection 11.2.7). Note that for the case where **Response Distribution = Exponential** and **Number of Hazard Pieces > 1** in the **Dropouts Model** tab a **Piecewise Dropouts Summary** table is provided at the bottom of the **Results** column on the right. Examples of **Dropouts Summary** sections are provided in Figure 11.184.

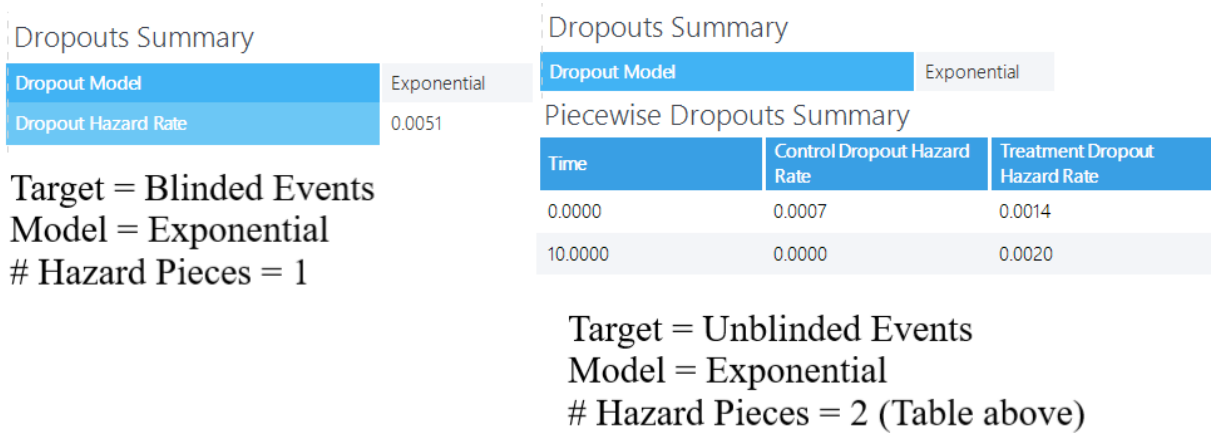


Figure 11.184: Target Events Summary Section Examples

The **Simulation Summary** section is shown for all predictions and provides a summary of the simulation setup parameters selected at the **Simulation Controls** step. It consists of three fields: **Seed**, **Simulations** and **Simulation Time**. These correspond to the random seed used in the current simulation, the total number of simulations used in the current simulation and the length of time (in seconds) the current prediction took to simulate. An example of a **Simulation Summary** section is provided in Figure 11.185.

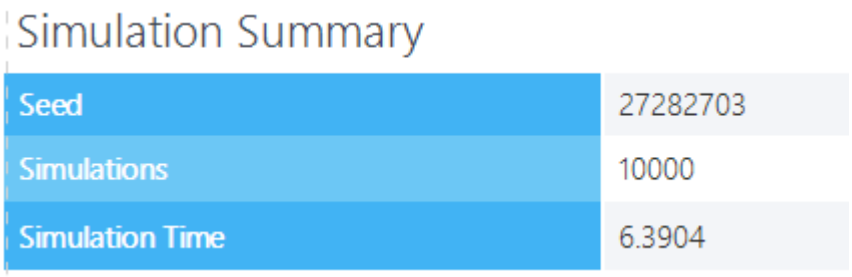


Figure 11.185: Simulation Summary Section Example

Results Column The **Results** sections shown and the information shown in a given section will change to reflect the inputs provided by the user during the **Setup** stage. The following sections (alongside their **Select the type of Prediction** step condition of appearance if any) is as follows:

- Overall Summary (All Predictions)
- Per-Group Summary (Target = Unblinded Events)
- Percentile Summary (All Predictions)

Inputs Column Sections The **Overall Summary** section is shown for all predictions and provides the average results for the main outputs of the prediction. Depending on the Target (**Enrollment Only** versus **Blinded Events / Unblinded Events**) and Inputs (**Subject Data Only/Summary Data** versus **Subject + Site Data**) the Overall Summary will include results for the average across all simulations for the **Sample Size (All), Accrual Period Duration (All), Study Duration (Blinded Events / Unblinded Events only), Events (Blinded Events / Unblinded Events only), Dropouts (Blinded Events / Unblinded Events only), Follow-up Time (Blinded Events / Unblinded Events only)** and **Number of Sites Opened (Subject + Site Data only)** as well as the **% of Simulations Target Reached** (**Blinded Events / Unblinded Events only**; where "target" is **Target Number of Events** (which may not be reached if **Dropout Hazard Rate(s)** are high enough for example). Examples of **Overall Summary** sections are provided in Figure 11.186.

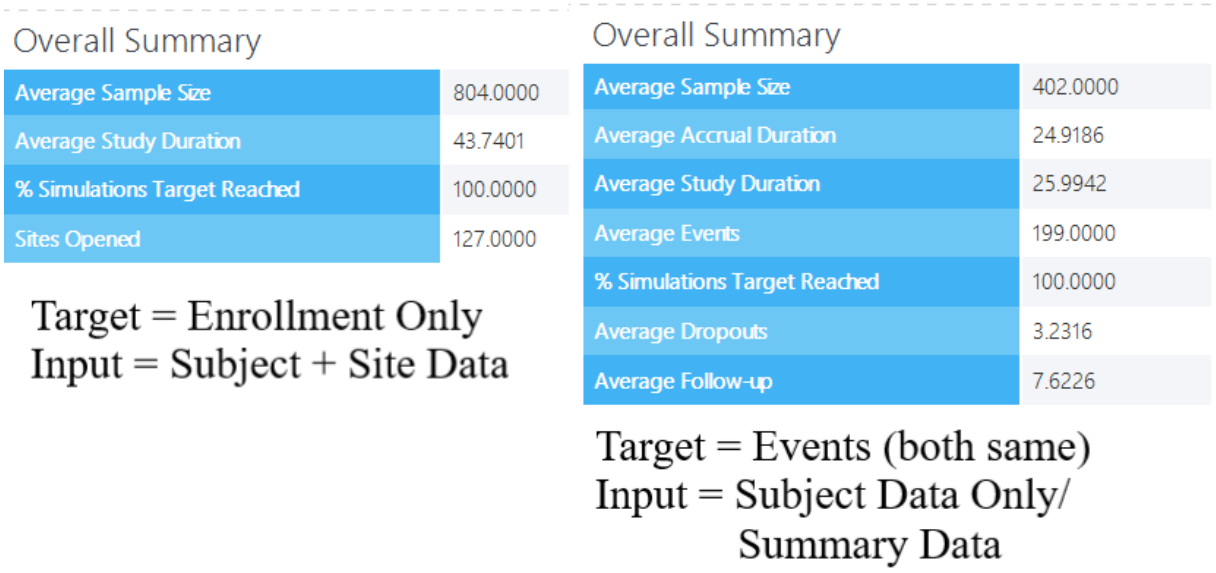


Figure 11.186: Overall Summary Section Examples

The **Per-Group Summary** section is shown for predictions where **Target = Unblinded Events** and provides the average results for the main outputs of the prediction for the **Control Group** and **Treatment Group**. For each group it provides the average **Sample Size, Events** and **Dropouts**. An example of the **Per-Group Summary** section is provided in Figure 11.187.

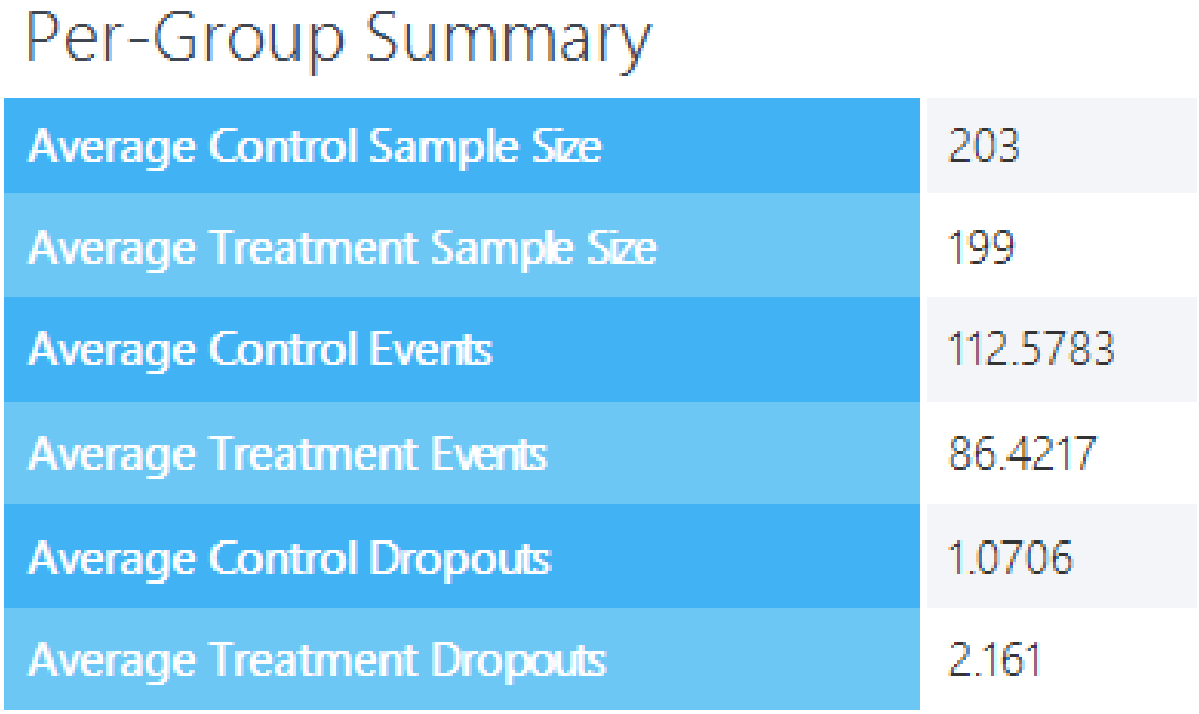


Figure 11.187: Per-Group Summary Section Example

The **Percentile Summary** section is shown for all predictions and provides the percentile results for the main outputs of the prediction. The required percentiles are specified

in the **Simulation Controls** step of **Setup**. Depending on the Target (**Enrollment Only** versus **Blinded Events / Unblinded Events**) and Inputs (**Subject Data Only/Summary Data** versus **Subject + Site Data**) the **Percentile Summary** will include percentile results for the **Sample Size (All), Accrual Events (Blinded Events / Unblinded Events only), Dropouts (Blinded Events / Unblinded Events only), Period Duration (All), Study Duration (Blinded Events / Unblinded Events only)** and **Number of Sites Opened (Subject + Site Data only).** Examples of **Percentile Summary** sections (top is **Target = Enrollment Only**, **Input = Subject + Site Data**; bottom is **Target = Unblinded Events** (note it would be same format for **Blinded Events**), **Input = Subject Data Only**) are provided in Figure 11.188.

Percentile Summary

Percentile	Sample Size	Study Duration	Sites Opened
5.00%	804	42.1003	127
25.00%	804	43.0285	127
50.00%	804	43.7222	127
75.00%	804	44.4059	127
95.00%	804	45.4795	127

Percentile Summary

Percentile	Events	Sample Size	Dropouts	Accrual Duration	Study Duration
5.00%	374	587	4	36.5928	36.6565
25.00%	374	601	5	37.2794	37.3398
50.00%	374	610	6	37.7507	37.8121
75.00%	374	620	7	38.2445	38.3030
95.00%	374	634	9	38.9979	39.0529

Figure 11.188: Percentile Summary Section Examples

Note as mentioned in **Inputs Column Section**, if the **Exponential Response Distribution** is used with a **Number of Hazard Pieces > 1** (i.e. piecewise exponential model) for the **Events Model** and/or **Dropout Model** then the piecewise exponential table will be shown below the results sections discussed above (examples given in **Inputs** section above).

Report Toolbar In nQuery Predict, each **Report** has a toolbar which allows the user to edit, save, print and export a report. The toolbar options available for nQuery Predict reports is shown in Figure 11.189.

Figure 11.189: Report Toolbar

These options are defined as follows:

1. Open: Open another nQuery Predict Report (.prnx)
2. Save: Save current nQuery Predict Report (.prnx)
3. Help: Unused
4. URL: Unused
5. Search: Search for text in current report. Select 14 to remove
6. Print: Open Print menu for current report
7. Quick Print: Print report using system defaults
8. Page Setup: Open Page Setup window to edit page size, orientation and margin sizes
9. Scale: Open Scale window to rescale size of report text by percentage or page size
10. First Page: Return to first page if report has multiple pages
11. Page Up: Go up one page if report has multiple pages
12. Page Down: Go down one page if report has multiple pages
13. Last Page: Go to last page if report has multiple pages
14. Navigation Pane: Open and close Navigation Pane. Contains Pages list and Search Results window
15. Zoom Out: Zoom out report by one increment
16. Zoom: Change the current zoom from list of options
17. Zoom In: Zoom in report by one increment
18. Page Layout: Set out how multiple pages are displayed (Single Page, Two Pages, Wrap Around)
19. Continuous Scolling: Enable or disable continuous scrolling in report
20. Show Cover Page: Show cover page
21. Export: Export report as other file type. Select arrow to see list in-report or select icon to open Export window
22. Send: Send report as email in export file type using system default email client.
23. Watermark: Add watermark to result using Watermark menu

The Export option can be used to save the report in the following file formats: PDF, HTML, MHT, RDF, DOCX, XLS, XLSX, CSV, Plain Text File (TXT), Image File (PNG, JPEG, BMP, GIF, EMF, WMF, TIFF).

11.2.8.3 Tables

nQuery Predict provides a number of tables to better explore and understand the results of a prediction. Note that these tables will be exported (as .csv files) when an nQuery Predict workspace is saved (see subsubsection 11.2.9.1). To open a given table, select the required table from under the **Tables** header in the Workspace Navigation Bar on the left-hand side of the nQuery Predict workspace after a prediction has been completed.

nQuery Predict can provide up to seven tables in the results output. These are:

- Enrollment Prediction Table (All Cases)
- Events Prediction Table (Target = Unblinded Events or Blinded Events)
- Dropout Prediction Table (Target = Unblinded Events or Blinded Events + Current Dropout or Dropout Hazard Rate(s) > 0)
- Summary Statistics Per-Simulation (Optional - All Cases)
- Per-Simulation Subject-level Data (Optional - All Cases)
- Per-Site Summary Statistics (Optional - Input = Subject + Site Data)
- Per-Simulation Site-level Data (Options - Input = Subject + Site Data)

The Enrollment Prediction, Events Prediction and Dropout Prediction tables are all self-similar and associated with their respective plots.

The Summary Statistics Per-Simulation and Per-Simulation Subject-level Data provide additional information for specific simulations on the subject-level. The Per-Site Summary Statistics and Per-Simulation Site-level Data provide additional information for specific simulations at the site-level. All four of these tables are optional and can be added or removed to the **Tables** header at the **Simulation Controls** step of **Setup** (subsubsection 11.2.9.4).

Multiple examples of each these tables is provided in the worked example above (Enrollment Demonstrations: subsection 11.2.6, Events Prediction: subsection 11.2.7). This section will provide a description of each table.

Enrollment Prediction Table The Enrollment Prediction Table provides a tabular summary of the actual and predicted accrual pattern alongside a 95% prediction interval for the projected accrual pattern. This table will consist of 100 **Time** points of which half are assigned before and after the **Current Time**. An example of an nQuery Prediction workspace with the Enrollment Prediction Table displayed is provided in Figure 11.190 in which the first projected future **Time** value of 25.344 has been highlighted.

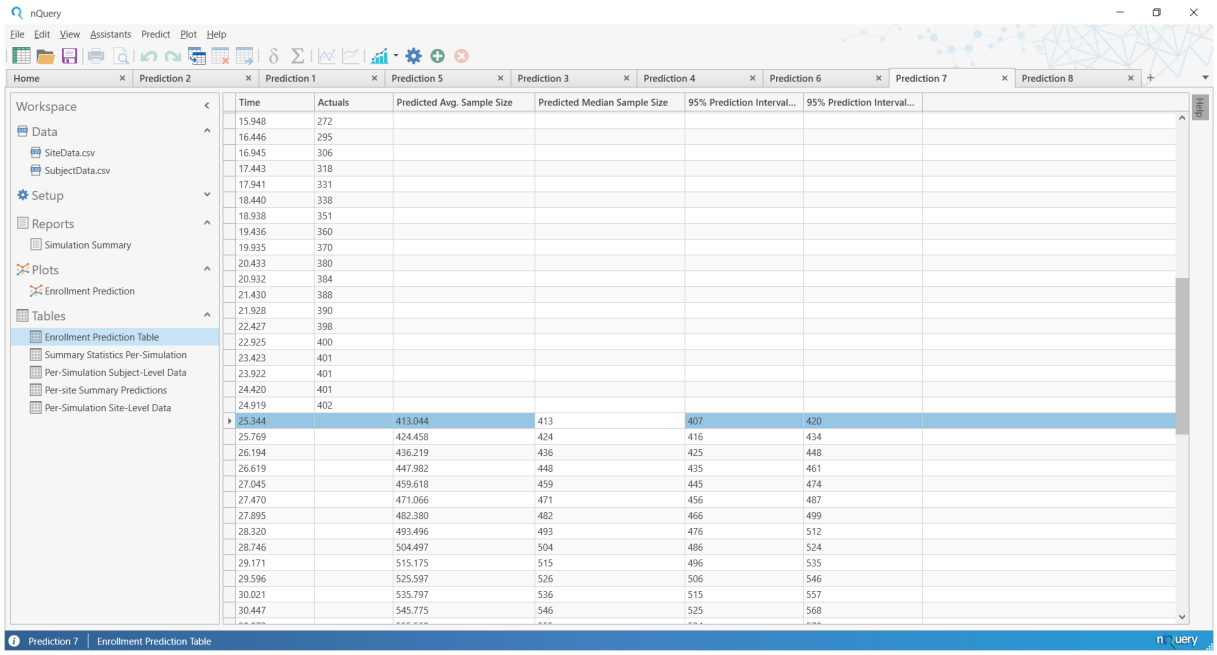


Figure 11.190: Enrollment Prediction Table Example

The Enrollment Prediction Table has six columns: **Time, Actual, Predicted Avg. Sample Size, Predicted Median Sample Size, 95% Prediction Interval LL, 95% Prediction Interval UL.**

Time is the length of time after the study start at which the enrollment process is being evaluated. The maximum **Time** value will be related to the largest **Accrual Duration** found across all simulations.

Actual is the actual number of subjects enrolled at a given past **Time**. Actual values are only shown for all values of **Time** less than or equal to the **Current Time**. All subsequent **Actual** cells are left blank.

Predicted Avg. Sample Size is the predicted (arithmetic) average (across all simulations) number of subjects enrolled at a given future **Time**. **Predicted Avg. Sample Size** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

Predicted Median Sample Size is the predicted median (i.e. 50% percentile over all simulations) number of subjects enrolled at a given future **Time**. **Predicted Median Sample Size** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

95% Prediction Interval LL is the lower limit of the 95% prediction interval (i.e. the 2.5% percentile over all simulations) for the number of subjects enrolled at a given future **Time**. **95% Prediction Interval LL** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

95% Prediction Interval UL is the upper limit of the 95% prediction interval (i.e. 97.5% percentile over all simulations) for the number of subjects enrolled at a given future **Time**. **95% Prediction Interval LL** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

Events Prediction Table The Events Prediction Table provides a tabular summary of the actual and predicted event pattern alongside a 95% prediction interval for the projected event pattern. This table will consist of 100 **Time** points of which half are assigned before and after the **Current Time**. An example of an nQuery Prediction workspace with the Events Prediction Table displayed is provided in Figure 11.191 in which the first projected future **Time** value of 24.958 has been highlighted.

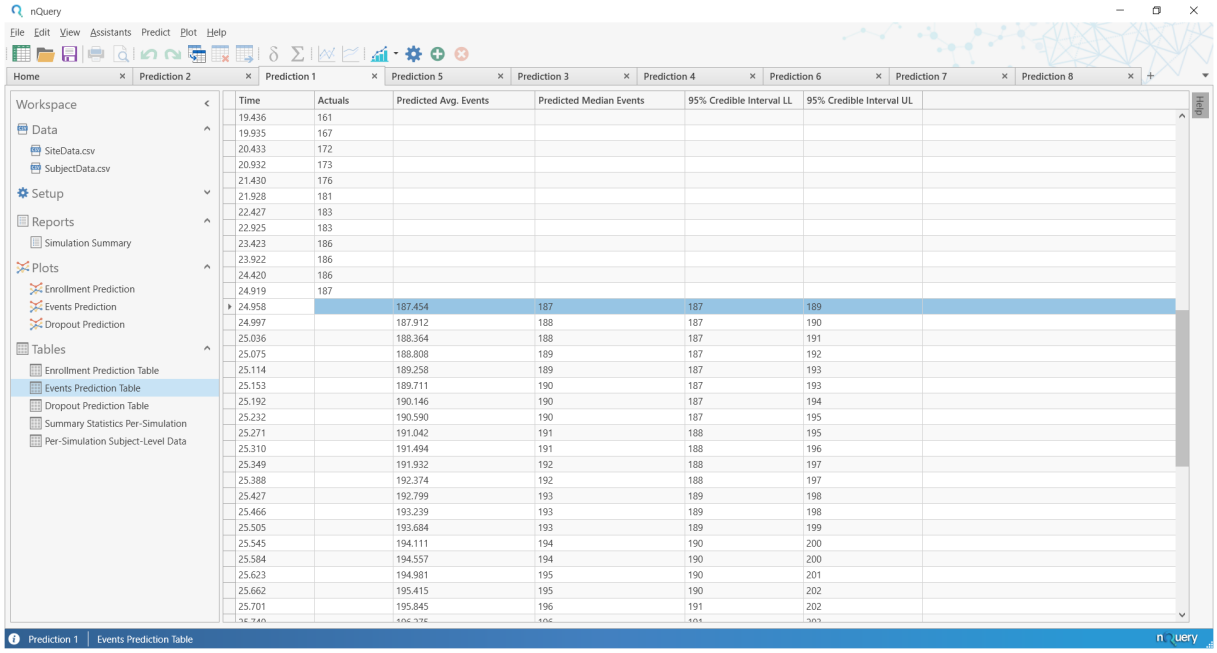


Figure 11.191: Event Prediction Table Example

The Events Prediction Table has six columns: **Time, Actual, Predicted Avg. Events, Predicted Median Events, 95% Prediction Interval LL, 95% Prediction Interval UL.**

Time is the length of time after the study start at which the event process is being evaluated. The maximum **Time** value will be related to the largest **Study Duration** found across all simulations.

Actual is the actual number of subjects who have had the event of interest at a given past **Time**. Actual values are only shown for all values of **Time** less than or equal to the **Current Time**. All subsequent **Actual** cells are left blank.

Predicted Avg. Events is the predicted (arithmetic) average (across all simulations) number of subjects who have had the event of interest at a given future **Time**. **Predicted Avg. Events** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

Predicted Median Events is the predicted median (i.e. 50% percentile over all simulations) number of subjects who have had the event of interest at a given future **Time**. **Predicted Median Event** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

95% Prediction Interval LL is the lower limit of the 95% prediction interval (i.e. the 2.5% percentile over all simulations) for the number of subjects who have had the event of

interest at a given future **Time**. **95% Prediction Interval LL** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

95% Prediction Interval UL is the upper limit of the 95% prediction interval (i.e. 97.5% percentile over all simulations) for the number of subjects who have had the event of interest at a given future **Time**. **95% Prediction Interval LL** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

Dropout Prediction Table The Dropout Prediction Table provides a tabular summary of the actual and predicted dropout pattern alongside a 95% prediction interval for the projected accrual pattern. This table will consist of 100 **Time** points of which half are assigned before and after the **Current Time**. Note that if there are no dropouts in the prediction (i.e. no dropouts in **Subject-level Data** or **Summary Data** and **Dropout Hazard Rate(s)** equal to zero) then this table will not be provided.

An example of an nQuery Prediction workspace with the Dropout Prediction Table displayed is provided in Figure 11.192 in which the first projected future **Time** value of 24.958 has been highlighted.

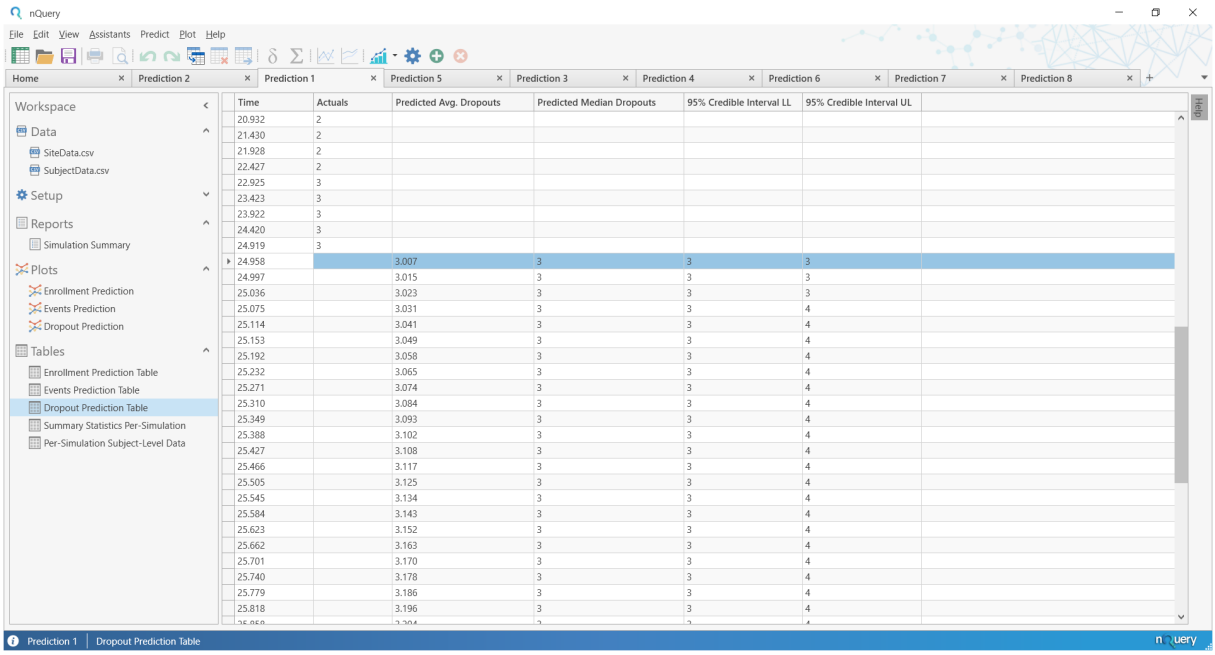


Figure 11.192: Dropout Prediction Table Example

The Dropout Prediction Table has six columns: **Time, Actual, Predicted Avg. Dropouts, Predicted Median Dropouts, 95% Prediction Interval LL, 95% Prediction Interval UL.**

Time is the length of time after the study start at which the dropout process is being evaluated. The maximum **Time** value will be related to the largest **Study Duration** found across all simulations.

Actual is the actual number of subjects who have dropped out at a given past **Time**. Actual values are only shown for all values of **Time** less than or equal to the **Current Time**. All subsequent **Actual** cells are left blank.

Predicted Avg. Dropouts is the predicted (arithmetic) average (across all simulations) number of subjects who have dropped out at a given future **Time**. **Predicted Avg. Dropouts** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

Predicted Median Dropouts is the predicted median (i.e. 50% percentile over all simulations) number of subjects who have dropped out at a given future **Time**. **Predicted Median Dropouts** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

95% Prediction Interval LL is the lower limit of the 95% prediction interval (i.e. the 2.5% percentile over all simulations) for the number of subjects who have dropped out at a given future **Time**. **95% Prediction Interval LL** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

95% Prediction Interval UL is the upper limit of the 95% prediction interval (i.e. 97.5% percentile over all simulations) for the number of subjects who have dropped out at a given future **Time**. **95% Prediction Interval LL** is only shown for **Time** values greater than the **Current Time**. All prior cells are left blank.

Optional Tables The next section will cover the optional tables which can be added or removed from a simulation in the **Output Options** section of the **Simulation Controls** step, with these options highlighted in Figure 11.193.

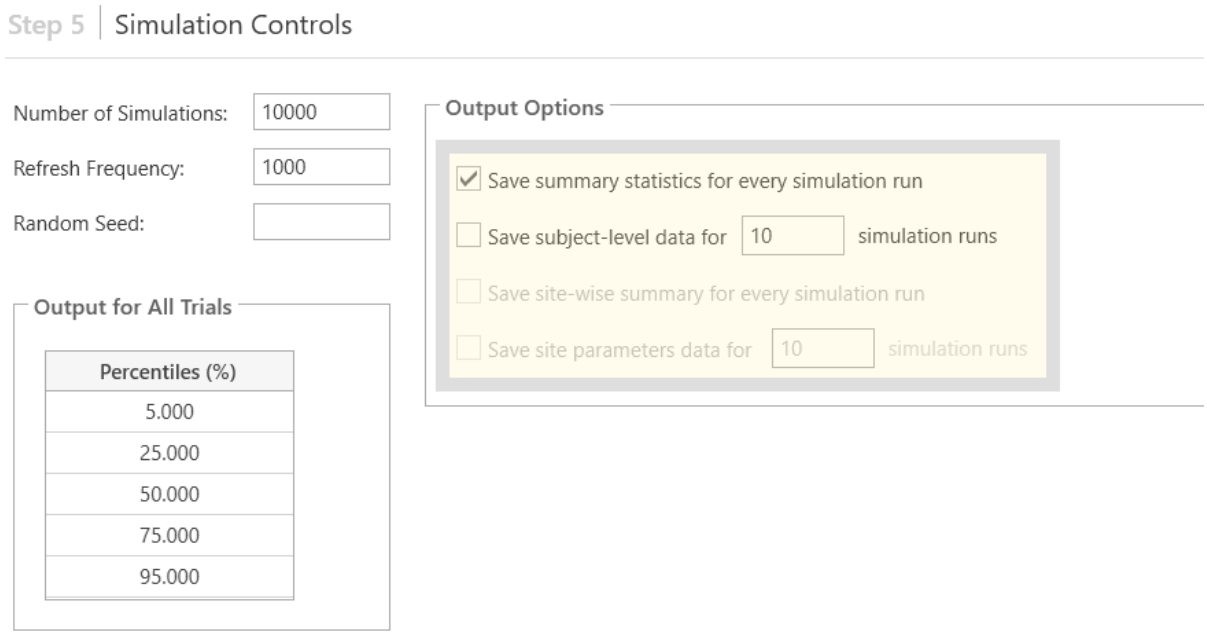


Figure 11.193: Optional Table fields in Simulation Controls

The **Output Options** for each table is as follows:

- Save summary statistics for every simulation run = Summary Statistics Per-Simulation table
- Save subject-level data for (X) simulation runs = Per-Simulation Subject-level Data table

- Save site-wise summary for every simulation run = Per-site Summary Predictions table
- Save site parameters data for (X) simulation runs = Per-Simulation Site-level Data table

The **(X)** value for the **Save subject-level data for (X) simulation** runs and **Save site parameters data for (X) simulation runs** allows the user the specify the number of individual simulations to output in their respective tables.

Save site-wise summary for every simulation run and **Save site parameters data for (X) simulation runs** will only be available if **Input = Subject + Site-level Data**. Otherwise, these options will be greyed out.

Summary Statistics Per-Simulation Table The Summary Statistics Per-Simulation Table provides the important inputs and summary statistic outputs for each individual simulation. The fields displayed will depend on the **Target** selected at the **Select the type of prediction** step of **Setup**. Definitions for each possible field are provided in the Help window on the right-hand side while the table is displayed in the nQuery Predict workspace.

Examples of the Summary Statistics Per-Simulation Table are provided in Figure 11.194. Examples can also be found in the Enrollment Prediction Demonstrations (subsection 11.2.6) and Events Prediction Demonstrations (subsection 11.2.7).

Simulation ID	Current Time	Current Sample Size	Target Sample Size	Accrual Duration
1	24.919	402	804	42.346
2	24.919	402	804	44.396
3	24.919	402	804	42.590
4	24.919	402	804	43.500
5	24.919	402	804	44.239
6	24.919	402	804	42.541

Enrollment Only

Censored	Control Sample Size	Control Events	Control Dropouts	Treatment Sample Size	Treatment Events	Treatment Dropouts	Accrual Duration	Accrual Duration Uncens...	Target Events Reached
	200	100	8	200	100	8	19.593	19.593	✔
	200	104	11	200	96	15	21.294	19.856	✔
	196	101	8	190	99	6	19.559	19.374	✔
	200	103	9	200	97	5	18.270	18.270	✔
	190	99	8	185	101	8	19.250	19.155	✔
	198	94	7	197	106	8	20.484	19.495	✔

Unblinded Events

Current Events	Current Dropouts	Current Available	Target Sample Size	Target Events	Study End Time	Total Sample Size	Total Events	Total Dropouts	Total Censored	Accrual Duration
50	0	150	400	100	17.889	349	100	0	249	17.879
50	0	150	400	100	17.281	349	100	0	249	17.213
50	0	150	400	100	17.694	344	100	0	244	17.657
50	0	150	400	100	18.190	376	100	0	276	18.025
50	0	150	400	100	18.709	368	100	0	268	18.632
50	0	150	400	100	17.572	366	100	0	266	17.524
50	0	150	400	100	18.667	364	100	0	264	18.585

Blinded Events

Figure 11.194: Summary Statistics Per-Simulation Table Examples

When **Target = Enrollment Only**, the Summary Statistics Per-Simulation Table will contain the following fields: **Simulation ID, Current Time**, **Current Sample Size, Target Sample Size**, **Accrual Duration**.

When **Target = Unblinded Events**, the Summary Statistics Per-Simulation Table will contain the following fields: **Simulation ID, Current Time, Current Sample Size, Current Events, Current Dropouts, Target Sample Size, Target Events, Study End Time, Total Sample Size, Total Events, Total Dropouts, Total Censored,**

Control Sample Size, Control Events, Control Dropouts, Treatment Sample Size, Treatment Events, Treatment Dropouts, Accrual Duration, Accrual Duration Uncensored, Target Events Reached

When **Target = Blinded Events**, the Summary Statistics Per-Simulation Table will contain the following fields: **Simulation ID, Current Time, Current Sample Size, Current Events, Current Dropouts, Target Sample Size, Target Events, Study End Time, Total Sample Size, Total Events, Total Dropouts, Total Censored, Accrual Duration, Accrual Duration Uncensored, Target Events Reached**

For the common **Sample Size, Event** and **Dropout** columns, the "Current" columns describe the number of subjects with a given status at the **Current Time** (based on the **Subject-level Data** or **Summary Data Fixed Parameters** inputs), the "Target" columns describe the targets specified for the simulation during **Setup**, the "Total" columns describe the total number of subjects with that status at the end of that simulation and the "Control" / "Treatment" columns give the total number subjects with that status at the end of that simulation for **Target = Unblinded Events**.

Other fields definitions are as follows:

Simulation ID is the simulation number/identifier, **Total Censored** is subjects who were administratively censored at study end due to not having an event or dropout at that point. **Study End Time** is the length of time after study start (Time = 0) at which the trial ended as **Target Number of Events** was reached, **Accrual Duration** is the length of time after study start at which the accrual process ended as the **Target Sample Size** was reached unless ended early for events prediction. **Accrual Duration Uncensored** is the accrual duration if the enrollment process had not been cut short due to the **Target Number of Events** being reached before the **Target Sample Size** during events prediction. **Target Events Reached** is an indicator for whether the **Target Number of Events** was reached in that simulation.

If **Target Events Reached** indicator is negative (X) then the **Study End Time** becomes the length of time at which there were no longer any remaining subjects left to have the event (e.g. due to high dropout rates, due to **Fixed Followup**). **Accrual Duration** and **Accrual Duration Uncensored** will be equal unless the enrollment process is ended early due to the **Target Number of Events** being reached before the **Target Sample Size** was reached.

Per-Simulation Subject-level Data Table The Per-Simulation Subject-level Data Table provides the simulated outcomes for each subject from a pre-specified number of simulations. The number of simulations is specified by editing the (X) value in the **Save subject-level data for (X) simulation runs** field of the **Output Options** section of the **Simulation Controls** step of **Setup.**

The fields and number of subjects (rows) displayed will depend on the **Target** and **Input** selected at the **Select the type of prediction** step of **Setup**. Definitions for each possible field are provided in the Help window on the right-hand side while the table is displayed in the nQuery Predict workspace.

Examples of the Per-Simulation Subject-level Data Table are provided in Figure 11.195. Examples can also be found in the Enrollment Prediction Demonstrations (subsection 11.2.6) and Events Prediction Demonstrations (subsection 11.2.7).

Simulation ID	Subject ID	Arrival Time	Site ID
1	399	22.717	366
1	400	22.866	101
1	401	22.942	204
1	402	24.919	322
1	403	24.980	127

Enrollment Only
Subject + Site Data

Simulation ID	Subject ID	Arrival Time	Event Time	Dropout Time	Final Status	Site ID	Group
1	1	0.186	5.479		1	103	0
1	2	0.226	3.728		1	108	1
1	3	0.341	6.546		1	121	0
1	4	0.726	25.275	662.214	1	103	0
1	5	1.495	9.656		1	103	1
1	6	2.209	5.447		1	103	0

Unblinded Events, Subject + Site Data

Simulation ID	Subject ID	Arrival Time	Event Time	Dropout Time	Final Status
1	56	10.000	0.027	105.428	1
1	57	10.000	18.747	364.962	0
1	58	10.000	0.655	79.015	0
1	59	10.000	2.096	309.335	0
1	60	10.000	6.171	327.186	0

Blinded Events, Subject Data Only

Figure 11.195: Per-Simulation Subject-level Data Table Examples

When **Target = Enrollment Only** and **Input = Subject Data Only** or **Summary Data**, the Per-Simulation Subject-level Data Table will contain information for each simulation with the following fields: **Simulation ID, Subject ID, Arrival Time**

When **Target = Enrollment Only** and **Input = Subject + Site Data**, the Per-Simulation Subject-level Data Table will contain information for each simulation with the following fields: **Simulation ID, Subject ID, Arrival Time, Site ID**

When **Target = Unblinded Events** and **Input = Subject Data Only** or **Summary Data**, the Per-Simulation Subject-level Data Table will contain information for each simulation with the following fields: **Simulation ID, Subject ID, Arrival Time, Event Time, Dropout Time, Final Status, Group**

When **Target = Unblinded Events** and **Input = Subject + Site Data**, the Per-Simulation Subject-level Data Table will contain information for each simulation with the following fields: **Simulation ID, Subject ID, Arrival Time, Event Time, Dropout Time, Final Status, Site ID, Group**

When **Target = Blinded Events** and **Input = Subject Data Only** or **Summary Data**, the Per-Simulation Subject-level Data Table will contain information for each simulation with the following fields: **Simulation ID, Subject ID, Arrival Time, Event Time, Dropout Time, Final Status, Group**

When **Target = Blinded Events** and **Input = Subject + Site Data**, the Per-Simulation Subject-level Data Table will contain information for each simulation with the following fields: **Simulation ID, Subject ID, Arrival Time, Event Time, Dropout Time, Final Status, Site ID**

Simulation ID is the simulation number/identifier, **Subject ID** is the subject identifier based on the order of **Arrival Time** (which the length of time after study start (Time = 0) at which a subject entered the study), **Event Time** is the actual or projected length of time after **Arrival Time** after which a subject had the event of interest, **Dropout Time** is the actual or projected length of time after **Arrival Time** after which a subject had dropped out, **Final Status** is the final status (**Event, Dropout** or **Censored**) of

a subject in the current simulation, **Site ID** is the site number/identifier a subject was recruited from and **Group** is the treatment group (**Control** or **Treatment**) a subject was assigned to.

Note that for **Input = Summary Data**, only the simulated subjects are provided in this table. When subject-level data is used, this will contain the subjects from the subject-level data and the fully simulated subjects.

For **Target = Enrollment Only**, simulated **Arrival Time** values are provided for all subjects alongside the **Arrival Time** column values from the subject-level data if used.

For **Target = Unblinded Events** or **Blinded Events**, the simulated **Arrival Time** values are generated for all fully simulated subjects (i.e. did not exist in subject-level data) and are provided alongside the subject-level data **Arrival Time** column values. The **Event Time** and **Dropout Time** are simulated for all fully simulated subjects AND those subjects who had **Censored Status** in the **Status Indicator** column in the subject-level data.

The **Final Status** is taken from the subject-level data for those subjects who had a **Event Status** or **Dropout Status** in the **Status Indicator** column. The **Event Time** will be empty if a subject was **Dropout Status** in the subject-level data and the **Dropout Time** will be empty if a subject was **Event Status** in the subject-level data.

For fully simulated subjects or **Censored Status** subjects from the subject-level data (i.e. subjects with a simulated **Event Time** and **Dropout Time**), the **Final Status** is based on the relationship between the simulated **Event Time** and **Dropout Time** and the **Study Duration/Study End Time** in that **Simulation ID** (**Study Duration/Study End Time** for given **Simulation ID** can be found in the **Summary Statistics Per-Simulation Table**). If a subject has an **Event Time** less than the **Dropout Time** and **Study Duration**, the **Final Status** will be **Event Status**. If a subject has a **Dropout Time** less than the **Event Time** and **Study Duration**, the **Final Status** will be **Dropout Status**. If a subject has both **Event Time** and **Dropout Time** greater than the **Study Duration**, the **Final Status** will be **Censored Status**. The one exception is if **For a Fixed Period** is selected from the **Subjects are Followed:** field in the **Accrual Options** step of **Setup** where in the rules above replace **Study Duration** with the specified **Followup Time**.

Site ID and **Group** will be generated for simulated **Arrival Time** subjects and taken from the subject-level data otherwise.

Per-site Summary Predictions table The Per-site Summary Predictions table provides the summary statistic outputs for each site from each individual simulation. This table is only available if **Input = Subject + Site Data**. Definitions for each field are provided in the Help window on the right-hand side while the table is displayed in the nQuery Predict workspace.

An example of the Per-site Summary Predictions Table is provided in Figure 11.196. Examples can also be found in the Enrollment Prediction Demonstrations (subsection 11.2.6) and Events Prediction Demonstrations (subsection 11.2.7).

Site ID	Avg. Accrual	Avg. Max Time	Avg. Start Time	Avg. Duration	Avg. Rate	Times Open
441	5.353	35.598	6.414	33.194	0.168	10000
442	11.903	40.817	5.428	38.609	0.309	10000
443	2.225	37.901	25.251	18.781	0.119	10000
444	4.455	39.426	9.013	33.264	0.138	10000
445	7.908	40.211	13.257	30.770	0.257	10000
446	7.999	27.623	5.829	21.828	0.371	10000
447	7.752	37.771	14.737	23.407	0.344	10000
501	4.823	40.299	6.842	37.189	0.130	10000
502	6.684	38.721	9.414	34.585	0.194	10000
503	2.343	31.142	10.395	33.643	0.070	10000
520	7.000	19.506	3.579	15.927	0.440	10000
521	5.940	32.185	8.783	24.012	0.258	10000
522	2.206	28.597	9.145	34.863	0.063	10000
523	2.080	26.995	7.184	36.853	0.056	10000
540	4.068	34.415	6.579	37.458	0.109	10000
541	2.049	26.518	6.579	37.368	0.055	10000
542	1.957	37.426	15.822	28.215	0.069	10000
543	4.786	42.280	34.577	9.451	0.512	7739
601	4.201	34.981	7.664	36.074	0.118	10000
602	3.928	34.546	4.868	39.169	0.100	10000
603	8.654	39.969	8.421	35.616	0.243	10000
604	5.739	37.025	4.178	39.631	0.146	10000
605	1.875	23.095	3.263	40.773	0.046	10000
606	10.191	40.445	6.579	37.459	0.272	10000
607	9.858	35.358	7.859	28.043	0.363	10000
608	5.289	40.491	10.066	33.672	0.159	10000
609	12.000	30.302	19.375	10.927	1.120	10000
610	6.514	38.392	8.684	35.353	0.184	10000
611	6.264	38.245	7.664	35.880	0.176	10000
620	2.507	38.188	9.243	34.793	0.072	10000
621	2.061	26.832	7.270	36.768	0.056	10000
622	1.992	27.124	5.691	38.347	0.052	10000
623	1.985	24.839	5.559	38.478	0.052	10000

Figure 11.196: Per-site Summary Predictions Table Example

The Per-site Summary Predictions Table has the following fields:

- Site ID: Site Identifier/Number
- Avg. Accrual: Average Number of accruals from this site across all simulations
- Avg. Max Time: Average time of the final enrollment from this site across all simulations
- Avg. Start Time: Average time a site opened at across all simulations
- Avg. Duration: Average length of time a site was open for across all simulations
- Avg. Rate: Average accrual rate (subjects enrolled per unit time) in a site across all simulations
- Times Open: The number of simulations in which a site opened

Note that the **Avg. Start Time** is the same for all simulations for **Opened Sites** in the **Site-level Data** but is randomly simulated for **Unopened Sites**. **Times Opened** will be equal to the number of simulations from the **Simulation Controls** step for all **Opened Sites** but will depend on if the simulated opening time was less than or greater than the **Study Duration** for **Unopened Sites**.

Per-Simulation Site-level Data Table The Per-Simulation Site-level Data Table provides the simulated summary outcomes for each site from a pre-specified number of individual simulations. This table is only available if **Input = Subject + Site Data**. The number of simulations is specified by editing the (X) value in the **Save site parameters data for (X) simulation runs** field of the **Output Options** section of the **Simulation Controls** step of **Setup.**

An example of the Per-Simulation Site-level Data Table is provided in Figure 11.197. Examples can also be found in the Enrollment Prediction Demonstrations (subsection 11.2.6) and Events Prediction Demonstrations (subsection 11.2.7).

Simulation ID	Site ID	Site Activation Time	True Enrollment Rate	Accruals	Observed Enrollment Rate	Final Enrollment Time	Enrollment Duration	Site Open
6	522	9.145	0.063	4	0.118	39.160	33.976	✓
6	523	7.184	0.056	1	0.028	8.902	35.936	✓
6	540	6.579	0.109	2	0.055	13.202	36.541	✓
6	541	6.579	0.055	2	0.055	32.148	36.541	✓
6	542	15.822	0.102	2	0.073	40.753	27.298	✓
6	543	0.000	0.500	0	0.000	0.000	0.000	✗
6	601	7.664	0.116	3	0.085	42.027	35.456	✓
6	602	4.868	0.100	3	0.078	38.043	38.252	✓
6	603	8.421	0.242	8	0.231	41.917	34.699	✓
6	604	4.178	0.145	7	0.180	38.998	38.943	✓
6	605	3.263	0.046	3	0.075	32.311	39.857	✓
6	606	6.579	0.273	8	0.219	35.518	36.541	✓
6	607	7.859	0.352	10	0.318	39.347	31.488	✓
6	608	10.066	0.281	3	0.091	42.778	33.055	✓
6	609	19.375	2.224	12	1.101	30.274	10.899	✓
6	610	8.684	0.185	7	0.203	41.625	34.436	✓
6	611	7.664	0.174	5	0.141	42.215	35.456	✓
6	620	9.243	0.131	1	0.030	30.714	33.877	✓
6	621	7.270	0.057	1	0.028	9.123	35.851	✓
6	622	5.691	0.052	3	0.080	41.439	37.430	✓
6	623	5.559	0.052	1	0.027	6.304	37.561	✓
7	101	3.184	0.506	15	0.510	32.567	29.383	✓
7	102	1.283	0.127	5	0.116	43.568	43.047	✓
7	103	0.000	1.605	45	1.710	26.308	26.308	✓
7	104	2.533	0.938	21	1.175	20.412	17.879	✓
7	105	3.257	0.185	7	0.170	35.205	41.073	✓
7	106	1.645	0.773	27	0.937	30.467	28.822	✓
7	108	0.213	0.526	13	0.609	21.542	21.329	✓
7	112	5.822	0.105	2	0.052	7.697	38.507	✓
7	113	6.941	0.222	5	0.134	28.421	37.389	✓
7	114	2.993	0.182	7	0.266	29.273	26.280	✓

Figure 11.197: Per-Simulation Site-level Data Table Example

The Per-Simulation Site-level Data has the following fields:

- Simulation ID: Simulation Identifier/Number
- Site ID: Site Identifier/Number
- Site Activation Time: Time at which site opened for enrollment in the current simulation
- True Enrollment Rate: User specified enrollment rate for site
- Accruals: Number of subjects enrolled in that site for this simulation
- Observed Enrollment Rate: Enrollment rate achieved in this site for this simulation based on number of Accruals
- Enrollment Duration: Length of time site was open for enrollment in that site for this simulation
- Site Open: Did site open during this simulation

Site Activation Time is taken from the **Subject-level Data** for **Opened Sites** (simulated for **Unopened Sites**). **True Enrollment Rate** is taken from the **Accrual**

Rates/Site column found in the **Accrual Infos/Site** tab at the **Accrual Options** step of **Setup,** with **Observed Enrollment Rate** being the actual rate achieved in a site in a given simulation. The **Enrollment Duration** will equal the **Accrual Duration** minus the **Site Activation Time** unless the **Enrollment Cap** is reached in a site. **Site Open** will always be a tick for **Opened Sites**.

11.2.9 Other Features

11.2.9.1 Saving and Exporting Workspace

nQuery provides the file format of **.nqp** to save and export an nQuery Predict Workspace. To save an nQuery Predict Workspace, select **Save** from the File Menu or select the **Save** icon from the toolbar or use the **CTRL+S** keyboard shortcut. This will open the **Save Workspace** window which is shown in Figure 11.198.

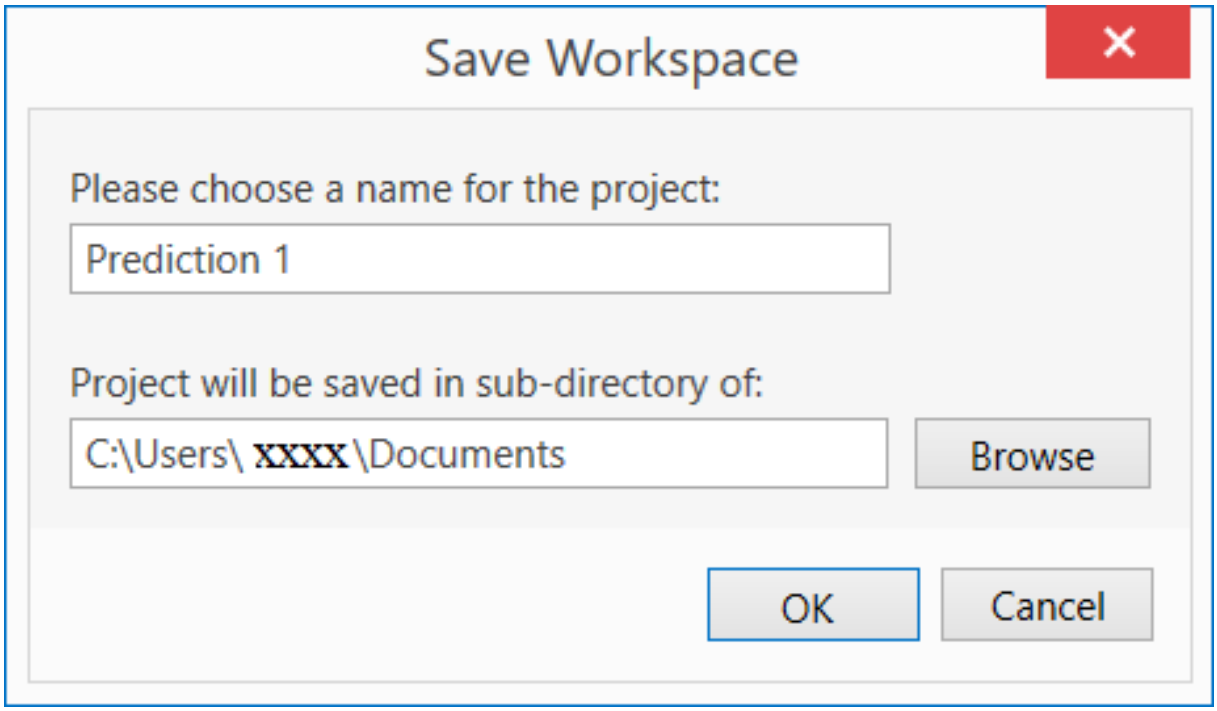


Figure 11.198: Save Workspace Window

The **Save Workspace** window allows the user to specify the name of the .nqp file in the **Please choose a name for the project:** field and the location to save the .nqp file in the **Project will be saved in sub-directory of:** field. The user can also edit the **Project will be saved in sub-directory of:** using the Browse button, which will open the **Browse for Folder** window. To save the project, select the OK button.

When a project is saved, a folder with the **Please choose a name for the project:** name will be present in the folder specified in the **Project will be saved in sub-directory of:** field. This project folder will contain the .nqp file alongside any datasets in the current workspace and all tables under the **Tables** header generated in the current prediction (all as .csv files).

After an nQuery Workspace is saved if a change is made to the workspace the user can save over the prior save using the Save options (see above) or save a separate version using Save As from the File menu.

To open a saved .nqp file, select the file in Window Explorer or find the file from the Open Menu which can be selected from the File Menu, the toolbar icon or **CTRL+O** keyboard shortcut. Opening a .nqp file works as for other nQuery file types (see subsection 1.7.5).

11.2.9.2 Editing and Saving Plots

nQuery Predict provides numerous tools to edit the plots and save those plots as separate image files. To edit, save or print a plot, open the context menu by right-clicking directly on plot while it is displayed in the workspace. An example of the context menu being open is shown in Figure 11.199.

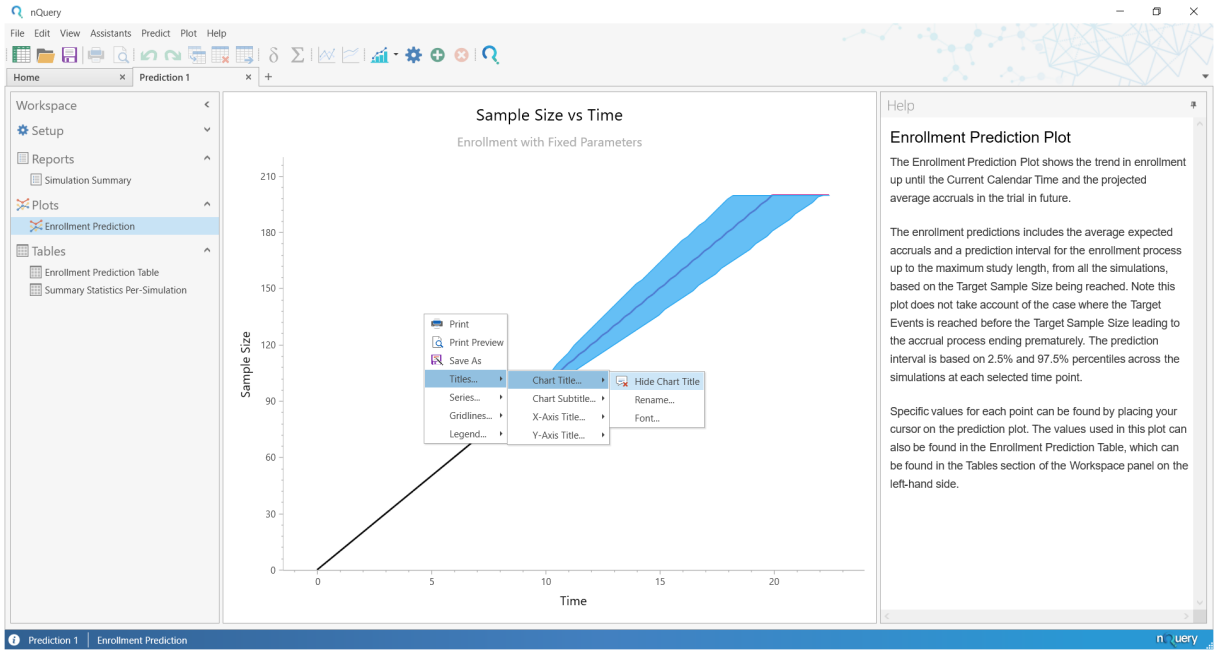


Figure 11.199: Plot Context Menu

The context menu contains the following options:

- Print: Open Print screen for current plot
- Print Preview: Create Print Preview of current plot
- Save as: Save current image as .pdf or .jpeg image file
- Titles: Hide, Rename or change font of all plot titles
- Series: Change color, add marker (including size and style) or rename any series line
- Gridlines: Add or remove X-axis or Y-axis gridlines (major only)
- Legend: Add/Remove legend and change location and outline

The majority of options for editing the plot under **Titles, Series, Gridlines** and **Legend** are selected directly from the context menu with ‣ indicating that a submenu is available if this option is selected. **Rename** and **Font** options will open additional pop-out windows to change these fields.

Save as will open the nQuery Save As screen where file type can changed from the **Save as Type** field at the bottom of the window.

Print and **Print Preview** will open up new windows for printing.

11.2.9.3 Error Checking

nQuery Predict provides error checking to ensure that all inputs during the **Setup** stage are appropriate. There are two primary error checks: data field checks, input field checks.

Data Field Checks relate to which columns can be selected from the subject or site-level data for a particular field at a **Data Field Selection** selection step when **Input = Subject Data Only** or **Subject + Site Data**. The **Subject-level Data** (Step 2 where available) and **Site-level Data** (Step 3 where available) steps are both **Data Field Selection** steps where the user chooses the required dataset and the columns which correspond to the fields required for the current prediction.

Data Field Checks ensure that only columns which have the appropriate characteristics are available for selection for a given field. For example, the **Arrival Time** field must all be numeric values greater than zero with at least 4 distinct values or the **Status Indicator** field must have no more than 3 unique alphanumeric values. For example, in Figure 11.200 the only two columns in **SubjectData.csv** which consist of numeric values only are **Arrival** (arrival times) and **Followup** (time on study).

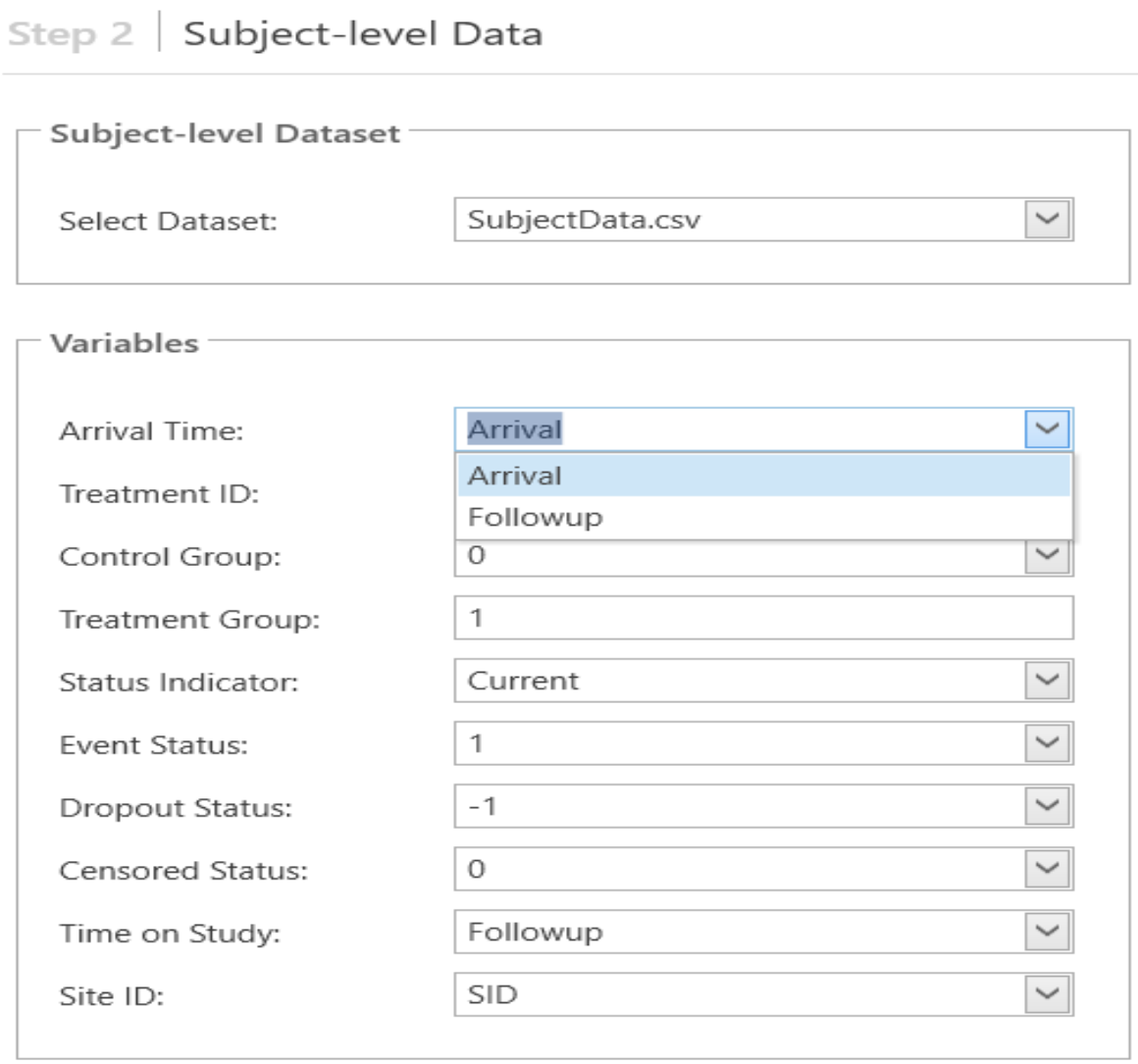


Figure 11.200: Data Field Check Example

If a required input is not being shown, the user may need to check if the criteria for that field (see subsection 11.2.4, subsection 11.2.6, subsection 11.2.7 for field requirements) have been fulfilled by, for example, checking and editing the data from the **Data** header in the Workspace Navigation Bar on the left side of the workspace window.

Note that an **Out of Range** error (see subsection 2.2.1) will be shown if the same column is selected in multiple fields at a **Data Field Selection** step.

Input Field Checks show an **Out of Range** error in any non-data field selection when a value that is not allowed is entered into a field. For example, **Target Number of Events** must be greater than the **Current Number of Events** for event prediction. These errors work the same as for standard nQuery errors (see subsection 2.2.1). An example is provided in Figure 11.201.

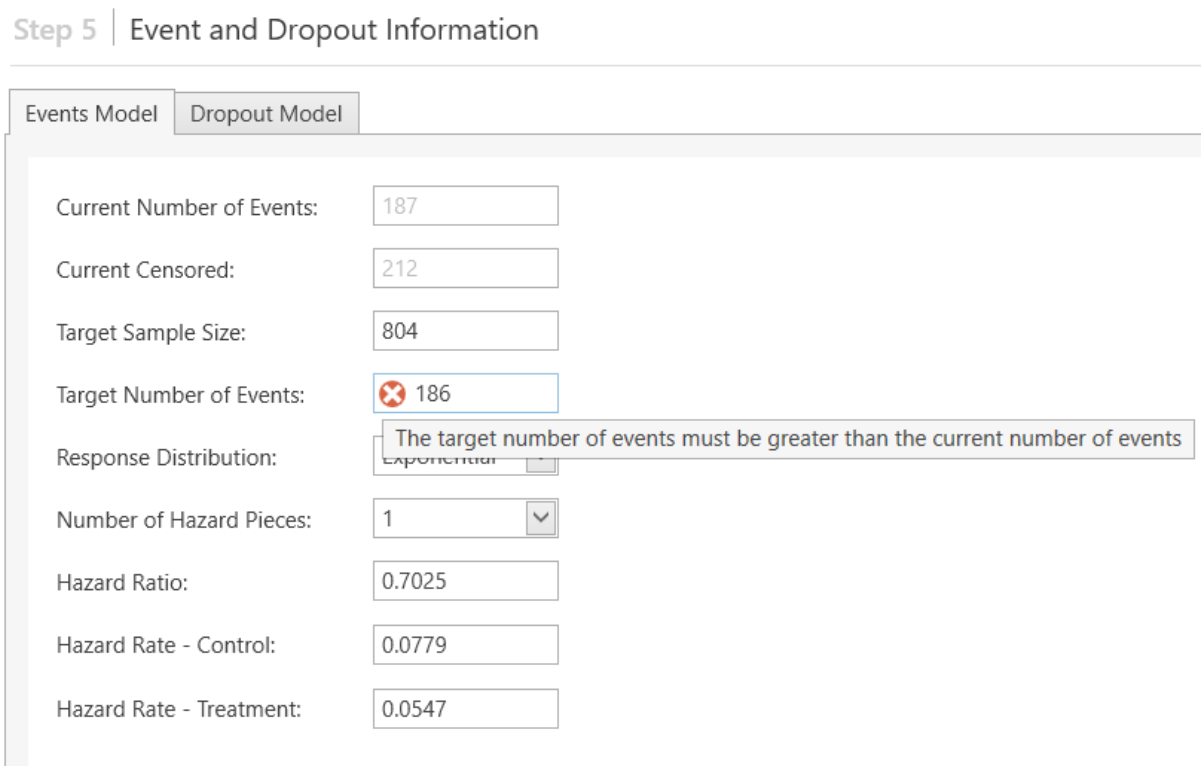


Figure 11.201: Input Field Check Example

11.2.9.4 Simulation Controls Overview

The **Simulation Controls** step is the common final step across all simulations during **Setup**. This step controls the overall simulation parameters, the percentiles of interest and the optional tables required by the user.

The **Simulation Controls** step consists of three main sections:

1. Simulation Controls
2. Output for all Trials (Percentile Controls)
3. Output Options

These sections are highlighted in Figure 11.202.

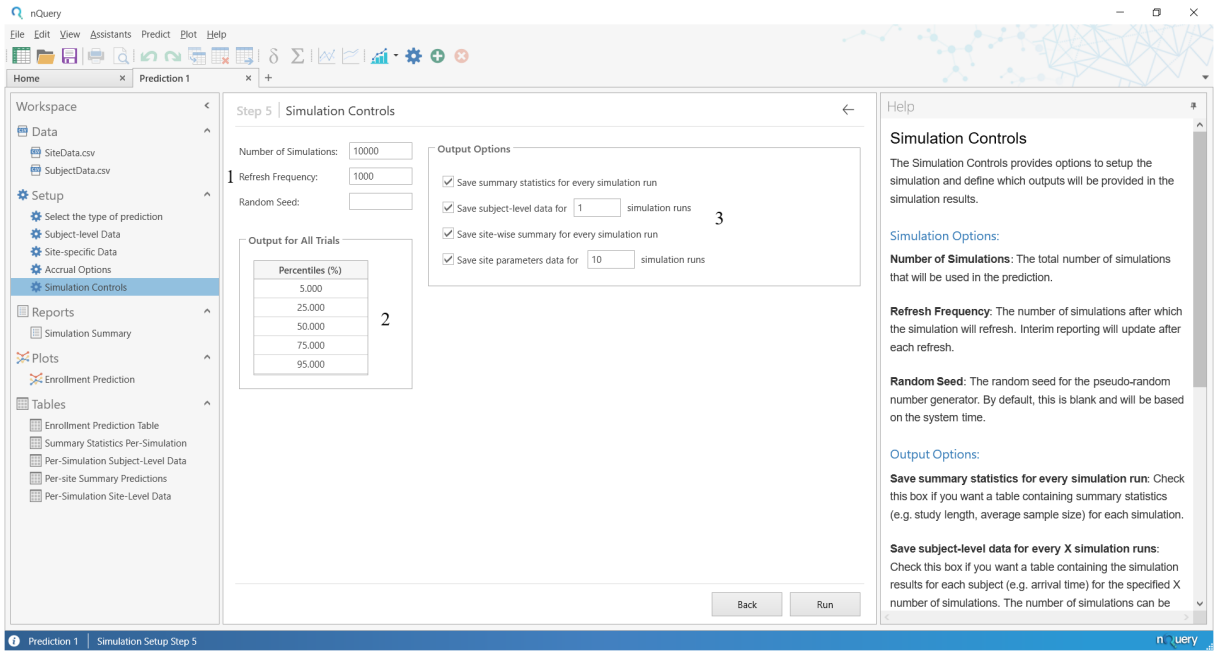


Figure 11.202: Simulation Controls

The **Simulation Controls** (1) section consists of the following fields (range in brackets): Number of Simulations (Integer > 100), Refresh Frequency (Integer > Number of Simulations) , Random Seed (Integer).

Number of Simulations is the required total number of simulations which will be run in the current simulation. **Refresh Frequency** is the number of simulations after which the summary statistics will be updated in the **Simulation in Progress** screen when Run is selected. **Random Seed** is used to specify the random seed for the pseudo-random number generator. If **Random Seed** is unspecified a random seed is selected for the user and will be shown in the **Simulation Summary** section of the **Simulation Summary Report**.

The **Output for all Trials / Percentile Table** (2) section consist of a 5 cell vertical table which specifies the percentiles of interest to display in the **Percentile Summary** section of the **Simulation Summary Report** results. By default this is set to 5th, 25th, 50th, 75th, 95th percentiles of the results across all simulations. This corresponds to the 90% Interval (5 - 95), Interquartile Range (25 - 75) and median (50) for the primary outcomes of interest. These values can be edited with any value between 0 and 100.

Output Options specifies the optional tables required in the current simulation. Details on these tables is provided in subsubsection 11.2.8.3. The **(X)** value for the **Save subject-level data for (X) simulation** runs and **Save site parameters data for (X) simulation runs** allows the user the specify the number of individual simulations to output in their respective tables.

11.2.9.5 nQuery Predict Options

There are additional options available to edit how nQuery Predict works from the Options menu. The Options menu can be opened by selecting Options from the File Menu.

nQuery Predict specific options can be found under the Predict header and are shown in Figure 11.203.

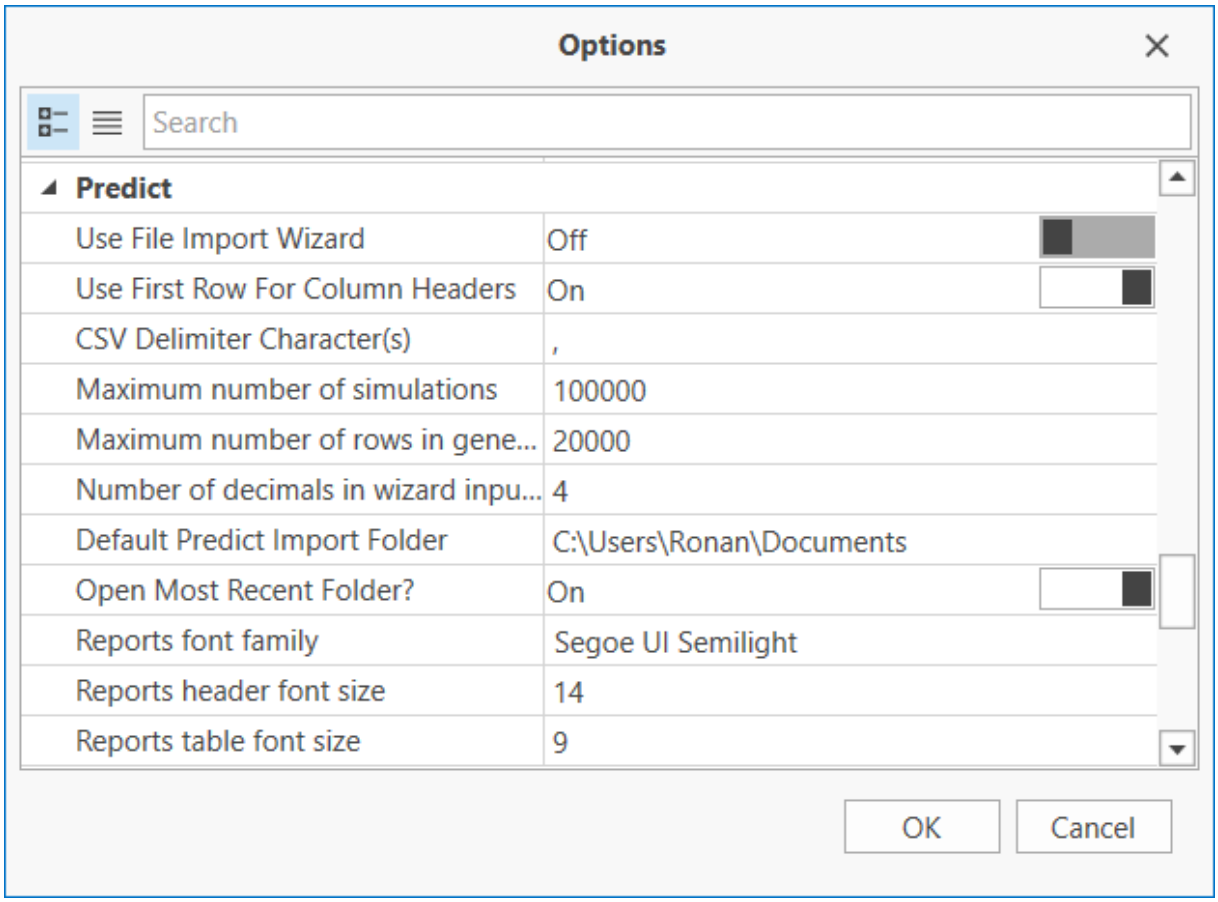


Figure 11.203: nQuery Predict Options

The options for nQuery Predict are as follows:

1. Use File Import Wizard: Toggle if Advanced File Import Wizard is needed
2. Use First Row for Column Headers: Toggle if first row of imported datasets should be assigned as column headers
3. CSV Delimiter Character(s): Enter delimiter between entries in imported CSV files
4. Maximum Number of Simulations: Maximum number of simulations allowed in nQuery Predict workspace
5. Maximum Number of Rows in Generated Reports: Maximum number of rows displayed in generated spreadsheet reports
6. Number of decimals in wizard input fields: Number of decimal places displayed in nQuery Predict numeric input fields and Report output fields
7. Default Predict Import Folder: Default folder displayed when importing datasets
8. Open Most Recent Folder?: Open most recently used folder in nQuery Predict workspace when importing datasets
9. Reports Font Family: Font used in nQuery Predict Reports

10. Reports Header Font Size: Font size of headers in nQuery Predict Reports
11. Reports Table Font Size: Font size of values in tables contained in nQuery Predict Reports

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