nQuery Advisor®
Version 7.0
User's Guide

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1. Introduction

This is the manual for nQuery Advisor version 7.0. Since most features described in the manual issued for nQuery Advisor version 5 remain the same, this manual describes the features new to Versions 6 and 7.0 and how you can utilize them.

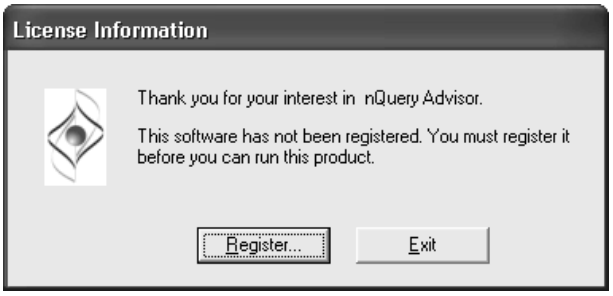
Chapters 1 and 2 are very much the same as those chapters in the version 5 manual, except that the new features and tables are included in the chapters in this manual. Chapters 3, 4, 5, and 6 in this manual are completely new to version 6, and Chapter 6 is new to Version 7.0, while the Appendix is an updated version of the previous Appendix.

If you are primarily interested in the new features in nQuery 6 and 7.0, you should find this manual to be sufficient to your needs.

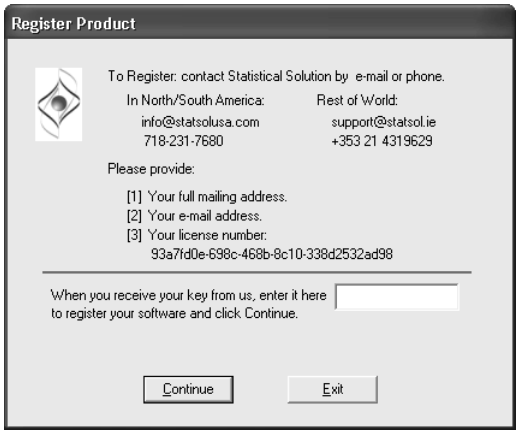
nQuery Advisor assists you in choosing an appropriate sample size for your research studies. nQuery Advisor also helps you to provide the standard deviation and effect size information which you need to make sample size and power computations.

The nQuery Advisor program was designed by professional statisticians with many years of experience in study design. They have created the nQuery Advisor program so that research investigators can compute appropriate sample sizes easily.

Running nQuery Advisor for the First Time



1. When you first run the nQuery Advisor software, a dialog box informing you that you have not registered nQuery Advisor will be displayed. Click on **Register…** to enter the license key that you have received from Statistical Solutions Ltd or to view your license number before contacting Statistical Solutions so that they can issue a license key.



2. The Register Product dialog allows you enter the license key that you have received from Statistical Solutions Ltd. Enter the license key and click **Continue** to unlock nQuery Advisor.

3. **Perpetual License.** If you have purchased a perpetual license, the **Thank you for registering your perpetual licensed copy of nQuery Advisor** message will be displayed before you can run nQuery Advisor.

3. **Annual License.** If you have purchased an annual license, a message containing the expiration date of your license will be displayed before you can run nQuery Advisor.

Uninstalling nQuery Advisor from Standalone Computer

Go to Add/Remove Programs in the Control Panel, click on **nQuery Advisor (Standalone Installation)** and then click on the **Add/Remove** button. Alternatively, you can run **setup.exe** again from either your CD or the web page, and setup will uninstall nQuery Advisor.

Uninstalling nQuery Advisor from Client Computer

Go to Add/Remove Programs in the Control Panel, click on **nQuery Advisor (Network - Client Installation)** and then click on the Add/Remove button. Alternatively, contact your administrator to find out the directory where the server version of nQuery Advisor has been installed and execute **setup.exe** from the \NetSetup folder off this directory.

Getting Started with nQuery Advisor

You have installed the nQuery Advisor program. Now you can spend a few minutes getting acquainted with the program.

You should start by doing the tutorial in Chapter 2. If you use the program to follow the tutorial, you can learn the basics of nQuery Advisor in a short period of time. The Chapter 2 tutorial may provide enough information for many users, but if you still have questions, you should follow the Analysis of Variance Tutorial in Chapter 12 in the nQuery 5 manual while using nQuery Advisor.

As questions arise, you can use the other chapters of this manual for reference. However, you have more than just this manual to help you understand nQuery Advisor. Each sample size table screen provides four different aids to understanding the workings and requirements of the program:

The guide card for each row of each sample size table and many side tables.
When you open a sample size table (and many of the side tables), the guide card for that table displays a short description of the type of entry expected for the row.

The tag for each icon.
When your cursor remains on an nQuery Advisor icon briefly, a tag appears with a description of that icon. For example, when you depress the File menu New option, you get the tag shown above.

The status line description for each menu item.
When your cursor lies on an icon or a menu item, a short description of that item appears on the left end of the status bar at the bottom of the screen.

The Help system.

When you choose the Help menu, you can access the Help Topics option to use the Contents, Index, or Find options. You also have a PDF Help file if you prefer to use PDF.

New Features and Tables in nQuery Advisor 6 and 7.0

The nQuery Advisor 7.0 program delivers 32 bit Windows architecture for Windows 98/NT/2000/XP/Vista.

New features:

- **Create randomization list (basic) for simple designs**
  You can create a randomization list for assignment of subjects to groups for designs with equal sample sizes. Simply specify the total sample size and the group names and click on the View List button. See Chapter 6 in the nQuery 7.0 manual for details.

- **Create randomization list (advanced) for designs with strata, unequal n's**
  You can create a randomization list for assignment of subjects to groups for designs with unequal sample sizes, and/or randomization within strata. You can also specify randomization block sizes to use. Simply specify the design details and group and strata names and click on the View List button. See Chapter 6 in the nQuery 7.0 manual for details.

- **Create randomization list (complex designs) (New in 7.0)**
  You can create a randomization list for assignment of subjects to groups for designs with unequal sample sizes, centers and strata, and have more user control over ID numbers. You can also specify randomization block sizes. Simply specify the design details and click on the View List button, then edit the default ID numbers if desired. See Example 5 in Chapter 6 in the nQuery 7.0 manual for details.

- **Random subset of cases**
  You can use this option to select a random subset of n cases from a total of N available cases. See Chapter 6 in this manual for details.

- **User control over number of decimal places displayed in table rows**
  You can specify the number of decimal places to display for each row in nQuery tables. These choices can be saved with the table and applied to other similar tables. These choices will also show in the printed copies of the tables. See Chapter 5 in the nQuery 7.0 manual for details.

- **Expanded right click edit menus**
  You have more options in the right click edit menus.

New Sample Size Tables in 6:

- **t-tests (ANOVA)**
  New table to compute power and sample size for the 2 x 2 crossover design

  t-test (ANOVA) for difference of means in 2 x 2 crossover design (MTT4)

- **Proportions**
  New table to compute sample size or confidence interval width for the relative risk (ratio of two independent proportions).

  Confidence interval for relative risk (ratio of two proportions) (PTC3, PTC3U)

- **Survival**
  New table to compute power or sample size for a non-inferiority test of the hazard ratio for two exponential survival curves, allowing for an accrual period, and dropouts

  Non-inferiority test for two exponential survival curves (STE0)

- **Agreement**
  New table to compute confidence interval width or sample size for the intraclass correlation

  Confidence interval for intraclass correlation for k measurements (AOC3)

  Update to formula for V(K) in side-tables for AOT2, AOC2 tables for Lin's concordance coefficient based on published correction.

Examples for each of the new tables are detailed in Chapter 4 of this nQuery 7.0 manual.

Customizing Regional Settings

You can change Windows settings to suit your locale, and if you tell Windows 98/2000/NT/XP/Vista that you want to use commas instead of periods for the decimal point, nQuery Advisor will honor your request. This is called internationalization or localization.

You do this in one of two ways:

1. From the **Start** menu, choose **Control Panel**. Within **Control Panel**, double click to activate **Regional Settings.** Choose the **Regional Settings** tab and choose a language/region in the drop-down box.

or

2. From the **Start** menu, choose **Control Panel**. Within **Control Panel**, double click to activate **Regional Settings.** Choose the **Number** tab. When you see the dialog box under the Number tab, enter your preferred decimal symbol in the **Decimal symbol** field.

Considerations:

a) If you use option 2 above, your edits change the system's configuration for that language. That is, if you're working in English (United States) and you change the decimal symbol to &, then change the language to French (France) and then back to English (United States), your decimal symbol will remain &. You can, however, return to the Number tab dialog box to change the Decimal symbol again.

b) The remaining settings in the dialog box under the Number tab have no apparent effect on the displays in the nQuery Advisor program. These are: No. of digits after decimal, Digit grouping symbol, No of digits in group, Negative sign symbol, Negative number format, Display leading zeroes, Measurement system, and List separator.

c) Files saved by nQuery Advisor should be entirely independent of the regional settings. This means that when you use commas as your decimal symbol, and you send a saved file to someone who uses periods, when he opens the file on his computer, the numbers will have periods.

d) Testing has uncovered no problems, but if you are changing the decimal symbol to any symbol other than the period or the comma, you may run into complications.

e) The printed date in the lower right corner of printed nQuery output respects the choices you make in Regional settings. As with decimal points, you can change the style in which the date is presented either by changing the language in the Regional Settings tab, or by making the change on the Date tab dialog box.

Please see Chapter 3, *The File and Options Menus*, in the nQuery 5 manual to read about the Preferences menu and its effect on your regional settings.

Troubleshooting

Some users experienced installation or runtime problems with the previous version of nQuery Advisor. Those problems were traced to particular versions of support DLLs and OCXs on their system. In order to resolve any future such problems quickly and effectively, we have provided a tool which determines the exact versions of all such files which nQuery Advisor is using on your system.

To use the troubleshooting tool:

Choose the **Help** menu **About nQuery** option.

In the **About nQuery Advisor** dialog box, click on the **Advanced Version Information** button.

The **Advanced Version Information** box will appear. This box lists the paths, versions and dates of the files which nQuery Advisor needs as those files exist on your computer.

Click on the **Save** button to save this information to a text file.

Send the saved text file to us so that we can advise you on any necessary updates to the files.

For this tool to work, you must have a particular file in the same folder as the executable file, nQuery7.0.exe. The file you need depends on the operating system you are using.

Operating System	File Required
Windows® 98	AdvVer.exe
Windows® NT	AdvVerNT.exe
Windows™ 2000	AdvVer.exe or AdvVerNT.exe
Windows™ XP	AdvVerNT.exe
Windows Vista	AdvVerNT.exe

2. Tutorial

Determination of the appropriate sample size is a crucial part of study design. We must choose sample size correctly to allow a study to arrive at valid conclusions for the scientific question. A study which is too small may produce inconclusive results, while a study which is too large will waste scarce resources.

Answering the question “What sample size do I need?” requires seven steps. Using an actual example of determining sample size for the two-sample t test, this chapter takes you through a step-by-step tutorial demonstrating some of the nQuery Advisor features. This chapter is not meant to be an exhaustive demonstration of nQuery Advisor options. Rather, the tutorial demonstrates the general methods of nQuery Advisor through one complete example. For a tutorial illustrating the use of the Compute Effect Size side tables, see Chapter 12 in the nQuery 5 manual, *Side Tables & Compute Effect Size*.

Ideally, evaluations of obtainable power or interval width are made prior to the start of a study. This is done to ensure that the chosen sample size is neither too small to be likely to detect important effects nor so large that the study is longer and more costly than necessary. However, evaluation of the power of a completed study which failed to find significance can be useful in deciding whether the intervention is ineffective or whether further study may be justified. The results of the completed study can provide information about variance. Nevertheless, the “effect size” used in retrospective power analyses should not be the effect size observed in the study, but should be an effect size that would be important to detect.

Step 1. Formulate the Study

The study question is: Does the new drug reduce anemia in elderly women after hip fracture?

Detail the study design

A two-group, randomized, parallel, double-blind study is planned. Patients will be studied for two weeks; each patient will be randomly assigned to receive either new drug or placebo 3 times per week. The sample sizes in the two groups will be equal.

Choose the outcome summary

The primary outcome measure will be the mean change in hematocrit level from pre-treatment to post-treatment. These changes will be compared between the two groups.

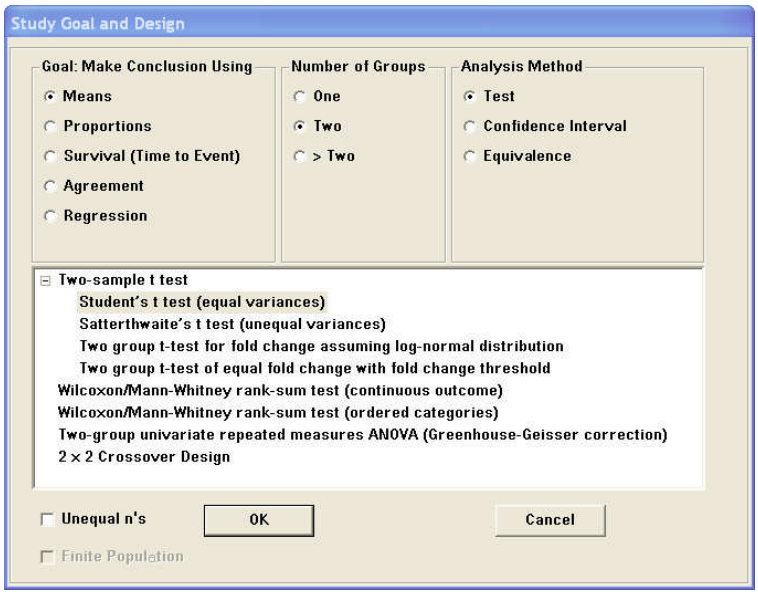
Specify the analysis method

The mean change in hematocrit level will be compared between the two groups of patients using the two-sample t test. The null hypothesis states that the mean change in hematocrit is the same in both groups.

Select **File menu New** option or click on the **New** button  . In the Study Goal and Design Box, you will see three columns of options.

Under **Goal: Make conclusion using**, select **Means.**

Under **Number of groups**, select **Two** groups.
Under **Analysis method**, select **Test**.
In the Study Goal and Design box below, the selections result initially in eight choices in the lower half of the Study Goal and Design dialog box**.**



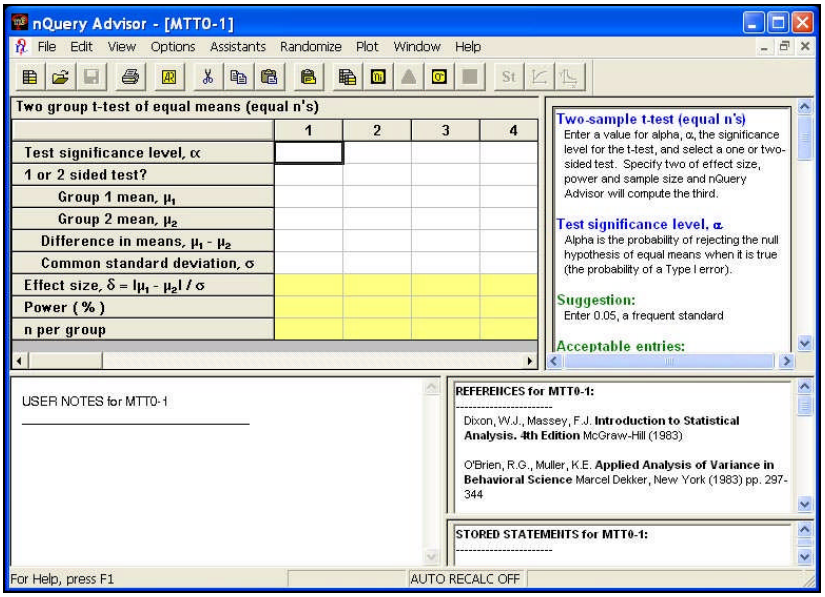
Different selections under "Goal" or "Number of Groups" or "Analysis Methods" bring up different lists of available sample size tables.

Note: This manual uses the ordering of the analyses within the Study Goal and Design box to determine an abbreviation for each analysis type. In this example, you are choosing analysis type MTT0. For a detailed explanation of the table abbreviation codes, please read the *Contents of the Study Goal and Design Dialog Box* section of Chapter 7 in the nQuery 5 manual, *The View and Windows Menus.*

(If you have set your screen resolution to a setting which is less than optimal for your monitor, some of the words in your display of the following figure may be cut off. The solution is to set the video display settings to the optimum for your monitor.)

Note that the Two-sample t test listing has a - sign beside it. To hide the listings under **Two-sample t test**, click on the – sign.

Select the Student's t test (equal variances) and click on the **OK** button to accept the choice. You will see the following screen:



This is the sample size table for the two group t test of equal means with equal n's. Before continuing with the example, this section discusses the general structure of the nQuery Advisor screen.

Title Bar

The title bar on the top of the sample size table window displays the name of the sample size table. The default name is the table abbreviation plus the number of the table. If you save the table using a different name, the next time you open the table, the title bar will display the name you used to save the table. For details on the nQuery table name abbreviations, see Chapter 7 in the nQuery 5 manual, *The View and Windows Menus*.

Menu Bar

The sample size table displays nine menus in the menu bar at the top of the window. The menus are: File, Edit, View, Options, Assistants, Randomize, Plot, Window, Help.

Icon Bar

Note that the icon bar beneath the menu bar offers 17 icon buttons. You can click on each of those icon buttons to gain direct access to the represented program option, rather than selecting the menu option. The icons are:


New


Copy


Estimate SD


Open


Paste

Specify Sigma


Save


Paste Unformatted

Statement


Print


Fresh Table


Plot Power vs n


Auto Recalculation


Unequal n’s


Plot user-selected rows


Cut


Compute Effect Size

If you rest the cursor on one of the icons, you will see a tag with a short description of the icon. A description of each icon also appears in the status line on the bottom of the window.

Table Title

Just below the icon buttons, the screen displays the title for this table: Two group t test of equal means (equal n's).

Column Numbers

Each column in the sample size table is labeled with a column number. You can change these default column names by using the Edit Column Names option from the Edit menu. Each table allows up to 20 columns for use. See Chapter 4 in the nQuery 5 manual, *The Edit Menu* for details.

Row Names

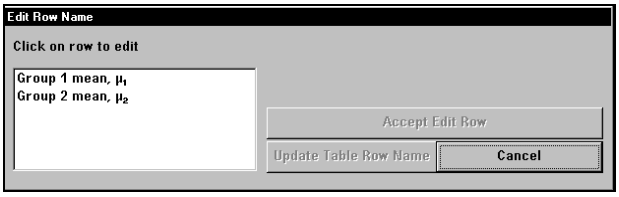
Below the table title, the screen displays nine row names. Each row name specifies the type of value to be found in the row, whether you enter the value, or the program calculates the value for you.

Changing Row Names or Labels

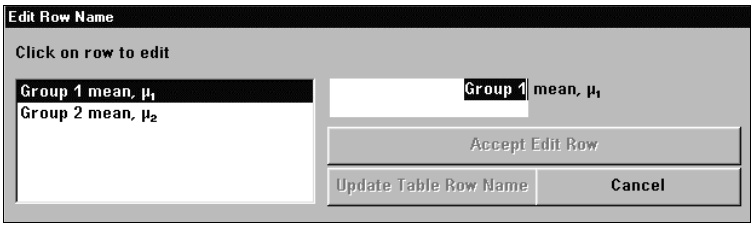
You can change the row labels to replace **Group 1** and **Group 2** with the specific names for your groups. This option allows you to enter customized row labels for the groups. Your new row labels will appear both on the screen and in the saved and printed versions of your sample size table.

To edit row names:

Click on the **Edit** menu **Edit Row Names** option. The Edit Row Name dialog box will appear.

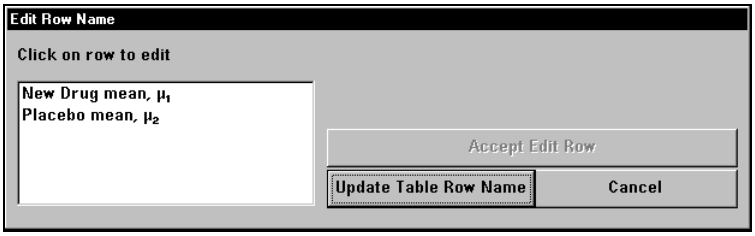


Click on **Group 1 mean, μ_1** and Group 1 will appear in the white rectangle in the center of the dialog box. Note that **mean, μ_1** appears to the right of the white rectangle so that you always know which mean you are specifying.



In the white rectangle, type New drug to replace Group 1, then click on the **Accept Edit Row** button.

Click on **Group 2 mean,** μ_2, enter **Placebo** in the white rectangle, and click on the **Accept Edit Row** button. The dialog box will show your new row name entries.



Click on the **Update Table Row Name** button to update the table, and the sample size table will appear with the new row names. You will see those names in the next figure, as you specify parameters in Step 2.

Note: You can use up to a maximum of 20 characters for the editable part of the row name.

Status Bar

The Status Bar lies at the bottom of your nQuery Advisor window. The Status Bar toggle in the View menu controls the display of the Status Bar. The bar presents a short description of each icon button as your cursor goes over the icon button. The status bar also presents the on/off status of the automatic recalculation option, along with the exact contents of any cell selected by the cursor.

Note: The status bar may show more significant figures than you can see in the cell. How the status bar figure compares with the cell depends on the number in the cell and the number of decimal places you have specified for the cell.

Colors in the Sample Size Table

The rows for power, sample size, effect size, interval width which provide the answers to your sample size queries are highlighted with yellow on the screen. In the sample size tables shown in grayscale in this manual, the yellow highlighting shows as a pale gray.

For example, Effect size, Power, and n per group are yellow when you have the table for the Two group t test on your screen. If you enter all required information in the white rows, you can fill in any two of the three yellow rows, and nQuery will compute the third. For this example, enter the group means and the common standard deviation, nQuery will compute the corresponding effect size. Then enter either power or n per group, and nQuery Advisor will calculate the other.

When you set the Auto Recalc option to **On**, the row(s) to be automatically recalculated will display green. For details on the Options menu Auto Recalc option, see Chapter 3 in the nQuery 5 manual, *The File and Options Menus*.

Guide Cards

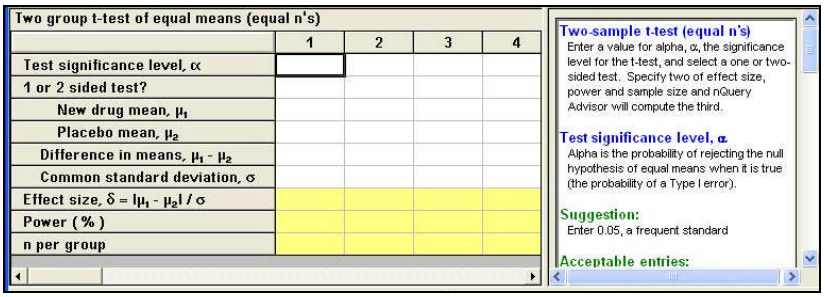
The guide cards in the right pane of the nQuery Advisor window provide statistical information on the row in which your cursor lies. If you are unfamiliar with the analytic procedure or with doing sample size computations, or you want some help with how to proceed while filling in values for the table, refer to the guide cards.

The default Guide toggle is set to **On** when you have an open sample size table. Thus, every new table appears with its guide card on. You can toggle the guide card to **Off** by choosing the **View** menu **Guide** option.

To view the guide card:

Click on any spreadsheet cell in the first row.

The guide card for the first row will appear in the upper right of the window.

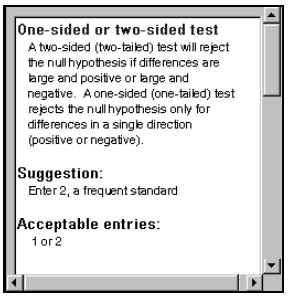


Note that the guide card corresponding to the top row provides general information about how to use the table. As you move the cursor from row to row, the guide cards display information appropriate for each row. You also get suggestions for row

values, details on limits for the values you can enter, and reminders about other helpful nQuery Advisor features.

To bring up the guide card for a different row:

Click on a cell in the second row, and the guide card will change to the card for the second row.



Every new table appears on the screen with its guide card On unless you turn off the guide card in the View menu.

To turn off the guide card:

Click on the **View** menu **Guide** option. The guide card pane will disappear from the window. (The guide card has been turned off for the rest of this example.)

To turn on the guide card after you have turned it off:

Click on the **View** menu **Guide** option. The guide card pane will appear in the window.

For details on copying, pasting and printing the Guide cards, please see the *Guide* section of Chapter 7 in the nQuery 5 manual, *The View and Windows Menus.*

References

The References pane is directly below the Guide Card pane of the nQuery Advisor window. There you will find the references for the current sample size table.

Statements

The Statements pane is directly below the References pane of the nQuery Advisor window. That pane is available for storing sample size justification statements generated by nQuery; these stored statements will be saved with the sample size table. This tutorial will demonstrate how to request Statements and store, print, or copy them to clipboard for pasting into other Windows applications.

Notes

The Notes pane is directly below the sample size table pane of the nQuery Advisor window. In the Notes pane you can enter all necessary notes to be saved with the sample size table.

Online Help

The nQuery online Help is available at all times. To access the Help through the menu bar, click on the **Help** menu **Help topics** option.

Step 2. Specify Parameters for Planned Analysis

For the two group t test example (MTT0), the parameters you must specify for the analysis method being planned are:

- the significance level for the test
- whether the test procedure is to be one or two-sided.

Plans call for a 5% ($\alpha = .05$) significance level and a two-sided test.

To enter the values:

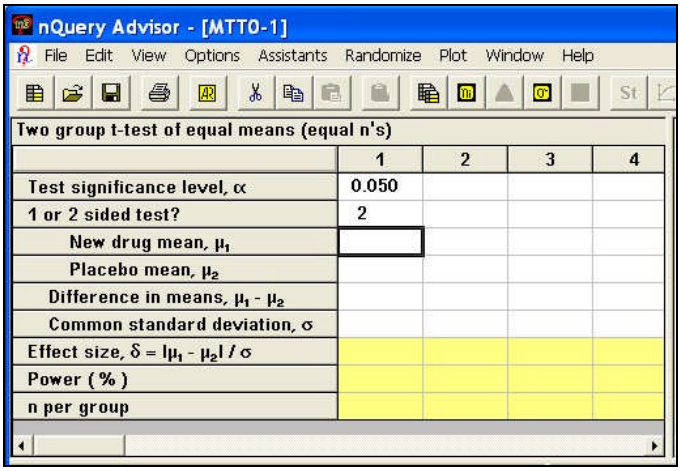
Click on the first cell of column 1. Enter **.05** into that cell.

Press <Enter> or the down arrow to register your entry. Your cursor will move to the cell in the second row.

Type **2** and press <Enter>.

The next screen shows the new values entered into the table after we have turned the Guide card option to **Off**. Note that the center section of the status bar at the bottom of the screen shows the exact contents of the chosen cell. The status bar will usually show more decimal places than appear in the table.

Note that we can change the number of decimals displayed for specific rows in the table by choosing the Format Decimal Displays for Selected Rows option in the right click menu after highlighting the chosen rows.



In preparation for the next step, repeat your row entries of .05 and 2 for columns 2 and 3. The next section will use the three columns.

To copy the values:

Use your cursor to select the first two rows of the first column.

Click on the **Edit** menu **Copy** option or use the Copy icon,  , in the icon bar, or use the **<Ctrl>-<C>** keyboard shortcut.

Select column two and use the Paste icon,  , in the icon bar, or click on the **Edit** menu **Paste** option, or use the **<Ctrl>-<V>** keyboard shortcut.

Select column three and use the Paste icon,  , in the icon bar, or click on the **Edit** menu **Paste** option, or use the **<Ctrl>-<V>** keyboard shortcut.

The row entries will display in columns two and three.

To fill several columns with values from current column:

See the Fill Right and Multi-factor section later in this chapter.

Using Mouse Buttons in Data Entry

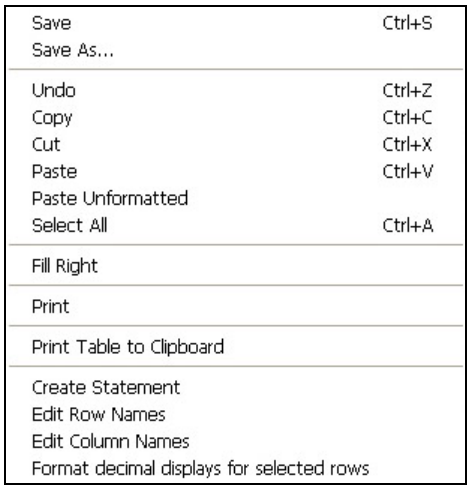
When you are entering data into a sample size table, you can select the cell in two ways:

- Use the left mouse button to single click on the cell. You can immediately start entering a value. Your new value will replace any existing cell contents.

- Use the left button to double click on the cell. Any existing number will be selected. You can press <Delete> to remove the number, or simply start typing the new number. In either case, the original number in the cell will disappear.

Right-click Menus

If you right click within the sample size table (or within other panes or views,) you will get a right-click menu. These menus provide another way to access the Save Save As, Undo, Copy, Cut, Paste, Paste Unformatted, Select All, Fill Right, Print, Print Table to Clipboard, Create Statement, Edit Row Names, Edit Column Names, and Format Decimal Displays for Selected Rows options.



These Edit options function in the same way whether you access them from the Edit menu or through the right-click menu for the sample size table.

Note that the right-click menus for the Guide Card, Statement, References, and User Notes panes differ from the menu shown above. Those right-click menu options include pane-specific options, such as: Undo, Copy, Cut, Paste, Print, Select All, Special Characters in the User Notes pane; Hide, Copy, Print in the Guide Card pane, and Copy, Print, Create Statement in the Stored Statements pane. See Chapter 4 in the nQuery 5 manual, *The Edit Menu* for details on the options available in the right-click menus.

Step 3. Specify Effect Size for Test

Specifying the effect size is often the hardest part of study planning.

For the two-sample t test, specifying the effect size has two parts: specifying the expected difference in means you would like to detect, and specifying the standard deviation expected within each group.

Specifying the difference in means expected for the two groups.

You should specify the expected mean changes, the worthwhile mean changes, or the important mean changes. People often say, “This study has never been done before, so how do I know what will happen?” However, previous use of the intervention is not the important question.

The important question is what is known about the outcome measure. What would be an important effect of treatment? What kinds of effects might be expected, given other information?

In this example, there was information on hematocrit from four prior studies:

1. From a small pilot study in six elderly females after hip fracture, the mean hematocrit was 32.3%. In the same institution, in 32 healthy elderly females, the mean hematocrit was 33.5%.
2. Two previous studies tested different doses of the new drug in other patient groups. In those studies, the placebo group showed no change in hematocrit. The treated group showed changes of 2.5% to 5%.

These data taken together suggest that we can expect a change of 0% in the placebo treated group, with treatment group changes lying in the range 2.5 to 5%. Thus, a conservative estimate of the possible effect of the new drug in elderly females might be in the range 2.0% to 2.4%. Such increases would be of real value to the patient.

To enter means:

Click on the cell in the first column of the **New drug mean** row and enter **2.0**.

Press the right arrow to move to the second column of the **New drug** row.

Enter **2.2**.

Press the right arrow to move to the third column of the **New drug** row.

Enter **2.4** and press <Enter>.

You have entered the treatment means.

Click on the first column of the **Placebo** mean row and type **0**.

Press the right arrow to move to the second column of the **Placebo** row.

Type **0** in the second and third columns of the **Placebo** row.

Note that nQuery Advisor automatically calculates the difference in means, as you can see in the next screen.

Two group t-test of equal means (equal n's)						
	1	2	3	4	5	6
Test significance level, α	0.050	0.050	0.050			
1 or 2 sided test?	2	2	2			
New Drug mean, μ_1	2.000	2.200	2.400			
Placebo mean, μ_2	0.000	0.000	0.000			
Difference in means, $\mu_1 - \mu_2$	2.000	2.200	2.400			
Common standard deviation, σ						
Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert / \sigma$						
Power (%)						
n per group						

Specifying the common standard deviation.

The next row in the table is **Common standard deviation,** so we must obtain information about variability between individuals within a group. The two-sample t test assumes that variability in the two groups is the same, so you enter a single value.

In determining the value of the common standard deviation, we again refer to previous studies. Standard deviations for hematocrit values were 3.2% in elderly females, and 3 to 6% for other groups.

The current study, however, requires the standard deviation for change in hematocrit, and less information is available. The information reported here required some additional calculations from the values given in the references. The standard deviation of change in hematocrit in the various placebo and treated groups ranged from about 1.5% to 2.5%. These data suggest that we can reasonably expect a standard deviation for change in hematocrit of about 2%.

The nQuery Advisor program helps you to utilize information from a variety of formats to obtain an estimate of the standard deviation. For details, see Chapter 9 in the nQuery 5 manual, *Determining a Value for the Standard Deviation*.

To enter Common standard deviation:

Click on the cell in the first column of the **Common standard deviation** row and enter **2.0**.

Type **2.0** in the second and third columns of the **Common standard deviation** row.

Note that nQuery Advisor automatically calculates the **Effect** size.

At this point, you may wish to enter notes concerning the origin of these values for the mean and standard deviation so that you can document them in your report. You can

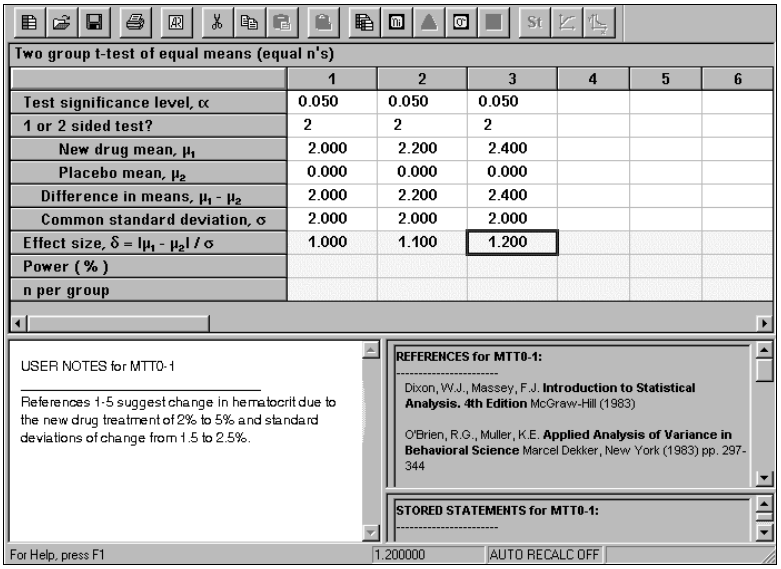
save any notes with the table, then print them out or copy them to the clipboard for future reference.

To add a note to the table:

Click in the white rectangle in the lower left of your screen below the title, USER NOTES for MTT0-1

Type: **References 1-5 suggest change in hematocrit due to the new drug treatment of 2% to 5% and standard deviations of change from 1.5 to 2.5%**.

Your nQuery Advisor table should look like the following screen.



Step 4. Compute: Sample Size or Power

Choose the value of power required for the study. The power is the probability that the results of your study will be statistically significant at the specified significance level if your assumptions about means, standard deviations, and effect size are true. The significance level is 5% for this example, and we are assuming that the values you have entered for means and standard deviation are the true values (not necessarily those observed in your study).

Investigators typically request study powers between 80% and 95%. The higher the required power, the larger the required sample size. Here, we assume that the investigator chooses 90% power.

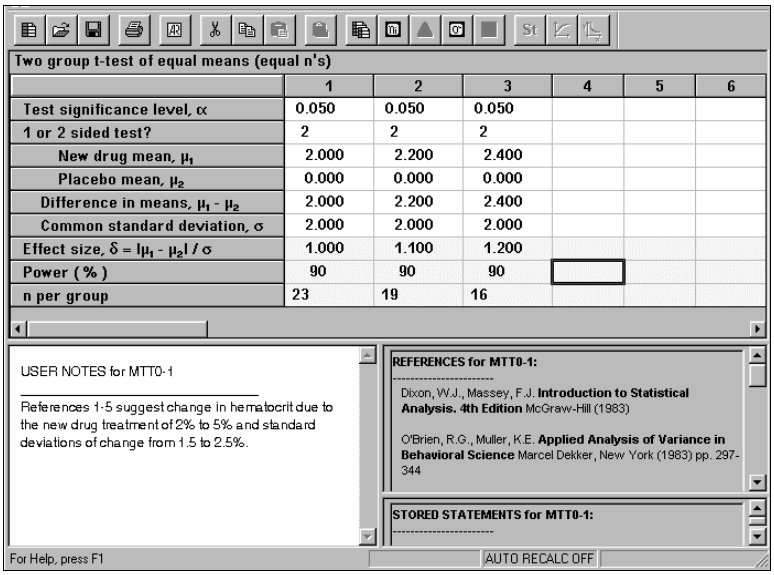
To enter a value for Power:

Click on the cell in the first column of the Power row and type **90**.

Press the right arrow to move to the second column.

Type **90** into the second and third columns of the Power row.

Note that, when you type the value **90** into the power row and press <Enter> or the right arrow, nQuery Advisor computes the necessary sample size and completes the column.



For the range of hypothesized changes in the new drug group, a sample size per group of 16 to 23 would be required (total study sample sizes of 32 to 46.) In the next section we illustrate easy ways to evaluate a variety of possibilities for other scenarios and sets of analysis parameters.

Step 5. Sensitivity Analysis

A sensitivity analysis allows you to assess variability in required sample size or in resulting power or interval width for a range of plausible parameter values. This section will discuss three approaches to sensitivity analysis.

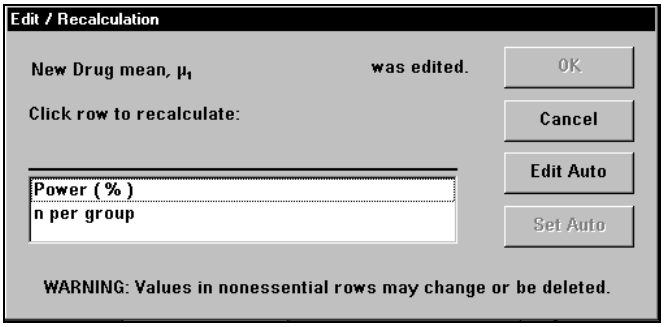
a. Edit Values in Filled-in Column

You might use this method after you have filled a sample size table and reviewed the results. For example, you might look at the screen above and wonder how the answer would change if the New drug mean were only 1.8. You can quickly get the answer to that question.

To edit a value in a filled-in column:

Click on the cell in the first column at the **New drug** row, type **1.8** and press <Enter>.

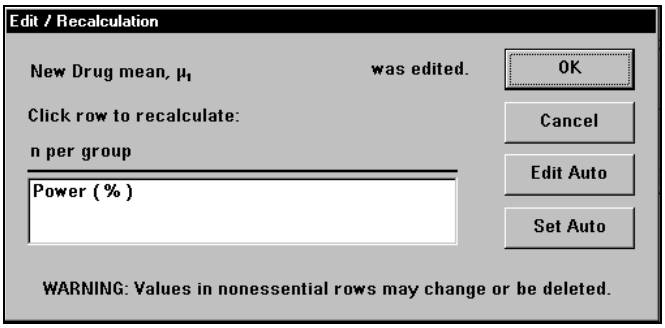
The **Edit/Recalculation** dialog box will appear.



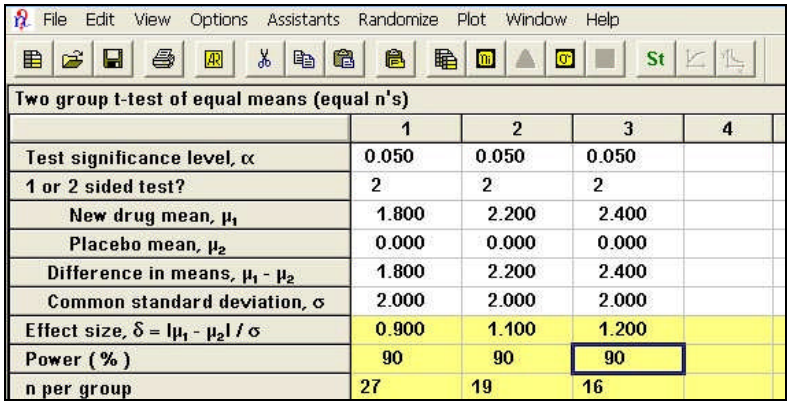
Because you have edited the New drug row, either the value for **Power** or the value for **n per group** must change. The choice is yours. In this example, we want to keep the power at 90%.

Click on **n per group.** The **OK** button and the **Set Auto** button will be enabled.

You could click on **Set Auto** to cause nQuery Advisor to automatically recalculate n per group every time you edit a row value. See Chapter 3 in the nQuery 5 manual, *The File and Options Menus*, for more details on that feature.



Click on **OK** to finish selecting the **n per group** row for recalculation. You can see the recalculated screen in the next figure. A New drug mean of 1.8 would require 27 per group to achieve 90% power.



	1	2	3	4
Test significance level, α	0.050	0.050	0.050	
1 or 2 sided test?	2	2	2	
New drug mean, μ_1	1.800	2.200	2.400	
Placebo mean, μ_2	0.000	0.000	0.000	
Difference in means, $\mu_1 - \mu_2$	1.800	2.200	2.400	
Common standard deviation, σ	2.000	2.000	2.000	
Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert / \sigma$	0.900	1.100	1.200	
Power (%)	90	90	90	
n per group	27	19	16	

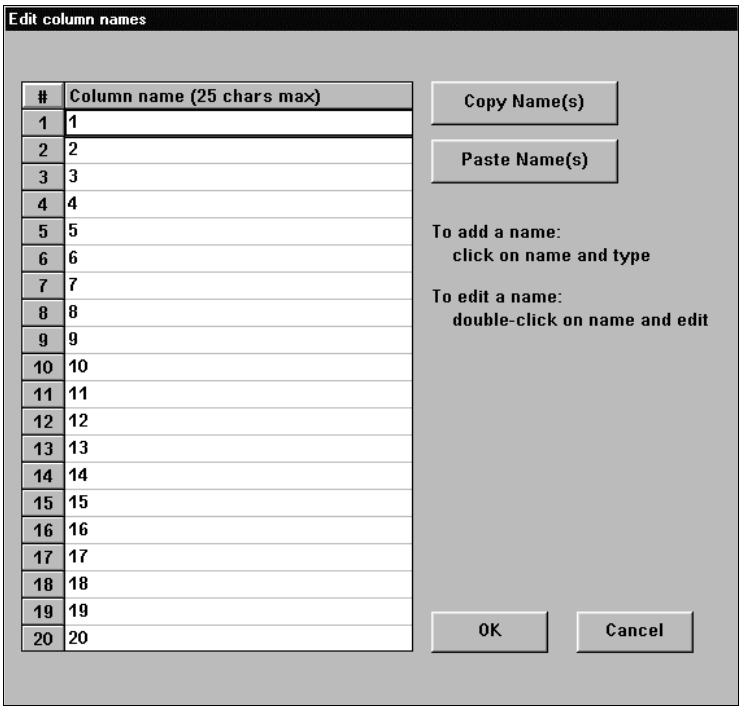
b. Edit a Column Name

Before you use the Plot options, you may want to edit a column name so that the column name will appear in the plot legend.

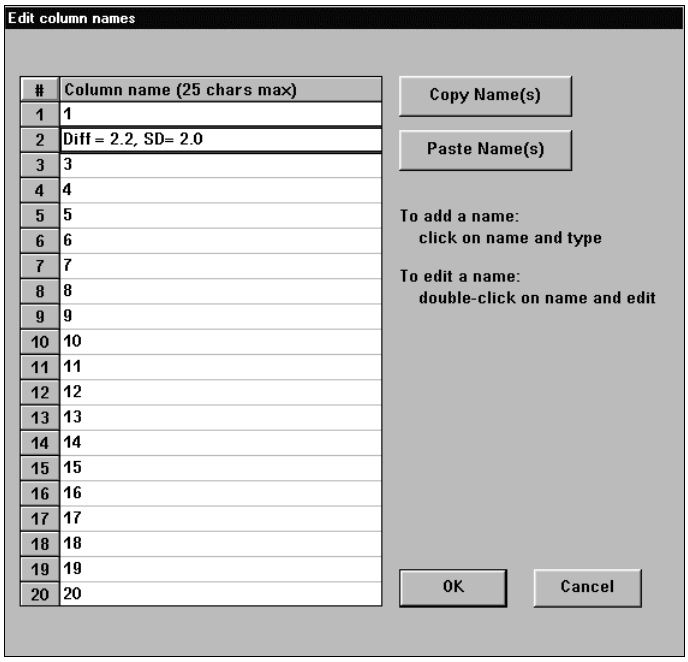
To change a column name:

Select the **Edit** menu **Edit Column Names** option or the right-click menu **Edit Column Names** option.

The **Edit Column Name** dialog box will appear. This box lists the column names that you can change in your sample size table. Column names are restricted to a maximum of 25 characters each; the names will not wrap.



Click on the second column name and type in the desired name. In this case, the name is Diff = 2.2, SD= 2.0. (If you wanted to use Special Characters in the column names, you would select the Special Characters box and paste the selected character into the notes, then copy it and paste it into the column name box. See Chapter 4 in the nQuery 5 manual, *The Edit Menu*.)

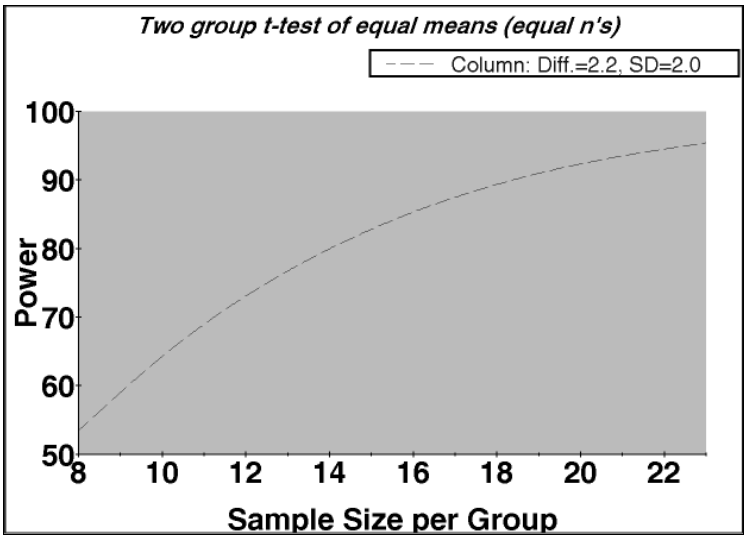


c. Use Plot Options

To use the Plot option to see n per group for different powers:

Use the mouse to highlight the entire second column of your sample size table.

Click on the **Plot** menu **Plot Power vs n** option or the **Plot Power vs n Plot** icon  . The plot for the chosen column will appear.



To use the Plot option to plot user-selected rows:

When you prefer more choice in axis parameters, you could choose the **Plot** menu **Plot User-selected rows** option or the **Plot User-selected rows** icon,  . See Chapter 6 in the nQuery 5 manual, *The Plot Menu*, for details on using the Plot option.

If you want to re-label your plot axes or title or change the appearance of the plotted lines or the background, read Chapter 6 in the nQuery 5 manual, *The Plot Menu*, for details.

d. Fill Table Rows Using Fill Right and Specify Multi-Factor Table

If you have been following this tutorial, you now have a table with three filled columns. Since we want an empty table for the next demonstration, you can open a New table, open a Fresh Table, or Clear the present table.

To open a new table using the File menu New option:

Choose the **File** menu **New** option or click on the **New** icon  . The Study Goal and Design box will appear.

Select your analysis and click **OK**. The new table will appear.

To open a new table using the Fresh Table option:

Choose the **File** menu **Fresh Table** option or click on  , the Fresh Table icon to get a new table for the same type of analysis as the current table. The new table window will appear; the table will contain no entries.

To clear the existing table:

Click on the **Edit** menu **Clear** option. A box will appear, prompting you to confirm that you want to clear the table.

Click on the **No** button if you want to refrain from clearing the table before you save it.

Click on the **Yes** button, and nQuery Advisor will clear your table.

The sample sizes necessary to detect differences in mean hematocrit change of 2.0, 2.2, 2.4 with a standard deviation of 2.0 were 23, 19, 16, respectively. Based on these values, the investigator decided to enroll 20 subjects per group. The investigator now wants to confirm that 20 subjects per group will give adequate power for these expected differences even for standard deviations larger or smaller than 2.0. The Edit options, Fill Right and Specify Multi-Factor Table, provide shortcuts for obtaining power or sample size for multiple sets of values.

Fill Right will quickly enter your chosen values in specified rows when you want to enter identical values in every column of any given row. The Specify Multi-Factor Table option accepts one-time entry of row values to be combined, then creates one column in your table for every combination of row values. These two options can substantially reduce the typing necessary to evaluate many sets of parameters or effect size values.

To use the Fill Right option:

Enter **.05** in the cell in the first row of the first column.

Enter **2** in the second row of the first column.

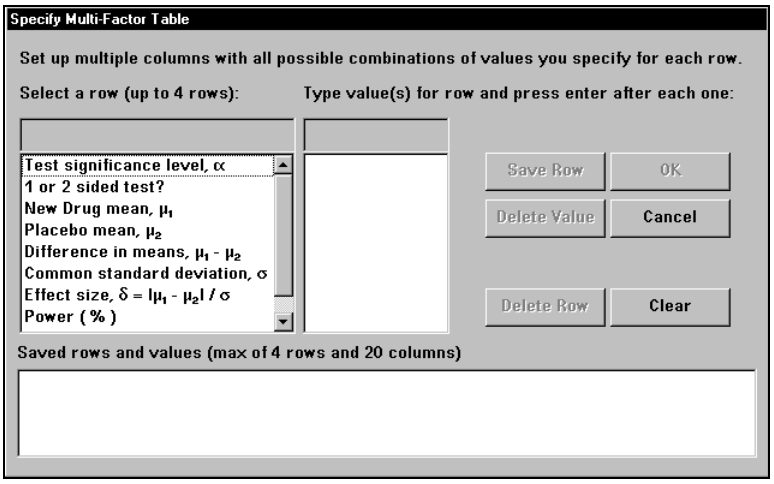
Enter **20** in the bottom row of the first column, n per group.

Select the first column.

Choose the **Edit** menu **Fill Right** option, and nQuery Advisor will enter the value from each of the three rows into every column of the table.

To use the Specify Multi-factor Table option:

Choose the **Edit** menu **Specify Multi-factor Table** option. The Specify Multi-factor Table dialog box will appear.



This option allows you to specify several values for one or more rows. The program will enter the values into your table in all possible combinations.

Click on **New drug mean**, and the cursor will blink in the value entry field in the second column.

Enter **2** and press <Enter>. The program will write the 2 to the column below the entry box.

Enter **2.2** and press <Enter>.

Enter **2.4** and press <Enter>.

Now that you have entered all three values, click on the **Save Row** button, and the three entries will be recorded in the bottom of the dialog box.

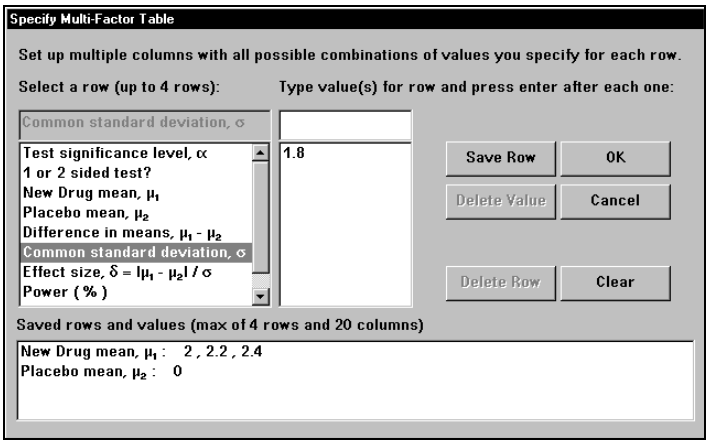
Click on **Placebo mean**.

Type **0** and press <Enter>.

Click on **Save Row**.

Click on **Common standard deviation**.

Type **1.8** and press <Enter>. The dialog box will be similar to the following figure. The bottom section displays the values entered for New Drug mean and Placebo mean.



Type **2.2** and press <Enter>.

Click on the **Save Row** button.

Click on **OK** to finish the entries and send them to the table. Your sample size table will appear with the columns filled as you have specified. Note that the nQuery Advisor Specify Multi-Factor Table option fills only as many columns as necessary to form all combinations.

Note: Values for the last row specified will change in the fastest moving fashion while values for the first row specified will change in the slowest moving fashion as they fill in the columns. See the screen below.

Two group t-test of equal means (equal n's)

	1	2	3	4	5
Test significance level, α	0.050	0.050	0.050	0.050	0.050
1 or 2 sided test?	2	2	2	2	2
New Drug mean, μ_1	2.000	2.000	2.200	2.200	2.400
Placebo mean, μ_2	0.000	0.000	0.000	0.000	0.000
Difference in means, $\mu_1 - \mu_2$	2.000	2.000	2.200	2.200	2.400
Common standard deviation, σ	1.800	2.200	1.800	2.200	1.800
Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert / \sigma$	1.111	0.909	1.222	1.000	1.333
Power (%)	92	79	96	86	98
n per group	20	20	20	20	20

Now that your table is almost completely filled in, you can see how the power varies with the changes in the mean difference and standard deviation.

Use the scroll bar to display columns lying to the right. Note that columns 7-20 contain the significance level, test sidedness, and n per group. That's because we used the Fill Right option for ease of filling the table. Since the Specify Multi-Factor Table option only filled columns 1-6, we should clean up the table.

To clean up the table:

Use the mouse to select columns 7-20.

Choose the **Edit** menu **Cut** option. The entries in columns 7-20 will be cut, and your table will contain only the columns necessary for the full multi-factor combinations.

Step 6. Choose Sample Size, Write Statement

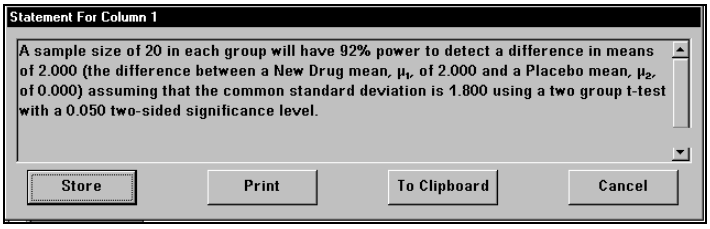
The nQuery Advisor program writes up the sample size decision for any chosen column. This feature makes it easy for you to report your sample size decisions in correct language.

To create a sample size justification statement:

Select any single completed column in your sample size table. For this example, select the first column.

Click on 

, the **Create statement** button, or the **Edit** menu **Create Statement** option. The statement will appear in the Statement dialog box.

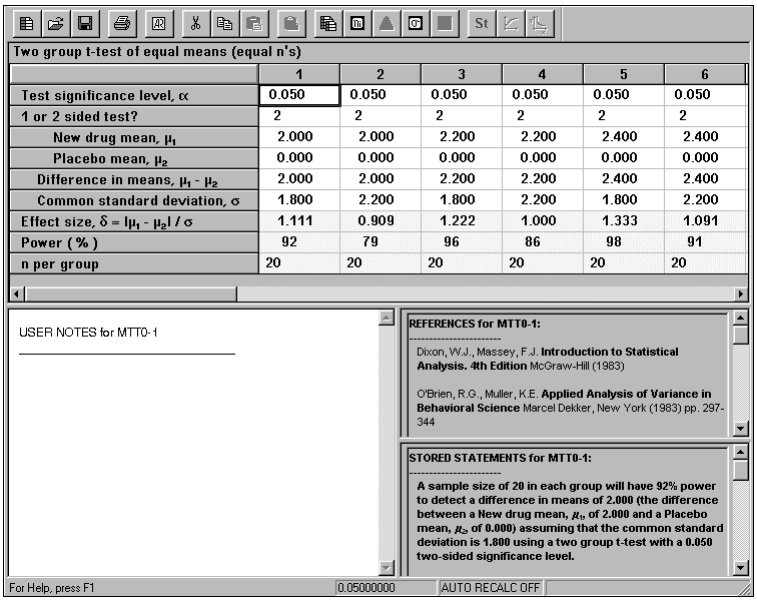


Buttons in the Statement Dialog Box

Store

To store the statement with the sample size table:

Click on the **Store** button to send the statement to the Statement pane of the sample size table.



Now when you save the sample size table, you will save the statement with the table.

After you have stored the statement with the sample size table, you can choose to print the statement or not, whenever you print the table.

Note: A stored statement is permanently associated with the sample size table and cannot be erased from the Stored Statements pane. For more information, see the Create Statements section of Chapter 4 in the nQuery 5 manual, *The Edit Menu*.

Print

To print the statement from the Statement dialog box:

Click on the **Print** button to bring up the **Print** dialog box.

Click **OK** to print the statement.

To print the stored statement and the table:

Choose the **File** menu **Print** option, and you will see the following dialog box. Note that the nQuery Advisor statements, notes, and side tables options will be grayed out when you have no statements, notes, or side tables for the current table.

Click in the appropriate check box to select **nQuery Advisor table** and **nQuery Advisor statements** for printing.

Click on **OK** to bring up the **Print** dialog box.

Click OK **to print the statement and table.**

To Clipboard

To use the statement in the statement dialog box with another Windows application:

Click on the **To Clipboard** button to send the statement to the clipboard for pasting into another Windows application.

To use the statement stored in the Statement pane in another Windows application:

Click on the right mouse button in the **Statement** pane to bring up the right-click menu.

Click on the **Copy** option to send the statement to the clipboard. The Font selection for pasting dialog box will appear. This box contains instructions on how to switch fonts. If this dialog box does not appear because it has been turned off, go to the **Options** menu, **Preferences** option, and select **Font for external pasting** or **Display font choice reminder upon copy**. For details on these options, see Chapter 4 in the nQuery 5 manual, *The Edit Menu*.

Click on the **OK, Complete Copy** button to save the fully formatted statement to the Clipboard.

Move to Microsoft Word or another word processing program, then paste the statement into the Windows word processing document. (Note that you can also paste to your sample size table from Windows applications. For details, see Chapter 4 in the nQuery 5 manual, *The Edit Menu*.)

The following text shows the statement pasted into this manual after a choice of the Arial font:

A sample size of 20 in each group will have 92% power to detect a difference in means of 2.000 (the difference between a Group 1 mean, μ_1, of 2.000 and a Group 2 mean, μ_2, of 0.000) assuming that the common standard deviation is 1.800 using a two group t-test with a 0.050 two-sided significance level.

Cancel

To exit from the statement dialog box:

Click on **Cancel** to discard the statement.

Step 7. Use Table, Statement, References, Plots in Study Protocol, and Save Table

You can insert the nQuery Advisor tables, statements, references and plots directly into your study protocol. You can print them directly (as described under Step 6), and you can save them to a file for later access and editing with nQuery Advisor.

To save the table:

Click on the File menu **Save** or **Save as** option or use the Save icon, or the right click menu to save (and name) the table.

The statements and notes are saved with the table.

Note that you must save any plots separately if you want them ready for immediate access. However, if you have the table, you can always reproduce the plots later.

To paste the table into your study protocol:

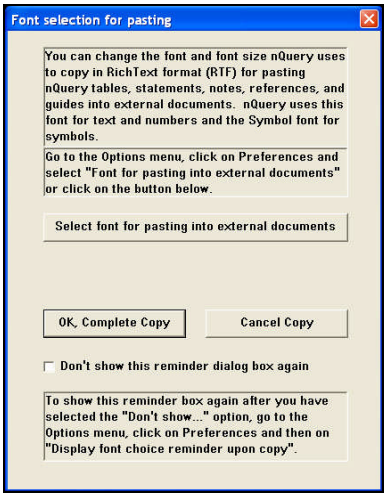
If you want to rename the treatment mean row before pasting, use the **Edit** menu **Edit Row Names** option described earlier in this chapter. If you want to provide column names, see Example 3 in Chapter 4 of the nQuery 7.0 manual.

If you need to display extra digits for a row or rows in the table, right click in the row to be updated, and select the **Edit** menu **Format Decimal Displays for Selected Rows** option. For more details, see Chapter 5 in this nQuery 7.0 manual.

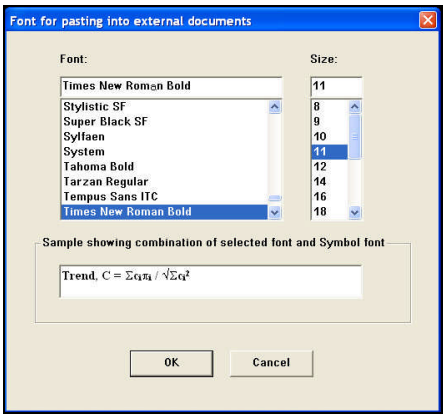
Choose the **File** menu (or right click menu) **Print table to clipboard** option.

The first time you do this, the **Font selection for pasting** dialog box will appear.

Note: At any time, you can change the chosen font by selecting **Options** menu **Preferences** option, and then the **Font for the external pasting** option.



Click on the **Select font for pasting into external documents** button and the **Font for pasting into external documents** dialog box will appear.



Choose the desired font and size. View a sample of that font with the symbol font or Greek letters in the Sample field. When satisfied with the choice of font, click on the **OK** button.

Open the word processing document and paste the table into the document.

We show the pasted table below. Note that symbols automatically appear in the symbol font. For this example we deleted columns 5-6 and chose Arial 8.

Two group t-test of equal means (equal n's)

	1	2	3	4
Test significance level, α	0.050	0.050	0.050	0.050
1 or 2 sided test?	2	2	2	2
New drug mean, μ_1	2.000	2.000	2.200	2.200
Placebo mean, μ_2	0.000	0.000	0.000	0.000
Difference in means, $\mu_1 - \mu_2$	2.000	2.000	2.200	2.200
Common standard deviation, σ	1.800	2.200	1.800	2.200
Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert / \sigma$	1.111	0.909	1.222	1.000
Power (%)	92	79	96	86
n per group	20	20	20	20

You can paste references, sections from guide cards, notes, and statements into your document in the same way.

Summary

This tutorial has introduced you to several of the nQuery Advisor features by using one complete example. You should now have a good overview of the nQuery Advisor program and its mode of operation. However, please keep in mind that nQuery Advisor offers many features not discussed in detail or even mentioned in

this chapter. See the other chapters of the nQuery 5 and 7.0 manuals for details and examples of the other available options.

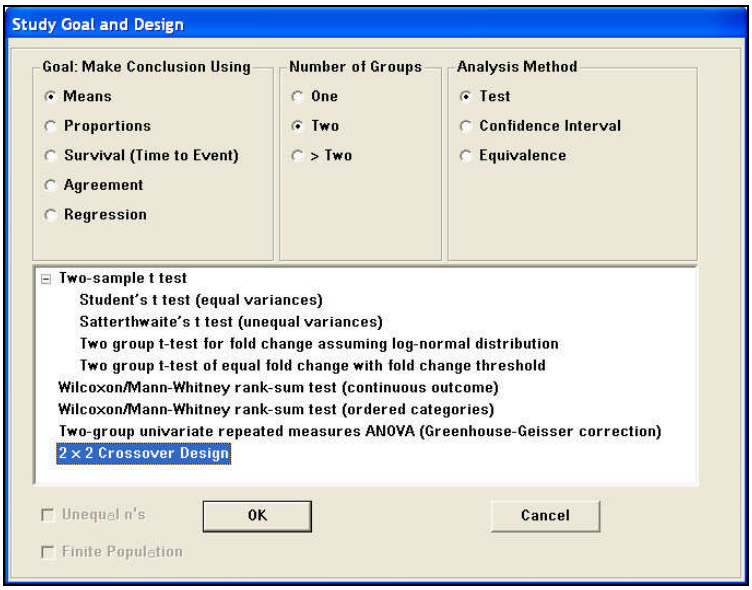
Chapter 6 of the nQuery 7.0 manual demonstrates how to produce a randomization list for your study using the randomization features new in Version 6 and the additional options for complex designs introduced in nQuery 7.0.

3. Overview of nQuery Tables and Examples

nQuery Advisor assists you in choosing an appropriate sample size for your research studies. nQuery Advisor also helps you to provide the standard deviation and effect size information which you need to make sample size and power computations.

Contents of Study Goal and Design Dialog Box

The Study Goal and Design dialog box allows you to choose the sample size table you want to use.



The nQuery Advisor program provides a sample size table for more than 80 different types of study plans. Codes will help you to find the analyses quickly.

The first letter of the code represents a goal from the first column:

Means, **P**roportions, **S**urvival, **A**greement, or **R**egression.

The second letter of the code represents the Number of Groups from the second column:

One, **T**wo, or **G**reater than two.

The third letter of the code represents the analysis method from the third column:

Test, **C**onfidence Interval, or **E**quivalence.

The fourth character in the code is the sequence number of the listed analyses, starting with 0.

For example, in the screen above, the code for Two-sample t test is MTT0. Most combinations of choices offer one or more analysis types for your selection, but a few do not.

Note that the Two-sample t test listing has a + sign beside it. In this case the sub-listings have already been expanded, but for other such menu items, you can click on the + to see the sub-listings.

Unequal n's

If your chosen nQuery table has an unequal sample sizes option, the Unequal n's checkbox in the lower left of the Study Goal and Design dialog box will be enabled. If you want unequal n's, click on the Unequal n's checkbox and click **OK**.

Finite Population

If your chosen analysis type has a Finite Population option, the Finite Population checkbox in the lower left of the dialog box will be enabled. If your design involves sampling from a Finite Population, click on the Finite Population checkbox and click **OK**.

The following tables have versions allowing for a finite population correction: MOT0, MOT1, MOC0, MOC1, MOC2, MOC3, POT0, POC0.

Sample Size Tables for Means in nQuery Advisor

This section of the Overview chapter briefly outlines all sample size tables available for analysis of means and refers you to examples in the nQuery 5 and 6 manuals.

The nQuery Advisor program provides a variety of sample size tables for determining sample size in problems where the group mean is the summary measure for analysis.

To select the appropriate sample size table, you first identify:

- the study design
- one, two, or multiple groups
- the intended analysis method, test, confidence interval, or equivalence test.

1. The most commonly used design for comparison of means is the two-group (independent sample) design. The most common analysis method for such designs is the two-group (two-sample) t test. The nQuery Advisor table choice would be:

MTT0 **Two-group t test of equal means**
See Chapter 2, *Tutorial*, nQuery 7.0 manual for a detailed tutorial on this table.

2. Another common design is one in which each subject is tested under two conditions. The usual analysis is the paired t test for situations in which each subject is tested under two conditions or provides a pre and post measurement.

MOT1 **Paired t test of mean difference equal to zero**
See Example 1 in Chapter 8 of the nQuery 5 manual.

Sample size tables for most designs with two or more groups allow sample size computations for designs utilizing unequal sample sizes in the groups. For an example, see Chapter 10 of the nQuery 5 manual.

For every sample size table used for analysis of means, the nQuery Advisor program requires an estimate of the within-group standard deviation. If you need help in determining an estimate of the standard deviation, refer to Chapter 9 of the nQuery 5 manual which details the options available under the **Assistants** menu to assist in estimating a value for the standard deviation.

One-group Tests and Confidence Intervals

MOT0 **One group t test that a mean equals a user-specified value**

MOC0 **Confidence interval for mean based on z (n large)**

MOC1 **Confidence interval for mean based on t (with coverage probability)**
This table makes allowance for uncertainty in estimation of the standard deviation. See Example 2 in Chapter 8 of the nQuery 5 manual for an example involving a confidence interval for the difference in means.

MOC5 **Confidence interval for percentile of a normal distribution**
See Example 3 in Chapter 8 of the nQuery 5 manual.

Versions of tables MOT0, MOC0, MOC1, are available for sampling from finite populations. See Chapter 19, *Sampling from Finite Populations*, nQuery 5 manual for details.

Two-group Tests and Confidence Intervals

MTT0 **Two group t test of equal means**

This table is for the ordinary pooled variance independent groups Student's t-test. See the example in Chapter 2, *Tutorial*, nQuery 7.0 manual.

.

MTT0uv **Two group Satterthwaite t-test of equal means (unequal variances)**

This table is for situations where a comparison between two means using the t-test would be applicable, but the variances for the two groups are expected to be unequal. See Example 4 in Chapter 8 of the nQuery 5 manual.

MTT0cv **Two group t-test for fold change assuming log-normal distribution**

This table is for situations where a comparison between two means using the t-test would be applicable, but the distribution of the data is expected to be log-normal and the user wants to specify the expected fold-change and the CV rather than the means and standard deviations after log transformation. This table is of special interest for planning and interpreting *DNA microarray* studies. See Example 5 in Chapter 8 of the nQuery 5 manual.

MTT0fct **Two group t-test of equal fold change with fold change threshold**

This table computes the probability of detection of specified fold-changes when the CV is specified and the result must exceed a specified *fold-change threshold*. This table is of special interest for planning and interpreting *DNA microarray* studies, see Example 6 in Chapter 8 nQuery 5 manual.

MTT1 **Wilcoxon (Mann-Whitney) rank-sum test that P(X<Y)=0.5 (continuous outcome)**

See Example 1 in Chapter 14, *Nonparametric Tests*, nQuery 5 manual.

MTT2 **Wilcoxon (Mann-Whitney) rank-sum test that P(X<Y)=0.5 (ordered categories)**

See Example 2 in Chapter 14, *Nonparametric Tests*, nQuery 5 manual.

MTC0 **Confidence interval for difference of two means based on z**

MTC1 **Confidence interval for difference of two means (coverage probability)**

This table makes allowance for uncertainty in estimation of the standard deviation. See Example 2 in Chapter 8 nQuery 5 manual.

One and two group paired, crossover, & repeated measures designs, tests and confidence intervals

MOT1 **Paired t test of mean difference equal to zero**

See Example 1 in Chapter 8 of the nQuery 5 manual

MOT2 **Univariate one-way repeated measures analysis of variance (constant correlation)**

See Examples 2 and 5 in Chapter 13 of the nQuery 5 manual

MOT3 **One-way repeated measures contrast (constant correlation)**

See Examples 2, 3 and 6 in Chapter 13 of the nQuery 5 manual

MOT4 **Univariate one-way repeated measures analysis of variance (Greenhouse-Geisser approximation)**

MOC2 **Confidence interval for difference in paired means based on z (n large)**

MOC3 **Confidence interval for difference in paired means based on t (coverage probability)**

This table makes allowance for uncertainty in estimation of the standard deviation.

MOC4 **Confidence interval for one-way repeated measures contrast (constant correlation)**

MTT3 **Two-group univariate repeated measures analysis of variance (Greenhouse-Geisser correction)**

See Example 7 in Chapter 13, nQuery 5 manual.

MTT4 **t-test (ANOVA) for difference in means in a 2 x 2 crossover design**

See Example 1 in Chapter 4 of this nQuery 7.0 manual.

Versions of tables MOT1, MOC2, MOC3, are available for sampling from finite populations. See Chapter 19, *Sampling from Finite Populations*, nQuery 5 manual, for details.

One and two group and crossover designs, equivalence and bio-equivalence tests

MOE0 **Paired t test of equivalence of means**

MTE0 **Two-group t test of equivalence in means**
See Example 1 in Chapter 11, *Demonstrating Equivalence,* nQuery 5 manual.

MTE1tg **Two-group t tests (TOST) of equivalence in means for two-group design**
See Examples 2 and 4 in Chapter 11, *Demonstrating Equivalence,* nQuery 5 manual.

MTE1co **t tests (TOST) of equivalence in means for crossover design**
See Example 3 in Chapter 11, *Demonstrating Equivalence,* nQuery 5 manual**.**

MTE2tg **Two-group t-tests (TOST) for ratio of means (using log scale)**
See Example 5 in Chapter 11, *Demonstrating Equivalence,* nQuery 5 manual.

MTE2co **t-tests (TOST) for ratio of means for crossover design (natural log scale)**
See Example 6 in Chapter 11, *Demonstrating Equivalence,* nQuery 5 manual.

MTE3 **Two-group t-tests (TOST) for ratio of means (using original scale)**
See Example7 in Chapter 11, *Demonstrating Equivalence,* nQuery 5 manual.

MTE4 **Crossover design TOST for ratio of means (using original scale)**
See Example 8 in Chapter 11, *Demonstrating Equivalence,* nQuery 5 manual.

Multiple group tests and confidence intervals

MGT0 **One-way analysis of variance**
See Example 1 in Chapter 12, *Analysis of Variance Tutorial,* nQuery 5 manual.

MGT1 **Single One-way between means contrast**
See Example 3 in Chapter 12, *Analysis of Variance Tutorial,* nQuery 5 manual.

MGT2 **Two-way analysis of variance**

MGC0 **Confidence interval contrast between means (large n's)**

MGC1 **Confidence interval for one-way contrast (with coverage probability)**
This table makes allowance for uncertainty in estimation of the standard deviation.

Sample Size Tables for Demonstrating Non-inferiority or Equivalence in nQuery Advisor

Chapter 11 in the nQuery 5 manual provides an introduction to sample size issues in equivalence testing, and give examples for sample size tables for equivalence testing for means . Non-inferiority and two one-sided equivalence tests are distinguished. At the end of the chapter we review the interrelationships between tests, confidence intervals, and equivalence demonstrations. Examples for equivalence tests for differences in proportions are given in Chapter 15 *Sample Size Tables for Proportions* in the nQuery 5 manual; see examples 9, 10, 11 in that chapter. An example for non-inferiority testing for survival analyses is given as Example 3 in Chapter 4 in this nQuery 7.0 manual.

nQuery Advisor provides sample size tables for the following non-inferiority or equivalence testing situations.

One-sided (non-inferiority) tests for difference of means

MTE0 **Two-group t test of equivalence in means**
See Example 1 in Chapter 11 in the nQuery 5 manual.

MOE0 **Paired t test of equivalence of means**

Two one-sided tests (TOST) for difference or ratio of means in two-group designs

MTE1tg **Two-group t tests (TOST) of equivalence in means**
See Examples 2 and 4 in Chapter 11 in the nQuery 5 manual.

MTE2tg **Two-group t tests (TOST) for ratio of means (using log scale)**
See Example 5 in Chapter 11 in the nQuery 5 manual.

MTE3 **Two-group t tests (TOST) for ratio of means (using original scale)**
See Example 7 in Chapter 11 in the nQuery 5 manual.

Two one-sided tests (TOST) for difference or ratio of means in crossover designs

MTE1co **t tests (TOST) of equivalence in means for crossover design**
See Example 3 in Chapter 11 in the nQuery 5 manual.

MTE2co **t-tests (TOST) of equivalence in ratio of means for crossover design (natural log scale)**
See Example 6 in Chapter 11 in the nQuery 5 manual.

MTE4 **Crossover design TOST for ratio of means (using original scale)**
See Example 8 in Chapter 11 in the nQuery 5 manual.

One-sided non-inferiority tests for difference of proportions

PTE0 **Two-group test of equivalence in proportions (large n)**
See Examples 10 and 11 in Chapter 15 in the nQuery 5 manual.

PTE1 **Two group test of equivalence in proportions using confidence interval:**

a) Lower confidence limit for difference in proportions (simulation)
See Example 10 in Chapter 15 in the nQuery 5 manual.

b) Upper confidence limit for difference in proportions (simulation)

POE0 **Paired test of equivalence of proportions (n large)**
See Example 9 in Chapter 15 in the nQuery 5 manual.

POE1 **Paired test of equivalence in proportions using confidence interval:**

a) Lower confidence limit for difference in paired proportions (simulation)
See Example 9 in Chapter 15 in the nQuery 5 manual.

b) Upper confidence limit for difference in paired proportions (simulation)

c) Two-sided confidence limits for difference in paired proportions (simulation)

Two sided equivalence for difference of proportions in paired or two-group design

PTE1 **Two group test of equivalence in proportions using confidence interval:**
c) Two-sided confidence limits for difference in proportions (simulation)
See Example 11 in Chapter 15 in the nQuery 5 manual.

POE1 **Paired test of equivalence in proportions using confidence interval:**
c) Two-sided confidence limits for difference in paired proportions (simulation)

One-sided non-inferiority test for survival hazard ratio

STE0 **Non-inferiority test for two exponential survival curves**
See Example 3 in Chapter 4 in this nQuery 7.0 manual.

One-sided non-inferiority test for slope of regression predictor

No nQuery sample size tables have yet been developed specifically for such an analysis. However, for a non-inferiority test for the slope of a single predictor, you can use the table RTT0. For a one-sided non-inferiority test, the answers for sample size are the same whether you specify alpha in the significance level row and 1-beta in the power row or beta in the significance row and 1-alpha in the power row. The answers are also the same when you are testing the null hypothesis that $\delta = 0$ versus the alternative that $\delta = \delta_1$ or whether, as in the non-inferiority situation, you are testing the null hypothesis that $\delta = \delta_1$ versus the alternative that $\delta = 0$. For a test of equivalence for regression slopes for a single predictor from two independent samples using the TOST approach, you could use MTE1tg. You would compute the value of σ for MTE1tg as SDresiduals/SDx (see rows in RTC0 and formula in guide card for the ω row). You also must make allowance for the fact that the error degrees of freedom used in MTE1tg is 2(n-1), while that used in regression problems is 2(n-2). So the resulting sample size from MTE1tg should be increased a bit to allow for this.

Sample Size Tables for Repeated Measures and Crossover Designs in nQuery Advisor

In Chapter 13 in the nQuery 5 manual, we discuss computing sample size and power for designs involving one or more groups of subjects in which the same continuous outcome variable is measured more than once. This is often called a repeated measures study. The simplest example of this type of study is a design with two measurements per subject where the two measurements occur sequentially in time as in a pre-post design, in which subjects are measured before and after an intervention. Other examples of repeated measures designs are:

- measurements are made at multiple sites in the same individual, such as measurements of visual acuity in both right and left eyes,
- a case-control study with individually pair-matched cases and controls,
- acid output is evaluated after a low dose of an acid suppressing drug and then after a high dose,
- subjects have been paired on background variables and then randomized so that one receives intervention A and one receives intervention B, or subjects have been surgically paired, such as in studies of pair-fed rats,
- measurements can be geographically contiguous as in split-plot designs,
- crossover studies in which each subject receives all interventions, but different groups of subjects receive the interventions in different orders.

nQuery Advisor has a number of sample size tables applicable for planning sample size for repeated measures designs.

The following categorization of repeated measures tables reflects their most common usage. However, it should be noted that tables for two or more repeated measures can also be used for power calculations for crossover designs, and some problems might properly be approached with any one of several different sample size tables. When based on the same underlying model, all of these approaches will give the same required sample size. The correspondences between approaches are illustrated in the examples in Chapter 13, *Repeated Measures and Crossover Designs* in the nQuery 5 manual and in Chapter 11, *Demonstrating Equivalence*, in the nQuery 5 manual.

Paired Designs, Tests, Confidence Intervals, and Equivalence Tests

MOT1 **Paired t test of mean difference equal to zero**

See Example 4 in Chapter 13 in the nQuery 5 manual and Example 1 in Chapter 8, *Sample Size Tables for Means*, in the nQuery 5 manual.

MOC2 **Confidence interval for interval in paired means based on z (n large)**

MOC3 **Confidence interval for difference in paired means based on t (coverage probability)**

MOE0 **Paired t test of equivalence of means**

POT1 **McNemar's test (χ^2) of equality of paired proportions**

See Example 2 in Chapter 15 in the nQuery 5 manual

POT1x **Exact sign test of equality of paired proportions**

See Example 2 in Chapter 15 in the nQuery 5 manual

POC1 **Confidence interval for ln(Ψ_M), odds ratio for paired proportions (n large)**

POE0 **Paired test of equivalence in proportions (n large)**

See Example 9 in Chapter 15 in the nQuery 5 manual

POE1abc **Paired test of equivalence in proportions using confidence interval: a) Lower confidence limit for difference in paired proportions (simulation), b) Upper confidence limit for difference in paired proportions (simulation), c) Two-sided confidence limits for difference in paired proportions (simulation)**

See Example 9 in Chapter 15 in the nQuery 5 manual

2x2 Crossover Designs, Tests and Equivalence Tests

MTT0 **Two group t test of equal means**
See Example 1 in Chapter 13 in the nQuery 5 manual. See also examples in Chapter 2, *Tutorial,* in this nQuery 7.0 manual, and Chapter 18, *Regression Tables,* in the nQuery 5 manual.

MTT4 **t-test (ANOVA) for difference in means in 2 x 2 crossover design**
See Example 1 in Chapter 4 in this nQuery 7.0 manual.

MTE0 **Two-group t test of equivalence in means**
See Example 1 in Chapter 11, *Demonstrating Equivalence,* in the nQuery 5 manual.

MTE1co **Two-group or crossover t test (TOST) of equivalence in means**
See Example 3 in Chapter 11, *Demonstrating Equivalence,* in the nQuery 5 manual.

MTE2co **Two-group or crossover t tests (TOST) for ratio of means (using log scale)**
See Example 6 in Chapter 11, *Demonstrating Equivalence,* in the nQuery 5 manual.

MTE4 **Crossover design TOST for ratio of means (using original scale)**
See Example 8 in Chapter 11, *Demonstrating Equivalence,* in the nQuery 5 manual.

Designs with Two or More Repeated Measures

MOT2 **Univariate one-way repeated measures analysis of variance (constant correlation)**
See Examples 2 and 5 in Chapter 13 in the nQuery 5 manual.

MOT3 **One-way repeated measures contrast (constant correlation)**
See Examples 2, 3 and 6 in Chapter 13 in the nQuery 5 manual.

MOT4 **Univariate one-way repeated measures analysis of variance (Greenhouse-Geisser correction)**

MOC4 **Confidence interval for one-way repeated measures contrast (constant correlation)**

MTT3 **Two-group univariate repeated measures ANOVA (Greenhouse-Geisser correction)**
See Example 7 in Chapter 13 in the nQuery 5 manual

Sample Size Tables for Nonparametric Tests in nQuery Advisor

A nonparametric approach to analysis of a two-group design uses the Wilcoxon/Mann-Whitney rank-sum test. The rank-sum test is a test of the null hypothesis that $P(X<Y) = 0.5$, where X is an observation from Group 1 and Y an observation from Group 2. It is equivalent to a test of equality of means when the two distributions have the same shape and equal variances. When the two distributions are normally distributed with equal variances, the rank-sum test will require about 5% more observations than the two-sample t-test to provide the same power against the same alternative.

For nonnormal populations, especially those with long tails, the rank-sum test may not require as many observations as the two-sample t-test. For example, the rank-sum test requires only about 80% of the sample size required by the t-test when the data are distributed like a t with 5 degrees of freedom.

Two nQuery Advisor tables are available for nonparametric tests, depending on whether the outcome variable is continuous or ordered categorical.

MTT1 **Wilcoxon/Mann-Whitney rank-sum test (continuous outcome)**
See Example 1 Chapter 14 in the nQuery 5 manual.

MTT2 **Wilcoxon/Mann-Whitney rank-sum test (ordered categories)**
See Example 2 in Chapter 14 in the nQuery 5 manual.

Sample Size Tables for Proportions in nQuery Advisor

Sample size tables for proportions assist you in determining the necessary sample size for studies in which:

- the outcome variable measure is dichotomous (success/failure, alive/dead, yes/no)
- you want to estimate or make tests on the proportion of "successes."

A number of sample size tables for proportions provide power using exact computations or simulation. However, formulas used by nQuery Advisor for sample sizes for many of the proportions tables use a normal approximation and are thus designed for large samples. For these, nQuery Advisor checks that the minimum expected cell size for the 2x2 or Gx2 table is greater than a preprogrammed default value. You will see a warning box if the minimum cell size falls below this value.

If you see the warning box, you must check that the sample size computed by nQuery Advisor will be adequate; see Example 4 for the two-group χ^2 test in Chapter 15 in the nQuery 5 manual. In some cases, the default value used by nQuery may be too conservative and lead to an unnecessarily large sample size. You may want to use the Change Minimum Expected Cell Count option from the Options menu to reduce the required minimum cell count for your nQuery Advisor session.

The nQuery Advisor program provides the following tables appropriate to studies in which the outcomes are proportions. Some of these tables have a version appropriate for sampling from finite populations. Those tables are denoted by an F at the end of the table code; see Chapter 19, *Sampling from Finite Populations*, for further details.

Note that for exact tests, the actual probability of rejecting the null hypothesis when it is true is less than or equal to alpha, and in some cases may be markedly less than the specified nominal level. For a two-sided test, nQuery uses the highest possible actual significance level for which the probability is less than or equal to $\alpha/2$ in both tails. Due to the fact that the attainable alpha level depends on the specified sample size, note that computed power may not increase monotonically with sample size for exact tests. See references for specific tables for details and advice.

Tests, Confidence intervals, and Equivalence Tests for single proportions or for differences in paired proportions in a single sample:

POT0 **One group χ^2 test that proportion equals user specified value (normal approximation)**

POT0x **Exact test for single proportion**

POT1 **McNemar's Test (χ^2) of equality of paired proportions**
See Example 2 in Chapter 15 in the nQuery 5 manual.

POT1x **Exact sign test of equality of paired proportions**
See Example 2 in Chapter 15 in the nQuery 5 manual.

POT2 **Chi-square test of specified proportions in C categories**

POC0 **Confidence interval for proportion using normal approximation (n large)**
See Example 1 in Chapter 15 in the nQuery 5 manual. and example in Chapter 19 in the nQuery 5 manual.

POC1 **Confidence interval for $\ln(\Psi_M)$, odds ratio for paired proportions (n large)**

POC2 **Confidence interval for probability of observing a rare event**

POE0 **Paired test of equivalence in proportions (n large)**
See Example 9 in Chapter 15 in the nQuery 5 manual.

POE1 **Paired test of equivalence in proportions using confidence interval: a) Lower confidence limit for difference in paired proportions (simulation), b) Upper confidence limit for difference in paired proportions (simulation), c) Two-sided confidence limits for difference in paired proportions (simulation)**
See Example 9 in Chapter 15 in the nQuery 5 manual.

See Chapter 19 *Sampling from Finite Populations* in the nQuery 5 manual for details for versions POT0F and POC0F.

Tests, Confidence Intervals, and Equivalence tests for comparisons of proportions in two independent groups:

PTT0 **Two group χ^2 test of equal proportions (odds ratio = 1) (Compute power or sample size)**
See Examples 3 and 4 in Chapter 15 in the nQuery 5 manual.

PTT0p **Two group χ^2 test of equal proportions (Compute one of two proportions)**
See Example 3 in Chapter 15 in the nQuery 5 manual.

PTT1 **Two group continuity corrected χ^2 test of equal proportions (odds ratio = 1) (Compute power or sample size)**
See Example 4 in Chapter 15 in the nQuery 5 manual.

PTT1p **Two group continuity corrected χ^2 test of equal proportions (Compute one of two proportions)**

PTT2 **Two-group Fisher's exact test of equal proportions (odds ratio=1)**
See Example 4 in Chapter 15 in the nQuery 5 manual.

Sample size and power for PTT0 are derived using the large sample normal approximation. Those obtained from PTT1 use a correction factor designed to approximate results for Fisher's Exact Test, and sample sizes will be larger and power lower than obtained using PTT0. Answers given by PTT2 are obtained using exact methods and will typically lie between those for PTT0 and PTT1.

PTT3 **Two-group Chi-square test comparing proportions in C categories**
See Example 6 in Chapter 15 in the nQuery 5 manual.

PTT4 **Mantel-Haenszel (Cochran) test of OR=1 for 2x2 tables in S strata**
See Example 7 in Chapter 15 in the nQuery 5 manual.

PTT4cc **Mantel-Haenszel (Cochran) test of OR=1 for 2x2 tables in S strata (Continuity Corrected)**

PTC0 **Confidence interval for difference of two proportions**

PTC1 **Confidence interval for difference of two proportions (continuity corrected)**

PTC2 **Confidence interval for ln(odds ratio)**
See Example 5 in Chapter 15 in the nQuery 5 manual.

PTC3 **Confidence interval for relative risk (ratio of two proportions)**
See Example 2 in Chapter 4 in this nQuery 7.0 manual.

PTE0 **Two group test of equivalence in proportions (large n)**
See Examples 10 and 11 in Chapter 15 in the nQuery 5 manual.

PTE1 **Two group test of equivalence in proportions using confidence interval: a) Lower confidence limit for difference in proportions (simulation), b) Upper confidence limit for difference in proportions (simulation), c) Two-sided confidence limits for difference in proportions (simulation)**
See Examples 10 and 11 in Chapter 15 in the nQuery 5 manual.

MTT2 **Wilcoxon (Mann-Whitney) rank-sum test that P(X<Y) = 0.5 (ordered categories)**
See Example 2 in Chapter 14, *Nonparametric Methods* in the nQuery 5 manual.

Tests for more than two groups

PGT0 **χ^2 test of equal proportions in G groups**

PGT1 **Trend across proportions, logistic model**
See Example 8 in Chapter 15 in the nQuery 5 manual.

PGT2 **G group Chi-square test comparing proportions in C categories**

Sample Size Tables for Survival Analysis in nQuery Advisor

Survival analysis methods are designed for studies in which patients are entered into a trial and followed until a specified event occurs, they are lost to followup, or the study ends. For example, researchers might follow patients until death, hospital discharge, cancer recurrence, or heart attack.

The essential difference between survival analysis methods and the methods appropriate for comparing means or proportions has to do with the outcome measure. For some patients in a survival study, the outcome measure, time to the event of interest, is known only to be larger than some followup interval.

For example, in a five year study, one patient who entered the trial 18 months before its termination is known not to have had a heart attack during the 18 months before the study ended. Another patient was followed only 3 months before he left the state and could not be contacted further. In the first case, time to heart attack is known to be longer than 18 months. In the second case, time to heart attack is known to be longer than 3 months. This type of data is called right censored.

If all patients are followed for the same fixed time period, say 3 years, we could simply analyze the proportion of patients surviving (not having the event of interest) during that time. We could use sample size methods based on comparison of proportions. However, even when the data are not censored at different time points, we may lose information by ignoring the time to the event. For example, survival under two treatment regimens might look much the same by three years when most of the patients have suffered a recurrence, but might differ considerably during the first year.

If the researchers followed all patients until the event of interest occurred, recording time to the event, we could analyze these continuous measurements of time to event by comparing groups on mean time to event. Thus, we could determine sample sizes by using methods for comparisons of means, although time to event data typically have distributions which are skewed to the right. For example, length of hospital stay is generally only 3-5 days, but some patients are hospitalized for weeks. In addition, following all subjects until the event of interest occurs is often not feasible.

We can base sample size computations for survival studies on:

- an estimate of the surviving proportions at some fixed time
- a model for the entire survival curve.

These selections bring up the four sample size tables for survival analysis. From each of the survival sample size tables, you can access a table which helps you to convert between different parameters characterizing expected survival times. See

Example 3 in Chapter 4 of this nQuery 7.0 manual or Example 2 in Chapter 16 in the nQuery 5 manual for details on using the parameter conversion table.

Tests Comparing Two Survival Curves

STT0 **Log-rank test for equality of survival curves**
See Example 1 in Chapter 16 in the nQuery 5 manual.

STT1 **Test based on exponential survival, accrual period**

STT2 **Test based on exponential survival, accrual period, dropouts**
See Example 3 in Chapter 16 in the nQuery 5 manual.

STT3 **Log-rank test with user specified survival, hazard, accrual, dropout rates, simulation**
See Examples 4, 5, 6, and 7 in Chapter 16 in the nQuery 5 manual.

One-sided non-inferiority tests for survival hazard ratio

STE0 **Non-inferiority test for two exponential survival curves**
See Example 3 in Chapter 4 in this nQuery 7.0 manual.

Sample Size Tables for Agreement in nQuery Advisor

Measures of agreement are designed to assess how closely two different measurement methods or two different raters agree on the values for an outcome measure. Often, one method is the "gold standard," and an investigator wants to study whether a new, cheaper method of measurement agrees well enough with the gold standard to warrant its use. The nQuery Advisor program provides sample size tables for tests or confidence intervals for several methods of measuring agreement. These are all one-sample problems.

Dichotomous outcome methods using Intraclass Kappa

AOT0 **Agreement between two dichotomous ratings (intraclass kappa)**

AOC0 **Confidence interval for intraclass kappa (n large)**
See example in Chapter 17 of the nQuery 5 manual

These sample size tables are applicable when two conditions hold:

- both the proposed version of the outcome/response variable and the gold standard version have only two possible categories (yes/no, success/failure, normal/abnormal)
- the intraclass version of the measure of agreement κ is to be used.

This version of κ is an index of the degree to which we can simply substitute one measure for the other. To assist you in computing values of kappa from proportions entered into a two-way table, nQuery Advisor provides a side table accessible from the Assistants menu Compute Effect Size option or from the Compute Effect Size icon; see example later in this chapter.

Continuous outcome methods using Pearson r

AOT1 **Correlation test that $\rho = \rho_0$ for x and y bivariate normal**

AOC1 **One-sided confidence interval for ρ for x and y bivariate normal**

These sample size tables are applicable when two conditions hold:

- both the proposed version of the outcome/response variable and the gold standard version are continuous measurements
- we can assume that their distributions are bivariate normal.

When those two assumptions are true, the Pearson correlation coefficient provides an index of the degree to which a linear relationship fits the data. Note that, even if the correlation coefficient is very close to 1.0, a scale change might be necessary before substituting one measure for the other.

Continuous outcome methods using Lin's concordance coefficient

AOT2 **Large sample test that Lin's concordance coefficient = K_0**

AOC2 **One-sided large sample confidence interval for Lin's concordance coefficient**

Lin, L.I., Hedayat, A.S., Sinha, B., Yang, M. "Statistical methods in assessing agreement: models, issues, and tools" *Journal of the American Statistical Association.* 97(2002) pp. 257-270.

Continuous outcome methods using intraclass correlation

AOC3 **Confidence interval for intraclass correlation for k measurements**
See Example 4 in Chapter 4 of nQuery 7.0 manual.

Sample Size Tables for Regression in nQuery Advisor

nQuery Advisor can help determine the required sample size for research studies involving correlation or regression analyses of the relationship between x variables (predictor variables, covariates, independent variables) and a y variable or dependent variable.

Choosing a Regression Table

Your choice of sample size table depends on:

- the nature of the y variable — whether it is a yes/no (dichotomous or two-level variable) or a continuous variable, such as cholesterol level
- the number and characteristics of the x variables — whether you have one or multiple x variables, and whether they are dichotomous, ordered, or continuous.

Dichotomous y (Logistic Regression)

When the y variable, the variable you wish to predict, has only two levels, success versus failure, alive versus dead, yes versus no, a logistic regression model is often used to assess the predictive value of covariates. nQuery Advisor provides several options for computing sample size for studies where logistic regression will be used.

For a single dichotomous covariate use:

PTT0U **Two-group χ^2 test of equal proportions (odds ratio = 1) (unequal n's)**
See Example 1a in Chapter 18 in the nQuery 5 manual.

For a single dichotomous covariate adjusted for p multiple covariates already in the model use:

PTT0U **Two-group χ^2 test of equal proportions (odds ratio = 1) (unequal n's)** and apply the variance inflation factor.
See Example 1b in Chapter 18 in the nQuery 5 manual.

For a single ordered covariate, that is for studies in which the predictor variable has several ordered levels (as for three dose levels), use:

PGT1 **Trend across proportions (logistic model)**
See Example 8 in Chapter 15, *Sample Size Tables for Proportions* in the nQuery 5 manual.

For a single continuous covariate, use:

ROT0 **Logistic regression test that $\beta = 0$ for one normally distributed covariate, x**
See Example 2 in Chapter 18 in the nQuery 5 manual.

MTT0U **Two group t test of equal means (unequal n's)**
See Example 3 in Chapter 18 in the nQuery 5 manual.

For a single continuous covariate adjusted for p multiple covariates already in the model use:

ROT1 or use MTT0U and apply the variance inflation factor.

ROT1 **Logistic regression test that $\beta = 0$ for one normal covariate x, adjusting for prior covariates**
See Example 3 in Chapter 18 in the nQuery 5 manual.

or

MTT0U **Two group t test of equal means (unequal n's)**
See Example 4 in Chapter 18 in the nQuery 5 manual.

Continuous y

When the variable to be predicted is continuous, and its relationship to the continuous predictor variable is expected to be linear, use linear regression models to determine the sample size necessary to assess the predictive value of continuous covariates.

For a single continuous covariate, use

ROT2 **Linear regression test that $\rho = 0$ for one normally distributed covariate, x**

This table provides sample size or power for the t test of the null hypothesis that the Pearson correlation coefficient, ρ, equals 0. That is, the t test tests a null hypothesis that there is no linear relationship between x and y.

To obtain the sample size required for a test of the null hypothesis that ρ is some value other than 0, or for a confidence interval of specified width for ρ, see sample size tables listed under **Agreement:**

AOT1 **Correlation test that $\rho=\rho_0$ for x and y bivariate normal**

AOC1 **One-sided confidence interval for ρ for x and y bivariate normal**

nQuery Advisor also provides sample size tables for tests and confidence intervals for regression slopes in one and two sample designs.

ROT5 **Linear regression test that $\beta=\beta_0$ for one x**
See Example 4 in Chapter 18 in the nQuery 5 manual.

ROC0 **Linear regression confidence interval for β**

RTT0 **Linear regression test that $\beta_1=\beta_2$ for one x**
See Example 5 in Chapter 18 in the nQuery 5 manual.

RTC0 **Linear regression confidence interval for $\beta_1 - \beta_2$**

For multiple covariates, use

ROT3 **Multiple linear regression test that $R^2 = 0$ for k normally distributed covariates.**

This table provides sample size or power for the F-test which tests the null hypothesis that a set of k predictor variables has no linear predictive relationship with y. That is, the F-test tests the null hypothesis that the squared multiple correlation between y and the x variables is 0.

For two sets of covariates, use

ROT4 **Multiple regression, test 0 increase in R^2 for B covariates adjusted for A covariates.**

This table provides sample size or power for the F-test of the null hypothesis that a set of B predictor variables has no linear predictive relationship with y, after y has been adjusted for A prior covariates. That is, the F-test will test the null hypothesis that the squared multiple correlation between y and the combined sets of A and B predictor variables is no larger than the squared multiple correlation between y and the initial set of A covariates.

4. Examples for Tables New in nQuery 6

The examples in this chapter demonstrate the four new tables in nQuery Advisor Version 6.

- t-test (ANOVA) for difference in means in 2 x 2 crossover design (MTT4)
  See Example 1 in this chapter.
- Confidence interval for relative risk (ratio of two proportions) (PTC3)
  See Example 2 in this chapter.
- Non-inferiority test for two exponential survival curves (STE0)
  See Example 3 in this chapter.
- Confidence interval for intraclass correlation for k measurements (AOC3)
  See Example 4 in this chapter.

In addition, these Examples are used to demonstrate use of some of the special features in nQuery Advisor

- Edit row names
  See Examples 1and 2 in this chapter; Tutorial in nQuery 5 manual and nQuery 7.0 manual; Chapter 4 in the nQuery 5 manual.
- Edit column names
  See Example 3 in this chapter; Tutorial in nQuery 5 manual and nQuery 7.0 manual; Example 6 in Chapter 8 in the nQuery 5 manual; Chapter 4 in the nQuery 5 manual.
- Change decimal display in table
  See Chapter 5 in the nQuery 7.0 manual and Example 3 in this chapter.
- Create sample size justification statement
  See any Example in this chapter; Tutorial in nQuery 5 manual and nQuery 7.0 manual; Example 1 in Chapter 17 in nQuery 5 manual.
- Paste table and statement into document preserving the Greek symbols
  See Examples 2 and 3 in this chapter; Tutorial in nQuery 5 manual and nQuery 7.0 manual; Chapter 3 in nQuery 5 manual.
- Copying and pasting from one column to another
  See Examples 2 and 3 in this chapter; Tutorial in nQuery 5 manual and nQuery 7.0 manual; Chapter 10 in nQuery 5 manual.

- Using other information to assist in estimating the standard deviation
  See Example 1 in this chapter; Chapters 5 and 9 in nQuery 5 manual.
- Printing table, statement, notes
  See Examples 1and 3 in this chapter; Tutorial in nQuery 5 manual and nQuery 7.0 manual; Chapter 3 in the nQuery 5 manual.
- Plotting sample size information
  See Example 3 in this chapter; Tutorial in nQuery 5 manual and nQuery 7.0 manual; Examples 1-5 in Chapter 6 in the nQuery 5 manual.

Example 1

2 x2 crossover (two-period, two treatment AB,BA) crossover using table t-test (ANOVA) for difference in means in 2 x 2 crossover design (MTT4)

The study design has a total sample size of 2n with n subjects receiving sequence AB, and n receiving BA. Thus, the A-B contrast is free of period effects on the average. The basis for the test of treatment effects will be the difference between treatments within each subject, $y_{diff} = y_1 - y_2$ where y_1 is the treatment 1 response and y_2 is the treatment 2 response.

Patients with cancer receive repeated chemotherapy cycles during which the number of neutrophils (a type of white blood cell) decreases. *Neutropenia* occurs when the number of neutrophils decreases below a fixed cut-off.

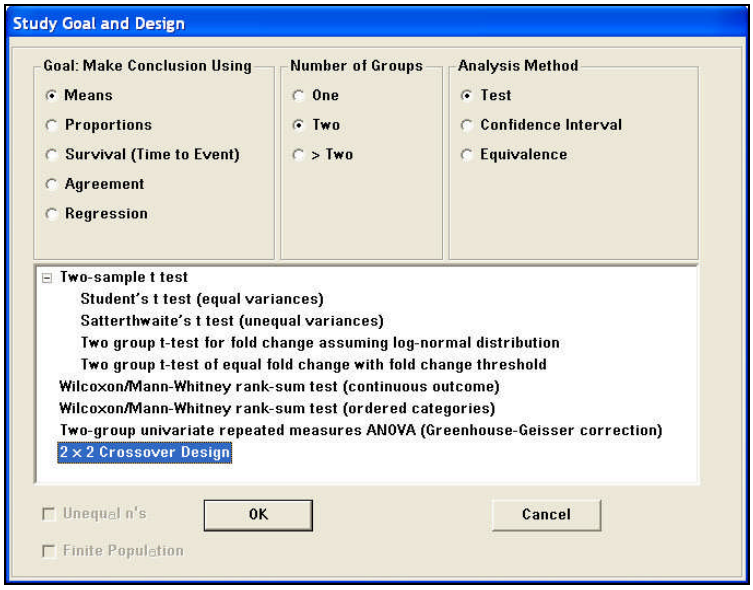
The study plan is to compare a new therapy to reduce the mean number of days of neutropenia with a placebo, using a 5% level two-sided t test appropriate for a crossover design, (or the crossover ANOVA). Each patient will get the new therapy during one chemotherapy cycle and placebo during another chemotherapy cycle. A new cycle of chemotherapy is not instituted until any previous neutropenia has resolved, and we assume that there are no carryover or residual effects.

The investigator asks whether 30 patients will provide adequate power to detect a drop of 3 days in the duration of neutropenia due to the new therapy. A previous study reported a median of 8 days of neutropenia in a control chemotherapy period with median durations of 3 and 4 days for two combination therapies. A small pilot study for patients receiving two cycles of chemotherapy with no treatment intervention showed median durations of about 6 days and a standard deviation of differences in neutropenia duration between the two cycles of 5.2.

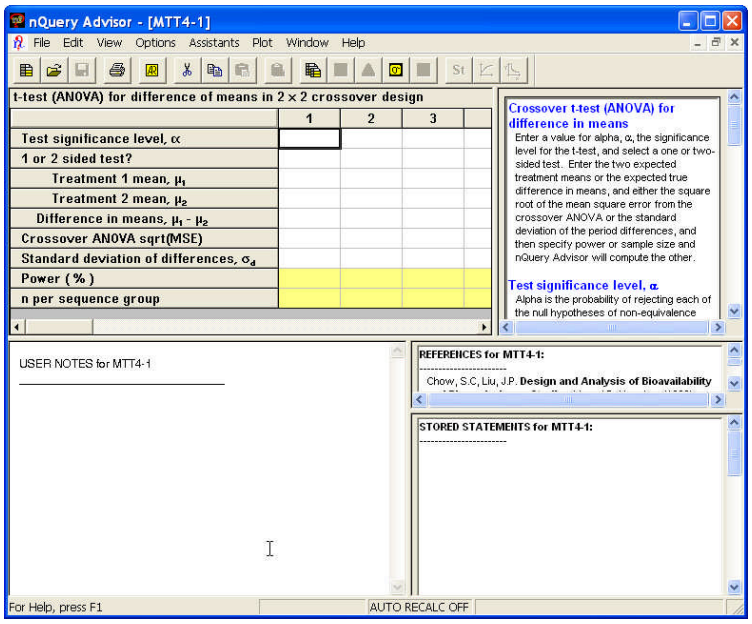
To run this example using nQuery Advisor 6.0:

In nQuery Advisor, choose the **File** menu **New** option or click on the **New** Icon button to obtain the Study Goal and Design dialog box.

Click on **Means**, **Two** group, and **Test** and select the bottom choice **2 x 2 crossover design.**



The sample size window for the 2 x2 crossover design for means appears.



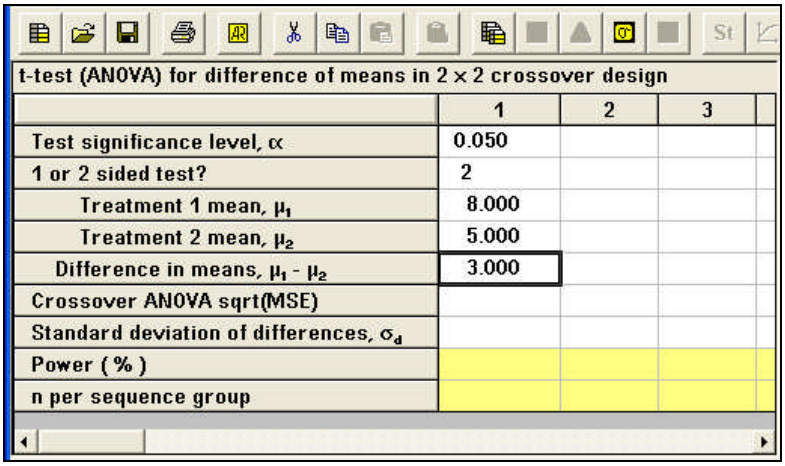
In the **Test significance level** row, enter **0.05**.

Enter **2** for a two-sided test.

In the **Treatment 1** row enter a mean of **8** days for the Placebo treatment.

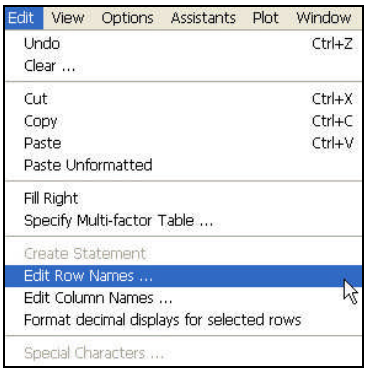
In the **Treatment 2** row enter a mean of **5** days (a decrease of 3 days) for the New therapy.

The difference in means will be calculated by nQuery.



To label the treatment rows as Placebo and New Therapy:

In the table, choose the Edit Row Names option from the table's right click menu or choose the **Edit** menu **Edit Row Names** option..



The **Edit Row Names** dialog box appears.

Click on **Treatment 1 mean**, and that name will appear in the editing field on the right.

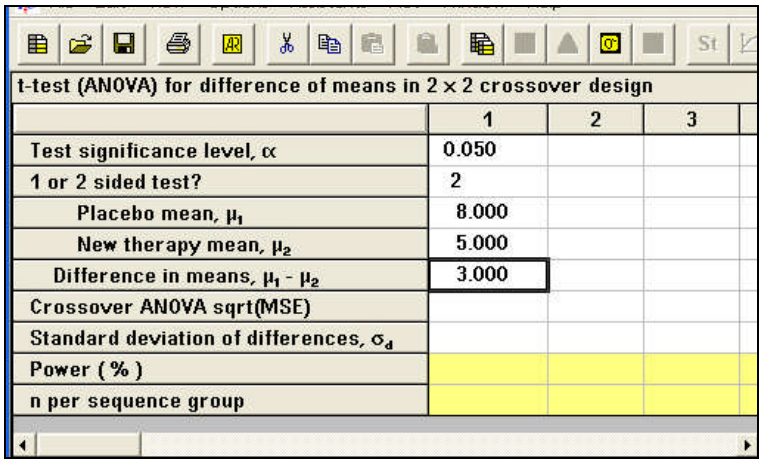
Type **Placebo** in the editing field, and the **Accept Edit Row** button becomes active.

Click on the **Accept Edit Row** to accept the new name, and the new name replaces the old in the left column.

Click on **Treatment 2 mean** and enter **New therapy** in the editing field on the right.

Click on the **Accept Edit Row** to accept the new name.

Click on the **Update Table Row Name** button to complete the editing.



t-test (ANOVA) for difference of means in 2 x 2 crossover design

	1	2	3
Test significance level, α	0.050		
1 or 2 sided test?	2		
Placebo mean, μ_1	8.000		
New therapy mean, μ_2	5.000		
Difference in means, $\mu_1 - \mu_2$	3.000		
Crossover ANOVA sqrt(MSE)			
Standard deviation of differences, σ_d			
Power (%)			
n per sequence group			

For this crossover design, you must enter either an estimate of σ_ε, the square root of the mean squared error from the crossover ANOVA, or an estimate of the standard deviation of differences,

$$\sigma_d = \sqrt{2}\sqrt{MSE}$$

and nQuery will compute the other. In this example, the standard deviation of differences was estimated to be 5.2.

Enter 5.2 in the **Standard deviation of differences** row and nQuery computes the Crossover ANOVA squareroot MSE as 3.677.

t-test (ANOVA) for difference of means in 2 x 2 crossover design

	1	2	3
Test significance level, α	0.050		
1 or 2 sided test?	2		
Placebo mean, μ_1	8.000		
New therapy mean, μ_2	5.000		
Difference in means, $\mu_1 - \mu_2$	3.000		
Crossover ANOVA sqrt(MSE)	3.677		
Standard deviation of differences, σ_d	5.200		
Power (%)			
n per sequence group			

To calculate power for this example:

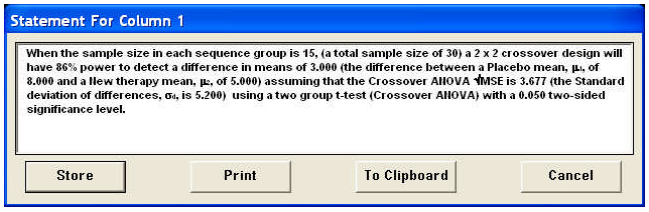
A total sample size of 30 is planned, so enter 15 in the n per sequence group row, and nQuery computes a power of 86%.

t-test (ANOVA) for difference of means in 2 x 2 crossover design

	1	2	3
Test significance level, α	0.050		
1 or 2 sided test?	2		
Placebo mean, μ_1	8.000		
New therapy mean, μ_2	5.000		
Difference in means, $\mu_1 - \mu_2$	3.000		
Crossover ANOVA sqrt(MSE)	3.677		
Standard deviation of differences, σ_d	5.200		
Power (%)	86		
n per sequence group	15		

To generate a statement for this result:

Click on the Statement icon, St, or choose the **Edit** menu **Create statement** option. The Statement dialog box will appear.

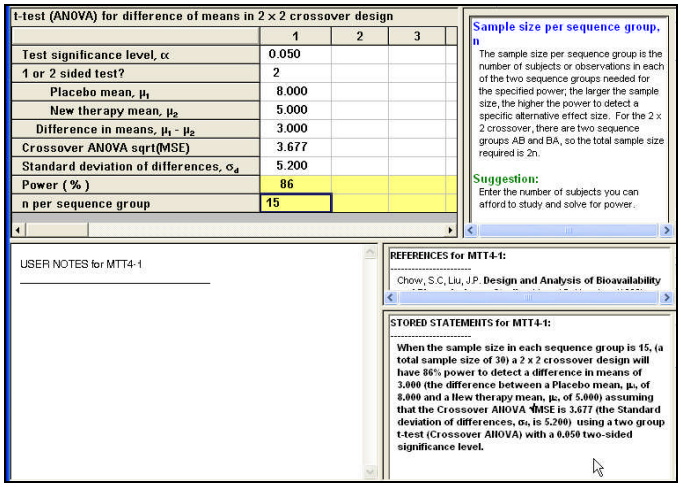


Use the **Print** button to print out the statement.

Use the **To Clipboard** button to copy the statement to the clipboard so that it can be pasted into a word processing document.

Use the **Cancel** button to cancel the operation.

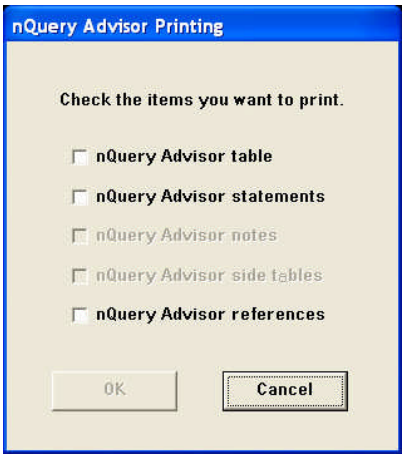
Use the **Store** button to store the statement so that it will display with the table, ready to be saved with the table.



Printing a Table

To print any filled section of the nQuery table:

Click on the **File** menu **Print** option. The Printing dialog box will appear.



Select from the items available to be printed: table, statements, and references. (There are no user notes for this table and no associated side tables.)

Click on the **OK** button to print.

Note: For details on creating a plot or pasting the table into a word processing document, see Example 3 in this chapter, STE0.

Estimating σ_d

In the MTT4 example above, we had an estimate for the standard deviation of differences. If we do not have that information, nQuery can calculate σ_d from:

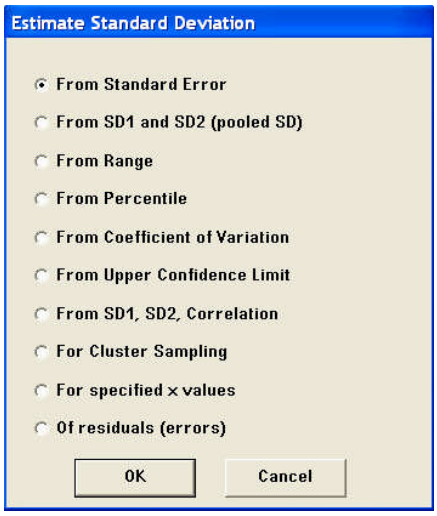
- within group mean squared error from the crossover (or repeated measures) ANOVA (just enter its squareroot in the nQuery table, and nQuery will calculate σ_d)

or

- between subject standard deviation and the between treatment/period correlation

To calculate standard deviation of differences from other information:

Click on the **Assistants** menu item **Estimate S.D.** The Estimate Standard Deviation dialog box will appear, displaying the default selection.



Select the option corresponding to the estimates available. In this case, we could compute an estimate of the standard deviation of differences from SD1, SD2, Correlation, the seventh option in the dialog box.

For more details on estimating standard deviation, see Chapter 9 in the nQuery 5 manual, Determining a Value for Standard Deviation, especially Example 7**.**

Example 2

Confidence interval for relative risk (ratio of two proportions) (PTC3)

In many epidemiologic applications, the investigator wishes to estimate the relative risk and a confidence interval for it.

In this example, the investigators plan to evaluate whether a prescription pain reliever increases the risk of cardiovascular adverse events in comparison with placebo. Previous studies on pain relievers in the same class of drugs suggest that the relative risk for cardiovascular events might be about 2. The study has been designed with 1000 patients per group for an efficacy endpoint. They want to assess the study's ability to distinguish a relative risk of 1 from a relative risk of 2. Based on previous studies, it is expected that the one-year cardiovascular adverse event rate will be about 1% in the placebo group.

Note: It would be preferable to analyze the study results using survival analysis methods to deal with dropouts and the possibility that the relative risk (or hazard ratio) is not constant over time.

Here we address the question:
How wide is the 95% two-sided confidence interval for the relative risk of cardiovascular adverse events likely to be in the planned study?

The appropriate table for this design is **Confidence interval for relative risk**.

To bring up the PTC3 sample size table in nQuery Advisor 6.0:

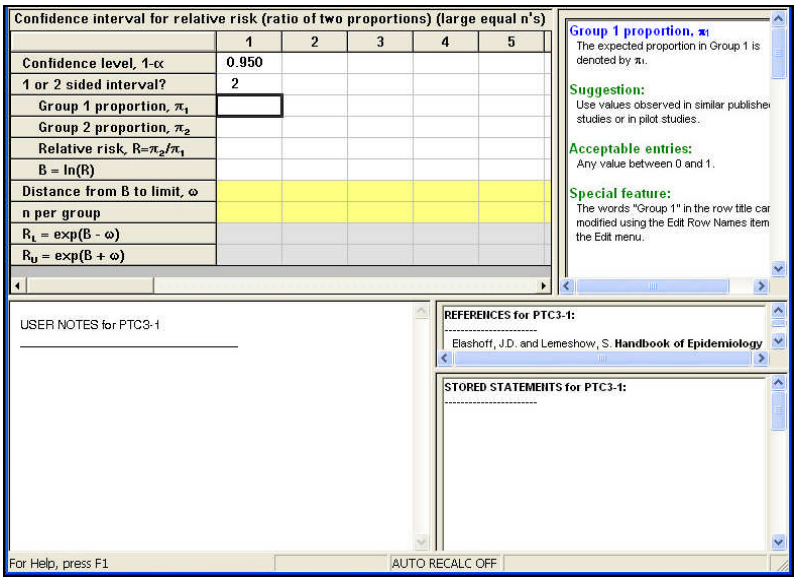
Click on the **File** menu **New** option or the **New** icon,  . The Study Goal and Design dialog box will appear.

Select **P**roportions, **T**wo, **C**onfidence Interval.

Select **Confidence interval for relative risk**, the fourth analysis method in the list of analysis methods.

Click **OK**. The Confidence interval for relative risk table will appear with no values entered.

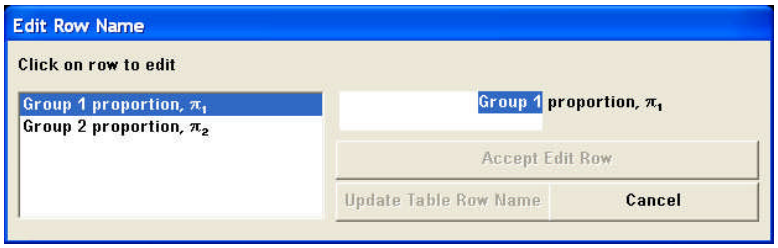
The following table shows the table with values for confidence level and 2-sided interval already filled in.



To label the treatment rows as Placebo and Pain reliever:

In the table, choose the **Edit Row Names** option in the Edit menu or in the right click menu.

The Edit Row Names dialog box appears. Click on **Group 1 proportion**, and that name will appear in the editing field on the right.



Type **Placebo** in the editing field, and the **Accept Edit Row** button becomes active.

Click on the **Accept Edit Row** to accept the new name, and the new name replaces the old in the left column.

Click on **Group 2 proportion** and enter **Pain reliever** in the editing field on the right.

Click on the **Accept Edit Row** to accept the new name.

Click on the **Update Table Row Name** button to complete the editing.

To complete the table using the information for this example:

Enter **.01** for the proportion of adverse events expected in the **Placebo** group.

We first look at the confidence interval width under the null hypothesis that the pain reliever does not increase the adverse event rate; that is for the situation where the true relative risk is 1.0. Enter **1.0** for the **Relative risk.** nQuery will calculate the proportion expected in the Pain reliever group as well as the remaining cells in the white section of the table.

Enter the planned sample size of **1000** for the **n per group** to get the following completed column.

Confidence interval for relative risk (ratio of two proportions) (large equal n's)					
	1	2	3	4	
Confidence level, 1-α	0.950				
1 or 2 sided interval?	2				
Placebo proportion, π_1	0.010				
Pain reliever proportion, π_2	0.010				
Relative risk, $R=\pi_2/\pi_1$	1.000				
$B = \ln(R)$	0.000				
Distance from B to limit, ω	0.872				
n per group	1000				
$R_L = \exp(B - \omega)$	0.418				
$R_U = \exp(B + \omega)$	2.392				

nQuery Advisor will calculate the natural log of the relative risk ratio, the expected distance from the log odds ratio to the upper or lower limit of the confidence interval, and the expected upper and lower limits of the confidence interval.

We see that with the planned sample size, even a true relative risk of 1.0 would be likely to result in a confidence interval for the relative risk extending above 2.0.

Determine the Effects of Changing Sample Size and/or Relative Risk

To see the effects of increasing the sample size or of postulating a true relative risk of 2, we start by copying some of the cells from column 1 to columns 2 and 3.

Select the first three cells in column 1.

Select the **Edit** menu **Copy** option or use the keys **<Ctrl>-<C>**.

To paste into the second column, click on the first cell of the second column and select the **Edit** menu **Paste** option or use the keys **<Ctrl>-<V>.**

To paste into the third column, click on the first cell of the third column and select the **Edit** menu **Paste** option or use the keys **<Ctrl>-<V**>.

In the second column, enter **.01** in the **Pain reliever proportion** cell, and nQuery will fill the remaining white cells in that column.

In the second column, enter an increased sample size of **1600** in the **n per group** row, and nQuery will calculate the results for all remaining rows. We see that with 1600 subjects per group, the expected upper limit of the confidence interval would be just below 2.0 for a true relative risk of 1.0.

In the third column, enter **.02** in the **Pain reliever proportion** cell, and nQuery will fill the remaining white cells in that column.

In the third column, enter **1000** in the **n per group** row, and nQuery will calculate the results for all remaining rows. Even when the true relative risk is 2.0, the lower limit of the confidence interval for the relative risk is likely to be below 1.0.

Confidence interval for relative risk (ratio of two proportions) (large equal n's)				
	1	2	3	4
Confidence level, 1-α	0.950	0.950	0.950	
1 or 2 sided interval?	2	2	2	
Placebo proportion, π_1	0.010	0.010	0.010	
Pain reliever proportion, π_2	0.010	0.010	0.020	
Relative risk, $R=\pi_2/\pi_1$	1.000	1.000	2.000	
B = ln(R)	0.000	0.000	0.693	
Distance from B to limit, ω	0.872	0.689	0.754	
n per group	1000	1600	1000	
$R_L = \exp(B - \omega)$	0.418	0.502	0.941	
$R_U = \exp(B + \omega)$	2.392	1.993	4.251	

To view the same three scenarios using a placebo rate of 2% per year:

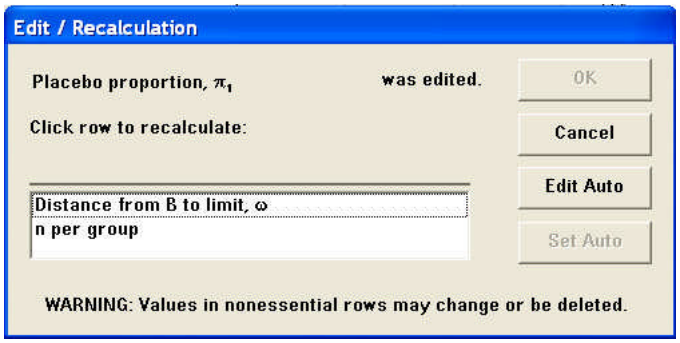
We want to start by filling the next three columns with the contents of the first three columns. We can do this in one copy/paste operation.

Select the cells in the rows of the first three columns, omitting only the gray rows.

To copy the contents of those cells, select the **Edit** menu **Copy** option or use the keys **<Ctrl>-<C>**.

To paste into the fourth through sixth columns, click on the first cell of the fourth column and select the **Edit** menu **Paste** option or use the keys **<Ctrl>-<V>**. nQuery will completely fill the fourth through sixth columns.

To change the **Placebo proportion**, click on the **Placebo proportion** row in column 4 and enter **0.02**. The Edit/Recalculation dialog box will appear.



Select **Distance from B to limit, ω** and click on the **OK** button. nQuery will recalculate the Distance.

To change the **Pain reliever proportion**, click on the **Pain reliever proportion** row in column 4 and enter **0.02**. The Edit/Recalculation dialog box will appear.

Select **Distance from B to limit, ω** and click on the **OK** button. nQuery will recalculate the Distance.

Carry out the same **Placebo proportion** and **Pain reliever proportion** edits in column 5.

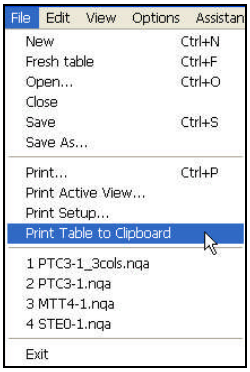
In column 6, change **Placebo proportion** to **0.20** and **Pain reliever proportion** to **0.40**. Columns 2 through 6 of the final table will be:

Confidence interval for relative risk (ratio of two proportions) (large equal n's)					
	2	3	4	5	6
Confidence level, 1-α	0.950	0.950	0.950	0.950	0.950
1 or 2 sided interval?	2	2	2	2	2
Placebo proportion, π_1	0.010	0.010	0.020	0.020	0.020
Pain reliever proportion, π_2	0.010	0.020	0.020	0.020	0.040
Relative risk, $R=\pi_2/\pi_1$	1.000	2.000	1.000	1.000	2.000
B = ln(R)	0.000	0.693	0.000	0.000	0.693
Distance from B to limit, ω	0.689	0.754	0.614	0.485	0.530
n per group	1600	1000	1000	1600	1000
R_L = exp(B - ω)	0.502	0.941	0.541	0.616	1.178
R_U = exp(B + ω)	1.993	4.251	1.847	1.624	3.396

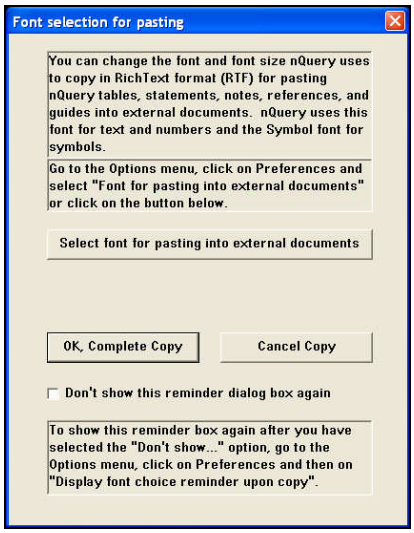
Pasting the Table into a Document

To send this table to the clipboard for pasting into a word processing document:

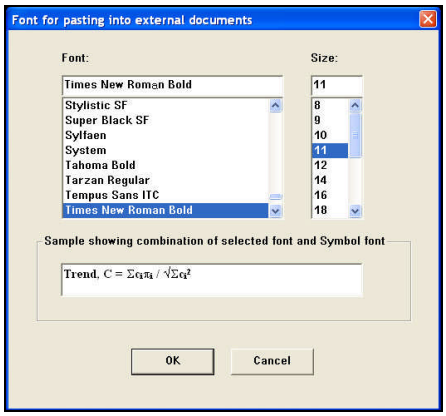
Choose the **File** menu or the table's right click menu **Print Table to Clipboard** option.



nQuery will present the **Font Selection for pasting** dialog box. This box lets you determine the font to be used for all text other than the characters in symbol font. This option makes it extremely easy to select any font on your computer for the text.



To choose a font, click on the **Select font for pasting** button. The **Font for pasting into external documents** dialog box will appear.



Choose a font and a size. Click on the **OK** button when satisfied.

Depending on your choice of font, when you paste the table contents into a document, the table will look similar to the following table:

Confidence interval for relative risk (ratio of two proportions) (large equal n's)

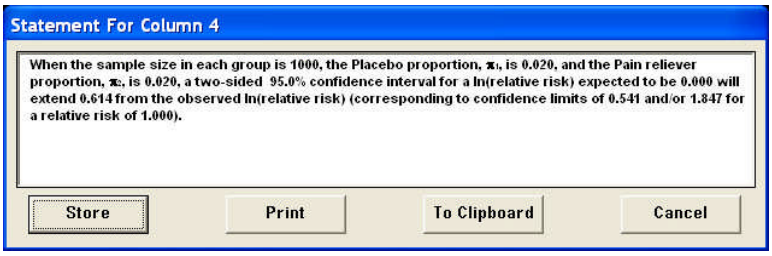
	1	2	3	4	5	6
Confidence level, 1-α	0.950	0.950	0.950	0.950	0.950	0.950
1 or 2 sided interval?	2	2	2	2	2	2
Placebo proportion, π_1	0.010	0.010	0.010	0.020	0.020	0.020
Pain reliever proportion, π_2	0.010	0.010	0.020	0.020	0.020	0.040
Relative risk, $R=\pi_2/\pi_1$	1.000	1.000	2.000	1.000	1.000	2.000
B = ln(R)	0.000	0.000	0.693	0.000	0.000	0.693
Distance from B to limit, ω	0.872	0.689	0.754	0.614	0.485	0.530
n per group	1000	1600	1000	1000	1600	1000
R_L = exp(B - ω)	0.418	0.502	0.941	0.541	0.616	1.178
R_U = exp(B + ω)	2.392	1.993	4.251	1.847	1.624	3.396

Generating a Statement

To get the statement for any column:

Click on any cell in the calculated column.

Click on the **Create Statement** button. The statement will appear.



You can save the statement to clipboard and paste it into your document, or you can print the statement, or store and save it with the table. For more details on this dialog box, please see Example 3, STE0, the next example in this chapter.

Example 3

Non-inferiority for two exponential survival curves (STE0)

Many cancer drugs which are effective in prolonging survival put patients at considerable risk for serious adverse events. A new drug with an improved safety profile would be of interest even if it did not increase survival as long as survival was not decreased in comparison with the standard. For example, suppose the standard drug results in a median survival of 12 months. The new drug might be considered to be not inferior as long as the median survival was not lower than 10 months.

The study will be designed as a non-inferiority trial with a survival outcome. The study plan has an accrual period of 18 months and a maximum followup time of 24 months. That is, the total trial length will be 24 months; those first to enter will be followed for 24 months and those entered at the end of the 18 months accrual period will be followed only 6 months. If all patients were to be followed for exactly 24 months no matter when they entered the trial, there is no need to specify the length of the accrual period.

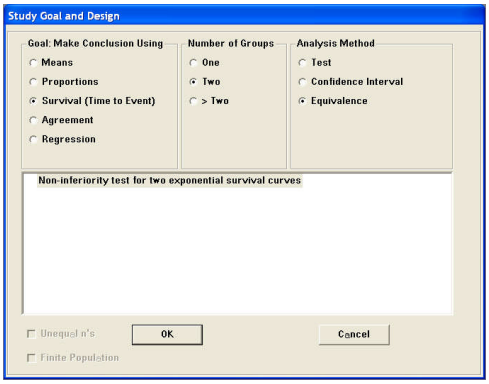
To select the appropriate sample size table in nQuery Advisor 6.0

Choose **File** menu **New** option

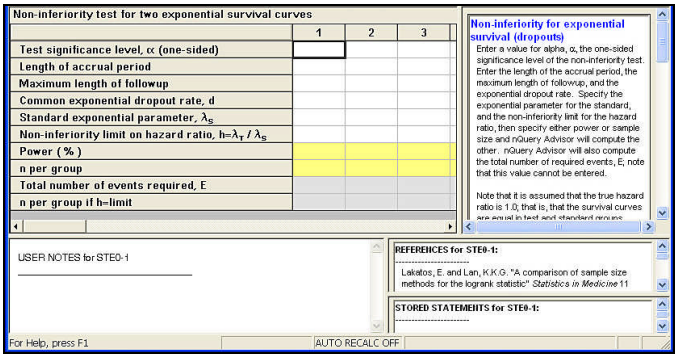
Click in the radio button to choose **Goal: Survival (Time to Event)**.

Click to choose **Number of Groups: Two**.

Click to choose **Analysis Method: Equivalence**.



The sample size table for **Non-inferiority test for two exponential survival curves** will appear.



Enter **0.050** for **Significance level**.

Enter **18** for **Length of accrual** period.

Enter **24** for **Maximum length of followup**. (In other words, those entered in the first month of the trial will be followed for 24 months and those entered at 18 months after the start of the trial will be followed only for 6 months.)

Enter **0.0** for **Common exponential dropout** rate; in this case we do not expect loss to followup for the survival outcome.

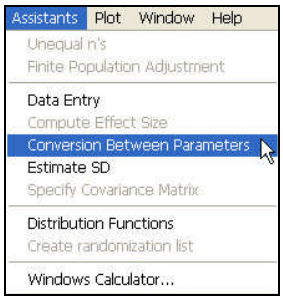
Note: Be sure to specify accrual period, followup period, and expected dropout rate in terms of months since the median survival is expressed in terms of months.

Non-inferiority test for two exponential survival curves			
	1	2	3
Test significance level, α (one-sided)	0.050		
Length of accrual period	18.00		
Maximum length of followup	24.00		
Common exponential dropout rate, d	0.0000		
Standard exponential parameter, λ_S			
Non-inferiority limit on hazard ratio, $h=\lambda_T / \lambda_S$			
Power (%)			
n per group			
Total number of events required, E			
n per group if h=limit			

Entering the values for standard exponential survival and the non-inferiority limit on the hazard ratio:

This table calls for specification of the exponential survival parameter for the standard and the non-inferiority limit on the hazard ratio; since we only know the values for median survival, we must use those values to calculate the exponential survival parameters.

Select the **Assistants** menu **Conversion Between Parameters** option.



The STT00 Conversion between Parameters side table will appear.

Enter **10** for **Group 1 median survival** and **12** for **Group 2 median survival**. The table automatically calculates the hazard ratio.

Conversion to alternate rates for exponential survival curves		
	1	2
Time t		
Group 1 proportion π_1 at time t		
median survival	10.000	
exponential parameter, λ_1	0.0693	
Group 2 proportion π_2 at time t		
median survival	12.000	
exponential parameter, λ_2	0.0578	
Hazard ratio, $h=\ln(\pi_1)/\ln(\pi_2)=med_2/med_1=\lambda_1/\lambda_2$	1.200	

We find that these values correspond to a hazard ratio no larger than 1.2 and that the exponential parameter for the standard treatment survival time expressed in months is 0.0578.

To bring the exponential parameter for the standard treatment 1 to the STE0 table:

Select the Group 2 **exponential parameter** corresponding to a median survival of 12 months and choose the **Edit** menu **Copy** option.

Switch to the STE0 table using the **<Ctrl>-<Tab>** keys or the **Window** menu list of open windows.

Click on the cell in the **Standard exponential parameter** row in column 1, and select the **Edit** menu **Paste Unformatted** option to paste the value from the side table.

To bring the hazard ratio to the STE0 table:

In the STT00 side table select the **hazard ratio** and choose the **Edit** menu **Copy** option.

Switch to the STE0 table using the **<Ctrl>-<Tab>** keys or the **Window** menu list of open windows.

Click on the cell in the **Non-inferiority limit on hazard ratio** row in column 1, and select the **Edit** menu **Paste Unformatted** option to paste the value.

Note that this table is for a test of the null hypothesis of inferiority (a hazard ratio of 1.2 in this example) versus the alternative hypothesis that the survival rates are the same in the two groups.

Enter **80**% power, and nQuery will calculate the rest.

Non-inferiority test for two exponential survival curves			
	1	2	3
Test significance level, α (one-sided)	0.050		
Length of accrual period	18.00		
Maximum length of followup	24.00		
Common exponential dropout rate, d	0.0000		
Standard exponential parameter, λ_S	0.0578		
Non-inferiority limit on hazard ratio, $h=\lambda_T / \lambda_S$	1.200		
Power (%)	80		
n per group	664		
Total number of events required, E	744		
n per group if h=limit	631		

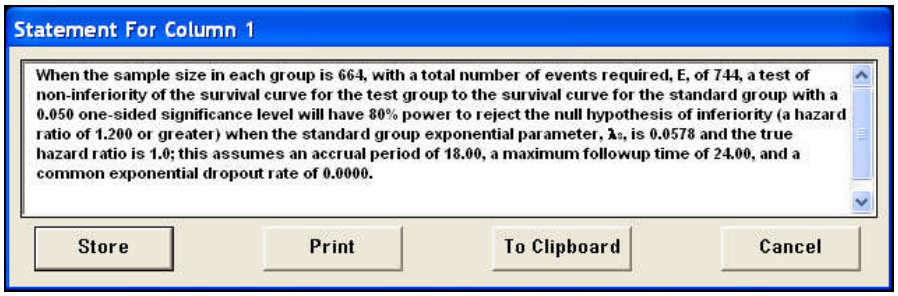
For such a trial to have 80% power, we find that it's necessary to observe a total of 744 events. To obtain that number of events would require about 664 patients per group (1328 patients total) if the alternate hypothesis that both test and standard have the same exponential parameter as that specified in the table were true.

If the null hypothesis were true, and the test were inferior by the amount specified, the required number of events would be obtained with a somewhat smaller sample size, see the last row in the table. Note that these estimates of required sample size depend on the assumptions that the survival curves do not deviate from the exponential model and that the hazard ratio is constant.

To get a statement for this result:

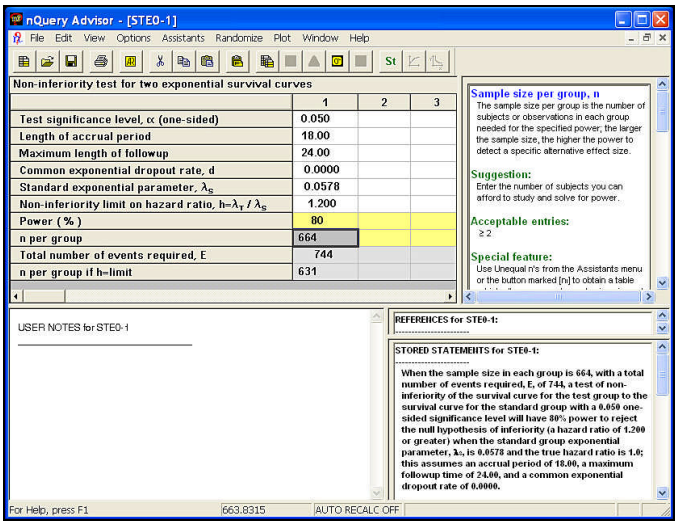
Click on the Statement icon, 

. The statement will appear in a separate dialog box.



Store Statement

Click on the **Store** button to store the statement with the STE0 table. The table below shows the stored statement in the table.

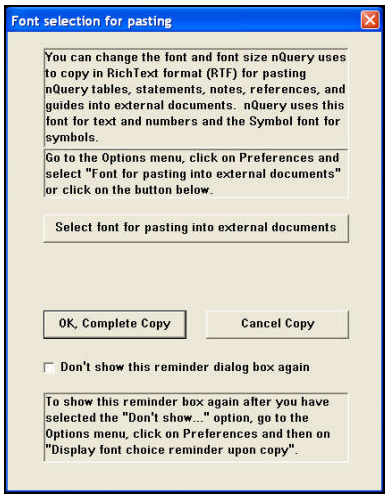


Print Statement

In the **Statement** dialog box, click on the **Print** button to print the statement. The usual Windows Print dialog box will appear.

Copy Statement to Clipboard

In the **Statement** dialog box, click on the **To Clipboard** button to copy the statement to the Clipboard. The **Font Selections for pasting** dialog box will appear.



For details on this dialog box, see Example 4, AOC3, the next example in this chapter. Here is the statement we obtain after choosing Arial 8 and pasting into this document, note that the Greek symbols have been maintained.

> When the sample size in each group is 664, with a total number of events required, E, of 744, a test of non-inferiority of the survival curve for the test group to the survival curve for the standard group with a 0.050 one-sided significance level will have 80% power to reject the null hypothesis of inferiority (a hazard ratio of 1.200 or greater) when the standard group exponential parameter, λ_S, is 0.0578 and the true hazard ratio is 1.0; this assumes an accrual period of 18.00, a maximum followup time of 24.00, and a common exponential dropout rate of 0.0000.

Adding additional columns and formatting the table

To request a different power, use the second column of the table:

Select the first 6 cells of the first column.

Choose the **Edit** menu **Copy** option.

Click on the first cell of the second column.

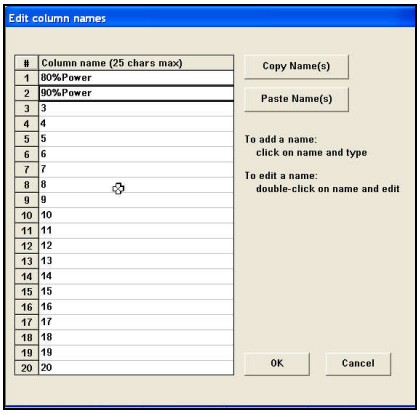
Choose the **Edit** menu **Paste** option to fill the first 6 cells of that column.

Enter **90** in the **Power** cell of the second column, and nQuery will calculate and fill the two remaining cells.

To rename the columns:

Choose the **Edit** menu **Edit Column Names** option and the Edit column names dialog box will appear.

Enter **80%Power** for Column 1 and **90%Power** for Column 2.

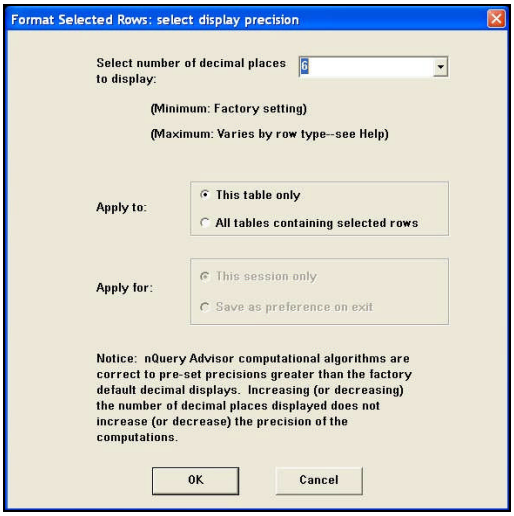


Click on the **OK** button to update the column names in STE0 with the new names.

To display more decimal digits in the row for the standard exponential parameter:

Right click in that row, and select the **Edit** menu **Format Decimal Displays for Selected Rows** option.

Enter **6** in the **Select number of decimal places** field.



Click on the **OK** button to update the table.

Non-inferiority test for two exponential survival curves		
	80%Power	90%Powe
Test significance level, α (one-sided)	0.050	0.050
Length of accrual period	18.00	18.00
Maximum length of followup	24.00	24.00
Common exponential dropout rate, d	0.0000	0.0000
Standard exponential parameter, λ_S	0.057762	0.057762
Non-inferiority limit on hazard ratio, $h=\lambda_T / \lambda_S$	1.200	1.200
Power (%)	80	90
n per group	664	920
Total number of events required, E	744	1031
n per group if h=limit	631	874

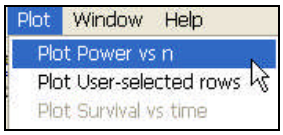
To achieve 90% power would require more than 1800 subjects total.

Plotting sample size information

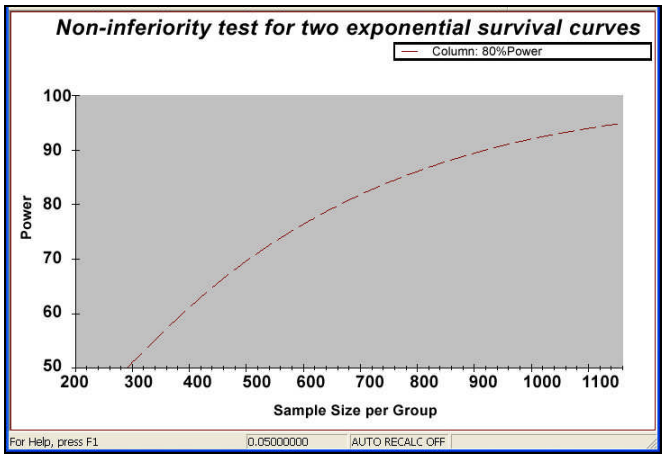
To get a plot of Power vs n for a column in the table:

Click on one of the two column titles to select the column for plotting.

Choose the **Plot** menu **Plot Power vs n** option or click on the leftmost of the two plot icons in the toolbar.



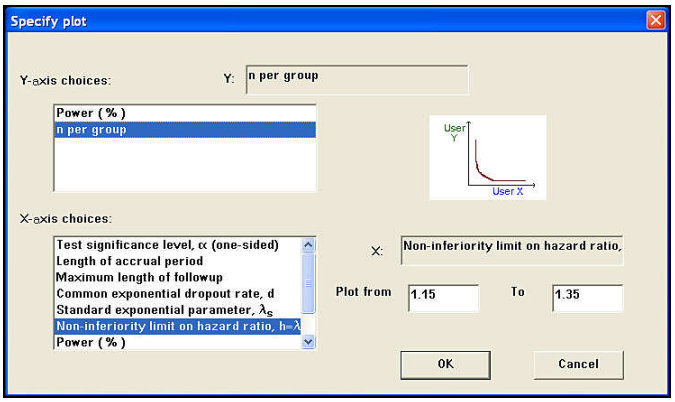
The plot will appear.



To get a plot relating the sample size to the specified hazard ratio for both selections of power:

Click on the two column titles to select the columns for plotting.

Choose the **Plot** menu **Plot User-selected rows** option or click on the rightmost Plot icon and nQuery will display the **Specify plot** dialog box.

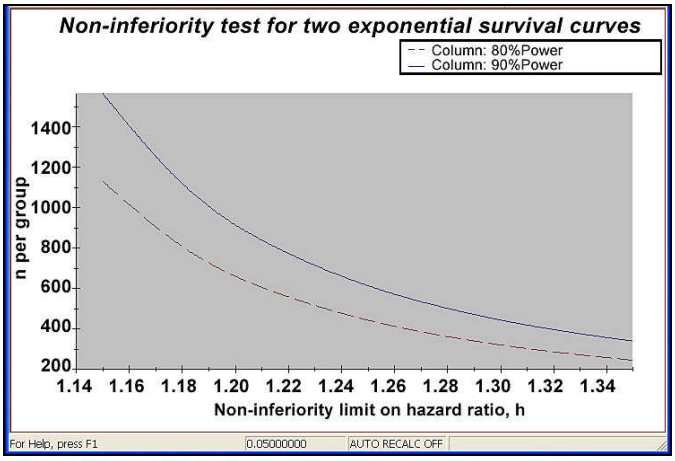


For **Y-axis**, click on **n per group**.

For **X-axis**, click on **Non-inferiority limit**.

Set a range of **1.15** to **1.35**.

Click on the **OK** button to finish the plot.



This plot shows that using a non-inferiority limit of 1.3 would require less than half the number of patients than a non-inferiority limit of 1.2. However, such a non-inferiority limit would imply that a median survival for the new drug potentially as low as 9.2 months would be acceptable.

Printing Plots

You can print plots by using the **File** menu **Print Current Page** option.

Copying and Pasting Plots

You can use the **Edit** menu **Copy** option to copy plots to the clipboard for pasting into documents.

Saving Plots

Use the **File** menu **Save as Metafile** option to save a plot to a graphic file readable by word processing programs and graphics programs.

Switching Between Plot and Table

To switch back to the STE0 table from the plot display, use the **<Ctrl>-<Tab>** keys or select the STE0 table from the listing of open windows in the Window menu.

Printing, Saving, and Pasting Table Results into Documents

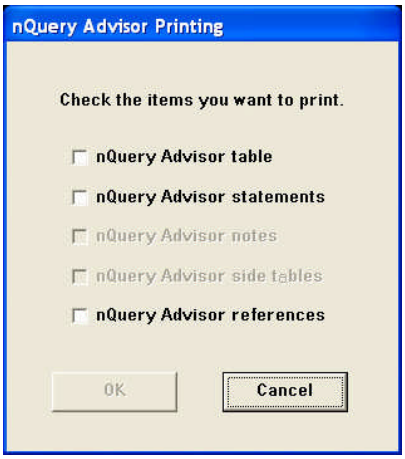
You can print the sample size tables (together with notes, statements, and references) or save the tables to a file (together with notes and statements).

To save the nQuery table:

Click on the **File** menu **Save** option. The nQuery program will save the table with its notes, statements, and side tables. Note that plots must be saved separately.

To print any filled section of the nQuery table:

Click on the **File** menu **Print** option. The Printing dialog box will appear.



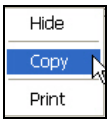
Select from the items available to be printed: table, statements, and references.

Click on the **OK** button to print.

To copy or print the nQuery table Guide cards:

Place the cursor in the Guide card pane.

Right click to bring up the Guide card right click menu.



Choose **Copy** to copy the Guide card to the clipboard for later pasting.

Choose **Print** to print the Guide card.

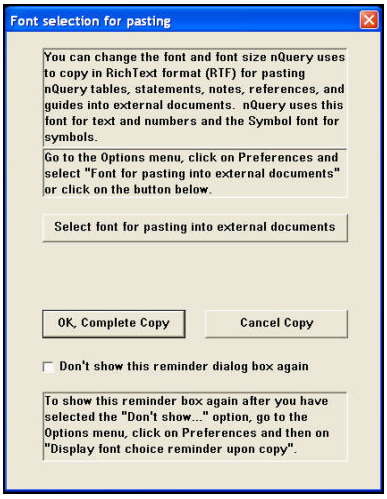
To prepare the nQuery table for pasting into another document:

Place the cursor in a cell in the table.

Click on the **File** menu **Print Table to Clipboard** option.

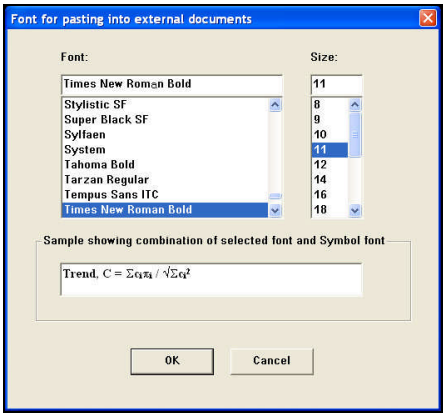
The first time you do this, the **Font selection for pasting** dialog box will appear.

Note: At any time, you can change the chosen font by selecting **Options** menu **Preferences** option, and then the Font for the external pasting option.



This dialog box allows you to choose the best font to emphasize the table within your document. The Greek symbols will appear in the symbol font and the rest of the text will appear in the font of your choice.

Click on the **Select font for pasting into external documents** button and the Font for pasting into external documents dialog box will appear. This dialog box gives you a display for every font you choose. This display gives you the opportunity to evaluate the effect of your selected font alongside the symbol font.



Choose the desired font and size, then click on the **OK** button.

Open the word processing document and paste the table into the document.

We show the pasted table and a pasted statement below.

Non-inferiority test for two exponential survival curves

	80%Power	90%Power
Test significance level, α (one-sided)	**0.050**	**0.050**
Length of accrual period	**18.00**	**18.00**
Maximum length of followup	**24.00**	**24.00**
Common exponential dropout rate, d	**0.0000**	**0.0000**
Standard exponential parameter, λ_S	**0.0578**	**0.0578**
Non-inferiority limit on hazard ratio, h=λ_T / λ_S	**1.200**	**1.200**
Power (%)	**80**	**90**
n per group	**664**	**920**
Total number of events required, E	**744**	**1031**
n per group if h=limit	**631**	**874**

STORED STATEMENTS for STE0-1

When the sample size in each group is 664, with a total number of events required, E, of 744, a test of non-inferiority of the survival curve for the test group to the survival curve for the standard group with a 0.050 one-sided significance level will have 80% power to reject the null hypothesis of inferiority (a hazard ratio of 1.200 or greater) when the standard group exponential parameter, λ_S, is 0.0578 and the true hazard ratio is 1.0; this assumes an accrual period of 18.00, a maximum followup time of 24.00, and a common exponential dropout rate of 0.0000.

Example 4

Confidence Interval for Intraclass correlation for k measurements (AOC3)

This example pertains to a study planned to assess the reliability of ratings of a functional measure in children. It will be assessed by four raters and it is hoped that the intraclass correlation will be about 0.85.

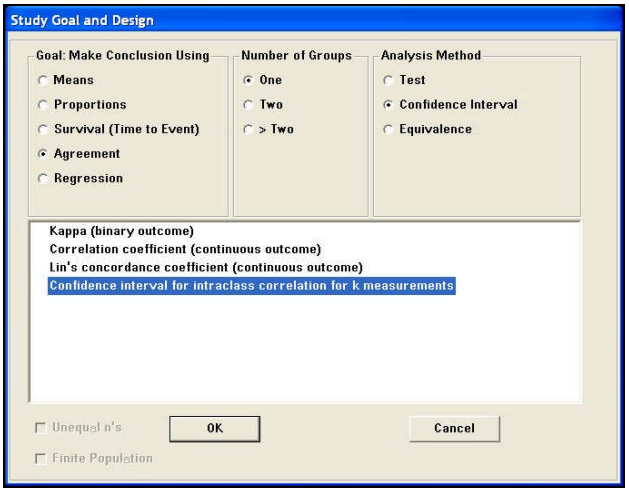
The investigator wants to know how many children must be rated by these four raters so that the 95% confidence interval width will be about 0.20 (the interval will extend about ± 0.1 from the estimate.) Or alternatively, how many children would be required so that the width would only be about 0.1 or about ± 0.05?

To bring up the AOC3 sample size table:

Click on the **File** menu **New** option or the **New** icon. The Study Goal and Design dialog box will appear.

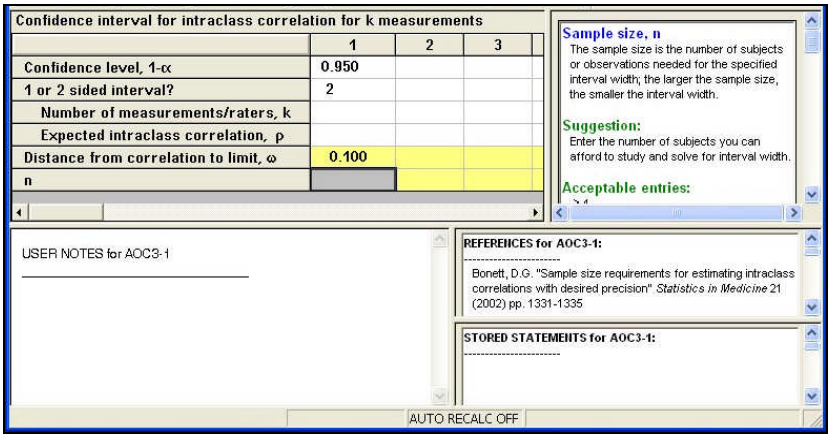
Select **A**greement, **O**ne, **C**onfidence interval.

Select the fourth table from the list of sample size tables.



Click **OK**. The Confidence interval for intraclass correlation for k measurements table will appear.

The following table shows the confidence level, 2-sided interval, and desired distance, ω, from the estimate to the confidence limit already filled in.



Type in **4** as the **Number of measurements/raters, k**.

Enter **0.85** as the **Expected intraclass correlation, ρ**, and the program calculates the required sample size.

Confidence interval for intraclass correlation for k measurements			
	1	2	3
Confidence level, 1-α	0.950		
1 or 2 sided interval?	2		
Number of measurements/raters, k	4		
Expected intraclass correlation, ρ	0.850		
Distance from correlation to limit, ω	0.100		
n	20		

Note that this table uses a normal approximation and that an exact confidence interval would not be symmetric around the estimate.

To determine the sample size required for a confidence interval width equal to one-half this width:

Select the first four rows in column 1 and choose the **Edit** menu **Copy** option.

Place the cursor in the first cell in column 2 and choose the **Edit** menu **Paste** option to paste the values into column 2.

In column 2, enter **0.05** in **the Distance from correlation to limit** row. The program calculates the n for the new distance.

Confidence interval for intraclass correlation for k measurements			
	1	2	3
Confidence level, 1-α	0.950	0.950	
1 or 2 sided interval?	2	2	
Number of measurements/raters, k	4	4	
Expected intraclass correlation, ρ	0.850	0.850	
Distance from correlation to limit, ω	0.100	0.050	
n	20	74	

To get the statement for the solution in the first column:

Click on any cell in the first column.

Click on the **Create Statement** icon, 

. The statement dialog box will appear. The dialog box allows you to copy the statement to clipboard for pasting in another document, print the statement, or store it in the stored statements panel on your screen. For more details on the Statement dialog box, see Example 1, MTT4, in this chapter. The following is the pasted statement from column 1 of the current table.

> **When the sample size is 20, a two-sided 95.0% confidence interval computed using the large sample normal approximation for an intraclass correlation based on 4 measurements/raters will extend about 0.100 from the observed intraclass correlation when the expected intraclass correlation is 0.850.**

To get a copy of the table to paste into your document:

Right-click in a table cell.

In the right-click menu, select **Print Table to Clipboard**.

When the **Font selection for pasting** dialog box appears, click on the **Select font** button and choose the exact font and size you want to use. For complete details on this option, please see Example 3 in this chapter, STE0.

After you choose the font, your table is available in the Windows clipboard for pasting.

Paste the table into a word processing document. The pasted table will be similar to the following table, depending on your choice of font.

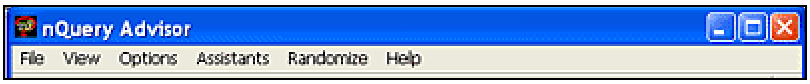
Confidence interval for intraclass correlation for k measurements

	1	**2**
Confidence level, 1-α	0.950	0.950
1 or 2 sided interval?	2	2
Number of measurements/raters, k	4	4
Expected intraclass correlation, ρ	0.850	0.850
Distance from correlation to limit, ω	0.100	0.050
n	20	74

For information on plotting sample size results, see Example 3, STE0, in this chapter.

5. The Options Menu and Format Decimal Display

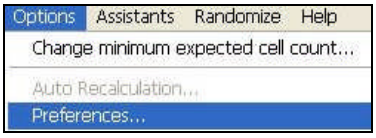
The first nQuery Advisor screen contains a menu bar with six choices: File, View, Options, Assistants, Randomize, and Help. The File, and View menus on this first screen are the initial menus. These initial menus are shorter than the File and View menus available after you open a table. The next figure shows the first nQuery Advisor menu bar.



See Chapter 3 in the nQuery 5 manual for a description of the File menu, Chapter 5 in the nQuery 5 manual for a description of the Assistants menu and Chapter 6 in the nQuery 7.0 manual for a description of the new Randomize menu, and Chapter 7 in the nQuery 5 manual for a description of the View menu. Note that when a table is open, there are three additional menus. See Chapters 4, 6, and 7 in the nQuery 5 manual for details.

Options Menu when no table is open

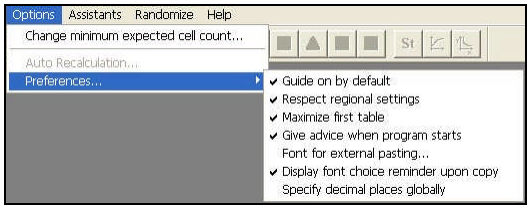
The Options menu provides three choices:



For a detailed discussion of the Change minimum expected cell count and Auto Recalculation options, see Chapter 3 in the nQuery 5 manual.

Preferences

When you choose the Options menu Preferences option before opening a table, you get a menu with seven options.



See Chapter 3 in the nQuery 5 manual for a description of the first six options.

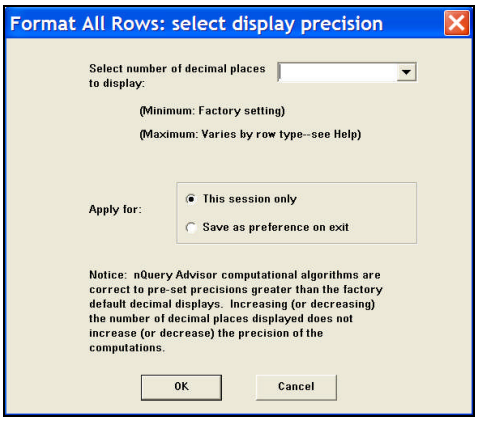
Specify decimal places globally

We can use this option to make a global shift up or down in the number of decimal places displayed. Generally, however, we will use it to restore the factory default setting for decimal places displayed throughout the program.

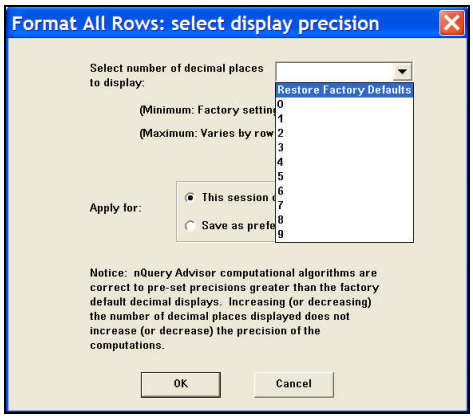
To specify decimal places globally:

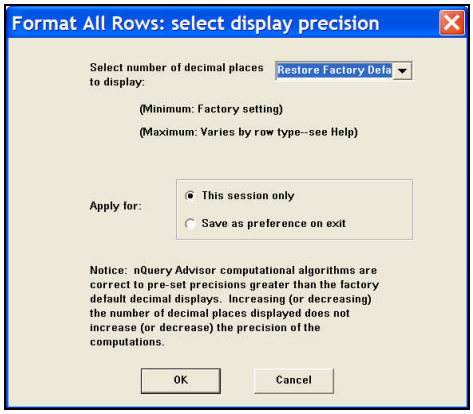
Select the **Options** menu **Preferences** option and the **Specify decimal places globally** option.

The **Format All Rows** dialog box will appear.



To restore the factory setting, click on the down arrow in the **Select number** box and select the option **Restore Factory Defaults**.





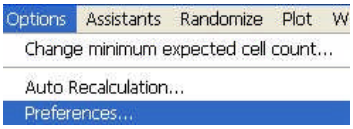
Select either **This session only** or **Save as preference on exit** and click on the **OK** button.

If you select **Save as preference on exit**, the program will have the factory defaults restored the next time you open it.

If you select **This session only**, the decimal displays will keep the factory default settings only for this session. The decimal displays will return to the settings they had prior to this session when you reopen the program.

Options Menu when a table is open

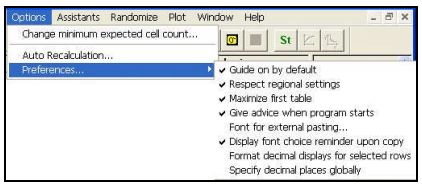
The Options menu provides three choices:



For discussion of the Change minimum expected cell count and Auto Recalculation options, see Chapter 3 in the nQuery 5 manual.

Preferences

When you choose the Options menu Preferences option when a table is open, you get a menu with eight options.



Format Decimal Displays for Selected Rows

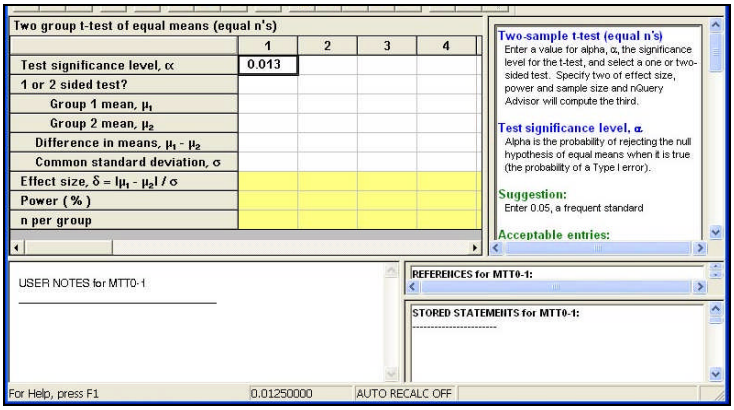
Note that this option is also available in the Edit menu and at the bottom of the right click menu when your cursor is in an nQuery table.

To illustrate use of this option, we provide an example. Suppose we plan to compare hormonal measurements between two groups. There are four different hormones of interest. To adjust for multiple testing we decide to use the Bonferroni correction and test each using an alpha level of .05/4 = .0125. For hormone A, we want to assess the power to detect the difference of interest using a two-sample t-test.

To compare measurements between two groups:

We bring up the appropriate sample size table for the t-test by choosing the **File** menu **New** option and choosing **Means**, **Two Group, Test**, and selecting **Student's t**.

For **Test significance level**, enter the value **0.0125**.

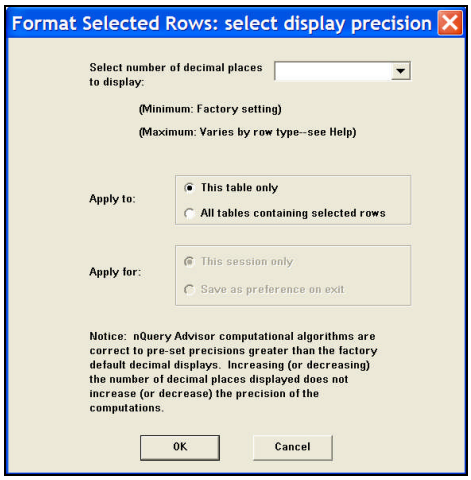


Note that the default decimal display for the significance level row shows only 3 decimal digits and shows the value rounded to 0.013. However, the actual value remains 0.0125, and you can see that in the status bar at the bottom of the nQuery screen.

To change the displayed value in the table:

Click on the **Test significance level** cell, and right click to get the right-click menu.

Select the option at the bottom of the right click menu, **Format Decimal Displays for Selected Rows.** The **Format Selected Rows** dialog box will appear.



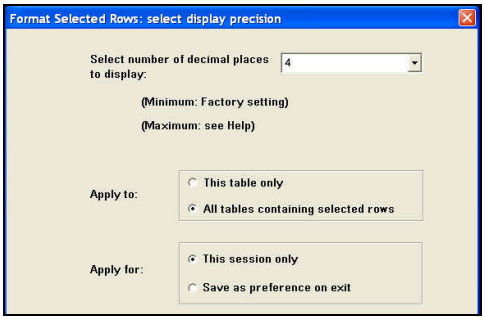
In the **Select number of decimal places to display** field, enter the number **4** into the dropdown box or click on the down arrow and select **4**.

You should pay special attention to the notice on the dialog box:

> Notice: nQuery Advisor computational algorithms are correct to pre-set precisions greater than the factory default decimal displays. Increasing (or decreasing) the number of decimal places displayed does not increase (or decrease) the precision of the computations.

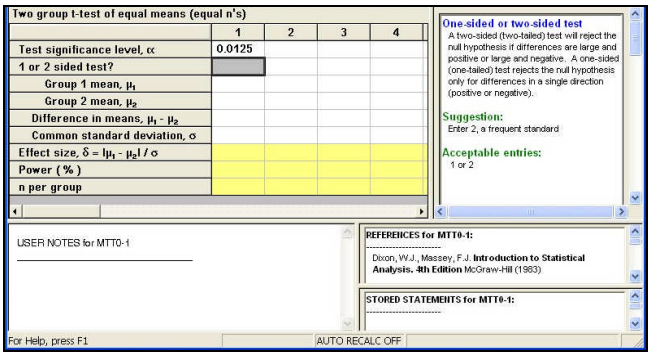
Specify whether you want this number of decimal places to apply only to the table on your screen or to all tables containing the significance level row. Here we will be using other tables for the other hormones, so we click on **All tables containing selected rows**.

That choice activates the **Apply for** options in the dialog box.



Click on the default choice of **This session only** and click on **OK**.

When you re-open nQuery at another session, the factory defaults will be in effect for that table. However, during this session all tables containing the significance level row will allow for four digits.



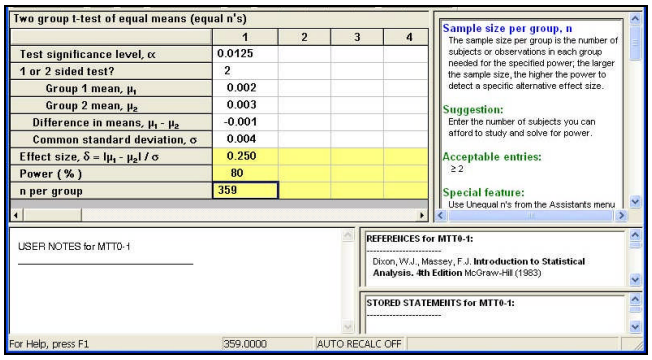
When you save the current table, you save any decimal display settings with it. You will see the same decimal display again when you open the table at a future session, no matter what the display setting is for that new session. The selected decimal display will also show up on printed and pasted tables.

Note: Minimum settings — You cannot reduce the number of displayed decimal places below the factory setting.

Maximim settings — The maximum available number of digits which can be displayed varies by row type:

- For integer rows, the decimal display cannot be changed
- For significance or confidence level rows the maximum number of decimal digits displayable is 6.
- For power rows the maximum number of decimal digits displayable is 2.
- For other rows, the maximum number of decimal digits displayable is 3 more than the default.

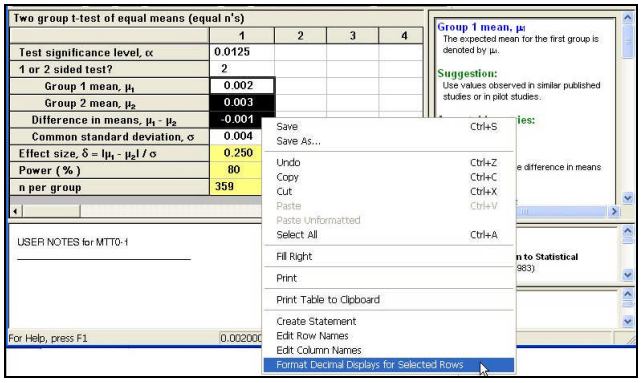
For this example we also suppose that the standard levels of the hormone are expected to be .0015 in the usual units. We expect an increase to .0025 in group 2. The common standard deviation is expected to be .004.



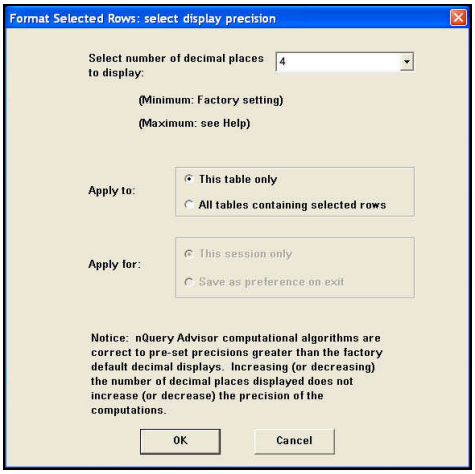
Although you could just enter these numbers and let nQuery proceed or multiply the means and SD by 10, 100, or 1000, you can adjust the number of decimal places displayed to keep the levels in the scale you prefer.

Highlight rows 3, 4 and 5.

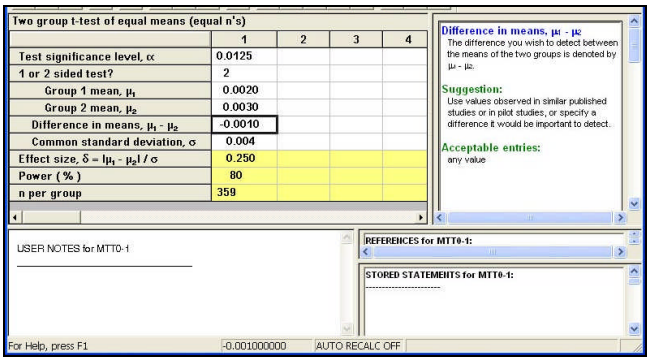
Use the right click menu to select **Format decimal display for selected rows.**



In the **Format Selected rows** dialog box, enter **4** and leave the default set to **This table only**, because this is the only hormone which is measured in this scale.



This change produces the following table.



When you save or print this table you will see the additional decimal places as shown on the screen.

6. Creating a Randomization List in nQuery 7.0

After we have finalized the study design and sample size, it is time to create a randomization list. We might need only a list to give to the pharmacist to use in creating the drugs and placebos required for each patient in the study. Or we might wish to create sealed envelopes to open when each patient has been entered into the study and it is time to administer the treatment (e.g. Swedish massage versus light touch massage).

Now, nQuery Advisor can create the randomization list for your study. nQuery Advisor has a new Randomize menu with four procedures to assist in creating a randomization list. In this chapter we take the user through examples for each of these procedures.

Create randomization list (basic)

Use for studies with equal sample sizes. Simply enter the names of the treatment groups, and the total sample size, and click on View List to get a randomization list to save, print, or copy into a document or spreadsheet. See Example 1.

Create randomization list (advanced)

Use for studies with unequal sample sizes, centers and/or strata, or user selection of randomization block sizes. See Examples 2 and 3 for details. The advanced version gives you more to specify:

- Specify treatment group names and randomization ratios.
- Specify stratum names, ID number prefixes, and the proportions of cases expected.
- Enter the total sample size.
- Specify a random seed for the simulation (optional).
- Choose a randomization block size or use nQuery's mixed block size default.
- Click on View List to get a spreadsheet style randomization list with ID numbers, stratum names, and treatment assignments.
- Save or print the list, or paste into a document or a spreadsheet. (Manual and Help list easy steps for making labels for envelopes or data form identification).

Create randomization list (complex designs)

Use for studies with unequal sample sizes, centers and strata, or user selection of randomization block sizes. See Example 5 for details. The complex designs options give you more to specify:

- Specify treatment group names, codes, and randomization ratios.
- Specify center names, and the proportions of cases expected in each center.
- Specify one or two stratifying factors, stratum names, and the proportions of cases expected in each stratum combination.
- Enter the total sample size.
- Specify a random seed for the simulation (optional.)
- Choose a randomization block size or use nQuery's mixed block size default.
- Click on View List to get a spreadsheet style randomization list with ID numbers, center and stratum names, and treatment assignments.
- Edit the default ID numbers.
- Save or print the list, or paste into a document or a spreadsheet. (The Help and Example 3 in this chapter list easy steps for making labels for envelopes or data form identification).

Random subset of cases

Use this option to select a random sample of n cases from N available subjects. See Example 4 in this chapter for details.

Example 1

Creating a randomization list (basic)

Use for studies with equal sample sizes. Simply enter the names of the treatment groups, and the total sample size, and click on View List to get a randomization list to save, print, or copy into a document or spreadsheet. See Example below.

Create Randomization List (Basic)

This option is for simple designs with 2 to 20 treatments/groups to which subjects must be assigned. Use this option if:

- the sample sizes in all the groups will be equal

- all subjects are from a single center
- there are no strata.

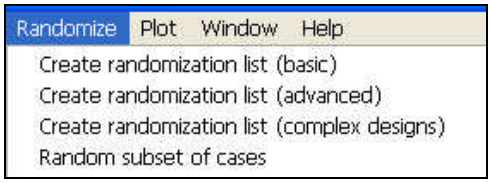
If different treatment groups will have different sample sizes, if there are multiple centers or strata, or if you wish to choose your own block sizes, **Create Randomization List (Advanced) or Create Randomization List (complex designs)** instead.

Suppose your planned study will have two treatment groups, New drug and Placebo, with 20 subjects per group (a total of 40 subjects). See Tutorial, Chapter 2, for details on how the sample size was selected for this particular example.

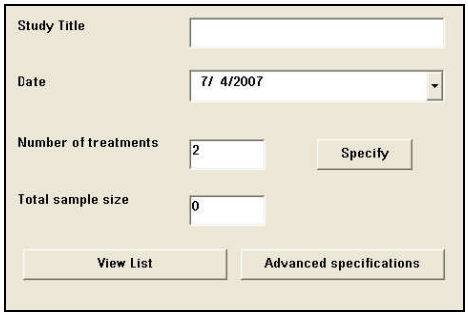
The pharmacist will need a list of patient ID numbers together with the treatment group to which each patient will be assigned in order to make up 40 bottles of pills. Each bottle will be labeled only with the patient ID and dispensing information, to maintain a double-blind study.

To create the randomization list for this study:

Select **Create Randomization List (Basic)** from the **Randomize** menu.

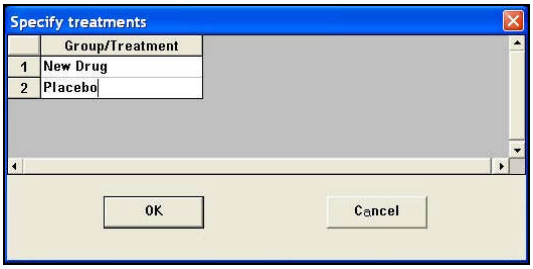


You will see the following screen. Note that nQuery supplies the date automatically.

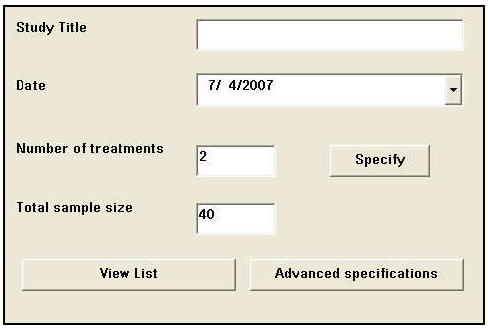


Fill in the study title and change the date if necessary. Clicking on the **Advanced specifications** button will take you to **Create randomization list (Advanced)** if you need to specify a more complex design. The information you have already typed in will be carried forward.

The default number of treatments is 2 so this box does not need to be changed. Click on the **Specify** button in order to specify the names of the treatments to which patients will be assigned. A Specify dialog box will appear. For this example, type in **New drug** and **Placebo** and click on **OK**.



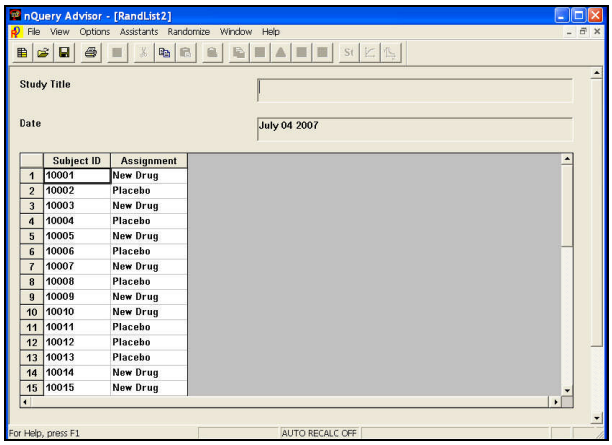
You will see the original screen again. The required sample size is 40, so type this in (or type in a somewhat larger number if you may need a few extra patient assignments just in case).



Click on the **View list** button. nQuery will create a randomization list using its own algorithm for mixing randomization block sizes.

For this example, block sizes will be 2 and 4. See **Computational Methods** at the end of this chapter for details.

The randomization list dialog box will appear with the study title, date, and a viewable spreadsheet with subject ID numbers and the treatment or group assignment for each subject.



You can examine the list on the screen by moving up and down using the slider bar. You can save the list to a file, you can copy it and paste it into a spreadsheet or word processing program, or you can print it. If you wish to change the specifications, click on re-specify and change the group names or the sample size. If you want to keep this list, you must save it before clicking on the re-specify button.

To save the list to a file:

Click on **Save** or **Save as.** The file will be saved as an nQuery file with the nQuery randomization list file extension .nqr. You can open this file again at a later time. In addition, you can save the header information and the treatment assignment list in a comma delimited text file (.csv file) or an ordinary text file (.txt file).

To copy the file for inclusion in documents:

Click on **Copy**. The list can be pasted directly into a spreadsheet or word processing program where it will appear as a table. Information about the study title, treatment names, sample size, and blocking method will appear in the pasted table. You can then edit the information at the top of the page and the column headers and/or subject ID numbers as desired and save or print from these programs.

Text below pasted into manual from nQuery:

July 4 2007
List created on July 4 2007 10:22:27
Group/Treatment Ratio
New drug 1
Placebo 1
Block size: Mixed
Random seed: 1189963347
Total sample size: 40

Subject ID	Assignment
100001	Placebo
100002	New drug
100003	New drug
100004	Placebo
100005	Placebo
100006	New drug
100007	Placebo
100008	New drug
100009	New drug
100010	Placebo
100011	New drug
100012	Placebo
100013	New drug
100014	Placebo ……..

If you want to create labels for sealed randomization envelopes, you can paste the file into Word and then use the Word Mail Merge Wizard. See details in Example 3 in this chapter.

To print the randomization list file:

Click on **Print.**

Example 2

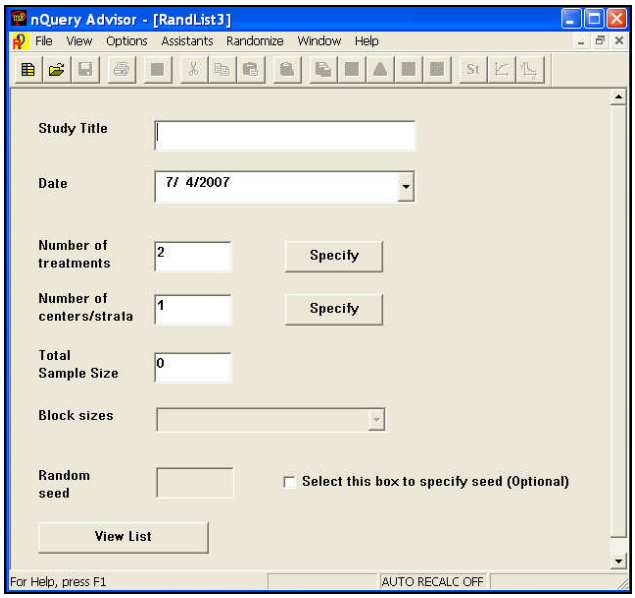
Creating a randomization list for a complex design using Create randomization list (advanced)

Consider an example in which there will be 3 treatment groups, placebo, new drug, standard drug. The ratio of sample sizes will be 1:2:2. That is, one-fifth of patients will be assigned to the placebo group, and two-fifths to each of the two active drugs. Patients will be entered at two sites, Center 1, and Center 2, and patients will be assigned to one of two strata: normal body weight and heavy. It is expected that the two Centers will enter about the same number of patients, and that about 20% of patients will be in the "heavy" category. The total sample size is planned to be 500.

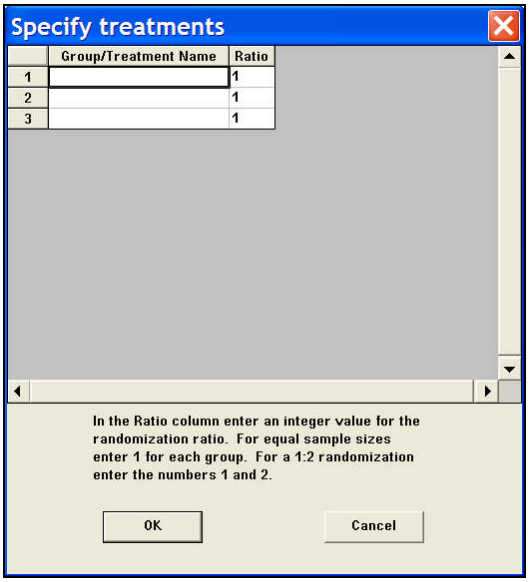
To create a randomization list for this example:

Select **Create Randomization List (Advanced)** from the **Randomize** menu.

In the Randomization dialog box, enter the study title, Example 2.



For our example, we specify that there are 3 treatments, and click on the **Specify** button. The **Specify** dialog box will appear with the **Ratio** column filled in for the default situation in which all treatments would have equal sample sizes.

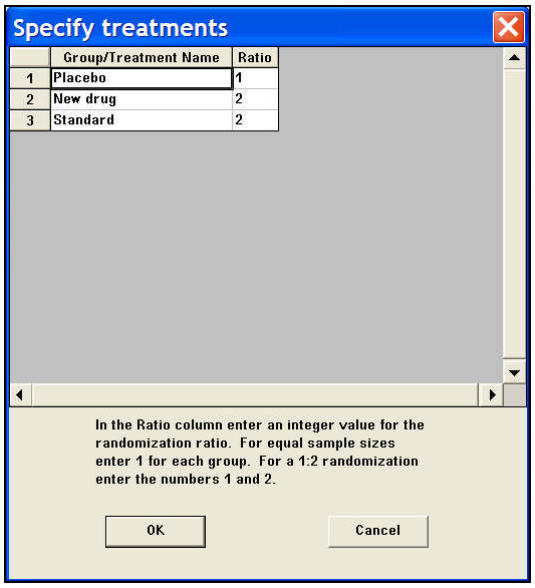


Type in the three treatment group names, **Placebo**, **New drug**, and **Standard**.

Edit the **Ratio** column for **New drug** and **Standard** to specify sample size ratios in these groups of twice the planned sample size for the **Placebo** group.

Note that the ratios must be whole numbers. If, for example, the ratios were 1 to 2.5, you would enter 2 and 5.

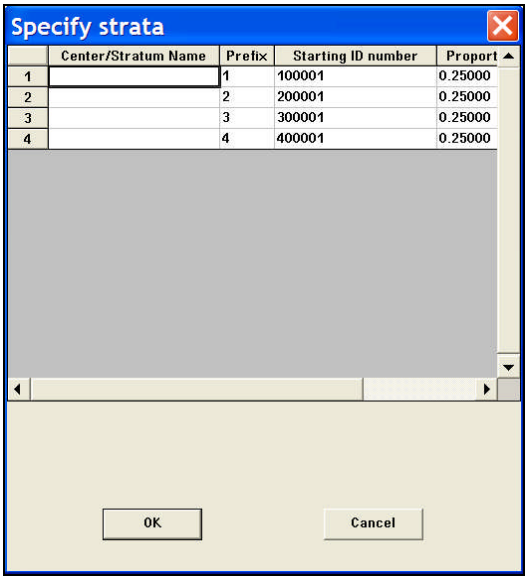
Enter **1**, **2**, and **2** in the **Ratio** column.



Click **OK** to return to the Randomization List dialog box.

You must now specify the number of centers/strata. In this example there are 2 centers and 2 strata, so we will need randomization lists for 4 center/stratum combinations. Alternatively, you could select **Create Randomization List (Complex Designs)** and specify the centers and strata separately; see Example 5.

In the **Number of strata** field, enter the number **4** and click on the **Specify** button. The **Specify strata** dialog box will appear.

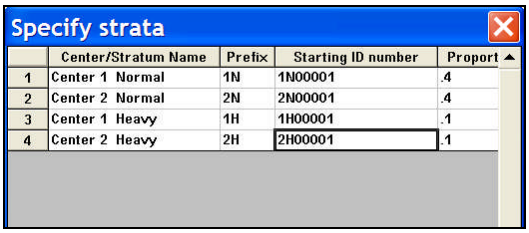


The **Specify strata** dialog box will display starting ID numbers and prefixes for each center/stratum. The dialog box is filled in for the situation where all centers/strata are expected to be about the same size.

Note: The proportions expected in each center/stratum must add to 1.

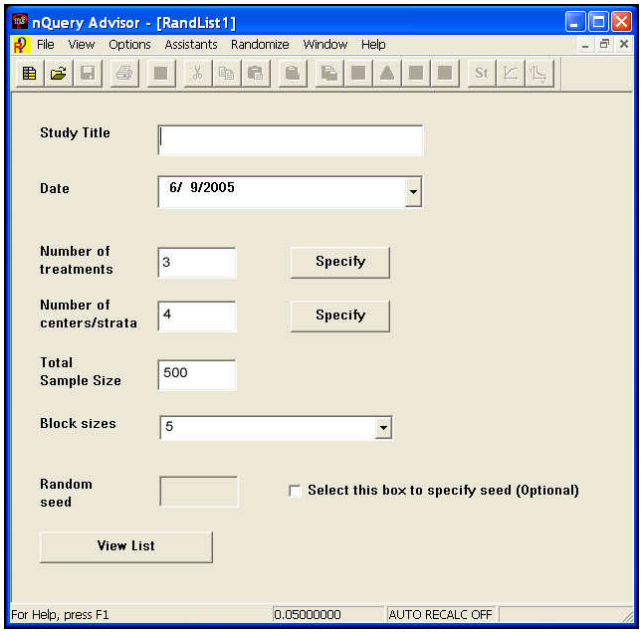
For this example we fill in the center/stratum names for the two center by two weight level strata. We enter names **Center 1 Normal**, **Center 2 Normal**, **Center 1 Heavy** and **Center 2 Heavy**. We want the ID numbers to start with prefixes specifying Center number and weight stratum, so we assign prefixes 1N, 2N, 1H, 2H. The Heavy category will be expected to have 20% of the total sample size or 10% in each Center, so enter the proportions, .4, .4, .1, .1.

Click **OK** and the Randomization dialog box will appear again.



We must specify the total sample size of 500. Or we can type in a somewhat larger sample size to allow for extra patients in one or more of the centers or strata.

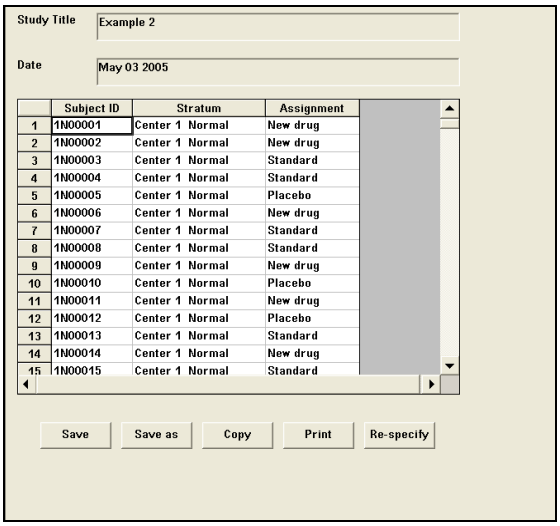
Specify whether you want all blocks to be size 5 (the minimum allowable with a 1:2:2 randomization), size 10, size 15, or size 20. Or you can use the nQuery mixed blocks randomization. If you choose the mixed block randomization, about 60% of the sample size within each center/stratum will be assigned using blocks of size 5 and the rest using blocks of size 10. See the **Computational Methods** section at the end of this chapter for details. Here we enter our choice of blocks of size 5. Note that you can select from the dropdown menu or enter a value.



For Create Randomization List (advanced), you do not have to specify a random seed, but may do so if you wish. If no random seed is specified, nQuery uses the clock on your computer to create the random seed to start the randomization. If you want to specify a random seed for the simulation, check the box labeled **Select this box to specify seed (optional)** and enter an integer value into the box labeled **Random seed**.

To see the randomization list, click on **View List**.

The **Randomization List** screen will appear with the study title, date, and a viewable spreadsheet with subject ID numbers, center/stratum labels, and the treatment or group assignment for each subject.



Use the slider bar to move down in the list to see the treatment assignments for the other center/stratum combinations.

You can save the list to a file, you can copy it and paste it into word processing program or a spreadsheet, or you can print it. If you wish to change the specifications, click on re-specify and respecify the desired information. If you want to keep this list, you must save it before clicking on the re-specify button.

To save the randomization list to a file:

Click on the **Save** or **Save as** button. The file will be saved as an nQuery file with the nQuery randomization list file extension .nqr. You can open this file again at a later time and can re-specify the list if desired. In addition, you can save the header information and the treatment assignment list in a comma delimited text file (.csv file) or an ordinary text file (.txt file).

To copy the file to be included in a document:

Click on the **Copy** button. Then you can paste the list directly into Excel or into Word where it will appear as a table. Information about the study title, treatment names, etc will appear in the pasted table. You can then edit the headers and/or subject ID numbers as desired and save or print from these programs. See Example 1 in this chapter for an example of a pasted list with header information.

To print the randomization file:

Click on the **Print** button.

To create labels for sealed randomization envelopes:

Paste the copied file into Word and then use the Word Mail Merge Wizard. See details in Example 3 in this chapter.

Example 3

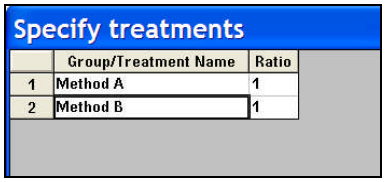
How to create labels for envelopes, cards, or form IDs from your randomization list.

For this example, let us use a simpler, smaller design. Suppose that patients will receive one of two surgical methods, Method A, or Method B and that the study will be done for patients with only a primary tumor and also for patients with metastatic disease. The total sample size will be about 60.

To create the randomization list:

Select **Create randomization list (Advanced)** from the **Randomize** menu.

Enter 2 treatments and specify the names **Method A** and **Method B**.



Enter **2** in **Number of strata**.

Specify the strata.

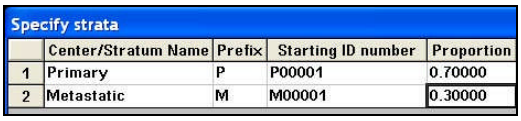
For **Primary** stratum, enter **P** in the Prefix field.

For **Metastatic** stratum, enter **M** in the Prefix field.

Each Starting ID number will change to reflect the prefix entered.

We expect that about 30% of patients will have metastatic disease. Enter **.7** in the **Primary Proportion** field.

Enter **.3** in the **Metastatic Proportion** field.



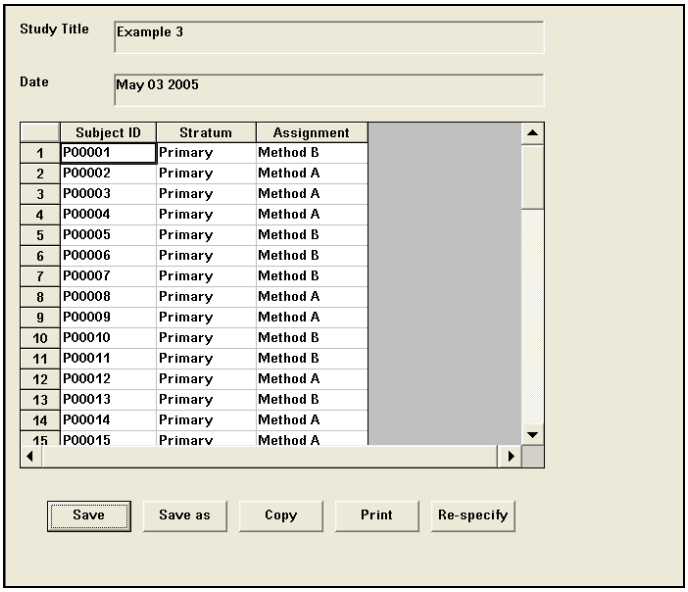
Click on **O**K to complete Strata Specification.

Enter a **Total Sample Size** of **60** or a somewhat larger number to provide for extras.

Select **Mixed** in the **Block sizes** field.

Click on the **View List** button, and the **Randomization list** dialog box will appear.

Scroll down, if necessary, to see the full list.



To create labels from the randomization list:

Click on the **Copy** button.

Open up Word and paste the list into Word.

In Word, delete all the header information except for the three column headers.

Delete the empty row under the column header.

Save the Word file, we named our file **Example3.doc**.

Close the Word document.

Note: Mail Merge options will vary in different versions of Word.

Open a new Word document and start the Mail Merge Wizard.

Depending on your version of Word, select the **Tools** menu **Mail Merge** option, or point to **Letters and Mailings**, and then click **Mail Merge Wizard**.

In the right hand panel, under **Select document type**, click **Labels**. Then click **Next** to continue.

Under **Select starting document**, click on **Change document layout** and then click on **Label Options.**

In the **Label Options** dialog box, select the correct printer type, and the type of label you are using. Then click OK.

The document will then show a layout for the label type. Click on **Next** at the bottom of the screen.

Under **Select recipients** click on **Use an existing list**,

Under the header **Use an existing list**, click on **Browse**. Find and select the saved list.

You will see a dialog box labeled **Mail Merge Recipients** complete with headers and a view of the assignment rows. Unless you want to print only part of the list, click on **Select All**, and click **OK**.

Under the Wizard **Use an existing list** header, it gives the name of the file. Click on **Next**.

Under **Arrange your labels**, click on a location in the first label, and click on the words **Address block** in the Wizard. In the **Insert Address Block** dialog box, click on the **Match Fields** button at the bottom.

Assign each of the columns to something Word recognizes (i.e. put Subject ID into “Last name” slot, Stratum into “company name” etc.) If you want Subject ID, Center/Stratum, and Assignment all on the same line, assign these to last name, first name, and title. If you want all 3 on different lines, put them in last name, company, and address1 or city. Click on **OK**. In the **Insert Address Block** box, click on **OK**.

Click on **Update all labels**.

Click on the **Next** button and preview the labels.

If the labels look good, click on **Complete the merge**.

Click on the **Next** button.

Click on the **Print** command to print out your labels.

Click on the **Edit individual labels** command to create a Word file containing all your labels which can be saved for future use.

Labels for Envelopes

Print one set of labels in which the column with treatment assignment has been deleted to paste on the outside of the envelopes.

Labels for Cards in the Envelopes

Print one set of labels with all columns to paste on cards to be inserted in the envelopes.

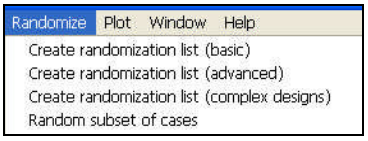
Example 4.
Random subset of cases

This option is useful when you have a list of subjects and want to select a random subset for an interview or a questionnaire.

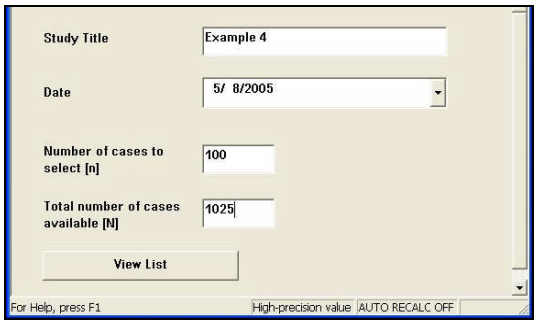
Suppose that 1025 patients with a specified diagnosis have been seen in the past 5 years. To evaluate whether recommended procedures were used in these cases, it is decided to review the medical records for a 10% random sample of individuals. The records are ordered by medical record number and a sequence number generated. Researchers need a list of which records to select in the sequence. They decide to select 100 records.

To create a list of which records to select for this study:

Choose **Random subset of cases** from the **Randomize** menu.

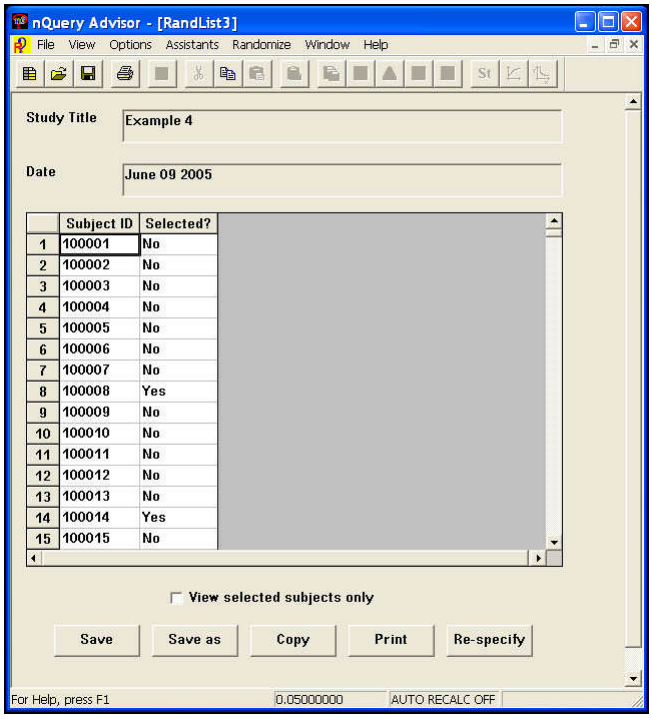


You will see the following screen. Note that nQuery supplies the date automatically. Fill in the study title. Enter **100** as the number of cases to select. Enter **1025** as the total number of cases available.



Click on **View List** button.

The randomization list dialog box will appear with the study title, date, and a viewable spreadsheet with the Subjects IDs numbered from 1 to 1025 and a Selected? column containing the word Yes for sequence numbers selected for the random sample and No for sequence numbers not selected for the random sample.



You can examine the list on the screen by moving up and down using the slider bar. You can save the list to a file, you can copy it and paste it into a word processing program or a spreadsheet, or you can print it. If you wish to change the specifications, click on re-

specify and change one or both of the sample sizes. If you want to keep this list, you must save it before clicking on the re-specify button.

If you only want to see a list of the cases which have been selected, check the **View selected subjects only** box.

To save the list to a file:

Click on **Save** or **Save as.** The file will be saved as an nQuery file with the nQuery randomization list file extension .nqr. You can open this file again at a later time and view either all the cases or only the selected cases by selecting or unselecting the **View selected subjects only** box. In addition, you can save the header information and the treatment assignment list in a comma delimited text file (.csv file) or an ordinary text file (.txt file).

To copy the file for inclusion in documents:

Click on **Copy**. The list can be pasted directly into a word processing program or a spreadsheet where it will appear as a table. Information about the study title and sample sizes will appear in the pasted table. You can then edit the information at the top of the page and the column headers and/or subject ID numbers as desired and save or print from these programs. The pasted list will contain either all the cases or only the selected cases depending on whether or not the **View selected subjects only** box has been selected.

You can see part of the current list copied and pasted below:

July 4 2007
List created on July 4 2007 10:22:27

Group/Treatment	Ratio
Yes	100
No	925
Block size:	1025
Random seed:	1730863952
Total sample size:	1025

Subject ID	Selected?
100001	No
100002	No
100003	No
100004	No
100005	No
100006	No

…

To print the randomization list file:

Click on **Print.**

Example 5

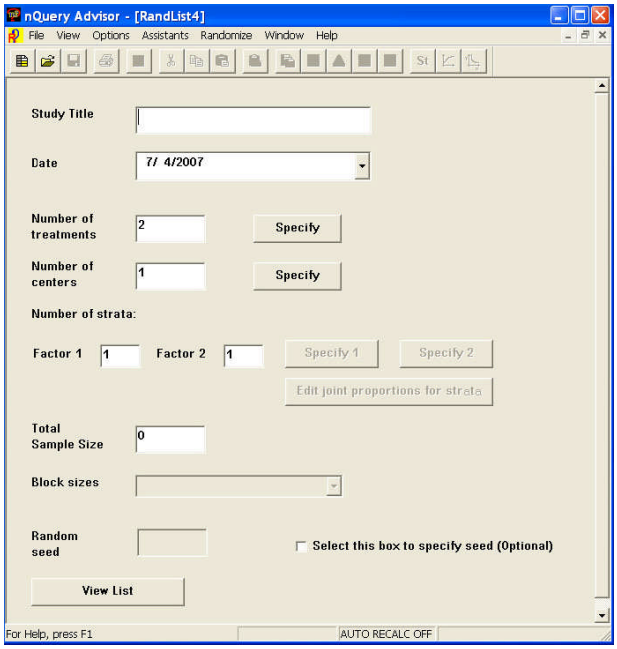
Creating a randomization list for a complex design using Create randomization list (complex design)

Consider an example in which there will be 3 treatment groups, placebo, new drug, standard drug. The ratio of sample sizes will be 1:2:2. That is, one-fifth of patients will be assigned to the placebo group, and two-fifths to each of the two active drugs. Patients will be entered at three sites, Center 1, Center 2, and Center 3, and patients will be stratified using two stratifying factors: gender (male or female) and smoking (smoker or non-smoker). It is expected that the three Centers will enter about the same number of patients, and that about 30% of patients will be in the "smoker" category. The total sample size is planned to be 500.

To create a randomization list for this example:

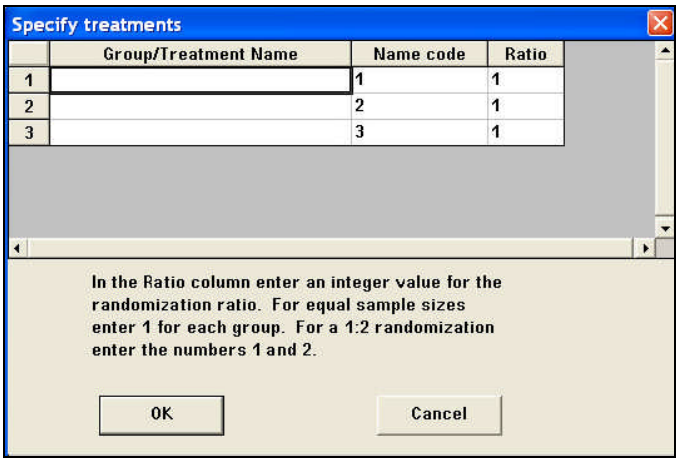
Select **Create Randomization List (Complex designs)** from the **Randomize** menu.

In the Randomization dialog box, enter the study title, Example 5.



For our example, we specify that there are 3 treatments, and click on the **Specify** button. The **Specify** dialog box will appear with the **Ratio** column

filled in for the default situation in which all treatments would have equal sample sizes.



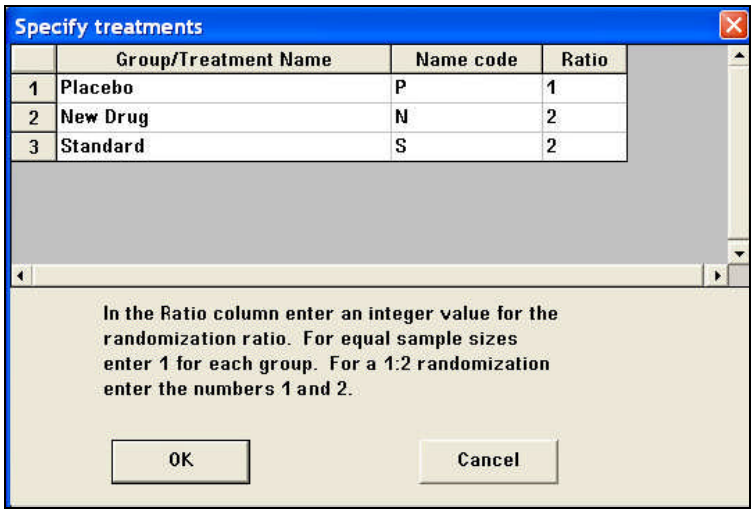
Type in the three treatment group names, **Placebo**, **New drug**, and **Standard**.

Leave the default treatment code numbers, or type in the other numbers or letters such as **P, N**, and **S**. They will appear as a column in the randomization list.

Edit the **Ratio** column for **New drug** and **Standard** to specify sample size ratios in these groups of twice the planned sample size for the **Placebo** group.

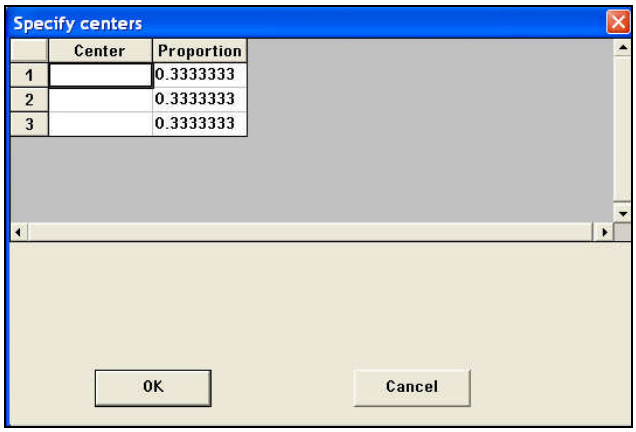
Note: The ratios must be whole numbers. If, for example, the ratios were 1 to 2.5, you would enter 2 and 5.

Enter **1**, **2**, and **2** in the **Ratio** column.

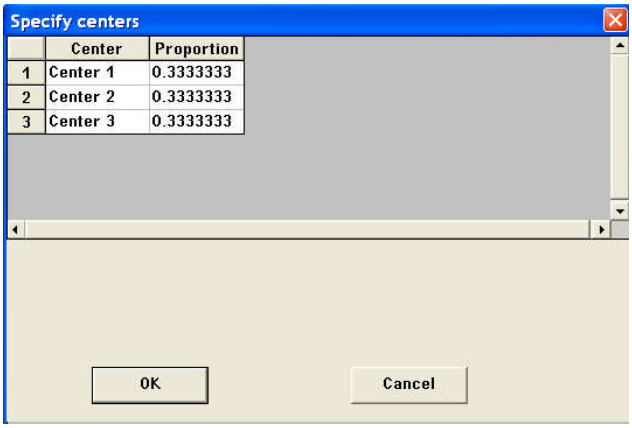


Click **OK** to return to the Randomization List dialog box.

You must now specify the number of centers. In this example there are 3 centers, so enter the number 3 and click on the **Specify** button. The **Specify centers** dialog box will appear.



Enter the center names and edit the proportions column if necessary. For this example, we expect the same sample size in each center, so the filled-in box will retain the default proportions.

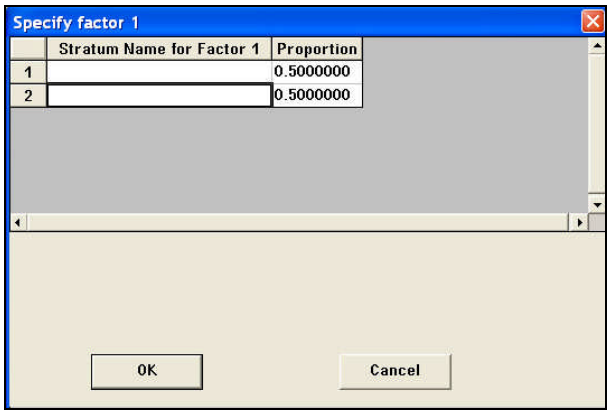


Note: The proportions expected in each center must add to 1.

Click **OK** to return to the Randomization List dialog box.

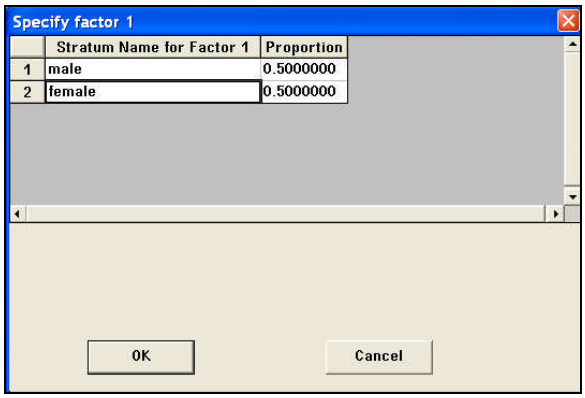
There are two stratifying factors, factor 1 is gender, and factor 2 is smoking status; each has two strata. Enter the number 2 for Factor 1, and click on the **Specify 1 button** to specify the strata for Factor 1.

The **Specify factor 1** dialog box will appear.



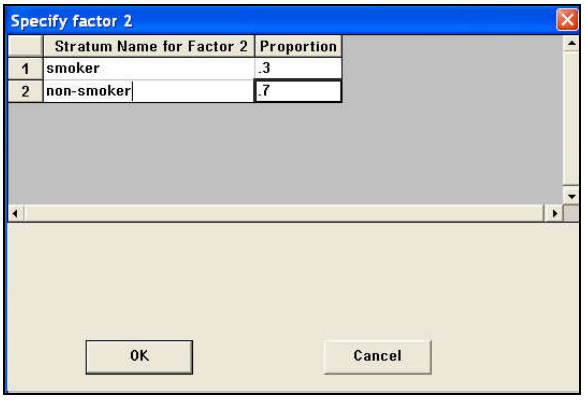
Enter the stratum names and the proportions of patients expected in each stratum. Here we expect an equal number of males and females, so we enter the names **male** and **female** and leave the default proportions.

Note: The proportions expected in each stratum must add to 1.



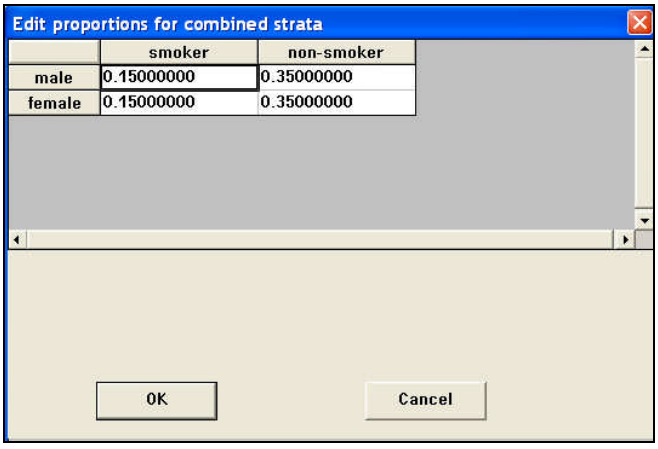
Click on **Ok** to return to the Randomization List dialog box.

Specify two strata for Factor 2. Now the **Specify 2** button is activated, so click on this to specify the strata for Factor 2. We enter **smoker** and **non-smoker** and change the proportions to **0.3** and **0.7.**



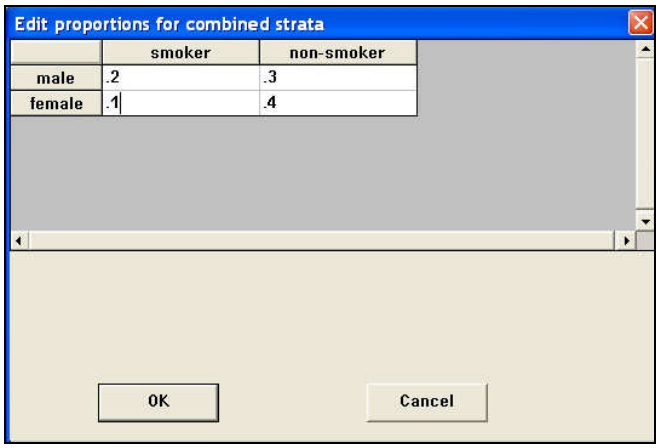
Click **OK** to return to the Randomization List dialog box.

If you expect that the proportions in the four combined strata are what would be expected if the stratifying factors were independent, continue on and specify the total sample size. If you want to check the proportions for the combined strata or to edit them, click on **Edit joint proportions for strata.**



For this example, we assume that fewer women smoke and change the proportions to

0.2 and **0.3** for males and **0.1** and **0.4** for females to maintain a 50-50 ratio of males to females.



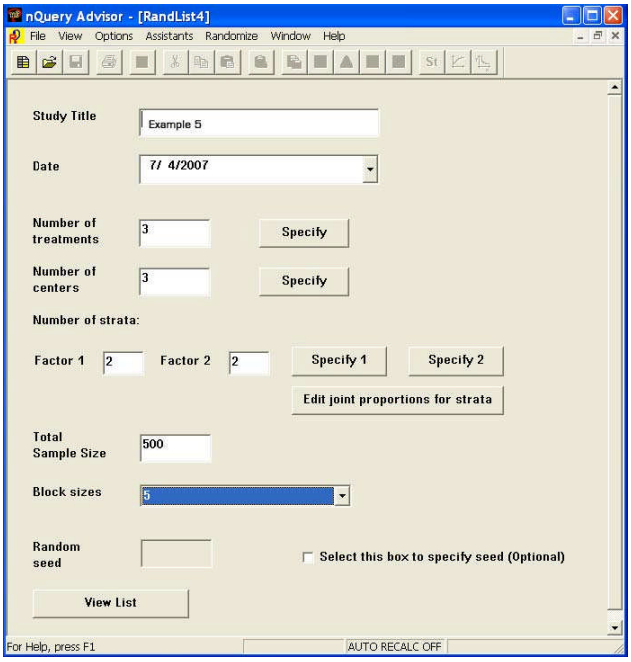
Note: The proportions expected in the combined strata must add to 1.

Click **OK** and the Randomization dialog box will appear again.

When you click on **OK** this automatically updates the proportions in the **Specify Factor 1** and **Specify Factor 2** dialog boxes if necessary.

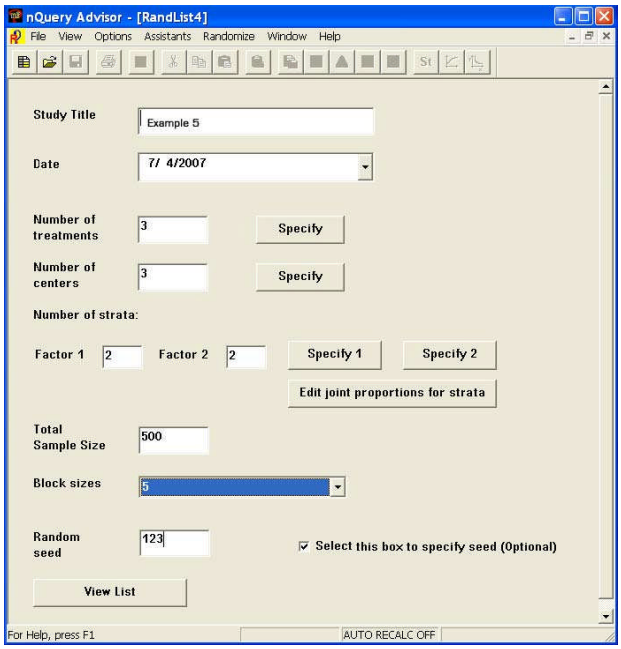
We specify a total sample size of 500. Or we can type in a somewhat larger sample size to allow for extra patients in one or more of the centers or strata.

Specify whether you want all blocks to be size 5 (the minimum allowable with a 1:2:2 randomization), size 10, size 15, or size 20. Or you can use the nQuery mixed blocks randomization. If you choose the mixed block randomization, about 60% of the sample size within each center/stratum will be assigned using blocks of size 5 and the rest using blocks of size 10. See the **Computational Methods** section at the end of this chapter for details. Here we enter our choice of blocks of size 5. Note that you can select from the dropdown menu or enter a value.



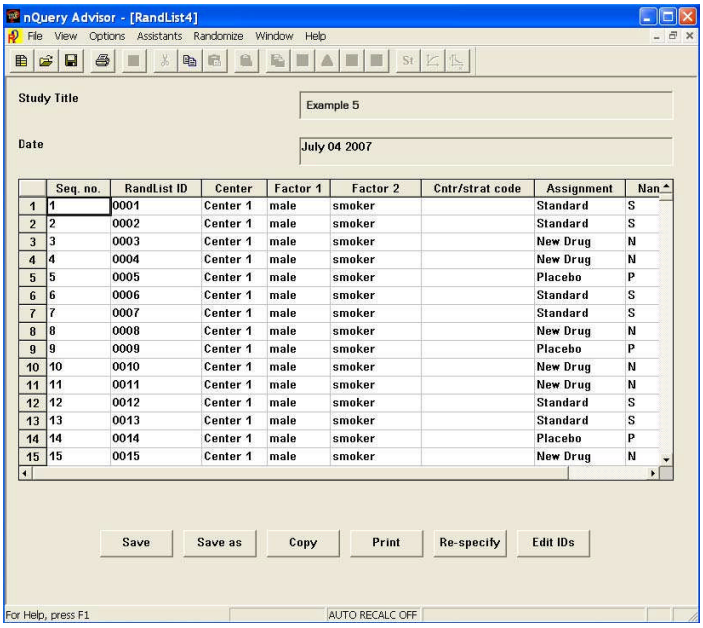
nQuery starts the randomization with a random seed to initiate the pseudo-random number generator used for the simulations. For **Create Randomization List (complex designs)**, you do not have to specify a random seed, but may do so if you wish. If no random seed is specified, nQuery uses the clock on your computer to create the random seed to start the randomization.

If you want to specify a random seed for the simulation, check the box labeled **Select this box to specify seed (Optional)** and enter an integer value greater than 0 into the box labeled **Random seed**. Here we specify a random seed of **123**.



To see the randomization list, click on **View List**.

The **Randomization List** screen will appear with the study title, date, and a viewable spreadsheet with subject ID numbers, center/stratum labels, and the treatment or group assignment for each subject.



Use the slider bar to move down in the list to see the treatment assignments for the other center/stratum combinations.

You can save the list to a file, you can copy it and paste it into a document of spreadsheet, or you can print it. If you wish to change the specifications, click on re-specify and re-specify the desired information. If you want to keep this list, you must save it before clicking on the re-specify button.

If you want to have Codes for the Center/stratum combinations appear in the List, click on **Edit IDs** to specify.

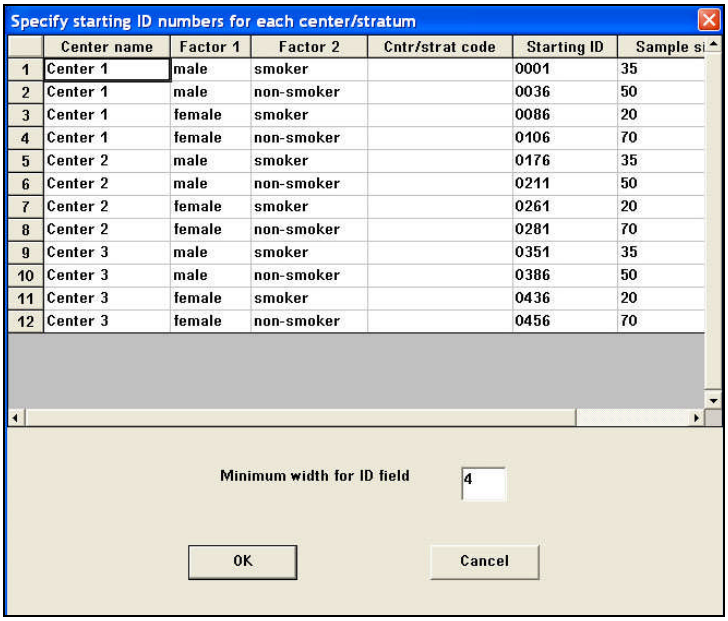
nQuery automatically creates RandList ID numbers for the subjects by using the sequence numbers (in this case the numbers 1 to 525 since more than 500 subjects were required to satisfy the treatment, center, and stratum specifications) and padding them with leading zeros. If you wish to edit these ID numbers, perhaps to number separately within each center or stratum, or to change the minimum width of the ID number, click on the button labeled **Edit IDs**. Note that the RandList ID numbers created using the **complex designs** option can not have alphabetic prefixes like those created using the **advanced** options.

Then we edit the starting IDs to begin the numbering for each center with a unique digit while allowing sequential numbering within each center.

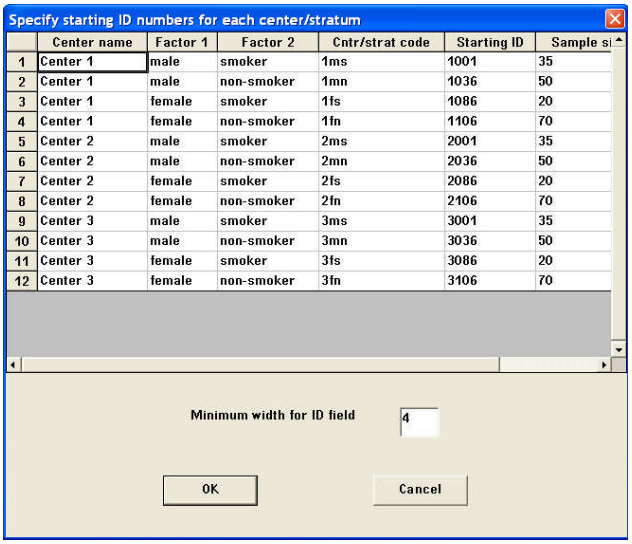
To edit the subject IDs.

Cick on the button labeled **Edit IDs**. The **Specify starting ID numbers for each center/stratum** dialog box will appear.

This box shows the center and stratum names, the starting IDs, and the sample sizes for each center/stratum combination.

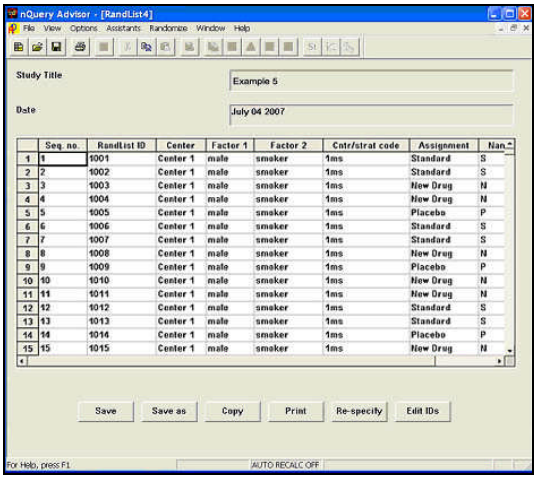


For this example, we edit the starting IDs to begin the numbering for each center with a unique digit but allow sequential numbering within each center. That is, we change the starting IDs for the four Center 1 strata to 1001, 1036, 1086, 1106; we change the starting IDs for the four Center 2 strata to 2001, 2036, 2086, 2106; and we change the starting IDs for the four Center 3 strata to 3001, 3036, 3086, 3106.



Note: It is assumed that numbering occurs from the top of the list down. nQuery will identify overlapping numbers if the starting ID in any succeeding center/stratum combination is not high enough. Hence, it will not allow numbering from the bottom up.

When you click **OK** you will see the randomization list with the changes in the codes and the ID numbers.



Note: If you choose to re-specify, the original list will be lost unless you specify the same random seed. When you change only a treatment,

starting IDs will still work, they will usually be kept. If you make changes which could create duplicate IDs, the ID specifications will be erased and the new list will be generated with sequential IDs starting with 0001 (if a width of 4 was selected). **If you have re-specified you should check to make sure the IDs have been altered as desired and that no duplicate IDs have been created.**

To save the randomization list to a file:

Click on the **Save** or **Save as** button. The file will be saved as an nQuery file with the nQuery randomization list file extension .nqr. You can open this file again at a later time. You also have the option to save the randomization list in a .csv or .txt format to use in other applications.

To copy the file to be included in a document:

Click on the **Copy** button. Then you can paste the list directly into a spreadsheet or into a document where it will appear as a table. Information about the study title, treatment names, etc will appear in the pasted table. You can then edit the headers and/or subject ID numbers as desired and save or print from these programs. The following listing shows the header information and selected portions of the randomization list as pasted into Microsoft Word from Microsoft Excel.

RandList4.nqr

Example 5

July 4 2007

List created on July 4 2007 17:01:56

Group/Treatment	Ratio
Placebo	1
New Drug	2
Standard	2

Center	Factor 1	Factor 2	Cntr/strat code	Starting ID	Target proportion	Sample size
Center 1	male	smoker	1ms	1001	0.067	35
Center 1	male	non-smoker	1mn	1036	0.100	50
Center 1	female	smoker	1fs	1086	0.033	20
Center 1	female	non-smoker	1fn	1106	0.133	70
Center 2	male	smoker	2ms	2001	0.067	35
Center 2	male	non-smoker	2mn	2036	0.100	50
Center 2	female	smoker	2fs	2086	0.033	20

Center 2	female	non-smoker	2fn	2106	0.133	70
Center 3	male	smoker	2ms	3001	0.067	35
Center 3	male	non-smoker	3mn	3036	0.100	50
Center 3	female	smoker	3fs	3086	0.033	20
Center 3	female	non-smoker	3fn	3106	0.133	70

Block size: 5

Random seed: 123

Total sample size: 525

Total sample size has been increased so that no centers/strata contain incomplete blocks; this may affect the relative proportions of the strata.

Seq no.	RandList ID	Center	Factor 1	Factor 2	Cntr/strat code	Assignment	Name code
1	1001	Center 1	male	smoker	1ms	Standard	S
2	1002	Center 1	male	smoker	1ms	Standard	S
3	1003	Center 1	male	smoker	1ms	New Drug	N
4	1004	Center 1	male	smoker	1ms	New Drug	N
5	1005	Center 1	male	smoker	1ms	Placebo	P
6	1006	Center 1	male	smoker	1ms	Standard	S
7	1007	Center 1	male	smoker	1ms	Standard	S
8	1008	Center 1	male	smoker	1ms	New Drug	N
9	1009	Center 1	male	smoker	1ms	Placebo	P
174	1174	Center 1	female	non-smoker	1fn	New Drug	N
175	1175	Center 1	female	non-smoker	1fn	Standard	S
176	2001	Center 2	male	smoker	2ms	New Drug	N
177	2002	Center 2	male	smoker	2ms	Standard	S
178	2003	Center 2	male	smoker	2ms	Standard	S
516	3166	Center 3	female	non-smoker	3fn	New Drug	N
517	3167	Center 3	female	non-smoker	3fn	Standard	S

518	3168	Center 3	female	non-smoker	3fn	New Drug	N
519	3169	Center 3	female	non-smoker	3fn	Placebo	P
520	3170	Center 3	female	non-smoker	3fn	Standard	S
521	3171	Center 3	female	non-smoker	3fn	Placebo	P
522	3172	Center 3	female	non-smoker	3fn	Standard	S
523	3173	Center 3	female	non-smoker	3fn	New Drug	N
524	3174	Center 3	female	non-smoker	3fn	Standard	S
525	3175	Center 3	female	non-smoker	3fn	New Drug	N

To print the randomization file:

Click on the **Print** button.

To create labels for sealed randomization envelopes:

Paste the copied file into Microsoft Word and then use the Word Mail Merge Wizard. See details in Example 3 in this chapter.

Computational methods

Assume that we have G groups to which we are assigning subjects. The randomization ratio is denoted as:

- 1:1 for two groups with equal sample sizes
- 1:2 for two groups with the larger sample size equal to twice the smaller
- 1:1:1 for three groups with equal sample sizes
- 1:2:2 with 3 groups in which groups 2 and 3 will have twice the sample size of the first group.

In general, these ratios are denoted as $r_1, r_2, \ldots, r_G$. Note that all the r's must be integers, so 1 to 2.5 would have to be defined as 2 to 5.

Let B_{min} denote the minimum block size for randomization; $B_{min} = \sum r_i$. So for two groups with equal sample sizes, $B_{min} = 2$, for three groups with equal sample sizes, $B_{min} = 3$, for a 1:2:2 design, $B_{min} = 5$.

Let the sample size in the group with the smallest sample size = n_1. Then the total sample size is $N= n_1B_{min}$. If the user specifies an N such that $n_1 = r_1N/B_{min}$ is not an integer, round up n_1 until it is an integer multiple of r_1 and redefine n_1 and N.

In the basic randomization, define B_{min} and $2B_{min}$ as the block sizes to be used. We will use b_1 blocks of size B_{min} and b_2 blocks of size $2B_{min}$. The order of the blocks will be randomized so the B_{min} and $2B_{min}$ sized blocks are intermixed, except that the last block should be the smaller size. The overall sample size should contain about 40% of subjects assigned using blocks of size 2 B_{min}. Therefore, $0.4N = b_2(2B_{min})$ and therefore b_2 is approximately $.2N/B_{min}$.

In the advanced or complex designs randomizations, we can choose B_{min} , $2B_{min}$, $3B_{min}$, 4 B_{min} or the same mixture used as the default for basic randomization. For advanced or complex designs randomization we do the randomization separately for each center/stratum combination and the relevant N is the center/stratum size.

For details of the random number generator used in nQuery Advisor, see discussion for table STT3 in Section 1 of the Appendix.

7. Appendix — References and Formulas

Every nQuery Advisor sample size table, distribution function table, standard deviation table, and table-specific side table has been tested for computational accuracy across table-specific ranges of parameters. Also, each table has been tested for full functionality of editing options and menu items (side tables, plots, statements) for one or more table-specific parameter sets.

You can review the methods used for testing. See the descriptions on the Statistical Solutions Ltd. Internet site, http://www.statsol.ie/valid.htm.

The first section of this appendix provides a brief description of the method used for computations in each table. These descriptions specify degrees of freedom and non-centrality parameters for each test based on non-central t, F, or χ^2. Definitions of the non-centrality parameters use the values for δ, Δ, or Δ^2 shown in the relevant row title of the specific table. Tables grouped together are tables for which nQuery uses the same computational method.

The second section provides details on methods used for computing statistical distribution functions.

Section 1

The nQuery program provides an inquiry table for more than 100 different types of analyses. To simplify table identification, nQuery uses abbreviations for each table name. These abbreviations create a unique abbreviation or code for each table without spelling out the table name in detail.

The first letter of the code represents the selection in the first column of the Study Goal and Design Box:

Means, **P**roportions, **S**urvival, **A**greement, or **R**egression

The second letter of the code represents the selection in the second column of the Goal and Design Box, denoting the number of groups in the design:

One, **T**wo, or **G** (>2 groups)

The third letter of the code represents the selected type of analysis from the third column:

Test, **C**onfidence Interval, or **E**quivalence

The fourth character in the code represents the number of the selection in the list box. The numbers start with 0 at the top of the list box.

For unequal n's tables, the code ends with the letter U. For example, the code for Two-sample t test with unequal n's is MTT0U.

Methods of computation for each table

Note: s=1 for a one-sided test and s=2 for a two-sided test. We define $z_{1-\alpha}$ as the 100(1-α) percentile of the normal (Gaussian) distribution.

MOT0 One-sample t test
MOT1 Paired t test for difference in means

Power, sample size, or effect size are computed using central and non-central t where the non-centrality parameter is $\sqrt{n}\,\delta$ and δ is defined in the table row title. See, for example, O'Brien, R.G., Muller, K.E. (1993) "Unified Power Analysis for t-tests through Multivariate Hypotheses", in Edwards, L.K. (Ed.), *Applied Analysis of Variance in Behavioral Science*, Marcel Dekker, New York. Chapter 8 (pp 297-344).

MOE0 Paired t test for equivalence of means

Power, sample size, or effect size are computed using central and non-central t where the non-centrality parameter is $\sqrt{n}\,\delta$ and δ is defined in the table row title. See, for example, Machin, D., Campbell, M.J. (1987) *Statistical Tables for Design of Clinical Trials*, Blackwell Scientific Publications, Oxford.

MOT2 Univariate one-way repeated measures analysis of variance
MOT3 One-way repeated measures contrast

Power, sample size, or effect size are computed using central and non-central F. For MOT2, the numerator and denominator degrees of freedom are (M-1) and (M-1)(n-1), and the non-centrality parameter is nM times the effect size. For MOT3, the numerator and denominator degrees of freedom are 1 and (M-1)(n-1), and the non-centrality parameter is n times the square of the effect size. The effect sizes are defined in the row titles in the respective tables. For MOT2, see Dixon, W.J., Massey, F.J. (1983) *Introduction to Statistical Analysis*. 4th Edition. McGraw-Hill. Chapter 14. For MOT3, see Overall, J.E., Doyle, S.R. (1994) Estimating Sample Sizes for Repeated Measures Designs, Controlled Clinical Trials 15:100-123.

MOT4 Univariate one-way repeated measures analysis of variance (Greenhouse-Geisser)

Power, sample size, or effect size are computed using methods taken from Muller, KE, Barton CN (1989) Approximate Power for Repeated-Measures ANOVA lacking Sphericity, *Journal of the American Statistical Association* 84:549-555.

MOC0 Confidence interval for mean based on z (n large)
MOC2 Confidence interval for difference in paired means (n large)
MOC4 Confidence interval for repeated measures contrast

Sample size or confidence interval width are computed using the large sample normal approximation, where the equations for interval width are given in the guide cards for the interval width row. See Dixon, W.J., Massey, F.J. (1983) *Introduction to Statistical Analysis*. 4th Edition. McGraw-Hill. Pages 80-85. For MOC4 see also Overall, J.E., Doyle, S.R. (1994) Estimating Sample Sizes for Repeated Measures Designs, Controlled Clinical Trials 15:100-123.

For MOC0 and MOC2, the formula for *n* is $n = \frac{z^2_{1-\alpha/s}\sigma^2}{\omega^2}$.

For MOC4, the formula for *n* is $n = \frac{z^2_{1-\alpha/s}\sigma^2(1-\rho)D^2}{\omega^2}$.

MOC1 Confidence interval for mean based on t (with coverage probability)
MOC3 Confidence interval for difference in paired means (coverage probability)

Sample size or confidence interval width are computed using iterative tolerance interval routines requiring central and non-central t and chi-square. See Kupper, L.L. and Hafner, K.B. (1989) How appropriate are popular sample size formulas? *The American Statistician* 43:101-105.

MOC5 Confidence interval for percentile of a normal distribution

Sample size or confidence interval width are computed based on section 4.4 in Hahn GJ, Meeker WQ (1991) *Statistical Intervals. A guide for practitioners.* John Wiley & Sons, Inc. New York. The P^{th} percentile of a normal distribution is estimated as the sample mean + k (sd) where sd is the sample standard deviation of the distribution and k is chosen to satisfy Prob(z < k) = P. The distance from the estimated percentile to the lower limit of the confidence interval is given by $- t_{1-\alpha}\,\sigma/\sqrt{(n)} + k\sigma$ where $t_{1-\alpha}$ is non-central t with n-1 degrees of freedom and non-centrality parameter $k\sqrt{(n)}$. The distance from the estimated percentile to the upper limit of the confidence interval is given by

$$+t_{1-\alpha}\sigma/\sqrt{(n)} - k\sigma$$

MOT0F **One group t-test that a mean equals user-specified value in finite population**

MOT1F **Paired t-test of mean difference equal to zero in finite population**

MOC0F **Confidence interval for mean based on z (n large) adjusted for finite population**

MOC1F **Confidence interval for mean based on t (with coverage probability) finite population**

MOC2F **Confidence interval for difference in paired means based on z (n large) adjusted for finite population**

MOC3F **Confidence interval for difference in paired means based on t (with coverage probability) finite population**

Computations for these tables are made in the same way as for the corresponding tables without the finite population correction except that the standard deviation is multiplied by the square root of one minus the sampling fraction. For explanation of the effects of finite sampling see Cochran, G. (1977) *Sampling Techniques* 3rd Edition. John Wiley & Sons Inc. New York. Pages 23-28.

MTT0 **Two-sample t-test**

MTE0 **Equivalence of two means**

Power, sample size, or effect size are computed using central and non-central t where the non-centrality parameter is $\sqrt{n}\,\delta/\sqrt{2}$and δ is defined in the table row title. See Dixon, W.J., Massey, F.J. (1983) Introduction to Statistical Analysis. 4th Edition. McGraw-Hill or O'Brien, R.G., Muller, K.E. (1993) "Unified Power Analysis for t-tests through Multivariate Hypotheses", in Edwards, L.K. (Ed.), *Applied Analysis of Variance in Behavioral Science*, Marcel Dekker, New York. Chapter 8 (pp 297-344).

MTT0cv **Two group t-test for fold change assuming log-normal distribution**

After taking ln(FC) as the difference in means and setting $\sigma = \sqrt{\left[\ln\left(1+CV^2\right)\right]}$,

the methods used for computing power and sample size are the same as for MTT0. See also Diletti, E., Hauschke D., Steinijans, V.W. "Sample size determination for bioequivalence assessment by means of confidence intervals" *Int. Journal of Clinical Pharmacology* 29(1991) p. 7.

MTT0fct Two group t-test of equal fold change with fold change threshold

After taking ln(FC) as the difference in means and setting $\sigma = \sqrt{\left[\ln\left(1+CV^2\right)\right]}$,

nQuery uses simulation methods based on the assumption of normally distributed independent samples to estimate the probability of detection. The probability of detection is the percent of simulations in which two conditions are both satisfied: the result is significant at the specified alpha level and the observed fold change exceeds the fold change threshold. It is assumed that the original distributions are log-normal and that the two groups have equal variances in the log scale (that is the CV is constant across groups). Michael Elashoff, personal communication. See also Diletti, E., Hauschke D., Steinijans, V.W. "Sample size determination for bioequivalence assessment by means of confidence intervals" *Int. Journal of Clinical Pharmacology* 29(1991) p. 7.

MTT0uv Two group Satterthwaite t-test of equal means (unequal variances)

Power and sample are computed using numerical integration methods based on the formulas from Moser, B.K., Stevens, G.R., Watts, C.L. "The two-sample t test versus Satterthwaite's approximate F test" *Commun. Statist.-Theory Meth.* 18(1989) pp. 3963-3975.

MTE1tg Two one-sided equivalence tests (TOST) for two-group design

Power or sample size are computed based on the bivariate non-central t-distribution with degrees of freedom 2(n-1) and non-centrality parameters

$$\delta_L = \frac{(\mu_T - \mu_S - \Delta_L)\sqrt{n}}{\sigma\sqrt{2}} \qquad \delta_U = \frac{(\mu_T - \mu_S - \Delta_U)\sqrt{n}}{\sigma\sqrt{2}}$$

using an algorithm due to Owen. When n per group > 5000, a large sample normal approximation is used. See Chow, S.C, Liu, J.P. *Design and Analysis of Bioavailability and Bioequivalence Studies,* Marcel Dekker, Inc. (1992), Schuirmann DJ (1987) A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability, *J. Pharmacokinet Biopharm* 15:657-680, Phillips KE (1990) Power of the two one-sided tests procedure in bioequivalence, *J. Pharmacokinet Biopharm* 18:137-143 and Owen DB (1965) A special case of a bivariate non-central t-distribution. *Biometrika* 52:437- 446.

MTE1co **Two one-sided equivalence tests (TOST) for crossover design**

After defining

$$\sigma = \frac{\sigma_d}{2} = \frac{\sqrt{MSE}}{\sqrt{2}}$$

the same methods are used as for MTE1tg.

MTE2tg **TOST for ratio of means (log scale) for two-group design**

Power or sample size are computed using the same methods as for MTE1tg except that the entered values for the ratio of means and the upper and lower limits are replaced by their natural logs, and the value

$$\sqrt{\left[\ln\left(1+CV^2\right)\right]}$$

is substituted for σ before computing the non-centrality parameters.

MTE2co **TOST for ratio of means (natural log scale) for crossover design**

After defining

$$\sigma = \frac{\sigma_d}{2} = \frac{\sqrt{MSE}}{\sqrt{2}}$$

the same methods are used as for MTE2tg.

MTE3 **TOST for ratio of means for two-group design (original scale)**

Power or sample size are computed using the same methods as for MTE1tg with non-centrality parameters

$$\delta_L = \frac{\left(\mu_T / \mu_S - \Delta_L\right)\sqrt{n}}{\sigma / \mu_S \sqrt{1+\Delta_L^2}} \qquad \delta_U = \frac{\left(\mu_T / \mu_S - \Delta_U\right)\sqrt{n}}{\sigma / \mu_S \sqrt{1+\Delta_U^2}}$$

In this case however this involves an approximation since the value 1 is substituted for the actual correlation between the two tests

$$\rho_{LU} = \frac{2}{\sqrt{1+\Delta_L^2}\sqrt{1+\Delta_U^2}}$$

See Hauschke D, Kieser M, Diletti E, Burke M (1999) Sample size determination for proving equivalence based on the ratio of two means for normally distributed data. *Statistics in Medicine* 18: 93-105.

MTE4 TOST for ratio of means for crossover design (original scale)

The exact methods for power and sample size computation are given in Hauschke D, Kieser M, Diletti E, Burke M (1999) Sample size determination for proving equivalence based on the ratio of two means for normally distributed data. *Statistics in Medicine* 18: 93-105. Here, we compute power or sample size using the same methods as for MTE1tg with non-centrality parameters:

$$\delta_L = \frac{(\mu_T / \mu_S - \Delta_L)\sqrt{2n}}{\sqrt{CV_B^2 (1-\Delta_L)^2 + CV_i^2 (1+\Delta_L^2)}} \qquad \delta_U = \frac{(\mu_T / \mu_S - \Delta_U)\sqrt{2n}}{\sqrt{CV_B^2 (1-\Delta_U)^2 + CV_i^2 (1+\Delta_U^2)}}$$

In this case, however, this involves an approximation, since the value 1.0 is substituted for the actual correlation between the two tests.

MTT1 Wilcoxon (Mann-Whitney) rank-sum test that P(X<Y) = .5 (continuous outcome)

Power, sample size, or p_1 are computed using a normal approximation formula from Noether GE (1987) Sample size determination for some common nonparametric statistics. *J. Am Stat. Assn* 82:645-647.

MTT2 Wilcoxon (Mann-Whitney) rank-sum test that P(X<Y) = .5 (ordered categories)

Power is computed based on approximating the unconditional distribution of the test statistic under the null and alternative hypotheses using the first four moments of the distribution; these approximation methods were developed by Kolassa J (1995) A comparison of size and power calculations for the Wilcoxon statistic for ordered categorical data. *Statistics in Medicine* 14: 1577-1581. A Cornish-Fisher approximation is used to approximate the critical value for a test of size alpha (equation 5 in Kolassa 1995); a continuity correction is made to this critical value—integer part of computed value +0.5 (or -0.5 if the critical value is negative) (Kolassa personal communication). An Edgeworth series approximation is used to approximate the power under the alternative distribution (equation 6 in Kolassa 1995).

MTT3 Two-group univariate repeated measures analysis of variance (Greenhouse-Geisser)

Power and sample size are computed using methods taken from Muller, KE, Barton CN (1989) Approximate Power for Repeated-Measures ANOVA lacking Sphericity. *Journal of the American Statistical Association* 84:549-555.

MTT4 t-test (ANOVA) for difference of means in 2 x 2 crossover design

Power and sample size are computed using methods taken from Senn, Stephen. **Cross-over Trials in Clinical Research (2nd Edition)** Wiley (2002) Page 285. In practice, methods are the same as for MTT0 except that σ is defined as $\sigma_d/2$ which equals √(MSE)/√(2).

MTC0 Confidence interval for difference of two means (N large)
MGC0 Confidence interval width for one-way contrast

Sample size or confidence interval width are computed using the large sample normal approximation, where the equations for interval width are given in the guide cards for the interval width row. See Dixon, W.J., Massey, F.J. (1983) *Introduction to Statistical Analysis*. 4th Edition. McGraw-Hill. Pages 80-85 and 130-131.

For MTC0 and MTC0U, the formula for the total sample size, $N = n_1 + n_2$, is

$$N = \frac{z^2_{1-\alpha/s}\sigma^2(1+r)^2}{\omega^2 r}$$

where $r = n_2/n_1$ is the ratio of the sample sizes in the two groups. For MGC0, the total sample size is $N = \dfrac{z^2_{1-\alpha/s}\sigma^2 \sum \frac{c_i^2}{r_i} \sum r_i}{\omega^2}$

where $r_i = n_i / n_1$ and the c_i are the contrast coefficients.

MTC1 Confidence interval for difference of two means (coverage probability)

Sample size or confidence interval width are computed using central and non-central t and chi-square with coverage probability constraints, see Kupper, L.L. and Hafner, K.B. (1989) How appropriate are popular sample size formulas? *The American Statistician*, 43:101-105.

MGT0 One-way analysis of variance
MGT1 Single one-way contrast

Power, sample size, or effect size are computed using central and non-central F. For MGT0, the numerator and denominator degrees of freedom are (G-1) and (N-G), and the non-centrality parameter is N times the effect size (for equal n's N=nG). For MGT1, the numerator and denominator degrees of freedom are 1 and (N-G), and the non-centrality parameter is the number of cases in group 1 times the square of the effect size. The effect sizes are defined in the row titles in the respective tables. See O'Brien, R.G., Muller, K.E. (1993) "Unified Power Analysis for t-tests through Multivariate Hypotheses", in Edwards, L.K.

(Ed.), *Applied Analysis of Variance in Behavioral Science*, Marcel Dekker, New York. Pages 297-344.

MGT2 **Two-way analysis of variance**

Power and sample size for the two main effects and the interaction effect are computed using central and non-central F. The numerator degrees of freedom are (a-1), (b-1), and (a-1)(b-1), respectively, and the denominator degrees of freedom are ab(n-1). The non-centrality parameters are nab times the respective effect sizes for factor A, factor B, and the interaction. The formulas for the effect sizes are defined in the guide cards for the table. See O'Brien, R.G., Muller, K.E. (1993) "Unified Power Analysis for t-tests through Multivariate Hypotheses", in Edwards, L.K. (Ed.), *Applied Analysis of Variance in Behavioral Science*, Marcel Dekker, New York. Pages 297-344.

MGC1 **Confidence interval for one-way contrast (with coverage probability)**

Sample size or confidence interval width are computed using central and non-central t and Chi-square with coverage probability constraints, see Kupper, L.L. and Hafner, K.B. (1989) How appropriate are popular sample size formulas? *The American Statistician*, 43:101-105.

POT0 **One sample Chi-square (normal approximation)**

Power or sample size are computed using the normal approximation to the binomial, see Dixon, WJ and Massey, F.J. (1983) *Introduction to Statistical Analysis*. 4th edition. McGraw-Hill. The sample size is given by

$$n = \frac{\left[z_{1-\alpha/s}\sqrt{\pi_0(1-\pi_0)} + z_{1-\beta}\sqrt{\pi_1(1-\pi_1)} \right]^2}{(\pi_0 - \pi_1)^2}$$

POT0x **Exact test for single proportion**

Power is computed using the cumulative binomial distribution. The cut-point for rejection is computed as the largest k for which the probability of observing k or fewer successes is $\leq \alpha$ when $\pi = \pi_0$ for a one-sided test in which $\pi_A < \pi_0$. For a one-sided test in which $\pi_A > \pi_0$, we choose the smallest k for which the probability of observing k or more successes is $\leq \alpha$. For a two-sided test we require both probabilities to be $\leq \alpha/2$. Power is computed for the rejection regions for $\pi = \pi_A$. See Dixon, W.J., Massey, F.J. (1983) Introduction to Statistical Analysis. 4th Edition. McGraw-Hill. Pages 281-284 and Chernick, M.R., Liu, C. Y. "The saw-toothed behavior of power versus sample size and software solutions: single binomial proportion using exact methods." *The American Statistician* 56(2002) pp 149-155.

POT1 **McNemar's test of equality of paired proportions**

Power or sample size are computed using equation (5.6) from Miettinen, O.S. (1968). On the matched-pairs design in the case of all-or-none responses. *Biometrics*, 24: 339-352. For POT1, the formula for *n* is

$$n = \frac{\left[z_{1-\alpha/s}\sqrt{\eta} + z_{1-\beta}\sqrt{\eta - \frac{\delta^2(3+\eta)}{4\eta}} \right]^2}{\delta^2}$$

where δ and η are defined in the row titles and the effect size side table.

POT1x **Exact sign test of equality of paired proportions**

For each sample size n, we generate the distribution of m, the number of discordant pairs, using the binomial distribution with parameters n, and proportion $\eta = \pi_{10} + \pi_{01}$. For each value of m the rejection region is computed for a test of the null hypothesis that the probability of a success =0.50 (see paragraph on methods for POT0x). Then the power of the test is computed based on the binomial for a sample size of m and a probability of success of $(1/2)(1+\delta/\eta)$. The powers are added up over the possible values of m weighting by their probabilities, except that we do not consider values of m less than m_0 or greater than m_1, where m_0 is such that $P(m<m_0) \leq 10^{-7}$ and m_1 is such that $P(m>m_1) \geq 10^{-7}$. See Dixon, W.J., Massey, F.J. (1983) *Introduction to Statistical Analysis*. 4th Edition. McGraw-Hill. Pages 388-389 and Chernick, M.R., Liu, C. Y. "The saw-toothed behavior of power versus sample size and software solutions: single binomial proportion using exact methods." *The American Statistician* 56(2002) pp 149-155.

POT2 **Chi-square test of specified proportions in C categories**

Power, sample size, or effect size are computed based on central and non-central chi-square, see Lachin, J. M. (1977). Sample size determinations for rxc comparative trials. *Biometrics*, 33: 315-324. The non-centrality parameter is $n \Delta^2$ where the effect size Δ^2 is defined in the side table and row title.

POC0 **Confidence interval for proportions (n large)**

Interval width or sample size are computed using the normal approximation to the binomial where the equation for interval width is given in the guide card for the interval width row. See Dixon, W.J., Massey, F.J. (1983) *Introduction to Statistical Analysis*. 4th Edition. McGraw-Hill. Pages 105-107. For POC0, the formula for n is

$$n = \left(\frac{z_{1-\alpha/s}}{\omega} \right)^2 \left[\pi(1-\pi) \right]$$

POC1 **Confidence interval for odds ratio for paired proportions (n large)**

Confidence limit or sample size computed based on normal approximation from Smith, J., Connett, J., McHugh, R. (1985). Planning the size of a matched case-control study for estimation of the odds ratio. *American Journal of Epidemiology* 122:345-347 where the equation for interval width is given in the guide card for the interval width row. For POC1, the sample size is given by

$n = \frac{z^2_{1-\alpha/s}(\Psi_M + 1)}{\omega^2 \pi_{01} \Psi_M}$ where the terms are defined in the row titles and the effect size side table.

POC2 **Confidence interval for probability of observing a rare event for**

The relationship between probability of an event, π, sample size, and the probability of observing one or more events, P, is given by

$$P = 1 - (1 - \pi)^n$$

See Machin, D., Campbell, M.J. (1987) *Statistical Tables for Design of Clinical Trials*, Blackwell Scientific Publications, Oxford. Section 6.2

POT0F **One group test for proportion (normal approximation) adjusted for finite population**

POC0F **Confidence interval for proportion using normal approximation (n large) adjusted for finite population**

Computations for these tables are made in the same way as for the corresponding tables without the finite population correction except that the adjusted sample size is nN/(n+N) where n is the unadjusted sample size. For explanation of the effects of finite sampling see Cochran, G. (1977) *Sampling Techniques* 3rd Edition. John Wiley & Sons Inc. New York. Pages 23-28.

POE0 **Paired responses: equivalence of π_1 and π_2**

Power or sample size are computed using the normal approximation given in the guide card for the first row in the table. This is obtained by noting that the maximum value of the variance of the difference in proportions under the null or alternative hypotheses is η. For POE0, the formula for *n* is

$n = \frac{\eta\left[z_{1-\alpha/s} + z_{1-\beta}\right]^2}{\left(\Delta_0 - \Delta_1\right)^2}$ where the terms are defined in the row titles and the effect size side table. These methods were developed based on personal communication with Gary G. Koch. See also Tango, T. (1998): Equivalence test and confidence interval for the difference in proportions for the paired-sample design. *Statistics in Medicine* 17:891-908.

POE1 **Paired test of equivalence in proportions using confidence interval**

a) Lower confidence limit for difference in paired proportions (simulation),
b) Upper confidence limit for difference in paired proportions (simulation),
c) Two-sided confidence limits for difference in paired proportions (simulation)

The power is calculated as the percentage of randomly-generated 2x2 tables for which the null hypothesis is rejected. The cells of the 2x2 table are filled in using the specified probabilities π_{11} (control yes, case yes), π_{10} (control yes, case no), π_{01} (control no, case yes), π_{00} (control no, case no). For each simulation the 2x2 table is generated using a number of trials equal to the sample size (to give the sum of the "control yes" entries) and choosing a random binomial variate with probability $\pi_{11} + \pi_{10}$. The sum of the "control no" entries is obtained by subtracting this value from the total sample size. The "yes, yes" cell is obtained as a random binomial variate with number of trials equal to the previously-computed sum of the first row and probability equal to $\pi_{11} /(\pi_{11} + \pi_{10})$. The "no, yes" cell is obtained similarly, and the other two cells are obtained by subtracting from the known row sums.

The Newcombe-Wilson score method (continuity corrected Method 10) is used for the confidence interval limits. (Newcombe RG (1988) Improved confidence intervals for the difference between binomial proportions based on paired data. *Statistics in Medicine* 17:2635-2650.) The power is computed as the proportion of simulations in which the observed confidence limits are within the specified equivalence range.

PTT0 **Two group χ^2 test of equal proportions (odds ratio = 1)**
PTT0p **Two group χ^2 test of equal proportions**

Power or sample size are computed using the normal approximation, see for example Machin, D, and Campbell M.J. (1987) *Statistical Tables for the Design of Clinical Trials*, Blackwell Scientific Publications, Oxford, or Fleiss, J.L., Tytun, A., and Ury, S.H.K. (1980) A simple approximation for calculating

sample sizes for comparing independent proportions. *Biometrics* 36:343-346. For PTT0, the formula for *n* is

$$n = \frac{\left[z_{1-\alpha/s}\sqrt{2\bar{\pi}(1-\bar{\pi})} + z_{1-\beta}\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)} \right]^2}{(\pi_1-\pi_2)^2} .$$

PTT1 **Two group continuity corrected χ^2 test of equal proportions (odds ratio = 1)**

PTT1p **Two group continuity corrected χ^2 test of equal proportions**

Power or sample size are computed starting with the answer from PTT0 and modifying n as shown in Fleiss, J.L., Tytun, A., and Ury, S.H.K. (1980) A simple approximation for calculating sample sizes for comparing independent proportions. *Biometrics,* 36:343-346. For PTT1, the sample size is given by

$$n' = \frac{n}{4}\left[1 + \sqrt{1 + \frac{4}{n|\pi_1 - \pi_2|}} \right]^2$$

PTT2 **Fisher's Exact Test**

The computed power is the expected power, obtained by summing the products of the conditional power given a particular first-column sum times the probability of that sum. The conditional powers are obtained by summing the bivariate binomial probability density over the critical region, where, to speed computation, all terms less than one-millionth of the estimated maximum term are dropped. See Fleiss, J.L. (1981) Statistical Methods for Rates and Proportions. 2nd Edition. Wiley, New York. Pages 24-26, and Thomas R.G., Conlon, M. (1992) "Sample size determination based on Fisher's exact test for use in 2 x 2 comparative trials with low event rates." Controlled Clinical Trials, 13 pp134-147,and Chernick, M.R., Liu, C. Y. "The saw-toothed behavior of power versus sample size and software solutions: single binomial proportion using exact methods." *The American Statistician*, 56(2002) pp 149-155.

PTT3 **Two-group Chi-square test comparing proportions in C categories**

Power, sample size, or effect size are computed based on central and non-central chi-square, see Lachin, J. M. (1977) Sample size determinations for rxc comparative trials. *Biometrics*, 33: 315-324. The non-centrality parameter is 2n Δ^2 where the effect size Δ^2 is defined in the side-table and row title.

PTT4 **Mantel-Haenszel (Cochran) test of OR=1 for 2x2 tables in S strata**

PTT4cc **Mantel-Haenszel (Cochran) test of OR=1 for 2x2 tables in S strata (continuity corrected) (Cochran)**

Power and sample size are computed using approximate formulas from Nam, Jun-Mo (1992) Sample size determination for case-control studies and the comparison of stratified and unstratified analyses. *Biometrics*, 38: 389-395. The terms used in the formulas are defined in the side-table row names.

PTC0 Confidence interval for $\pi_1-\pi_2$ (n large)

Interval width or sample size are computed based on the normal approximation where the equations for interval width are given in the guide cards for the interval width rows. For PTC0, the formula for *n* is

$$n = \frac{z^2_{1-\alpha/s}\left[\pi_1(1-\pi_1)+\pi_2(1-\pi_2)\right]}{\omega^2}.$$

See Dixon, W.J., Massey, F.J. (1983) *Introduction to Statistical Analysis*. 4th Edition. McGraw-Hill. Pages 286-288.

PTC1 Confidence interval for $\pi_1-\pi_2$ (continuity corrected)

Interval width or sample size are computed based on the normal approximation for a continuity corrected interval given in Fleiss, J.L. (1981) *Statistical Methods for Rates and Proportions* 2nd edition. Wiley, New York .

PTC2 Confidence interval for ln(odds ratio) (n large)

Interval width or sample size are computed based on the normal approximation from O'Neill, R.T. (1984) Sample size for estimation of the odds ratio in unmatched case-control studies. *American Journal of Epidemiology* 120:145-153. For PTC2, the formula for *n* is

$$n = \frac{z^2_{1-\alpha/s}\left[\dfrac{1}{\pi_1(1-\pi_1)}+\dfrac{1}{\pi_2(1-\pi_2)}\right]}{\omega^2}.$$

PTC3 — Confidence interval for relative risk (ratio of two proportions) (n large)

Interval width or sample size are computed based on the normal approximation from Elashoff, J.D. and Lemeshow, S. **Handbook of Epidemiology** Springer Publishers (2004) Chapter 2.1.

$$\omega = z_{1-\alpha/s}\left[\frac{(1-\pi_1)}{n_1\pi_1}+\frac{(1-\pi_2)}{n_2\pi_2}\right].$$

PTE0 **Two-sample Chi-square test for equivalence**

Power or sample size are computed based on the normal approximation. See for example Machin, D., Campbell, M.J. (1987) *Statistical Tables for the Design of Clinical Trials*, Blackwell Scientific Publications, Oxford, for the equal n case, and Farrington & Manning (1990) Test statistics and sample size formulae for comparative binomial trials with null hypotheses of non-zero risk difference for non-unity relative risk. *Statistics in Medicine* 9: 1447-1454 for the unequal n case. For PTE0, the formula for *n* is

$$n = \frac{(z_{1-\alpha} + z_{1-\beta})^2 \left[\pi_S(1-\pi_S) + \pi_T(1-\pi_T)\right]}{(\Delta_1 - \Delta_0)^2}$$

where the terms are defined in the row titles.

PTE1 **Two-group test of equivalence in proportions using confidence interval**

a) Lower confidence limit for difference in proportions (simulation),
b) Upper confidence limit for difference in proportions (simulation),
c) Two-sided confidence limits for difference in proportions (simulation)

The binomial results are simulated separately for each group. The Newcombe-Wilson score method (uncorrected) is used for the confidence interval limits. (Newcombe RG (1988) Interval estimation for the difference between independent proportions: comparison of eleven methods. *Statistics in Medicine* 17:873-890.) The power is computed as the proportion of simulations in which the observed confidence limits are within the specified equivalence range.

PGT0 **Chi-square for Gx2 table**

Power or sample size are computed based on central and non-central chi-square using the formulation given as Case 2 in Lachin, J. M. (1977). Sample size determinations for rxc comparative trials. *Biometrics*, 33: 315-324.

PGT1 **Test for linear trend in Gx2 table (logistic model)**

Power or sample size are computed using the equation from Nam, J. (1987). A simple approximation for calculating sample sizes for detecting linear trend in proportions. *Biometrics*, 43: 701-705. For PGT1, the formula for n_1 , the sample size in group 1 is

$$n_1 = \left[\frac{z_{1-\alpha/s}\sqrt{\bar{\pi}(1-\bar{\pi})\sum r_i(x_i - \bar{x})^2} + z_{1-\beta}\sqrt{\sum r_i \pi_i (1-\pi_i)(x_i - \bar{x})^2}}{\sum r_i \pi_i (x_i - \bar{x})} \right]^2 \text{ and}$$

the other terms are defined in the table and the compute effect size side table

and $\bar{\pi} = \sum \frac{n_i \pi_i}{N}$.

PGT2 **G group Chi-square test comparing proportions in C categories**

Power, sample size, or effect size are computed based on central and non-central chi-square, see Lachin, J. M. (1977) Sample size determinations for rxc comparative trials. *Biometrics*, 33: 315-324. The non-centrality parameter is $N\,\Delta^2$ where the effect size Δ^2 is defined in the side-table and row title and N is the total sample size (Gn for the equal n's case).

STT0 **Log-rank test for equality of survival curves in two groups**

Power or sample size are computed based on approximation from Freedman, L.S. (1982). Tables of the number of patients required in clinical trials using the logrank test. *Statistics in Medicine*, 1:121-129. For STT0, the sample size formula is

$$n = \frac{(z_{1-\alpha/s} + z_{1-\beta})^2 (h+1)^2}{(2-\pi_1-\pi_2)(h-1)^2}$$ where the terms are defined in the row titles.

STT1 **Test based on exponential survival, accrual period**

STT2 **Test based on exponential survival, accrual period, dropouts**

Power or sample size are computed based on equations from Lakatos, E. and Lan, K.K.G.1992. A comparison of sample size methods for the logrank statistic. *Statistics in Medicine*, 11: 179-91. For STT1 and STT2, the sample size is

$$n = \left(\frac{z_{1-\alpha/s} + z_{1-\beta}}{\ln(\lambda_E) - \ln(\lambda_C)} \right)^2 \left(\frac{1}{E(P_E)} + \frac{1}{E(P_C)} \right)$$

where $E(P_i) = \frac{\lambda_i}{\lambda_i + d}\left[1 - \frac{e^{-(\lambda_i+d)(T-T_0)} - e^{-(\lambda_i+d)T}}{(\lambda_i + d)T_0} \right]$, T_0 is the length of the accrual period and T the total length of followup, and the other terms are defined in the row titles.

For STT0, STT1, and STT2, the required number of events, E, can be obtained approximately from the equation

$$E = \frac{4(z_{\alpha/2} + z_\beta)^2}{[\ln(h)]^2}$$

where $z_{\alpha/2}$ and z_{β} are the upper $\alpha/2$ and upper β points, respectively, of the standard normal distribution and h is the hazard ratio. See Collett, D. (1994) *Modelling Survival Data in Medical Research*, Chapman & Hall, Formula 9.2

STT3 Log-rank test of survival in two groups, simulation with specified rates

Power is computed by simulating two groups of individuals following the course of the experiment and subject to accrual, hazard, and dropout rates specified in the corresponding side table. In each simulation, the fate of each individual is controlled by the output of the random number generator. The test statistic is computed according to the method specified in Chapter 5, pages 127-128, of Lee, E.T. (1980) *Statistical Methods for Survival Data Analysis*. Lifetime Learning Publications. Belmont, California. The number of simulations in which the test statistic indicated a significant outcome is divided by the total number of simulations, and the quotient is reported as the power. If a one-sided test is specified, the program tracks separately the simulations that are significant in the positive direction and in the negative direction and reports the quotient that gives the greater power. As long as the power is reasonably high, the number of simulations that appear significant in the "wrong" direction should be very small.

The data for each individual are simulated using a deterministic pseudo-random number generator, so for the same inputs and the same seed, the computed power will always be the same. The particular generator used is called r250 and is described in *Journal of Computational Physics* v. 40, pp. 517-526 (1981). The random number generator r250 is a Tausworthe-style shift-register random number generator, based on a primitive trinomial in which the state is initialized using some other random number generator, and a trick is then used to make certain that the columns are linearly independent. The cited paper describes various statistical tests to validate the output.

The present implementation differs from that of the authors cited in that we initialize the state of r250 using the default random number generator in Microsoft Visual C++, which is a mixed linear congruential random number generator. In contrast, the authors use GGL, which is a multiplicative congruential random number generator. Our approach has the advantage that pure-multiplicative random number generators perform very poorly with regard to the independence of sequences generated by different seeds. To test our implementation of this generator, we compared the results of simulations done with r250 to those done with the default Microsoft generator, and also to the Wichmann-Hill generator (*Applied Statistics*, v. 31, pp. 188-190). For several examples with 10,000 simulations, all three generators produced values for power agreeing to within .005.

STE0 — Non-inferiority test for two exponential survival curves

Power or sample size are computed based on the approximate formula for the required number of events

$$E = \frac{4(z_{\alpha/2} + z_{\beta})^2}{[\ln(h)]^2}$$

where $z_{\alpha/2}$ and z_{β} are the upper $\alpha/2$ and upper β points, respectively, of the standard normal distribution and h is the hazard ratio. See Collett, D. *Modelling Survival Data in Medical Research* Chapman & Hall (1994) Section 9. 2 and Rothman, M., Li, N., Chen, G., Chi, G.Y.H., Temple, R., Tsou, H.H. "Design and analysis of non-inferiority mortality trials in oncology" *Statistics in Medicine* 22(2003) pp. 239-264. The following formula, adapted from equations in Lakatos, E. and Lan, K.K.G.1992. A comparison of sample size methods for the logrank statistic. *Statistics in Medicine*, 11: 179-91 is used to compute the n required in each group to achieve the specified power

$$n = \frac{E}{4}\left(\frac{2}{E(P_S)}\right)$$

where $E(P_S) = \frac{\lambda_S}{\lambda_S + d}\left[1 - \frac{e^{-(\lambda_S+d)(T-T_0)} - e^{-(\lambda_S+d)T}}{(\lambda_S + d)T_0}\right]$, T_0 is the length of the accrual period and T the total length of followup, and the other terms are defined in the row titles. The "n per group for h=limit" is given by

$$n_h = \frac{E}{4}\left(\frac{1}{E(P_S)} + \frac{1}{E(P_T)}\right)$$

AOT0 Agreement between two dichotomous ratings (intraclass kappa)

AOC0 Confidence interval for intraclass kappa (n large)

Power or confidence interval width, or sample size are computed using the large sample standard error of estimated kappa from Block, D.A. and Kraemer, H.C. (1989). 2x2 kappa coefficients: measures of agreement or association. *Biometrics*. 45:269-287.

AOT1 Test for value of correlation coefficient

AOC1 Confidence interval for correlation coefficient

Power or confidence interval width, or sample size are computed based on the large sample normal approximation using Fisher's z transformation; see Dixon, W.J., Massey, F.J. *Introduction to Statistical Analysis*. 4th Edition McGraw-Hill (1983) p. 224. The sample size for AOT1 is given by

$$n = \frac{(z_{1-\alpha/s} + z_{1-\beta})^2}{[FZ(\rho_1) - FZ(\rho_0)]^2} + 3$$ where FZ denotes the Fisher's z transform, $\mathbf{FZ}(\rho) = \frac{1}{2}\ln\left[\frac{1+\rho}{1-\rho}\right]$.

AOT2 **Lin's concordance coefficient (continuous outcome)**
AOC2 **Confidence interval for Lin's concordance coefficient (continuous outcome)**

Power or interval width, or sample size are computed using normal approximation formulas given in Lin, L., Hedayat, A.S., Sinha, B., Yang, M. (2002). Statistical methods in assessing agreement: models, issues, and tools. *Journal of the Amer. Stat. Assn* 97 (2002) pp.257-270.

AOC3 — Confidence interval for intraclass correlation for k measurements

Interval width or sample size are computed using normal approximation formulas given in Bonett, D.G. "Sample size requirements for estimating intraclass correlations with desired precision" *Statistics in Medicine* 21(2002) pp. 1331-1335.

$$n = \frac{2(z_{1-\alpha/s}(1-\rho)[1+(k-1)\rho])^2}{k(k-1)\omega^2} + 1$$

The value of n calculated from ω may be an underestimate for k=2 and ρ>0.6 or k≥10 and ρ<0.2. (Bonett 2002 recommends adding 5 to n for k=2 and ρ≥0.7). As a consequence, the value of ω calculated from n may be an underestimate for k=2 and ρ>0.6 or k≥10 and ρ<0.2.

ROT0 **Logistic regression (binary outcome), single x**
ROT1 **Logistic regression, x_1 adjusted for p X's (binary outcome),**

Power or sample size are computed using normal approximation formulas given in Hsieh, F.Y. (1989). Sample size tables for logistic regression. *Statistics in Medicine* 8:795-802.

The sample size for ROT0 is:

$$n = \frac{\left[z_{1-\alpha/s} + z_{1-\beta}\exp(\frac{-\beta^2}{4})\right]^2}{p_M\beta^2}\left[1 + 2p_M\Delta\right]$$

where

$$\Delta = \frac{\left[1 + (1+\beta^2)\exp(\frac{5\beta^2}{4})\right]}{1 + \exp(\frac{-\beta^2}{4})}$$

For ROT1, $n = \frac{n_1}{1-\rho^2}$

where n_1 is the sample size obtained in the case of a single covariate.

ROT2 **Linear regression (continuous outcome), single x**
ROT3 **Multiple linear regression with k covariates,**
ROT4 **Multiple linear regression, x_1 adjusted for A covariates**

Power, sample size, and detectable correlation coefficient are computed using central and non-central F with numerator and denominator degrees of freedom 1 and n-2 for ROT2, k and (n-k-1) for ROT3, and b and (n-a-b-1) for ROT4 based on a conditional power viewpoint. Non-centrality parameters are nf^2 where $f^2 = \rho^2/(1-\rho^2)$ for ROT2, $f^2 = R^2/(1-R^2)$ for ROT3, and $f^2 = (R_{AB}^2 - R_A^2)/(1-R_{AB}^2)$ for ROT4. See Gatsonis, C., Sampson, A.R. (1989) Multiple Correlation: Exact Power and Sample Size Calculations. *Psychological Bulletin* 106:516-524.

ROT5 **Linear regression test that $\beta=\beta_0$ for one x**

Power, sample size, or effect size are computed based on central and non-central t, with n-2 degrees of freedom. The non-centrality parameter is the effect size, δ, times $\sqrt{n}$, where δ is defined in the guide card for the effect size row. See Dupont, W., Plummer, W. (1998) Power and sample size calculations for studies involving linear regression. *Controlled Clinical Trials* 19:589-601.

ROC0 **Linear regression confidence interval for $\beta=\beta_0$**

Interval width and sample size are computed using the large sample normal approximation; the formula for the interval width is shown in the guide card for that row. See Dixon, W.J., Massey, F.J. (1983) *Introduction to Statistical Analysis.* 4th Edition. McGraw-Hill. Pages 214-219.

RTT0 **Linear regression test that $\beta_1=\beta_2$ for one x**

Power, sample size, or effect size are computed based on central and non-central t with 2n-4 degrees of freedom. The non-centrality parameter is the effect size, δ, times $\sqrt{n/2}$, where δ is defined in the guide card for the effect size row. See Dupont, W., Plummer, W. (1998) Power and sample size calculations for studies involving linear regression. *Controlled Clinical Trials* 19:589-601.

RTC0 **Linear regression confidence interval for $\beta_1 - \beta_2$ for two groups**

Interval width and sample size are computed using the large sample normal approximation; the formula for the interval width is shown in the guide card for that row. See Dixon, W.J., Massey, F.J. (1983) *Introduction to Statistical Analysis*. 4th Edition. McGraw-Hill. Pages 227-229.

Section 2
Central functions (computing cumulative distribution function)

Normal distribution z

The method used to compute the cumulative value of the normal distribution up to x will differ, depending on the value of x. Specifically:

1. If x is between -1.5 and 3.0, the c.d.f. is computed via the Taylor series centered at 0.
2. If x is between 3.0 and 10.0 or between -10.0 and -1.5, the program uses a continued fraction given by A. G. Adams in his 1969 communication in *CACM* vol. 12 pp. 565-566.
3. If x is less than -10.0 or greater than 10.0, the value of the c.d.f. is set as 0.0 or 1.0, respectively.

F distribution

The cumulative value of the F distribution up to x with m numerator degrees of freedom and n denominator degrees of freedom is usually calculated by a call to the function that computes the incomplete beta function with a equal to m/2 and b equal to n/2, integrating up to n/(n +mx), and subtracting the result from 1.

However, if either n or m is particularly large, the value may be calculated from the cumulative χ^2distribution function. This will occur when lgamma(m+n) – lgamma(m +1) – lgamma(n) + m*log(y) + n*log(1 – y) is greater than or equal to 500, where lgamma is the logarithm of the gamma function and y equals n/(n +mx), or when the value calculated in the paragraph above is equal to zero and at least one of m,n is greater than 100.

t distribution

There is no separate computation for the c.d.f of the central t distribution. Instead, it is computed from the F distribution with 1 numerator degree of freedom, using the square of the t value and distinguishing between positive and negative values of t.

χ^2 distribution

If the degrees of freedom exceed 150, the c.d.f of the χ^2 distribution up to x is computed via the Wilson-Hilferty approximation (see N.C. Severo and M. Zelen, *Biometrika* vol. 47 pp. 411-416, 1960); that is, one computes the cumulative normal distribution up to:

$$\left[\left(x/\nu\right)^{\frac{1}{3}} - \left(1 - 2/\left(9\nu\right)\right)\right]\sqrt{2/\left(9\nu\right)}.$$

Otherwise use is made of a recurrence relation that reduces degrees of freedom by 2 (see Abramowitz and Stegun, 1970, equation 26.4.8); this reduces the problem to calculating the χ^2 distribution with 1 or 2 degrees of freedom (according to whether the original degrees of freedom are odd or even); this is easily done exactly in terms of the normal distribution function or the exponential function.

Incomplete beta function I_x (a,b)

The incomplete beta function may be computed either by a power series or by a continued fraction derived from the power series. The power series is described in *Numerical Recipes in C* 2nd Edition, equation 6.4.4. Equation 6.4.5 describes the continued fraction

nQuery Advisor makes several tests to see if for the given values of x, a and b, the value of $I_x(a,b)$ is negligibly close to zero or one; if so, the program returns zero or one as appropriate. If not, then nQuery checks to see if the power series can be predicted to converge rapidly; if so, nQuery uses the power series. Otherwise, nQuery uses the continued fraction.

Cumulative binomial

If π is the probability of success on a single trial, then the probability that the number of successes is less than or equal to k, given n independent trials, is calculated as $1 - I_\pi(k+1, n-k)$, see definition of the incomplete beta function above. If k=n, however, the probability is taken to be 1.

Non-Central functions (computing cumulative distribution function)

Non-central F

In the usual case the c.d.f. of the non-central F distribution is computed via a call to the non-central beta function, which is a Poisson mixture of incomplete beta values in the same way that non-central F is a Poisson mixture of values of the c.d.f for the central F distribution.

Just as in the central F case, there are approximations for use for large degrees of freedom. When numerator degrees of freedom are large, we compute the desired value from the c.d.f for central X^2. When the denominator degrees of freedom are large, we use the non-central X^2.

Non-central beta

The non-central beta function Ix (a,b,δ) is defined as the sum as i ranges from 0 to infinity of

$P_i(\delta)\, I_x(a + i, b)$,

where $P_i(\delta)$ is the Poisson probability for i with Poisson parameter δ, and

$I_x(a + i, b)$

is the incomplete beta function as before. This sum is computed from a minimum value of i to a maximum value, where the contribution of terms outside this range is considered negligible. For this purpose the incomplete beta distribution is considered negligible past 100 standard deviations from the mean, and the Poisson distribution is considered negligible past 10 standard deviations to the left, or 100 standard deviations to the right, of the mean. Also the summation is terminated if the value of $I_x(a + i, b)$ falls below 10^{-12}.

Non-central t

Following exercise 23.24 of Stuart and Ord, *Advanced Theory of Statistics*, vol. 2, p. 904, it is possible to compute the c.d.f. of the non-central t in a manner quite analogous to the computation of non-central beta detailed above. That is, you can use a generalized Poisson mixture of values of incomplete beta, where for successive terms the value of one of the parameters for incomplete beta changes by 1/2 rather than by 1. Similarly for the Poisson factor, the Poisson distribution is generalized to non-integer values. We sum until the integer Poisson values sum to within $5 * 10^{-13}$ of 1. Since the half-odd-integer Poisson values should be about the same, this should be within about 10^{-12} of the right answer.

The x value for the values of incomplete beta going into the series is the reciprocal of

$1 + t^2/\nu$,

where t is the upper value of the c.d.f. and ν is degrees of freedom. If this value is too small, i.e. less than 10^{-8}, we risk losing information due to roundoff error. Therefore, we approximate our result as the normal c.d.f up to t—δ, and add a correction term linear in t. Note that the quadratic term is correct already.

Non-central χ^2

The c.d.f. of the "non-central χ^2 distribution" is a Poisson mixture of central χ^2 c.d.f's, and much the same considerations apply as for non-central beta.

Percentage points and non-centrality parameters

Percentage points of normal distribution

For probability p < 0.5, one computes $y = \sqrt{(\log(1/p^2))}$. Then the percentage point z is computed as y + P(y) / Q(y) where P and Q are fourth-degree polynomials in y with appropriate coefficients. For p>0.5, the situation is symmetrical. This method is due to Odeh and Evans, *Applied Statistics* v. 23(1974), pp. 96-97.

Percentage points of central F distribution

An initial estimate of the percentage point is obtained via an approximate formula. The code then searches for another value that falls on the opposite side of the true percentage point from the estimate already obtained (i.e. the two estimates bracket the true value).

Then the Illinois method (more fully described below) is used to find a value of F such that the c.d.f. up to F differs from the desired value by at most 0.01.

Finally, Halley's method (See Huh, *Communications in Statistics--Simulation and Computation* v. 15(1986).pp.1191-1198) is used until two criteria are met:

a) The c.d.f. up to F differs from the desired value by at most 0.0001.

b) Successive estimates of F differ from one another by at most 0.0001 proportionally, that is to say, by at most 0.0001 times the absolute value of the more recent estimate. (In the F case, of course, all estimates are nonnegative.)

It is also worth noting that if numerator degrees of freedom are greater than denominator degrees of freedom, we reverse the degrees of freedom and take the reciprocal of the percentage point.

Percentage points of central t distribution

Again there is no separate computation. We take the square root of the F percentage point, first doubling the probability and using 1 numerator degree of freedom, and assigning the sign as appropriate.

Percentage points of central χ^2 distribution

First, an initial estimate is obtained via the Wilson-Hilferty approximation referenced above. If degrees of freedom exceed 150, this is used as the answer.

Otherwise, a modification is used of Halley's method (referenced above). Again the iteration is continued until the c.d.f. up to the estimate differs from the desired value by at most 0.0001 and two successive estimates differ proportionally by at most 0.0001.

Percentage points of non-central F distribution

The Illinois method (see Kennedy and Gentle, *Statistical Computing*, Marcel Dekker: New York(1980)) is used. That is, two initial estimates are chosen. Those estimates ideally should bracket the true solution, but this is usually not critical. We then find successive estimates by linear interpolation, splitting the interval as appropriate so that our two estimates continue to bracket the true solution. The only exception is that if the older of the two estimates remains fixed, its corresponding ordinate is adjusted (halved, if we think of ourselves as looking for the zero of a function). That is, if we're looking for the value of the monotonic function f , we choose x_0 and x_1 such that f (x_0) and f (x_1) have opposite sign, then compute x_2 as

$$[x_0 \, f(x_1) - x_1 \, f(x_0)] / [f(x_1) - f(x_0)]$$

Then if f (x_1) and f (x_2) have opposite sign we replace x_0 by x_1 and x_1 by x_2 and continue. If on the other hand they have the same sign we again replace x_1 by x_2 but we leave x_0 as it is. However on the next round, we shall use a value half as large for f (x_0).

The iteration continues until both f (x_1) has absolute value less than 0.0001 and x_0 and x_1 differ proportionally by at most 0.0001 (i.e. they differ by less than 0.0001 times the arithmetic mean of their absolute values).

In the case of percentage points of non-central F there seems to be no need for subtlety in choosing the initial estimates; they are chosen to be 0.0 and 100000.0.

Percentage points of non-central t distribution

The Illinois method is used as described above. If δ is the non-centrality parameter, then the bracketing values are chosen to be δ-100 and δ+100, except in the one-degree-of freedom-case, when they are chosen to be δ-1000 and δ+1000.

Percentage points of non-central χ^2 distribution

The Illinois method is used as described above. The initial bracketing values are chosen to be 0.0 and 100000.0.

Non-centrality parameter of the non-central F distribution
(given both the probability and the percentage point)

The Illinois method is used as described above. The bracketing values are obtained as follows: The program first tries the upper limit 5000. If this value is not large enough, an error message is produced. (An error message is also generated if the probability given by central F is larger than the desired value, since that indicates the value zero for the non-centrality parameter to be too large.)

Otherwise we start with $\lambda_0 = 0.0$ and $\lambda_1 = 1.0$. If the true value is between these, we continue with the Illinois method; otherwise we replace λ_0 by λ_1 and double λ_1, and repeat.

Non-centrality parameter of the non-central t distribution

The Illinois method is used. The initial estimates are chosen as -100.0 and 100.0.

Non-centrality parameter of the non-central χ^2 distribution

The Illinois method is used. The initial values are chosen as for the non-centrality parameter of non-central F and the same error checking is performed.

Use of distribution functions in computing power, sample size, and effect size, or interval width and sample size

Power

We are given the desired significance level of the test, an "effect size" or values from which it may be calculated, and the sample size. We wish to determine the power of the study to reject the null hypothesis.

First one determines the appropriate percentage point of the central t, F, or χ^2 distribution, depending on the problem at hand, where the degrees of freedom depend on the sample size in a manner that depends on the test being considered (see Methods of Computation for each table). The "appropriate" percentage point means the $100(1-\alpha)\%$ point, in a one-sided test, or the $100(1-\alpha/2)\%$ point in a two-sided test. Then the non-centrality parameter of the distribution of the test statistic under the alternative hypothesis is calculated from the effect size in a manner depending on the test being considered (see Methods of Computation for each table). Finally the power is computed as the c.d.f. of non-central distribution with the degrees of freedom and non-centrality parameter as in Methods of Computation for each table.

Sample sizes for tests

The section above describes how power is computed from effect size and sample size. When given power and effect size, one can compute the required sample size by searching for the minimum integer value required to produce (at least) the requested power. This is done, essentially, via the Illinois method. The initial values are obtained by trying the values 100, 10 and 2 in that order. If two values are found that bracket the desired value they are used; otherwise (i.e. if a sample size of 100 is too small) linear extrapolation is used to find an upper bound.

Another feature to note is that the iteration will terminate under two conditions:

1. If the calculated power is within 0.0001 of the requested value.
2. If we have two estimates within 1 of each other (since we're only looking for the least integer that is large enough).

Effect sizes for tests

To calculate effect size from power and sample size, one simply reverses the procedure given above for computing power. That is, one calculates as before the central percentage point corresponding to significance, then the non-centrality parameter of the t, F , or χ^2 that gives a c.d.f. equal to one minus the specified power at the calculated percentage point. Then one solves for the effect size from the non-centrality parameter in a manner depending on the particular test being considered (see Methods of Computation for each table).

Interval width for means confidence intervals with tolerance probability

We obtain the half-width of a confidence interval for a mean (or difference between means, or means contrast) by multiplying a t—percentage point (corresponding to a confidence level) by an estimate for the standard deviation. (Also there may be a scaling factor for the difference or contrast case.)

Since the estimate for the variance is distributed as χ^2, the tolerance probability is the c.d.f. of the χ^2 distribution. Note that the tolerance probability is the chance that the confidence interval obtained from the study will be no wider than the specified value.

Therefore, we multiply the relevant t-percentage point by the square root of the relevant χ^2 -percentage point, and multiply by the standard deviation, the scaling factor, and other factors depending on sample size (corresponding to the factors necessary to make the distribution of estimated standard deviation be χ^2).

Sample size for means confidence intervals with tolerance probability

As in the case of the means t -tests, we have a quantity that increases with sample size, and that we want to be at least a certain value. This quantity is not power, but tolerance probability. The same variation on the Illinois method is used to determine the minimum necessary sample size.

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