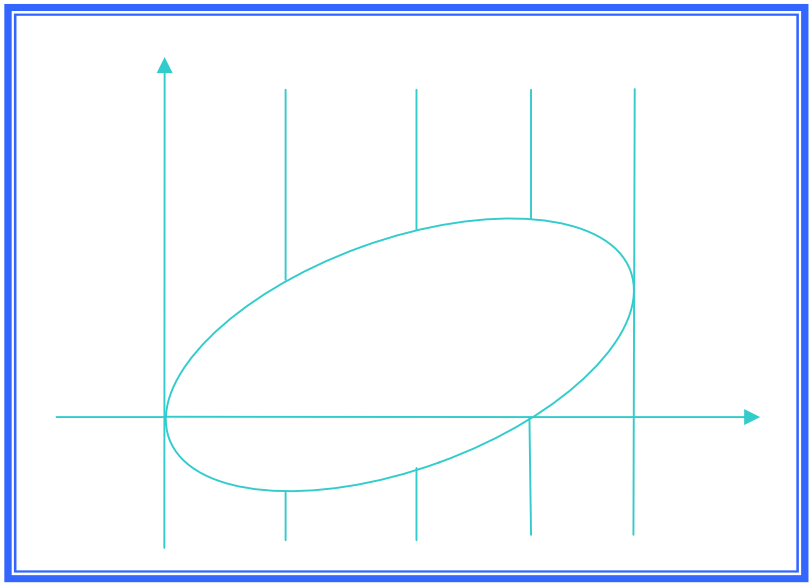
A Computer Program for

SCPRT on Information Time

Version 1.0



Xiaoping Xiong, Ph.D.

February 1, 2007

Table of Contents

1. Introduction

1.1 Sequential Conditional Probability Ratio Tests

A clinical trial is usually designed to detect a given difference in parameters of interest with given power and significance level. The sequential designs of clinical trials allow a trial to be stopped early when data collected at an early stage of the trial have produced enough, in one sense or another, evidence for the conclusion of testing about the hypotheses.

Different sequential designs are available for the same requirement of significance level and power. On the other hand, the same set of observed data can be interpreted as outcomes of different sequential designs with the same significance level and power. Therefore for the same observed data, the conclusion of a test may be significant by one sequential design but insignificant by another. This phenomenon may lead to the question that whether applying sequential test design to clinical trials is rational.

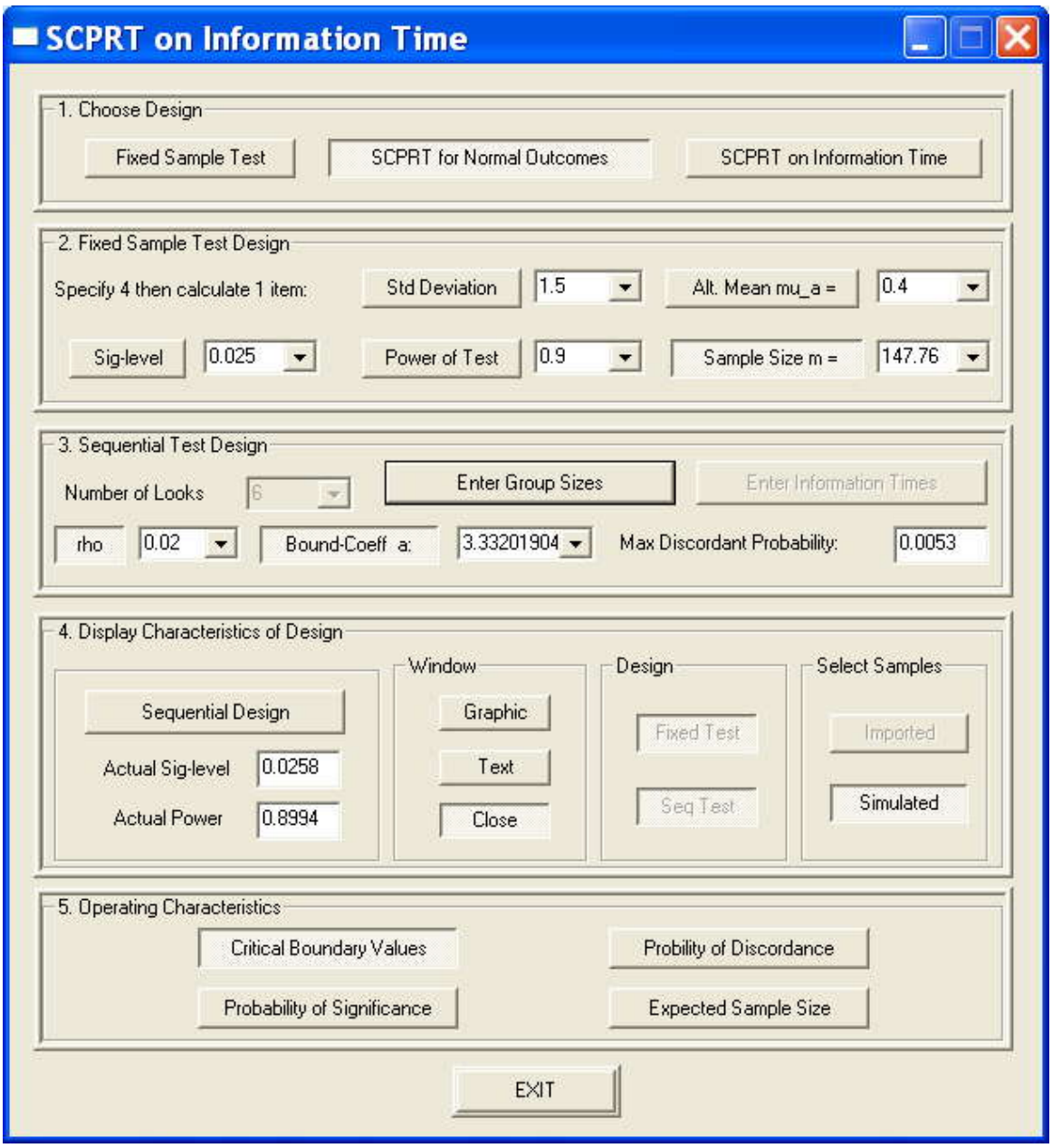
Withstanding this challenge, the sequential conditional probability ratio test (SCPRT) proposed by Xiong (1993, 1995) offers a special feature, i.e., a conclusion made at an early stopping is unlikely to be reversed if the trial were not stopped but continued to the planned end. The SCPRT gives a sound reason to stop a trial early: i.e., if the trial were not stopped as it should be, adding more data and continuing the trial to the planned end would not change the conclusion. With an SCPRT procedure, a sequential clinical trial is designed with not only given significance level and power, but also with a given probability of discordance, which controls the chance that a conclusion made at an early stage would differ from that at the final stage of the trial.

1.2 Computer Program for SCPRT

This computer program is created for the design procedure of *SCPRT on Information time*, which is generally applicable to designs of clinical trials in which the sequential test statistics can be approximated by a standard Brownian motion on information interval [0, 1]. Implemented on Microsoft Windows, this computer program is interactive, intuitive, and simple to use. This computer program is initiated, designed, and coded in *Compaq Visual Fortran* by Dr. Xiaoping Xiong.

You may copy the executable file of this computer program to any directory of your computer with operating system *MS Windows XP*, and then start the program by double clicking the executable file. In the front page of the program, click button ***Start Program*** to open the main dialog box ***SCPRT on Information Time***, in which there are 5 numbered panels:

1. Choose Design
2. Fixed Sample Test Design
3. Sequential Test Design
4. Graphic Display of Design
5. Operating Characteristics



The design procedure proceeds from panel 1 to panel 5:

- In the *1st* panel ***Choose Design***, you may choose one of three designs: 1) ***Fixed Sample Test***; 2) ***SCPRT for Normal Outcomes***; 3) ***SCPRT on Information Time***. The default choice is 2.
- In the *2nd* panel ***Fixed Sample Test Design***, you may design a fixed sample test for a one-sided test. The fixed sample test has 5 parameters: 1) the standard deviation, 2) the alternative, 3) the significance level, 4) the power of test, and 5) the sample size. You need to specify values for any four of the five parameters, and then calculate the remaining parameter by clicking its button. If you want to design a sequential test and had selected ***SCPRT for Normal Outcomes*** or ***SCPRT on Information Time*** in the *1st* panel ***Choose Design***, you still need to enter parameters in the *2nd* panel as above before you proceed to the *3rd* panel.
- In the *3rd* panel ***Sequential Test Design***, you design a sequential test (SCPRT) after you had made choices in the first and second panels. You choose a value for the number of looks and then click the button ***Enter Group Sizes*** or ***Enter Information Times*** to open a dialog box. After entering information into this dialog box, close the box and then click the button ***Bound-Coeff*** to calculate the boundary coefficient "***a***" and the maximum probability of discordance ($\boldsymbol{\rho}_{max}$). The maximum conditional probability of discordance "*rho"* (or $\boldsymbol{\rho}$) is specified with a default value of 0.02**.** You can change "*rho"* to other values, but remember to click the button ***Bound-Coeff*** to update "***a***" and "$\boldsymbol{\rho}_{max}$".
- In the *4th* panel ***Graphic Display of Design***, you can graphically display the sequential boundaries, the power function, and the expectation function of the design that you specified in the third panel. You first click the button ***Sequential Design*** to calculate the actual significance level and power of the sequential design, then click the button ***Graphic*** in the sub-panel ***Window*** to open a graphic window labeled ***Graphic Window: Plotting***. In the graphic window, you can select ***Applications*** → ***Plot Design…*** → ***Sequential boundary*** <u>or</u> ***Power function*** <u>or</u> ***Expected sample size*** to display the plot of selected item.
- In the *4th* panel, you can also simulate sample paths and display them in the graphic window. From the main dialog box, click the button ***Simulated*** in the sub-panel ***Select Samples*** to open a dialog box ***Setting Simulation***. In this dialog box, click the button ***Select Set*** repetitively until the desired number of records is displayed, and then click ***Simulate*** and then ***Done*** to close this dialog box. You return to the graphic window and select ***Applications*** → ***Plot Samples…*** → ***By simulation*** to display the simulated samples overlaying on the sequential boundaries of design made in earlier panels.

- In the *5th* panel ***Operating Characteristics***, you can display the numeric results of characteristics of the sequential design specified in earlier panels. You click one of the four buttons: 1) ***Critical Boundary Values***; 2) ***Probability of Discordance;*** 3) ***Probability of Significance***; 4) ***Expected Sample Size*** to open a dialog box displaying information about the selected item.

1.3 Applications with this computer program

This program is applicable to designs of any study for which the sequential test statistic behaves stochastically as same as or approximately as the Brownian motion on the (information) time interval [0, 1]. The sequential procedure for **one population with normal distribution** is imbedded easily into the SCPRT procedure for Brownian motion; the procedures are illustrated in Sections 2 to 6. Though only the **one-sided test** is illustrated this program, the **two-sided test** with significance level α and power $1-\beta$ can be implemented by utilizing a one-sided test with significance level $\alpha/2$ and power $1-\beta$. Let S_{t_k} be the sequential test statistic at the kth look with information time t_k for a one-sided test. A two-sided sequential test is accomplished through a procedure of performing two one-sided sequential tests simultaneously with S_{t_k} and $-S_{t_k}$ sharing common sequential boundaries of one-sided test. The procedure of two-sided sequential test stops when, for the first time, either one of the one-sided tests has reached the significance (across upper boundaries) or both of the one-sided tests have reached the futility (across lower boundaries). This sequential procedure is appropriate in particular to compare the means of two populations even when the distributions for which are not normal. In most situations, the distribution of the difference between samples from two populations approximates well to the normal distribution even when sample sizes are very small. Thus the stochastic process induced by sequential test statistic approximates well the Brownian motion on all information times setting on [0, 1]. For normal, binary, and survival populations, the procedures for **comparison of two populations** are illustrated in Section 7, and the procedures for **comparison with historical population** are illustrated in Section 8. For each sequential test design, a fixed sample test is designed first for given significance level and power and other requirements; then an SCPRT sequential procedure is developed based on the fixed sample test design. For designs in Sections 7 and 8, the sample sizes of fixed sample tests can be either obtained using any other software, or be calculated using equations provided there in this manual.

2. A Starting Example

"Show me an example", you might ask. Yes, we certainly do, because it is usually easier for anyone to learn from examples. You will have a good experience of this computer program after you walking through the starting example, with your hands on the computer program and following the steps illustrated in this section.

Hands on example to help get you started.

2.1 A Fixed Sample Test

The SCPRT design is started with a design of a fixed sample test for testing hypotheses

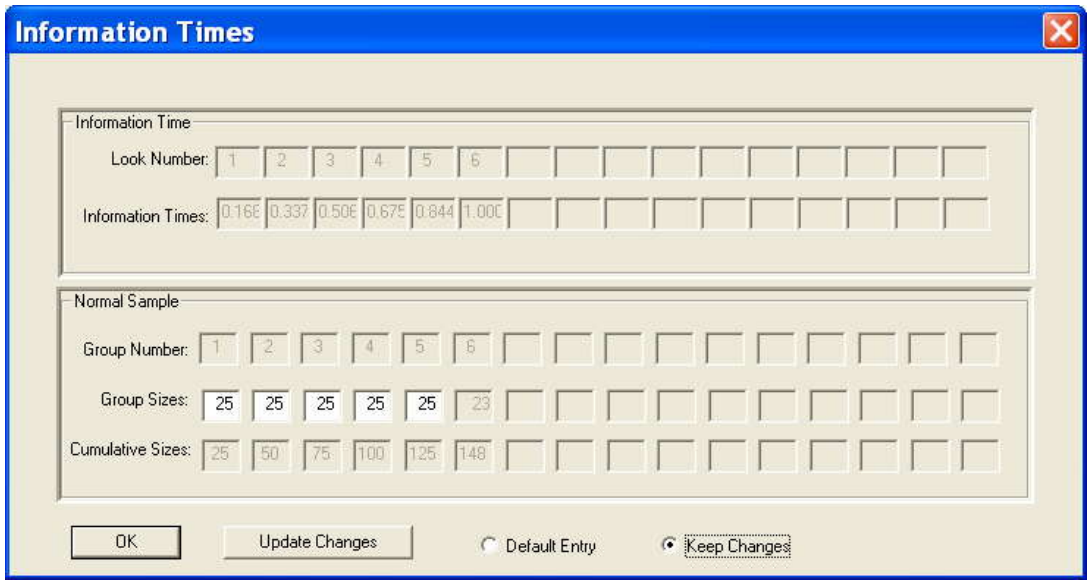
$$H_0: \mu \le 0 \quad vs. \quad H_a: \mu > 0$$

Suppose you want to detect an alternative $\mu_a=0.4$ with a significance level $\alpha=0.025$ and power $1-\beta=0.9$, assuming the standard deviation of observations is $\sigma=1.5$. In the 1st panel, click the button ***SCPRT for Normal Outcomes***. In the *2nd* panel, enter 0.025 for ***Sig-level***, 1.5 for ***Std Deviation***, 0.9 for ***Power of Test***, and 0.4 for ***Alt. Mean mu_a =***, and then click the button ***Sample Size m =***. The sample size for this design will be calculated as *m=147.7*.

2.2 Number of Looks, Group Sizes, and Information Times

The sample size for the fixed sample test is *m = 148*, a rounding-off of *147.7,* and is also the maximum sample size of the sequential test. Assume you want to have five interim looks and the final look (six looks in total) when the cumulative sample size reaches 25, 50, 75, 100, 125, and 148 in the sequential procedure. In the 3rd panel, enter 6 for ***Number of Looks***, and then click the button ***Enter Group Sizes*** to open a dialog box labeled ***Information Times*** as below. In this dialog box, you change the sizes for the first two groups from 24 to 25, and then click the button ***Update Changes***. The updated cumulative sample sizes and information times of looks will be presented in this dialog box. You may click the button ***Keep Change*** before closing this dialog box; otherwise the sample sizes or information times will take default values when you reopen this dialog box. To cancel the effect of ***Keep Change*** when you reopen this dialog box, just click ***Default Entry*** and close and then reopen the dialog box. After finishing with this dialog box and returning to the main dialog box ***SCPRT on Information Time***, you **need** to click the button ***Bound-Coeff a:*** to update or calculate the boundary coefficient ***a=3.33185*** and the maximum probability

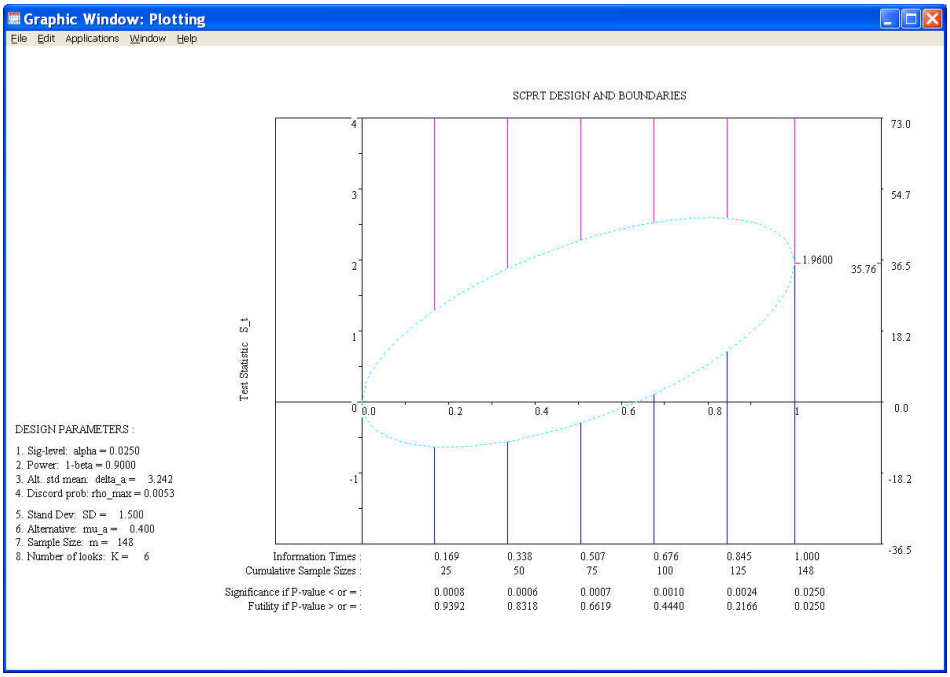
of discordance ρ_{max}***=0.0053;*** otherwise subsequent calculations will be based on an incorrect value of boundary coefficient ***a***.



2.3 Sequential Boundaries

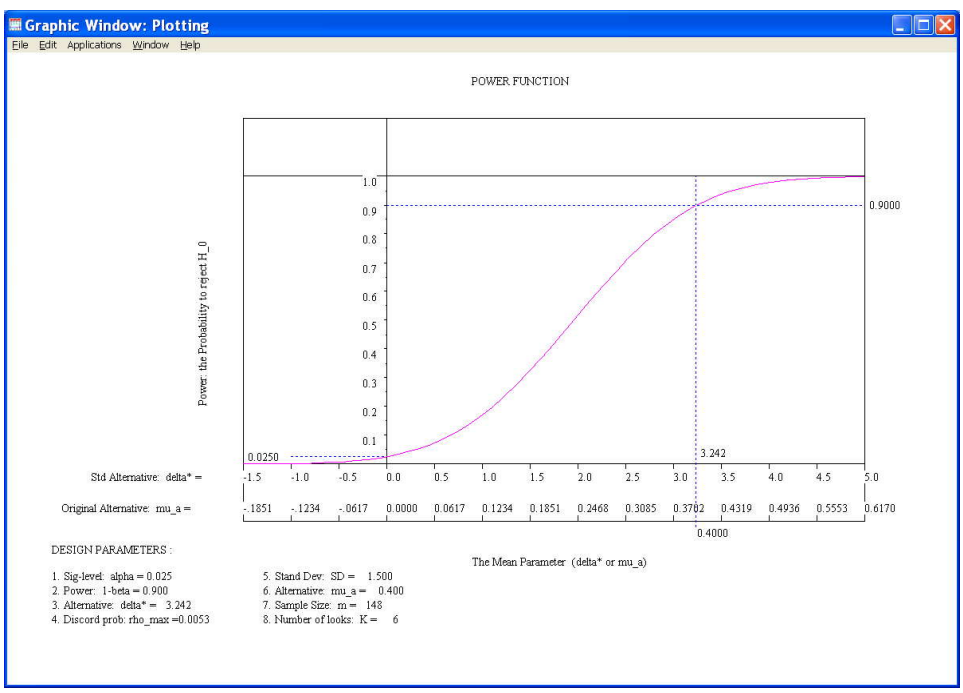
In the 4th panel, click the button ***Sequential Design*** to calculate the significance level and power of the sequential design, which are ***α = 0.0258*** and ***1-β = 0.8994***. Click the button ***Graphic*** to open a graphic window ***Graphic Window: Plotting***. In this window, you select ***Applications*** → ***Plot Design...*** → ***Sequential boundary*** from drop-down menus to open a small dialog box ***Plot***.

Click the button ***Refresh Plot*** in this dialog box, the system will plot the sequential boundaries as shown below. Some of the design parameters and operating parameters such as information times and critical P-values for upper and lower boundaries are reported in this plot. To close the window, you may select ***File*** → ***Close*** from drop-down menus, or click the button **-** in the right upper corner of the window, or click the button ***Close*** in the 4th panel of the main dialog box ***SCPRT on Information Time***, to minimize the window. **Do Not** click the button **x** in the right upper corner of the window to kill it because once the window is killed, it cannot be reopen.



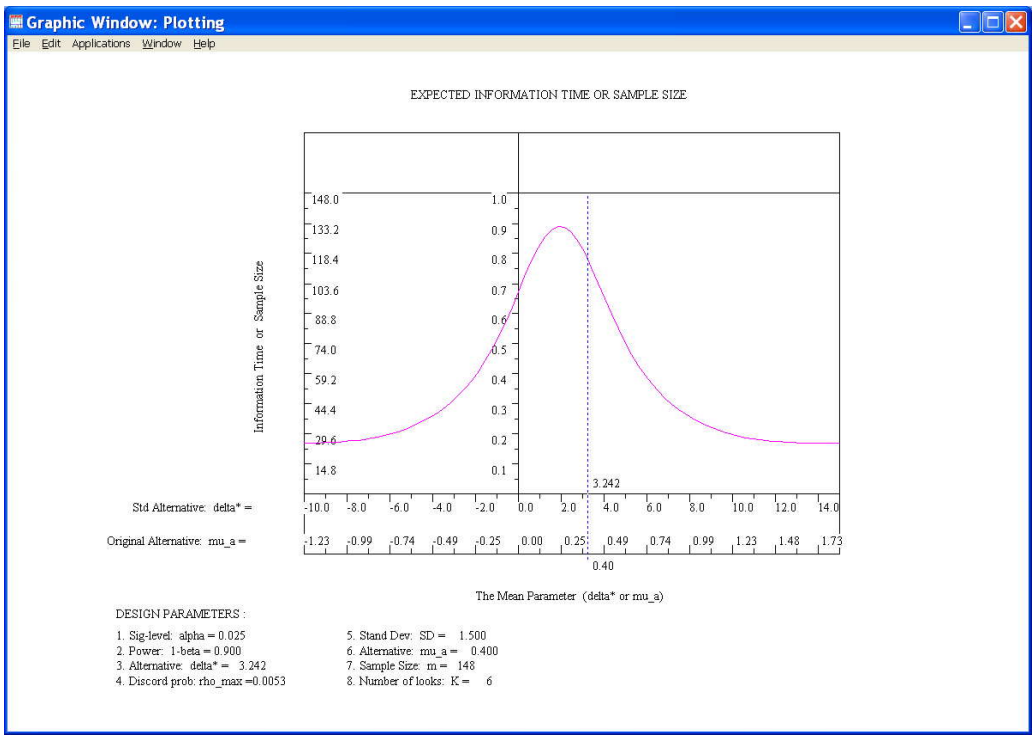
2.4 Power Function

In the window ***Graphic Window: Plotting***, select the following from the drop-down menu: ***Applications*** → ***Plot Design...*** → ***Sequential boundary*** to open a dialog box labeled ***Plot***. Clicking the button ***Refresh Plot*** will display a plot of power function as shown below.



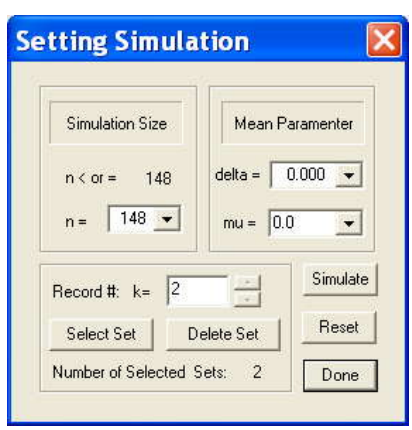
2.5 Expected Sample Size

In the window ***Graphic Window: Plotting***, select the following from the drop-down menu: ***Applications*** → ***Plot Design…*** → ***Sequential boundary*** to open a dialog box labeled ***Plot***. Click the button ***Expected sample size*** to display a plot of power function as shown below.



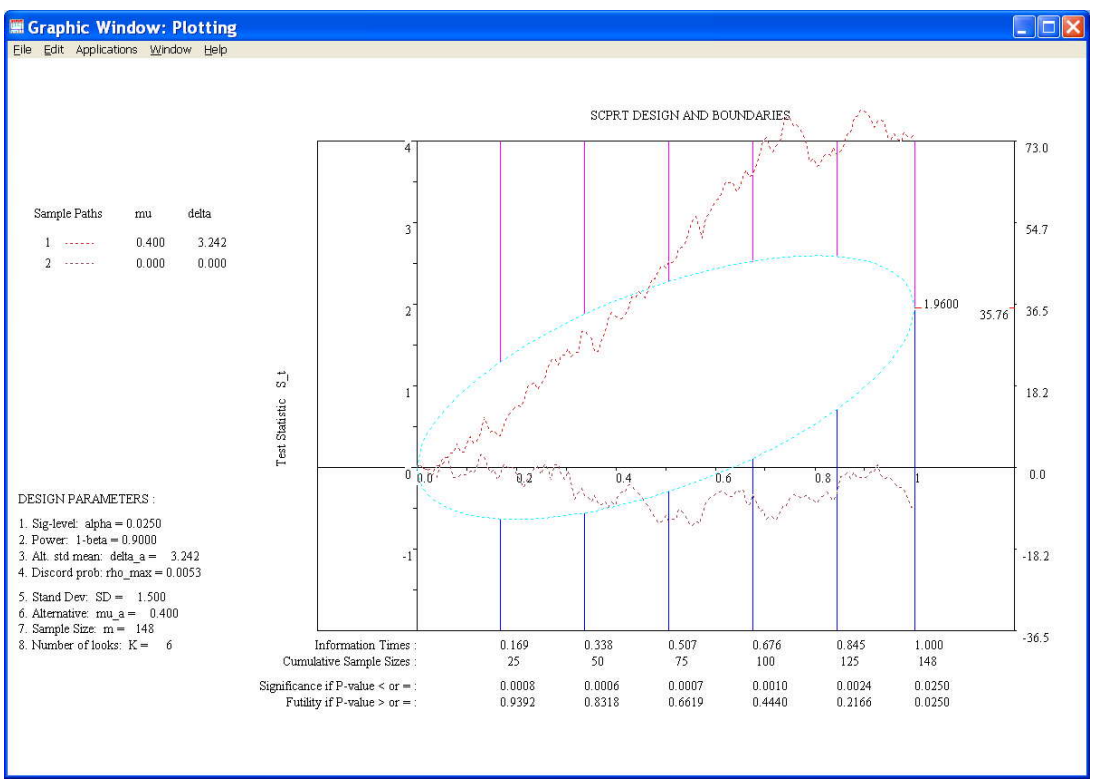
2.6 Simulating Sample Path

In the 4th panel of the main dialog box, click the button labeled ***Simulated*** (in sub-panel ***Select Samples***) to open a dialog box labeled ***Setting Simulation*** as below.



In this dialog box, click the button ***Select Set*** once after selecting ***mu*** = ***0.40***, and then click ***Select Set*** once again after selecting ***mu*** = ***0.0***. You see ***Record # k*** = ***2*** which indicates that two sets of data have been selected for simulation. One set of data will be simulated with true mean = *0.40* (*i.e.*, under H_a), and the other set of data will be simulated with true mean = *0.0* (under H_0). Click the button ***Simulate*** and then close this dialog box by clicking the button ***Done***. In the window ***Graphic Window: Plotting***, select the following from the drop-down menu: ***Applications*** → ***Plot Samples…*** → ***By simulation***. The dialog box shown below is displayed.

Select the button ***Saved*** and then click the button ***Refresh Plot***, the system will display a plot of two simulated sample paths laying over on sequential boundaries as shown below. By selecting the button ***New*** in the dialog box, you can simulate a series of new sample paths by clicking the button ***Refresh Plot*** repetitively.



3. Procedure for SCPRT Design

The procedure of SCPRT design using this computer program can be summarized as the following main steps.

3.1 Select type of sequential design

In the *1st* panel:

1) Select the design of your choice

3.2 Step one: Design a fixed sample test

In the *2nd* panel:

1) Enter your chosen values for any 4 of 5 parameters.
2) Click the button of the *5th* parameter to calculate its value.
3) Anytime you make any changes by 1), remember to redo 2).

3.3 Step two: Set information time

In the *3rd* panel:

1) Enter number of looks.
2) Click button ***Enter Group Sizes*** or button ***Enter Information Times*** to open a dialog box labeled ***Information Times***, then enter group sizes or information times into the dialog box.
3) Click ***Update Changes*** in the dialog box to update the sample size for the last group and information times for all looks.
4) **Optional:** Click ***Keep Changes*** to preserve the group sizes and information times in case of accidentally reopening this dialog box. To cancel the effect of ***Keep Changes*** when reopening the dialog box, click ***Default Entry*** and close and then reopen the dialog box.
5) Click ***OK*** to close the dialog box.

3.4 Step three: Control sequential boundaries

In the *3rd* panel again:

1) Enter value for "*rho*", the maximum conditional probability of discordance (***ρ***); its default value is 0.02.
2) Calculate the boundary coefficient "a" by clicking the button ***Bound-Coeff a***.

3) If the maximum probability of discordance (ρ_{max}) is too small or too large, change "*rho*" in 1), and redo 2) until you are satisfied with ρ_{max}.

3.5 Check sequential design

In the *4th* panel:

1) Display the significance level and power of test for the sequential design by clicking the button ***Sequential Design.***
2) Open this graphic window by clicking the button ***Graphic.***
3) Display boundaries, power functions, and expected sample sizes by clicking drop-down menu ***Applications*** of the graphic window and then select ***Plot Design… .***

3.6 Get numeric values of sequential design

In the 5th panel:

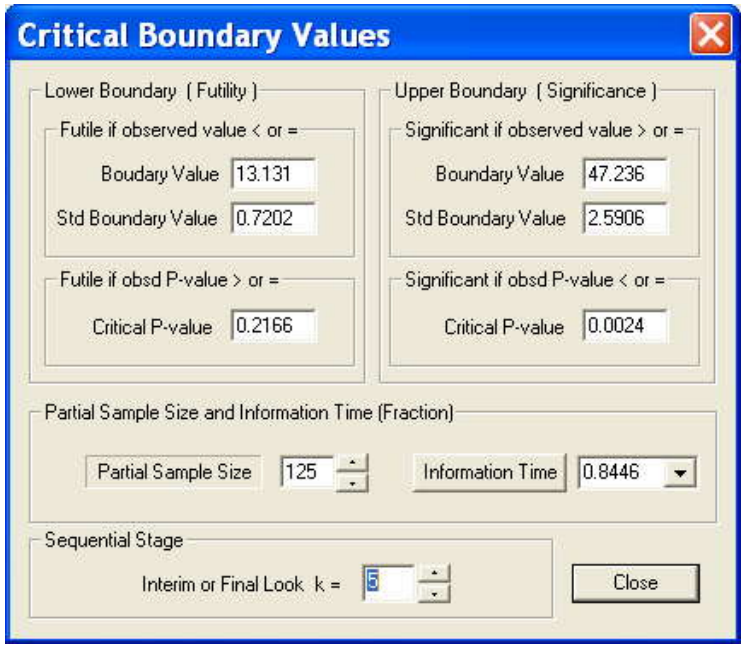
1) Click ***Critical Boundary Values*** to open a dialog box from which you can obtain information time, sequential boundaries, and critical P-values for any look *k*.
2) Click ***Probability of Discordance*** to open a dialog box from which you can obtain the maximum probability of discordance and the probabilities of discordance for any value of the mean parameter.
3) Click ***Probability of Significance*** to open a dialog box, from which you can obtain the probability of significance (i.e., the probability to reject H_0) for any value of the underlying mean parameter, including the significance level at *mu = 0* and the power of test at *mu = mu_a*. This is the power function.
4) Click ***Expected Sample Size*** to open a dialog box from which you can obtain the expected sample size and expected information time for any value of the underlying mean parameter.

4. Characteristics of Sequential Design

4.1 Sequential Boundaries and Critical P-values

The original test statistic at k^{th} look is S_{n_k}, the sum of first n_k original observations $X_1 \cdots X_{n_K}$. The standardized test statistic is $S^*_{t_k}$, obtained by dividing S_{n_k} with the standard deviation of S_{n_K} at the final stage *K*. For practical convenience, the upper

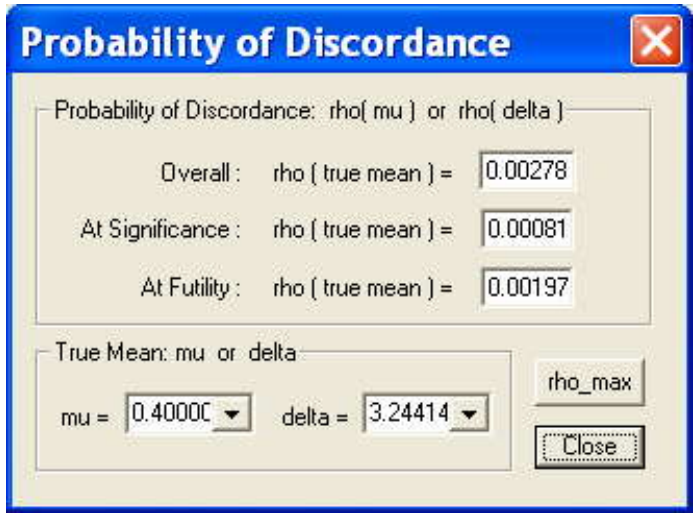
and lower sequential boundaries can also be represented in terms of critical *P* values.



The sequential test statistic has crossed the boundary and the sequential test should be stopped if the observed *P*-value (for S_{n_k} or $S^*_{t_k}$ as a fixed sample test at k^{th} look) is either smaller than the critical *P*-value of the upper boundary or larger than the critical *P*-value of the lower boundary. Click ***Critical Boundary Values*** in the 5th Panel to open a dialog box as shown above. In the panel ***Upper Boundary (Significance)*** of the dialog box, the upper boundary for S_{n_k} is ***Boundary Value 47.236*** when ***Interim (or Final) Look k = 5*** in the panel ***Sequential Stage***; the upper boundary for $S^*_{t_k}$ is ***Std Boundary Value 2.5906***; the ***critical P-value*** is ***0.0024***. The lower boundary values can be obtained similarly from the panel ***Lower Boundary (Futility)***. By changing the ***Interim or Final Look k*** in the panel ***Sequential Stage***, the boundary values and critical values can be obtained for different look *k*'s.

4.2 Probability of Discordance

When a sequential test is stopped on the basis of partially collected data, two questions naturally arise: "Is this conclusion as reliable as the one drawn from all data?" and "Would the conclusion have been reversed if the trial had not stopped but continued to the planned end?" The probability of discordance is a quantitative measurement for answering this question. Click ***Probability of Discordance*** in the 5th panel to open a dialog box as below.



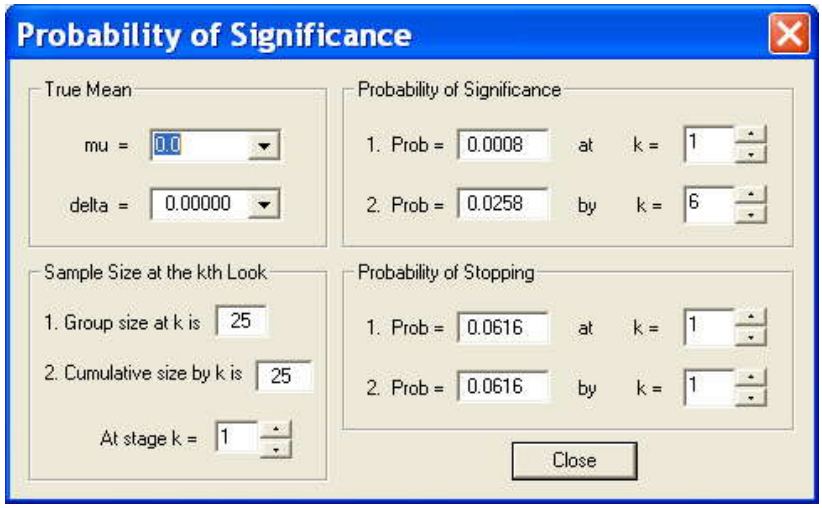
In the panel ***Probability of Discordance*** of the dialog box above, the (overall) probability of discordance is ***rho (true mean) = 0.00278*** when ***mu = 0.4*** in the panel ***True Mean***. The discordance between conclusions of sequential test and the fixed sample test results from two situations: 1) the sequential test is significant and the fixed sample test is futile (or insignificant), which is named as ***At Significance***; 2) the sequential test is futile (or insignificant) and the fixed sample test is significant, which is named as ***At Futility***. In the dialog box above, ***rho (true mean) = 0.00081*** for ***At Significance***, ***rho (true mean) = 0.00198*** for ***At Futility***, and the sum of the two components equals the overall *rho*. The probabilities of maximum discordance are the probabilities of discordance when true mean ***mu = 0.24166*** (***delta = 1.95996*** = z_α), and can be obtained by clicking the button ***rho_max*** in the dialog box. The ***delta*** in the panel above is the drift parameter of Brownian motion, and also the mean of standardized test statistic at the last stage, i.e., ***delta*** = $E(S_{t_K})$ = $m^{1/2}mu/\sigma$. The mean ***mu***, the standard deviation ***σ***, and the sample size ***m*** are those entered or calculated in the 2nd panel of the main dialog box.

4.3 Probability of Significance

The significance level is the probability of rejecting H_0 when the true mean = *0*; the power of the test is the probability of rejecting H_0 when the true mean = *mu_a.* The power function is the probability of rejecting H_0 as the function of the true mean. The significance level and the power of the test are two special values of the power function when the true mean equals *0* and *mu_a*, respectively.

In general, the significance level of SCPRT design is slightly higher than that of the fixed sample test design, and the power of the test for SCPRT is slightly lower

than that of the fixed sample test. In the example in Section 20, the significance level is 0258 for the former and 0.025 for the latter, and power is 0.8994 for the former and 0.90 for the latter. The entire power functions of sequential test design and the fixed sample test design are very close. It can be shown that the difference between the two power functions is less than the probability of discordance for any true mean and thus is less than the maximum probability of discordance ρ_{max}. Click ***Probability of Significance*** in the 5th Panel to open a dialog box as shown below.

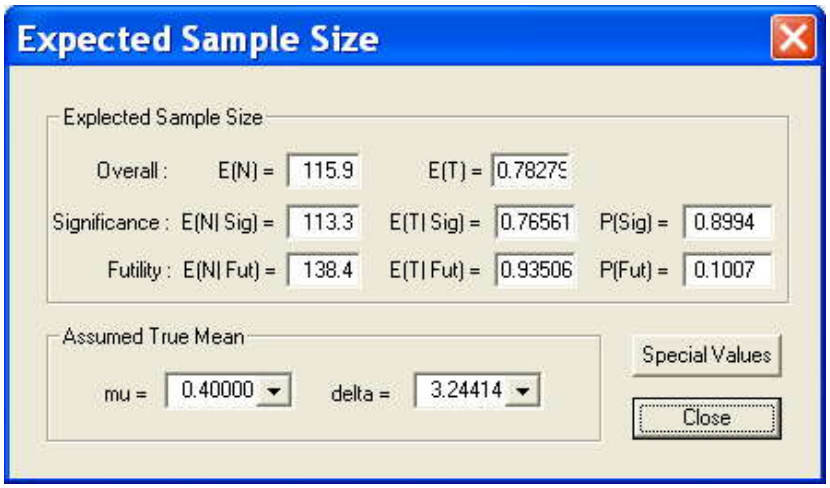


In the panel ***Probability of Significance*** of the dialog box above, the significance level ***Prob = 0.0258 by k = 6*** is obtained by entering ***mu = 0*** in the panel ***True Mean***. The power of the test ***Prob = 0.8994 by k = 6*** is obtained by entering ***mu = 0.4***. The probabilities that the sequential test to stop **at** or **by** the kth look are in the panel ***Probability of Stopping***. For example, let ***mu = 0.4*** in the panel ***True Mean*** and let ***k = 5*** in the panel ***Sample Size at the kth look***, then the probabilities of stopping ***Prob = 0.2248*** **at** ***k = 5*** and ***Prob = 0.6023 by k=5*** are presented in the panel ***Probability of Stopping***.

4.4 Expected Sample Size and Expected Information Time

The sample size of a sequential test is random, not predetermined. Therefore the efficiency of sequential tests is usually judged by their expected sample sizes such that a smaller expected sample size means greater efficiency. However, a sequential design with a larger maximum sample sizes usually has a smaller expected sample size. For example, the Wald's SPRT has the smallest expected sample size, but it has the largest maximum sample size which equals infinity. The SCPRT has the smallest maximum sample size which equals the sample size of

fixed sample test, and its expected sample size is a little larger than that of Wald's SPRT. Click ***Expected Sample Size*** in the 5th panel to open a dialog box as below.



In the panel ***Expected Sample Size*** of the dialog box, the expected sample size is ***E(N) = 115.9*** and the expected information time is ***E(T) = 0.78275*** when ***mu = 0.4***, where *E(T)=E(N)/m* and *m* is the maximum sample size. Given that the result of test is ***Significance*** (i.e., the sequential test statistic has fallen into the rejection region of H_0), the conditional expected sample size is ***E(N|sig) = 113.3*** and the conditional expected information time is ***E(T|sig) = 0.76561.*** Given that the result of the test is ***Futile*** (i.e., insignificant, or the sequential test statistic has fallen into the acceptance region of H_0), the conditional expected sample size is ***E(N|Fut) = 138.4*** and the conditional expected information time is ***E(T|sig) = 0.93506.*** By clicking ***Special Values*** repetitively, the expected sample sizes and information times will be calculated in sequence for special values of true mean: ***mu = 0 (mu_0 = 0)***, ***mu = 0.4 (mu_a = 0.4)***, and ***mu = 0.24166 (delta = 1.95996 =*** z_α***)***.

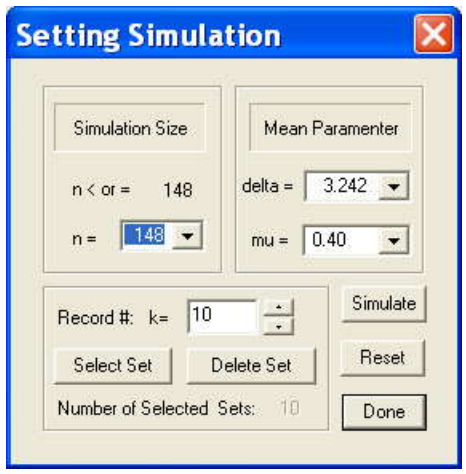
5. Simulation of Sample Paths

For a statistical inference problem in reality, observations are sampled from an unknown distribution or a distribution with unknown parameters. By statistical analysis, the distribution or its parameters are estimated from the observations. Simulation is opposite to the statistical inference, in which the true distribution or its parameter is assumed known and observations are simulated or artificially sampled from this distribution. It can be viewed that the observations in a statistical inference problem in reality are simulated by **nature** which has used a distribution to do simulations but hided the true distribution or its parameters away from our knowledge.

This computer program provides the functionality of simulation by which users can simulate observations in different situations (e.g., under H_0 or under H_a). The simulation helps users to understand intuitively the stochastic behaviors of sequential test statistics over the sequential boundaries of various designs and simulation parameters chosen.

5.1 Setting Parameters for Simulation

Click the button ***Simulated*** in the sub-panel ***Select Samples*** of the *4th* panel to open a dialog box as shown below.

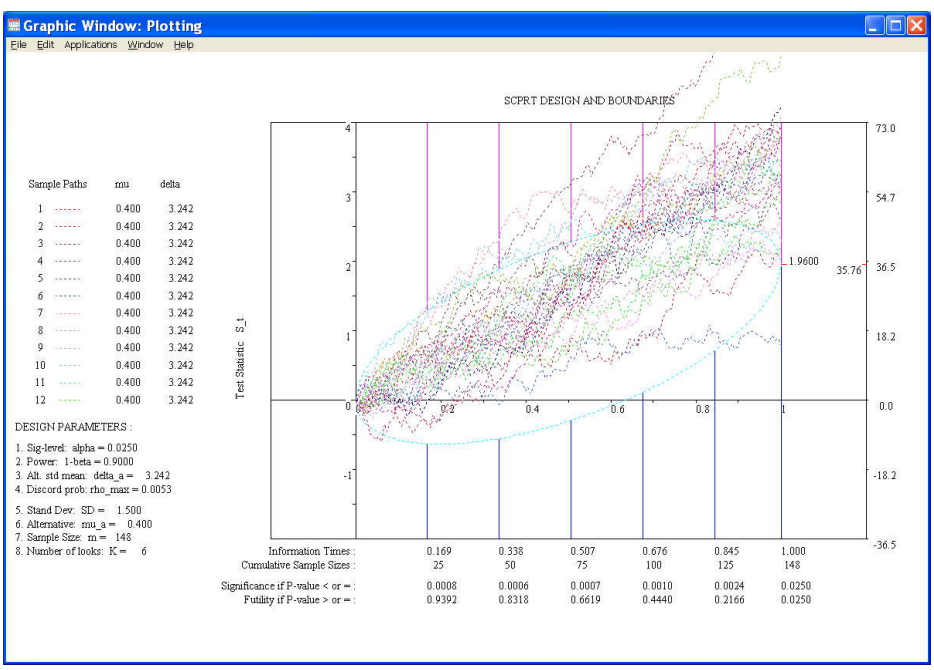


In the dialog box above, click the button ***Select Set*** to select a number of data sets for simulation. For a data set to be selected, the number of observations in this set is specified by ***n =***; the mean parameter of observations in this set is specified by ***mu =*** or ***delta =***; the ordinal number of this set is specified by ***Record #: k =***. You can delete a selected set by clicking the button ***Delete Set***. After a set is deleted, the ordinal numbers of selected sets will be updated and reassigned to the remaining sets. The design parameters except the mean parameters used for simulation are that set previously in the *2nd* panel ***Fixed Sample Test Design*** in the main dialog box. If you made changes in the *2nd* panel and want to simulate data sets with new parameters, you need to click the button ***Reset*** in the dialog box and restart the selection process for simulation. The total number of sets selected is indicated by ***Number of Selected Sets*** which is gray until you click the button ***Simulate*** to make it black. By clicking ***Simulate***, the data sets are simulated and ready for being displayed and/or saved.

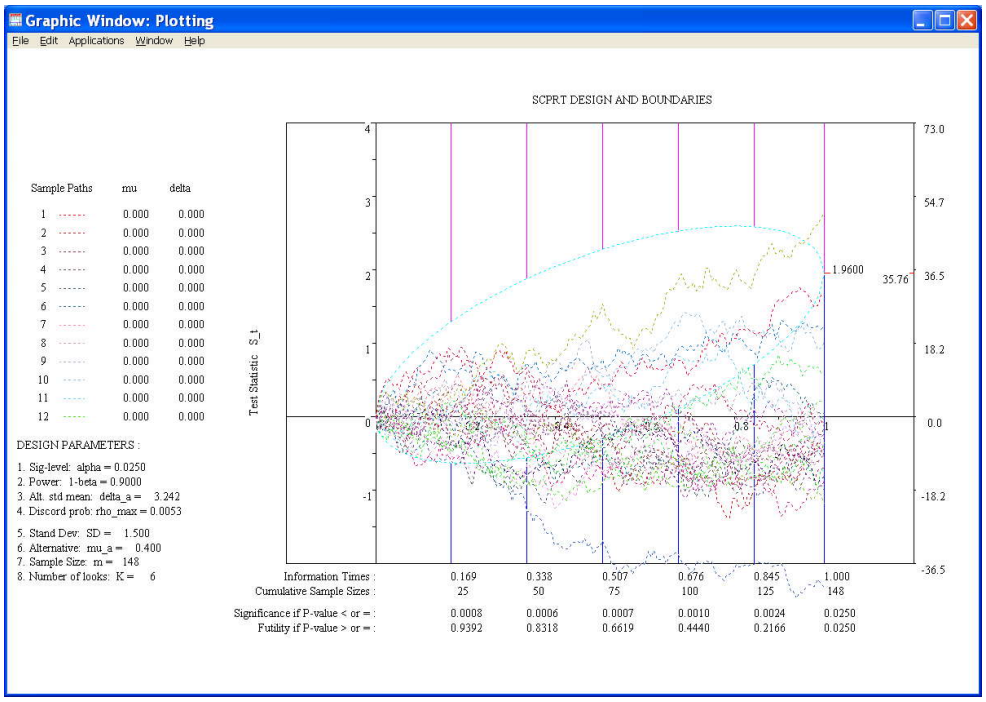
5.2 Simulating Samples and Interpreting Results

After having selected sets as explained above, click ***Graphic*** in the *4th* panel of the main dialog box to open a graphic window labeled ***Graphic Window: Plotting***. Select the following from the drop-down menu: ***Applications*** → ***Plot Samples...*** → ***By simulation*** to open a dialog box ***Plot Simulation***.

If the radio button ***New*** is selected each time you click the button ***Refresh Plot***, new sets of sample paths will be simulated and plotted in ***Graphic Window: Plotting***. If ***Saved*** is selected each time you click ***Refresh Plot***, the saved set of sample paths will be plotted in ***Graphic Window: Plotting***. The mean parameters of those paths are those set by the dialog box ***Setting Simulation*** (Section 5.1). For simulation example, assume 30 sets are selected (hence *k=30*) and ***mu = 0.4*** is selected as the mean parameter for each of them. The simulated 30 sample paths are plotted in the figure below. The colors of the first 10 sample paths are listed to the left of the figure.



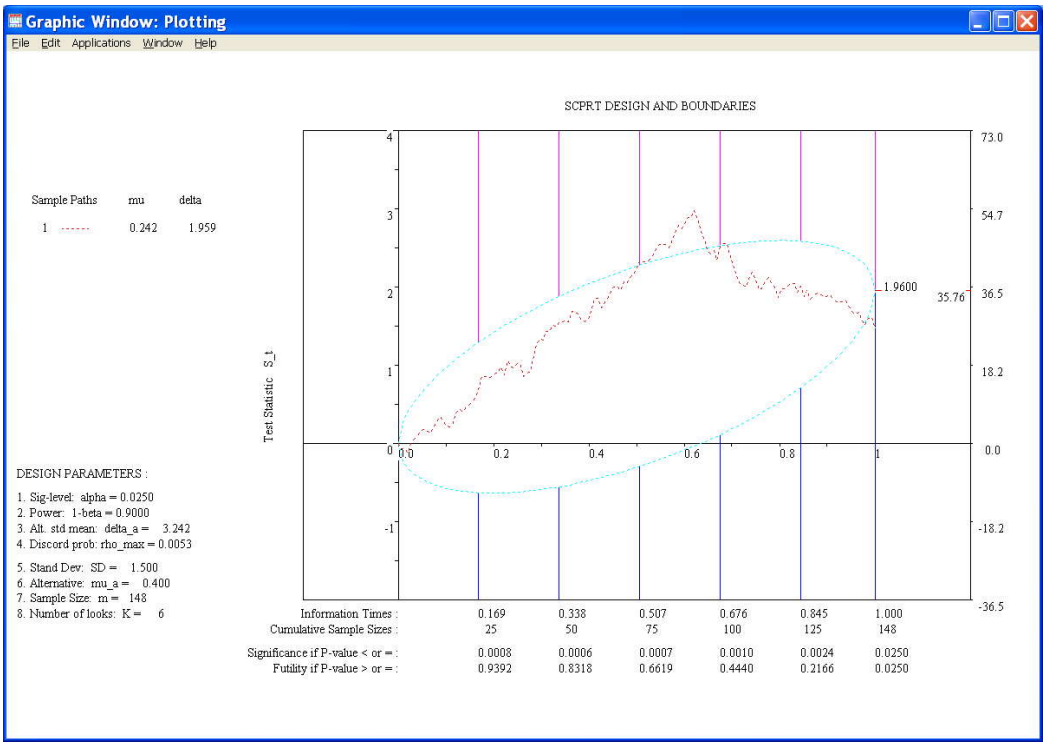
For another simulation example, assume 30 sets are selected with ***mu = 0*** as the mean parameter for each of them. The simulated 30 sample paths are plotted in the figure below.



For the two simulation examples above, significance level $\alpha = 0.025$ and power of test $1-\beta=0.9$ (hence $\beta=0.1$) were set. Under H_a ($mu=0.4$), the number of simulated paths failed to reach significance (i.e., with endpoints below cutoff value $z_\alpha = 1.96$) at the planned end (information time $t=1.0$) is random, on average, it equals $k\times\beta = 30\times0.1 = 3$. Under H_0 ($mu = 0.0$), the number of simulated paths that falsely reached significance (i.e., those with the endpoint above cutoff value $z_\alpha = 1.96$) at the planned end (information time $t = 1.0$) is random, on average, it equals $k\times\alpha = 30\times0.025 = 0.75$. You may repeat the two simulations many times and check if the numbers of paths ending above (or below) $z_\alpha = 1.96$ is about 3 (or 0.75) in average for the first (or the second) simulation example.

A major concern regarding early stopping of clinical trials is the possible later reversal of the early conclusion. Suppose a trial could be stopped according to the sequential design and the partially collected data, but the trial was not stopped and continued to the planned end. The conclusion of a test carried out with all data could be opposite to that of a sequential test at the earlier look. As shown in the figure below, the sequential test statistic crossed the upper boundary at the 3rd look with the first 75 observations and hence, the test should be stopped with a conclusion of significance. Suppose the trial were not stopped as it should have

been, but had continued to the planned end and stopped at the 6th look with 148 observations. The test statistic crossed the lower boundary at the 6th look, and hence the test should be concluded with finding of insignificance. This is a typical example of discordance between the conclusion at an early stage drawn from partially collected data and that at the planned end drawn from full data.



For an SCPRT design, the probability of discordance depends on the true mean ***mu***, and is maximized at the ***mu*** (μ) that its standardization ***delta*** (δ) is equal to the cutoff value (i.e., ***delta*** = z_α). You may obtain this value of ***mu*** or ***delta*** for each design by clicking ***Probability of Discordance*** in the *5th* panel of the main dialog box and then clicking ***rho_max*** in the dialog box ***Probability of Discordance***.

In the dialog box ***Setting Simulation*** (see Section 5.1), let ***mu*** or *delta* equal the value that maximizes the probability of discordance (discussed above). Click ***Select Set*** only once to select one data set. After selecting ***New*** in the dialog box ***Plot Simulation***, you can get a new sample path in the window ***Graphic Window: Plotting*** each time you click ***Refresh Plot***. Assume ***rho_max*** = *0.0053* and suppose you have clicked ***Refresh Plot*** repetitively 100 times. The number of incidences of discordance happened among the 100 sample paths is random, on average, equal to *k* × ***rho_max*** = *100×0.0053 = 0.53*. In other words, you need to simulate 200 sample paths in average to get one incidence of discordance as the one shown in the figure above.

5.3 Saving Simulated Data

After did simulation as in Section 5.2, click ***text*** in the 4th panel to open a text window labeled ***Text Window: Save and Import Data***. If the graphic window ***Graphic Window: Plotting*** is open, click the drop-down menu ***Window*** → ***Text Window*** to switch the graphic window to a text widow ***Text Window: Save and Import Data***. From the text window, click the drop-down menu ***Applications*** → ***Save Simulation*** to open a *Microsoft* dialog box ***Save As***. Select a directory and enter a file name, and click ***Save*** to save the simulated data into a text (*.txt*) file. The data will be displayed in the text window simultaneously if the size of data is large. The data can not be shown in the text window if the size is large. If the size is large but not larger than *200k*, then the data is saved, however, an external text editing tool such as *Notepad, WordPad,* or *Microsoft Word* is required to view it. In a simulated data set includes 7 (variables in) columns: 1) *ordinal numbers of simulated sets*; 2) *ordinal numbers of observations* (within a set); 3) *simulated observations* (in original scale); 4) *information times* (of observations within a set); 5) *standard deviation* (of distribution used for simulating a set of observations); 6) ***delta*** (the standardized mean parameter used for simulating a set of observations); and 7) ***mu*** (the mean parameter used for simulating a set of observations).

5.4 Restarting Simulation

If you are doing simulation and then changed the design parameters in the *2nd* panel, then you have to update sequential boundaries and setting of simulation before starting new simulations. Click ***Enter Group Sizes*** or ***Enter Information Times*** in the *3rd* panel of the main dialog box to update group sizes or information times; click button ***Bound-Coeff*** to recalculate the boundary coefficient ***a***. In the *4th* panel, click ***Sequential Design*** to update the ***Actual Sig-level*** and ***Actual Power*** for the sequential test design. Click ***Simulated*** to open the dialog box ***Setting Simulation***, in which click ***Reset*** and then enter new choices of mean parameter and number of observations for each set, and click ***Select Set*** repetitively to select sets for simulation. After all steps above, you are ready to simulate new sample paths with updated designs and parameters by clicking ***Graphic*** in the *4th* panel.

6. Graphic Display

6.1 Sequential Boundaries

Refer to Section 2.3 for the steps to display the sequential boundaries. In the plot of sequential boundaries, the ***x*-axis** of the plot is presented with two scales: one is by the cumulative sample sizes; another is by the information times. The information time at each look is the ratio of the cumulative sample size at this look to the planned total sample size. The ***y*-axis** of the plot is presented in two scales: the scale on the right side of the plot is for the original test statistic S_{n_k}, which is the sum of n_k original observations collected **by** the kth look. The scale on the left side of plot is for the standardized test statistic $S^*_{t_k}$, which equals S_{n_k} divided by $n_K^{1/2}\sigma$ which is the standard deviation of S_{n_K} at the final stage K. The $t_k = n_k/n_K$ is the information time at the kth look, and σ is the standard deviation of the original observation. The n_K (= m) is the sample size at the planned end of the sequential test. At the kth look, the mean and variance of S_{n_k} are $n_k\mu$ and $n_k\sigma^2$, respectively; the mean and variance of $S^*_{t_k}$ are $t_k\delta$ and t_k, respectively.

6.2 Power Function

Refer to Section 2.4 for the steps to display the power function. In the plot of power function, the ***x*-axis** of the plot is for the mean parameter, which is presented with two scales: one is for mean of *original observations*; another is for the mean of *standardized observations*. The ratio of the scale for original data to the scale of standardized data is equal to $\sigma/m^{1/2}$. The power function of the sequential design is presented by the pink curve. The mean parameter under H_a is marked on the vertical blue dotted line with the two scales. The significance level and power for the fixed sample test design are marked by the two horizontal blue dotted lines.

6.3 Expected Sample Size

Refer to Section 2.5 for the steps to display the expected sample size. In the plot of expected sample size, the ***x*-axis** of the plot is for the mean parameter, which is presented with two scales: one is for mean of *original observations*; another is for the mean of *standardized observations*. The ratio of the scale for original data to

the scale of standardized data is equal to $\sigma/m^{1/2}$. The ***y*-axis** of the plot is presented with two scales: the scale on the right side of the plot is by the *sample size*; the scale on the left side of the plot is by the *information time*. The pink curve is the expected sample size as a function of mean parameter in the two scales. The mean parameter under H_a is marked on the vertical blue line with the two scales. The expected sample size under H_0 (***mu = 0*** or ***delta = 0***) and H_a (***mu = mu_a*** or ***delta = delta_a***) can be visually identified from the plot.

6.4 Simulated Data

Refer to Section 2.6 for the steps to display the simulated data, and then refer to Section 5.2 for more detailed instructions. In the plot of simulated sample paths, the ***x*-axis** of the plot is presented with two scales: one is by the cumulative sample sizes; another is by the information times. The ***y*-axis** of the plot is presented with two scales: one is for the original test statistic S_{nk}, which is the sum of n_k original observations by the kth look; another is for the standardized test statistic $S^*_{n_k}$ which equals S_{nk} divided by $(n_K)^{1/2}\sigma$, the standard deviation of S_{nK} at the final stage K. The $t_k=n_k/n_K$ is the information at the kth look, and σ is the standard deviation of the original observation. The n_K (= m) is the sample size at the planned end of the sequential test. A simulated sample path can be interpreted in either of the two scales.

6.5 Imported Data

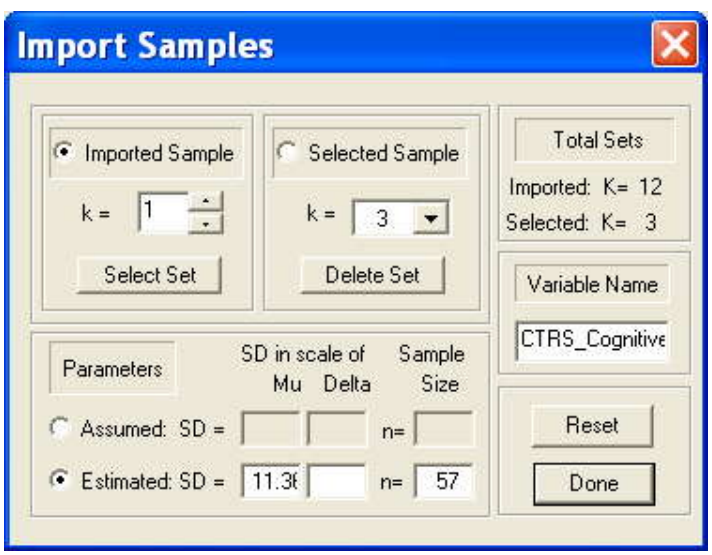
For a clinical trial or an experiment designed with SCPRT, sequentially collected data can be displayed graphically against the sequential boundary for a visual monitoring of the trial or experiment. If there are several variables in the trial or experiment, the sample paths for all variables can be displayed in a same plot. To display imported data, you first need to design sequential boundaries; second, to *import the data* from a text window; third, to *select sets* from the imported data for simulation; and finally, to *display* the selected sample paths.

- **Designing Sequential Boundaries:** Refer to Sections 2 and 3 for the steps to design the sequential boundaries. If you want to represent two or more variables from an observed data (see ***Note 1*** below) in the same plot, then enter four parameters in the 2nd panel of the main dialog box: the significance level, the power, the (maximum) sample size (same for all variables), and the standard deviation (let it equal 1). Then click ***Alternative***

mu_a to calculate the mean parameter. For each set, observations will be rescaled by being divided by the assumed or estimated standard deviation of the set, by which the standard deviation of rescaled observations from each set equals one.

- **Import Data:** Refer to Section 5.2 for the steps to open a text window ***Text Window: Save and Import Data***. From this window, click the drop-down menu ***Applications*** → ***Import Data*** → ***Sample*** → ***Simulated*** or ***Observed*** to open a *Microsoft* dialog box ***Open***. From this box, find the (.txt) file of your interest and then click "***Open***" to import a simulated data or an observed data (see **Note 1** below). Once imported, the data will be listed in the text window if the size of the data is not too large. If the data does not appear in the text window, it could be due to the large size of data. If the size of data not exceeding 200*k*, then plots of the data still can be displayed in the graphic window, even though the data did not appear in the text window. The observed data should be preprocessed according to **Note 2** below. For an imported data, you may import variable names for the columns of data. To import the list of variable names, from the **text window** you click the drop-down menu ***Applications*** → ***Import Data*** → ***Variable Names*** to open a *Microsoft* dialog box ***Open*** from which you can open a (.txt) file that contains a list of variable names for the imported observed data (see **Note 1** below).

- **Select Sets:** Click ***Imported*** in the sub-panel ***Select Samples*** of the *4th* panel to open a dialog box ***Import Samples*** as below. If the button ***Imported*** is gray (not responsive to clicks), then you need first to import the data using the procedure above.



In the dialog box ***Import Samples***, click ***Select Set*** to select sets from imported sets for display. The ordinal number of an imported set is indicated by ***k* =** in the panel ***Imported Sample***. The ordinal number of a selected set is indicated by ***k* =** in the panel ***Selected Sample***. The total numbers of imported sets and selected sets are indicated by the two numbers in the panel ***Total Sets***. Click ***Selected Sample*** and then click ***Delete Set*** to delete a set, the ordinal number of which is prefixed by ***k* =**, from the selected sets. The assumed or estimated standard deviation (prefixed by ***SD* =**) and sample size (prefixed by ***n* =**) for each imported or selected set are shown in the panel ***Parameter***. For each set, the assumed ***SD*** came with the imported list of variables, and the estimated ***SD*** is computed from observations from the imported data. Select ***Assumed: SD* =** or ***Estimated: SD* =**, depending on whether the standard deviation is assumed or estimated for each set selected.

- **To display:** Open the graphic window by clicking ***Graphic*** in the 4th panel, or switch the open window from a text widow (***Text Window: Save and Import Data***) to a graphic window (***Graphic Window: Plotting***) by clicking the drop-down menu ***Window*** → ***Graphic Window***. From the graphic window, click the drop-down menu ***Applications*** → ***Plot Samples...*** → ***Imported Data*** to open a dialog box labeled ***Plot Imported...***.

In the dialog box ***Plot Imported...***, select ***All*** and then click ***Refresh Plot***. All imported sets of sample paths will be displayed in ***Graphic Window: Plotting***. Selecting ***Selected***, click "***Refresh Plot***" to display only sets of sample paths previously selected through the dialog box ***Import Samples*** shown above.

Note 1: The imported data can be a data that was simulated and saved using this computer program, or a real data from clinical trials or experiments. We call the former a **simulated data**, and the latter an **observed data**. For a **simulated data**, the true mean and standard deviation of each set are known, and there are **7 columns** (see Section 5.3). For an **observed data**, the true mean and standard deviation of each set are unknown, and there are only **3 columns**: 1) the ordinal number of set (or path); 2)

the ordinal number of observation (in each set); 3) the observation (in original scale). An example for the data structure of file for observed data is given as below.

```
1    1    2.74100
1    2   -2.82478
:    :    :
2    1    1.24490
2    2   -0.04851
:    :    :
3    1    0.49472
3    2    0.79912
```

The file above can include only numerical items. If you want to display variable names for the variables of an imported **observed data**, then you need to import them from a separate .txt file which contains **3 columns**: 1) the ordinal number of imported set; 2) the variable names of imported set; 3) the standard deviation of imported set. An example for the data structure of the file for variable names is given as below.

```
1  name_variable_one    2.0
2  name_variable_two    1.5
3  name_variable_three  1.0
```

The total number of sets should be the same for the two files.

Note 2: For each set or variable in the observed data, if the hypothesis is H_0: $\mu \le \mu_0$ *vs.* H_a: $\mu > \mu_0$, then the imported observations should be $X_i = X_i^* - \mu_0$, where X_i^* is the original observation from trial or experiment. If the hypothesis is H_0: $\mu \ge \mu_0$ *vs.* H_a: $\mu < \mu_0$, then the imported observations should be $X_i = -X_i^* + \mu_0$.

7. Comparison of Two Populations

The SCPRT procedure described above is about one-population comparison, in which an unknown mean is compared to a known constant. For comparing the means of two populations, we can easily transform the problem to one-population comparison by comparing the difference of two means to *0*. However, the calibration of information times for interim analyses may not be in the simple form of proportions on cumulative sample sizes of interim analyses to the total sample size at the planned end. The sequential test statistic and information times of looks are given in section 7.1 for comparing two normal populations, in section 7.2 for comparing two binary populations, and in section 7.3 for comparing two survival populations. To obtain the sequential boundaries, critical p-values, and other operating characteristics for the sequential test statistic in these situations using this computer program are demonstrated in section 7.4.

7.1 Two Normal Populations

Let μ_1 and μ_2 be the unknown means, and σ_1^2 and σ_2^2 known variances, of two normal distributions. The hypothesis H_0: $\mu_1 \le \mu_2$ vs. H_a: $\mu_1 > \mu_2$ is equivalent to H_0: $d \le 0$ vs. H_a: $d > 0$, where $d = \mu_1 - \mu_2$. Suppose you want to test the hypothesis with significance level α and power $1-\beta$ to detect a given d_a (> 0). For a fixed sample test, the sample size is $m_1 = (z_\alpha + z_\beta)^2(\sigma_1^2 + r\sigma_2^2)/d_a^2$ for the first population (X_1), and is $m_2 = m_1 / r$ for the second population (X_2), where r is a number specified by the user as the ratio of two sample sizes. If you want to minimize the total sample size $m = m_1 + m_2$, then you may choose $r = \sigma_1 / \sigma_2$. If you want to minimize the total cost of accruals, $C = m_1 + cm_2$, then you may choose $r = \sqrt{c}\sigma_1 / \sigma_2$, where c is the proportional cost of individual accrual for X_2 assuming the cost for X_1 is 1. For the sequential test, let n_{1k} and n_{2k} be sample sizes of two populations at the kth look; assume $n_{1k} / n_{2k} = r$ for all $k = 1, \ldots, K$, where K is the total number of interim and final looks. The n_{1k}'s are specified by you, the designer of study, and the n_{2k}'s are calculated by $n_{2k} = rn_{1k}$. Let $S_{t_k}^* = U_k / V_K^{1/2}$, where $U_k = \sum_{j=1}^{n_{1k}} X_{1j} - r\sum_{j=1}^{n_{2k}} X_{2j}$, and $V_k = n_{1k}(\sigma_1^2 + r\sigma_2^2)$. Then the hypothesis of interest became H_0: $\delta \le 0$ vs. H_a: $\delta > 0$ with the sequential test statistic $S_{t_k}^*$ distributed with $N(t_k\delta, t_k)$, where $t_k = n_{1k} / n_{1K}$, $n_{1K} = m_1$, and $\delta = (z_\alpha + z_\beta)d / d_a$.

For example, assuming $\sigma_1 = 1$ and $\sigma_2 = 1.2$, and $c = 1$, let $r = 5/6$ which minimizes the total sample size. Assume with significance level $\alpha = 0.05$ and power $1-\beta = 0.85$ to detect a difference of $d_a = 0.5$. The calculated sample size is $m_1 = 63.27$ for X_1, and $m_2 = 75.92$ for X_2; hence $m_1 = 64$ and $m_2 = 76$ by being rounded up to the nearest integers. Assume $K = 4$ and the cumulative sample sizes for the first population at the four looks are assigned as $n_{11} = 15$, $n_{12} = 30$, $n_{13} = 45$, and $n_{14} = 64$, then the cumulative sample sizes for the second population at the four looks are $n_{21} = 18$, $n_{22} = 36$, $n_{23} = 54$, and $n_{24} = 76$, calculated by $n_{2k} = n_{1k} / r = 6n_{1k} / 5$ for k =1, 2, 3, and 4. The information times are $t_1 = 0.234375$, $t_2 = 0.468750$, $t_3 = 0.703125$, and $t_4 = 1$, calculated by $t_k = n_{1k} / n_{14}$ for k =1, 2, 3, 4. Under H_a, the parameter of drift for Brownian motion to be detected with power $1-\beta = 0.85$ is $\delta_a = 2.6968$, calculated by $\delta_a = d_a[m_1/(\sigma_1^2 + r\sigma_2^2)]^{1/2}$. If m_1 is not rounded up, then $\delta_a = z_\alpha + z_\beta$.

7.2 Two Binary Populations

Let p_1 and p_2 be the parameters of response for two binary distributions, respectively. The hypothesis H_0: $p_1 \le p_2$ vs. H_a: $p_1 > p_2$ is equivalent to H_0: $d \le 0$ vs. H_a: $d > 0$, where $d = p_1 - p_2$. Suppose you want to test the hypothesis with significance level α and power $1-\beta$ to detect a given d_a (> 0). For a fixed sample test, the sample size is $m_1 = (z_\alpha + z_\beta)^2[(p_2 + d_a)(1 - p_2 - d_a) + rp_2(1 - p_2)]/d_a^2$ for the first population (X_1), and is $m_2 = m_1 / r$ for the second population (X_2), where r is the ratio of two sample sizes, a number specified by user. If you want to minimize the total sample size $m = m_1 + m_2$, you may choose $r = \sqrt{(p_2 + d_a)(1 - p_2 - d_a) / p_2(1 - p_2)}$. If you want to minimize the total cost of accruals, $C = m_1 + cm_2$, you may choose $r = \sqrt{c(p_2 + d_a)(1 - p_2 - d_a) / p_2(1 - p_2)}$, where c is the proportional cost of individual accrual for X_2 assuming the cost for X_1 is 1. Let n_{1k} and n_{2k} be cumulative sample sizes of two populations at k^{th} look of a sequential test. Assume $n_{1k} / n_{2k} = r$ for all $k = 1, \ldots, K$, where K is the total number of interim and final looks. Assume n_{1k}'s are specified, and n_{2k}'s are calculated by $n_{2k} = n_{1k} r$. Let $S_{t_k}^* = U_k / V_K^{1/2}$, where $U_k = \sum_{j=1}^{n_{1k}} X_{1j} - r\sum_{j=1}^{n_{2k}} X_{2j}$ and $V_k = n_{1k}((p_2 + d_a)(1 - p_2 - d_a) + rp_2(1 - p_2))$. The hypothesis of interest is now H_0: $\delta \le 0$ vs. H_a: $\delta > 0$ with the sequential test statistic $S_{t_k}^*$ distributed approximately with $N(t_k\delta, t_k)$, where $t_k = n_{1k} / n_{1K}$, $n_{1K} = m_1$, and $\delta = (z_\alpha + z_\beta)d / d_a$.

For example, assuming significance level $\alpha = 0.05$ and power $1 - \beta = 0.85$ for detecting a difference of $d_a = 0.2$. Assume nuisance parameter $p_2 = 0.6$ and $c = 1$; $r = 0.8165$ minimizes the total sample size; hence let $r = 4/5$ for simplicity. The calculated sample size is $m_1 = 63.27$ for X_1, and is $m_2 = 79.08$ for X_2; hence $m_1 = 64$ and $m_2 = 80$ by rounded up to the nearest integers. Assume $K = 4$ and the cumulative sample sizes for the first population at the four looks are $n_{11} = 16$, $n_{12} = 32$, $n_{13} = 48$, and $n_{14} = 64$, then the cumulative sample sizes for the second population at the four looks are $n_{21} = 20$, $n_{22} = 40$, $n_{23} = 60$, and $n_{24} = 80$, calculated by $n_{2k} = n_{1k} / r = 5n_{1k} / 4$ for k =1, 2, 3, and 4. The information times are $t_1 = 0.2$, $t_2 = 0.4$, $t_3 = 0.8$, and $t_4 = 1$, calculated by $t_k = n_{1k} / n_{14}$ for k =1, 2, 3, and 4. Under H_a, the parameter of drift for Brownian motion to be detected with power $1 - \beta = 0.85$ is $\delta_a = 2.6968$ by $\delta_a = d_a[m_1 / ((p_2 + d_a)(1 - p_2 - d_a) + rp_2(1 - p_2))]^{1/2}$.

7.3 Two Survival Populations

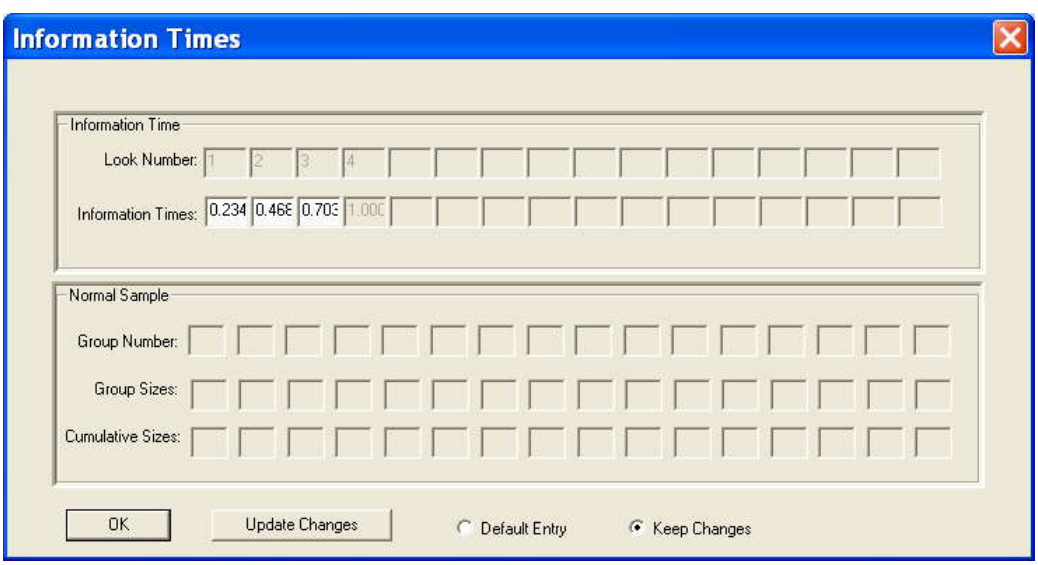
Let λ_1 and λ_2 be hazards of survival functions $G_1(t)$ and $G_2(t)$ for two populations, X_1 and X_2, respectively. Let $r = \lambda_2 / \lambda_1$ be the hazards ratio and assume r is a constant independent of time, which means that λ_1 and λ_2 should be proportional to each other if λ_1 and λ_2 are functions of time t. The hypothesis of interest is H_0: $r \le 1$ vs. H_a: $r > 1$ with significance level α and power $1-\beta$ to detect a given alternative r_a. Let m_1 and m_2 be the samples sizes of the two populations, and let $\pi = m_1/(m_1+m_2)$ and $1-\pi = m_2/(m_1+m_2)$ be proportions of the two groups. Let $A = \frac{1}{6}\{G_1(f) + 4G_1(0.5a+f) + G_1(a+f)\}$, $B = \frac{1}{6}\{G_2(f) + 4G_2(0.5a+f) + G_2(a+f)\}$, where a is the length of enrollment period and f the length of followup period in the clinical trial, for sample size calculation assuming they are the same for both groups. The sample size for the first group is $m_1 = m_2\pi/(1-\pi)$, and the sample size for the second group is $m_2 = (z_\alpha + z_\beta)^2 / \{\pi(1-B-\pi(A-B))(\ln(r_a))^2\}$. You may choose $\pi = \left(1-2B+A-\sqrt{(1-A)(1-B)+(A-B)^2}\right)\Big/3(A-B)$ if you want to minimize the total sample size $m = m_1 + m_2$. Assume distinct event times across two groups are $\tau_1 < \tau_2 < \cdots < \tau_j \cdots$, where the event time is defined as the length of time from the accrual to the event for a patient. At time τ_j, let d_{1j} be the number of events from the first population and d_{2j} the number of events from the second population. Let n_{1j} and n_{2j} be numbers of subjects at risk just before time τ_j from the two populations. Consequently, $d_j = d_{1j} + d_{2j}$ is the total number of events at time τ_j among a total of $n_j = n_{1j} + n_{2j}$ subjects just before τ_j , and $e_{1j} = n_{1j} d_j / n_j$. Let $\tau^*(k)$ be calendar time at the kth look, at which the log-rank score is $U_k = \sum_j (d_{1j\tau^*(k)} - e_{1j\tau^*(k)})$, where $d_{1j\tau^*(k)}$, $e_{1j\tau^*(k)}$, $n_{1j\tau^*(k)}$, $n_{2j\tau^*(k)}$ $d_{j\tau^*(k)}$, and $n_{j\tau^*(k)}$ are those as d_{1j}, e_{1j}, n_{1j}, n_{2j} d_j, and n_j but calculated from the data up to $\tau^*(k)$. Let $v_{1j\tau^*(k)} = n_{1j\tau^*(k)} n_{2j\tau_k^*(k)} d_{j\tau^*(k)} (n_{j\tau^*(k)} - d_{j\tau^*(k)}) / n^2_{j\tau^*(k)} (n_{j\tau^*(k)} - 1)$, then the variance of U_k is $V_k = \sum_j v_{1j\tau^*(k)}$. The sequential test statistic is $S^*_{t_k} = -U_k / \sqrt{V_K^*}$ for $k = 1, \cdots, K-1$, where $V_K^* = \{(z_\alpha + z_\beta)/(\ln(r_a)\}^2$; $t_k = V_k / V_K^*$ is the projected information time and V_K^* is the projected variance of U_K. At the final stage K, the true variance V_K is used instead of V_K^*, hence $t_K = 1$ and $S^*_{t_K} = -U_K / \sqrt{V_K}$. The information time t_k is

not specified in advance but calculated from V_k with data up to the stage k, with all looks determined according to the calendar time or the number of subjects enrolled since the start of clinical trial.

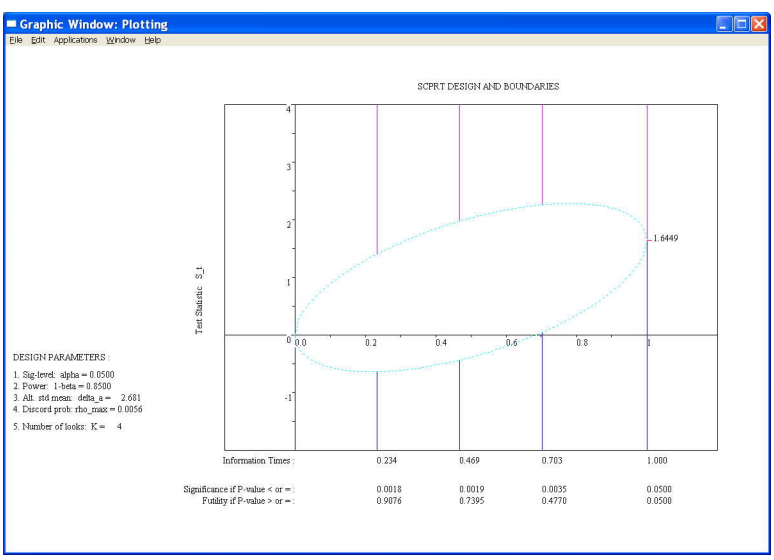
For example, assume $G_1(t) = \exp(-\lambda_1 t)$ and $G_2(t) = \exp(-\lambda_2 t)$, and with significance level *α* = 0.05 and power *1-β* = 0.80 to detect $r_a = 1.6$ ($r = \lambda_2 / \lambda_1$) under H_a. Assume the accrual period is from 0 to *4*th year, and the follow-up period is from *4*th year to *5*th year, of study; thus $a = 4$ (years) and $f = 1$ (year). Assume a nuisance parameter $\lambda_2 = 0.2$ ($EX_2 = \mu_2 = 1/\lambda_2 = 5$), then under H_a, $\lambda_1 = \lambda_2 / r_a = 0.125$ ($EX_1 = \mu_1 = 1/\lambda_1 = 8$), hence A=0.6945 and B=0.5636. The total sample size $m = m_1 + m_2$ can be minimized by $\pi = 0.457$. Let $\pi = 0.5$ for the simplicity of balanced sample sizes, the calculated sample sizes are $m_1 = m_2 = 150.9$; hence $m_1 = m_2 = 151$ by rounded up to the nearest integers. Assume looks are planned at the 2nd, 3rd, 4th, and 5th years from the start of trial. Information time t_k of the kth interim analysis will be calculated from data for $k = 1, \cdots, 4$.

7.4 Sequential Boundaries

For any sequential test statistic that behaves like a Brownian motion on the information interval [0, 1], including those in Sections 7.1, or 7.2, or 7.3, the SCPRT sequential boundaries and critical p-values can be obtained as following. For illustrative purpose, we will use the numerical example in Section 7.1 for comparing two normal populations.



In the 1st panel of the main dialog box labeled ***SCPRT on Information Time***, click the button ***SCPRT on Information Time***. In the *2nd* panel, enter 0.05 for ***Sig-level*** and 0.85 for ***Power of Test***. In the 3rd panel, enter 4 for ***Number of Looks***, and then click the button ***Enter Information Times*** to open a dialog box labeled ***Information Times*** as above. In this dialog box, change the default information times to the values of $t_1 = 0.234375$, $t_2 = 0.468750$, $t_3 = 0.703125$ for the first three looks calculated in Section 7.1, and then click the buttons ***Update Changes*** and ***Keep Changes***. The updated information times of looks should be as that in the dialog box above. Click the button ***OK*** to close the dialog box and return to the main dialog box. Remember to click the button ***Bound-Coeff a***, by which the boundary coefficient is calculated as ***a = 2.9420***, and the maximum probability of discordance is calculated as ρ_{max} ***= 0.0056***. In the 4th panel, click the button ***Sequential Design*** to calculate the significance level and power of the sequential design, which are ***α = 0.0511*** and ***1-β = 0.8489***. In the sub-panel ***Window***, click the button ***Graphic*** to open a graphic window ***Graphic Window: Plotting***. In this window, select ***Applications*** → ***Plot Design...*** → ***Sequential boundary*** from drop-down menus to open a small dialog box ***Plot***. By clicking the button ***Refresh Plot*** in the box, the system will plot the sequential boundaries, as shown below, with the critical P-values for upper and lower boundaries listed in the plot. The critical p-values listed in the plot are p_{a_k}'s = (0.0018, 0.0019, 0.0035, 0.05) for upper boundaries and p_{b_k}'s = (0.9076, 0.7395, 0.4470, 0.05) for lower boundaries, respectively, for reaching significance and futility. In the plot, $\delta_a = 2.681$ calculated by $\delta_a = z_\alpha + z_\beta$, which differs slightly from $\delta_a = 2.6968$ calculated in Section 7.1. The former is calculated using sample size $m_1 = n_{14} = 63.27$, and the latter is calculated using $m_1 = n_{14} = 64$ which is the actual sample size used in trial.



Click ***Critical Boundary Values*** in the *5th* Panel of the main dialog box, the sequential boundaries for $S^*_{t_k}$'s are obtained as (1.413, 1.9815, 2.2648, 1.6449) and (-0.642, -0.4395, 0.0483, 1.6449), respectively, for upper and lower boundaries. The critical p-values and the sequential boundaries for S_{n_k}'s are presented as well in the dialog box. At the *k*th look, the observed P-value p_{S_k} can be obtained as the p-value from regular non-sequential test of comparing two populations applying to data collected up to stage k. If p_{S_k} is less than or equal to p_{a_k}, or greater than or equal to p_{b_k} at some stage k for the first time, then the trial can be stopped. The power function, the probability of discordance, and the expected information time of SCPRT design can be obtained with similar procedures by clicking other three buttons in the *5th* Panel: ***Probability of Significance***, ***Probability of Discordance***, and ***Expected Sample Size***, respectively.

8. Comparison with Historical Population

The SCPRT procedure for comparing a current population with a historical population is similar to that for comparison of two current populations in Section 7. The main difference distinguishing this situation from the previous one is that the samples for the current population (X_1) are collected and sequentially compared at each look of the study with all samples from the historical population (X_2). The SCPRT procedure for this situation differs from that in Section 7 in three aspects: 1) calculation of sample size (see Section 8.1); 2) definition of sequential test statistic (see Section 8.2); 3) calculation of information time (see Section 8.3).

8.1 Sample Size Calculation

There are two scenarios for sample size calculation for design of comparison with historical population. The **first scenario** is the conventional way of comparing two means, namely, to detect $d_a = \mu_{1a} - \mu_2$ with power *1-β*. The sample size of the historical population m_2 is given. The sample size for the current population for **normal populations** is by $m_1 = \sigma_1^2 / [d_a^2 / (z_\alpha + z_\beta)^2 - \sigma_2^2 / m_2]$, and that for ***binary populations*** is by $m_1 = (p_2 + d_a)(1 - p_2 - d_a) / [d_a^2 / (z_\alpha + z_\beta)^2 - p_2(1 - p_2) / m_2]$. For **survival populations**, $m_1 = m_2 \pi / (1 - \pi)$, where m_2 is given and π is the solution of

equation $m_2 = (z_\alpha + z_\beta)^2 / \{\pi(1 - B - \pi(A - B))(\ln(r_a))^2\}$; or equivalently, $\pi = \left(1 - B - \sqrt{(1-B)^2 - 4(A-B)(z_\alpha + z_\beta)^2 / m_2(\ln(r_a))^2}\right) \Big/ 2(A - B)$.

The **second scenario** is to detect alternative $\hat{d}_a = \mu_{1a} - \hat{\mu}_2$ with power $1-\beta$. Since the mean of historical controls had already been estimated by $\hat{\mu}_2 = \overline{X}_2$ prior to the current study, and investigators may take it as a priori information for design of the trials. The appeal of the scenario is that the alternative hypothesis with μ_{1a} against a visible $\hat{\mu}_2$ rather than an invisible μ_2 sometimes conveys important practical information. For the **normal populations**, with the sample size of the historical population m_2 given, the sample size m_1 for the current population for the current study is the solution of equation $z_\beta = \hat{d}_a \sqrt{m_1} / \sigma_1 - z_\alpha \sqrt{1+R}$, where $R = (\sigma_2^2 / m_2)/(\sigma_1^2 / m_1)$ is a function of m_1. Equivalently, the sample size can be calculated by $m_1 = \left[\left(\sigma_1 / \hat{d}_a\right)\left(z_\beta + z_\alpha \sqrt{1 + \sigma_2^2 (z_\beta^2 - z_\alpha^2) / m_2 \hat{d}_a^2}\right) \Big/ \left(1 - \sigma_2^2 z_\alpha^2 / \hat{d}_a^2 m_2\right)\right]^2$. For the **binary populations**, $m_1 = \dfrac{(p_2 + \hat{d}_a)(1 - p_2 - \hat{d}_a)\left(z_\beta + z_\alpha \sqrt{1 + p_2(1-p_2)(z_\beta^2 - z_\alpha^2)/m_2 \hat{d}_a^2}\right)^2}{\left(\hat{d}_a - p_2(1-p_2) z_\alpha^2 / m_2 \hat{d}_a\right)^2}$. The m_1 obtained from the second scenario is smaller than that obtained from the first scenario. However, the SCPRT procedure and the sequential test statistic are the same for the two scenarios.

8.2 Sequential Test Statistic

For **normal populations**, the sequential test statistic is defined as $S_{t_k}^* = \dfrac{\sqrt{1+R}}{\sqrt{m_1}\sigma_1(1 + R(n_k / m_1))} \sum_{i=1}^{n_k} \left(X_{1i} - \overline{X}_2\right)$, where X_{1i} 's are observations from the current population, and $\overline{X}_2$ is the sample mean of all data from the historical population. For **binary populations**, the sequential test statistic is the same as above equation except that σ_1 is replaced by $\sqrt{(p_2 + \hat{d}_a)(1 - p_2 - \hat{d}_a)}$. For the **survival populations**, similar to that in Section 7.3, the sequential test statistic is $S_{t_k}^* = -U_k / \sqrt{V_K^*}$ for $k = 1, \cdots, K-1$, where $U_k = \sum_j (d_{1j\tau^*(k)} - e_{1j\tau^*(k)})$, $V_k = \sum_j v_{1j\tau^*(k)}$, $V_K^* = \{(z_\alpha + z_\beta)/(\ln(r_a)\}^2$, $t_k^* = V_k / V_K^*$ (see Section 8.3); $\tau^*(k)$ is the calendar time at

k^{th} look. In equation $v_{1j\tau^*(k)} = n_{1j\tau^*(k)} n_{2j} d_{j\tau^*(k)} (n_{j\tau^*(k)} - d_{j\tau^*(k)}) / n^2_{j\tau^*(k)} (n_{j\tau^*(k)} - 1)$, the component items different from those in Section 7.3 are $d_{j\tau^*(k)} = d_{1j\tau^*(k)} + d_{2j}$, $n_{j\tau^*(k)} = n_{1j\tau^*(k)} + n_{2j}$, $e_{1j\tau^*(k)} = n_{1j\tau^*(k)} d_{j\tau^*(k)} / n_{j\tau^*(k)}$. Same as in Section 7.3, the true variance V_K at the final stage K is used instead of V_K^*, and hence $t_K^* = 1$ and $S_{t_K}^* = -U_K / \sqrt{V_K}$. The transformed information time t_k^* is not specified in advance but calculated from V_k with data collected up to the kth look. The looks are determined according to the calendar time of study or the number of patients enrolled since the start of clinical trial.

8.3 Transformed Information Time

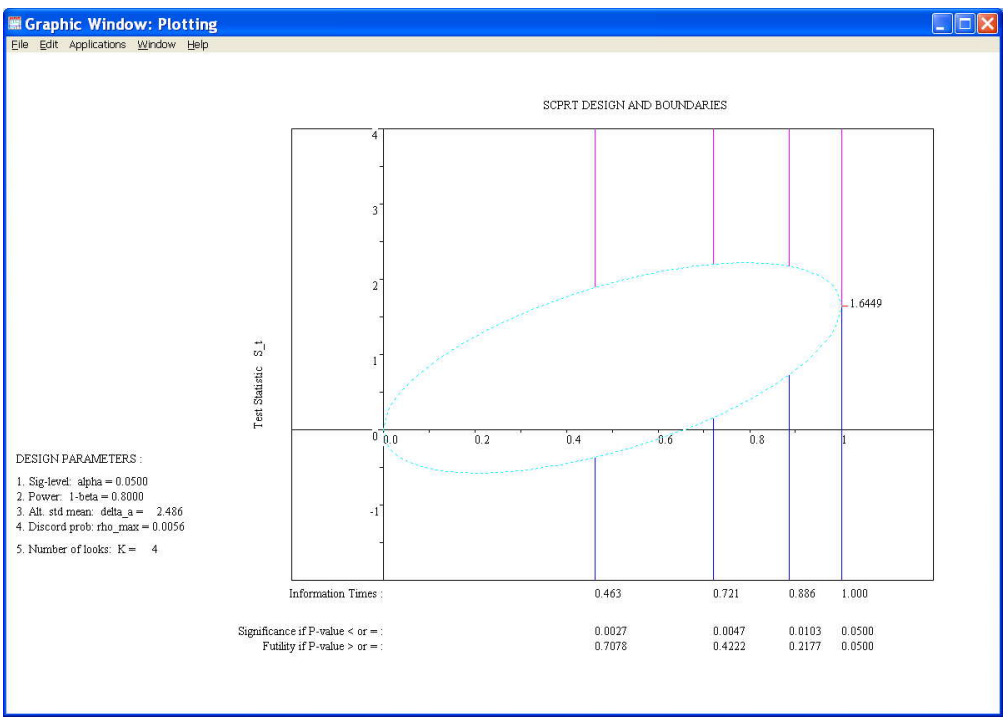
For comparison against historical data, the *original information time* measures the information accumulation for data from the current population, and the *transformed information time* measures the information accumulation for data from both current and historical populations. For **normal** and **binary distributions**, the **original information time** at the kth look is $t_k = n_{1k} / n_{1K}$, and the **transformed information time** is $t_k^* = t^*(t_k) = (1+R)t_k / (1+Rt_k)$, where $R = (\sigma_2^2 / m_2)/(\sigma_1^2 / m_1)$ for normal distribution and $R = \left((p_2(1-p_2)/m_2\right) / \left((p_2 + \hat{d}_a)(1-p_2-\hat{d}_a)/m_1\right)$ for binary distribution. For **survival populations**, the information time can not be predetermined but be calculated from data at each look. As shown in Section 8.2, the **transformed information time** t_k^* can be directly estimated from data at the kth look, thus does not need to be transformed from the original information time t_k which is also random and needs to be estimated from data at the kth look. The presentation and calculation of sequential boundaries are much simpler by using the transformed information time.

8.4 Sequential Boundaries

For a sequential test statistic defined in Section 8.2, the sequential boundaries and critical p-values can be obtained by follow steps in Section 7.4. However, the information times entered in the program procedure should be the **transformed information time** defined in Section 8.3.

Example for normal populations: To test hypothesis H_0: $\mu_1 \le \mu_2$ vs. H_a: $\mu_1 > \mu_2$, assume $\sigma_1 = 1$, $\sigma_2 = 1.5$, $m_2 = 148$, and $\hat{\mu}_2 = \overline{X}_2 = 0.0337$. With significance level

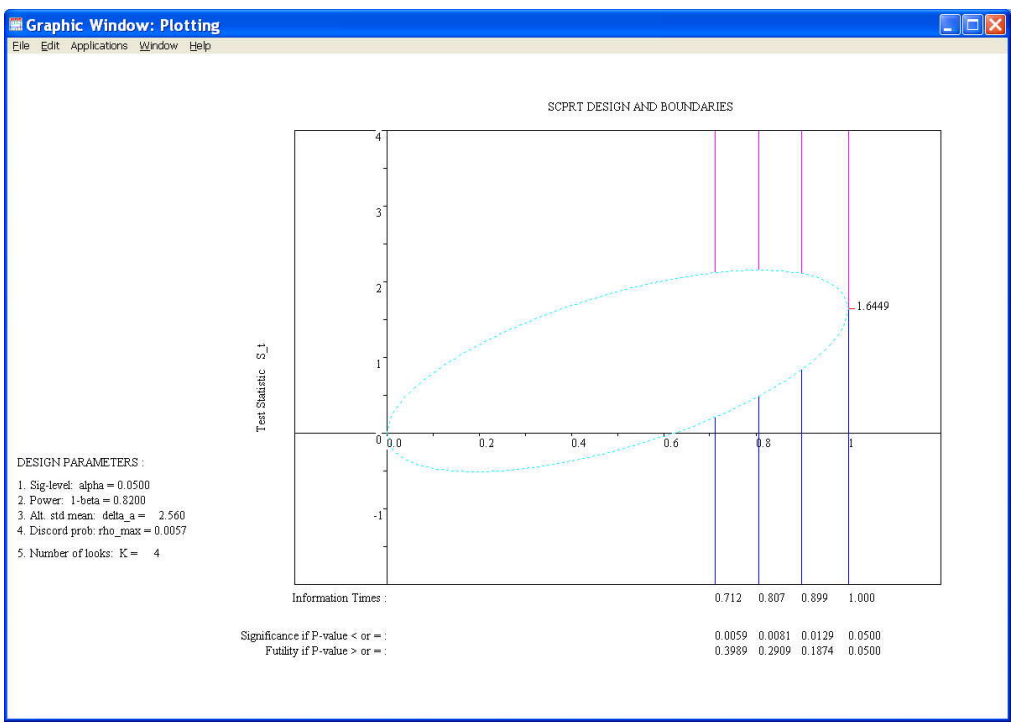
$\alpha = 0.05$ and power $1-\beta = 0.80$ to detect a difference of $d_a = 0.4$ (for the first scenario), we have $m_1 = 100$ and hence $R = 1.584507$. Assume $K = 4$ and at the 4 looks the cumulative sample sizes are $n_{11},\cdots,n_{14} = 25,\ 50,\ 75,\ 100$ for the current population. The original information times are $t_1,\ldots,t_4 = 0.25,\ 0.5,\ 0.75,\ 1$, and the transformed information times are $t_1^*,\cdots,t_4^* = 0.46280, 0.72102, 0.88576, 1$ calculated by $t_k^* = (1+R)t_k/(1+Rt_k)$. Referring to Section 7.3, in the 1st panel of the main dialog box ***SCPRT on Information Time***, click the button ***SCPRT on Information Time***. In the *2nd* panel, enter 0.05 for ***Sig-level*** and 0.80 for ***Power of Test***. In the 3rd panel, enter 4 for ***Number of Looks***, and then click the button ***Enter Information Times*** to open a dialog box labeled ***Information Times***. In this dialog box, change the default information times to the values of $t_1 = 0.46280$, $t_2 = 0.72102$, $t_3 = 0.88576$ for the first three looks in Section 7.1, and then click the buttons ***Update Changes*** and ***Keep Changes***. Click the button ***OK*** to close the dialog box and return to the main dialog box labeled ***SCPRT on Information Time***. Set ***ρ=0.03*** and click the button ***Bound-Coeff a***, by which the boundary coefficient is calculated as ***a= 2.582826*** and the maximum probability of discordance is calculated as ρ_{max}***=0.0056***.



In the 4th panel, click the button ***Sequential Design*** to calculate the significance level and power of the sequential design, which are ***α = 0.0507*** and ***1-β = 0.7993***. In the sub-panel ***Window***, click the button ***Graphic*** to open a graphic window ***Graphic***

Window: Plotting. In this window, select ***Applications*** → ***Plot Design...*** → ***Sequential boundary*** from drop-down menus to open a small dialog box ***Plot***. After clicking the button ***Refresh Plot***, the system will plot the sequential boundaries, as shown above, with listed the critical P-values for upper and lower boundaries. The critical p-values are listed in the plot as p_{a_k}'s = (0.0027, 0.0047, 0.0103, 0.05) on upper boundaries and p_{b_k}'s = (0.7078, 0.4222, 0.2177, 0.05) on lower boundaries, respectively, for significance and futility.

An example for binary populations: To test hypothesis H_0: $p_1 \le p_2$ vs. H_a: $p_1 > p_2$, we assume $m_2 = 35$ and $\hat{p}_2 = \overline{X}_2 = 0.62857$. With significance level $\alpha = 0.05$ and power $1-\beta = 0.82$ to detect a difference of $\hat{d}_a = 0.2$ (for the second scenario), we have $m_1 = 62$ and hence $R = 2.9117$. Assume $K = 4$ and the cumulative sample sizes of current population at 4 looks are $n_{11},\ldots,n_{14} = 24,\ 32,\ 43,\ 62$. The original information times are $t_1,\cdots,t_4 = 0.3871,\ 0.5161,\ 0.6935,\ 1$ and the transformed information times are calculated as $t_1^*,\cdots,t_4^* = 0.7118, 0.8067,\ 0.8985,\ 1$.

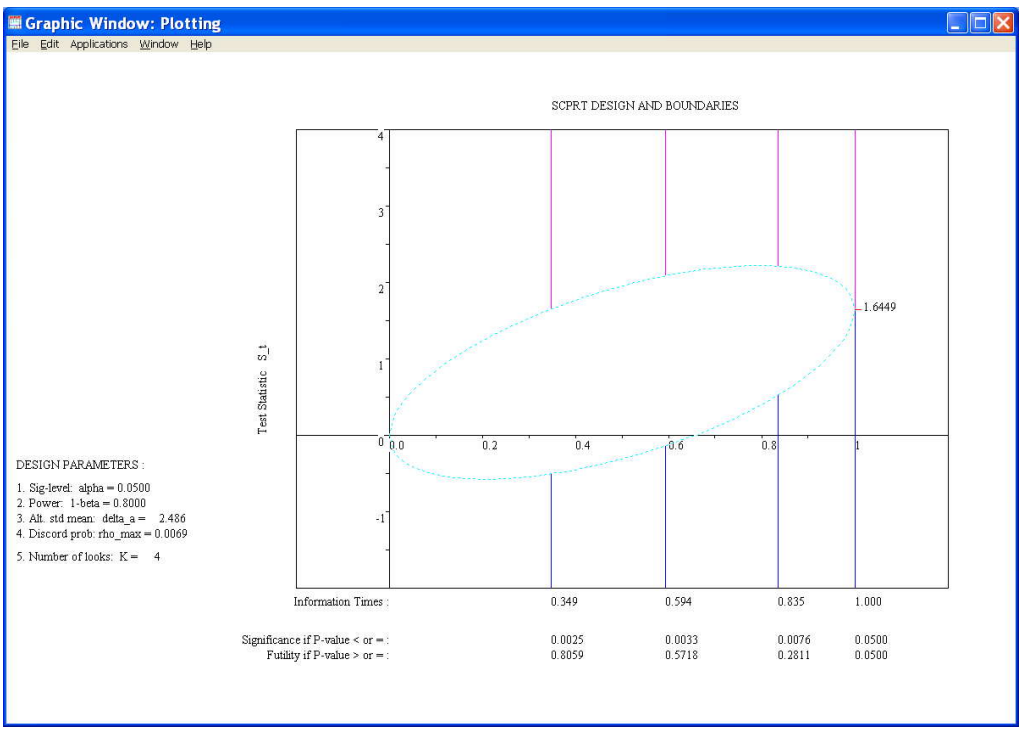


Follow the steps of computer program for the example above and set ***α = 0.05*** and ***1-β = 0.82*** in the second panel, and ***ρ = 0.04*** in the second panel, of the main dialog box. We have boundary coefficient ***a = 2.22137*** and the maximum probability of discordance ρ_{max} ***= 0.0057***. In the 4th panel, the significance level and power are ***α =***

0.0505 and ***1-β = 0.8195***, updated by clicking the button ***Sequential Design***. The sequential boundaries are plotted as above, and by which the critical P-values are p_{a_k}'s = (0.0059, 0.0081, 0.0129, 0.05) on upper boundaries and p_{b_k}'s = (0.3989, 0.2909, 0.1874, 0.05) on lower boundaries, respectively, for significance and futility. Click ***Critical Boundary Values*** in the *5th* Panel, the sequential boundaries for S_{t_k}'s are obtained as $(a_{t_1},\ldots,a_{t_4}) =$ (2.1255, 2.1592, 2.1144, 1.6449) and $(b_{t_1},\ldots,b_{t_4}) =$ (0.2161, 0.4946, 0.8414, 1.6449) for upper and lower boundaries, respectively. Let $S_{n_{1k}}^{X_1} = \sum_{i=1}^{n_{1k}} X_{1k}$ be the number of responses in n_{1k} binary observations from the current population at the *k*th look. Then the sequential boundaries for $S_{n_{1k}}^{X_1}$ are $a_k^* = [a_k]^+$ and $b_k^* = [b_k]_-$ for upper and lower boundaries, respectively, where $a_k = a_{t_k}\sqrt{(p_2+d_a)(1-p_2-d_a)m_1}(1+Rn_{1k}/m_1)/\sqrt{1+R} + n_{1k}\overline{X}_2$ and $b_k = b_{t_k}\sqrt{(p_2+d_a)(1-p_2-d_a)m_1}(1+Rn_{1k}/m_1)/\sqrt{1+R} + n_{1k}\overline{X}_2$; $[x]^+$ is the smallest integer greater than or equal to x; and $[x]_-$ is the largest integer less than or equal to x. For this example, the sequential boundaries for $S_{n_{1k}}^{X_1}$'s are $(a_1^*,\ldots,a_4^*) =$ (22, 29, 37, 49) as the upper boundaries for significance, and $(b_1^*,\ldots,b_4^*) =$ (15, 21, 30, 48) as the lower boundaries for futility, with partial cumulative sample sizes $(n_{11},\ldots,n_{14}) =$ (24, 32, 43, 62) at the four looks.

An example for survival populations: Assume the survival functions are $G_1(t) = \exp(-\lambda_1 t)$ and $G_2(t) = \exp(-\lambda_2 t)$ for current population and historical population, respectively. To test hypothesis *H0*: *r ≤1* vs. *Ha*: *r >1* ($r = \lambda_2/\lambda_1$) with significance level $\alpha = 0.05$ and power $1-\beta = 0.80$ to detect alternative $r_a = 1.6$ (for the first scenario), we assume $m_2 = 140$ for the sample size for the historical population, and $a = 4$ (years) and $f = 1$ (year) for the durations of accrual and follow-up, respectively. Assume the nuisance parameter $\lambda_2 = 0.2$, then $\lambda_1 = 0.125$ under *Ha* and thus $m_1 = 170$. Assume looks are planned at the 2nd, 3rd, 4th, 5th years from the start of trial. Information time t_k is not specified by be calculated from data at the *k*th interim analysis for $k = 1,\cdots,4$. For example, by simulation with parameters set under *Ha* by letting $\lambda_2 = 0.2$ and $\lambda_1 = 0.125$, we have the transformed information times $(t_1^*,\ldots,t_4^*) =$ (0.349, 0.594, 0.835, 1.0). Follow the steps in computer program for the two examples above in Section 8.4, enter these $t_1^*,\ldots,t_4^*$ and set ***ρ= 0.03***, we have boundary coefficient ***a= 2.584797*** and the maximum

probability of discordance ***ρmax=0.0069***. In the 4th panel, the significance level and power are ***α = 0.0510*** and ***1-β = 0.7989***. The sequential boundaries are plotted as below, and the critical P-values are p_{a_k}'s = (0.0025, 0.0033, 0.0076, 0.05) on upper boundaries and p_{b_k} 's = (0.8059, 0.5718, 0.2811, 0.05) on lower boundaries, respectively, for significance and futility. Click ***Critical Boundary Values*** in the *5th* Panel, the sequential boundaries for $S_{t_k^*}$'s are obtained as $(a_{t_1^*},\ldots,a_{t_4^*}) =$ (1.6578, 2.0936, 2.2174, 1.6449) and $(b_{t_1^*},\ldots,b_{t_4^*}) =$ (-0.5097, -0.1395, 0.5295, 1.6449) for upper and lower boundaries, respectively.



References

1. Xiong X. Sequential Analysis for Hypergeometric Distribution, *Ph.D. dissertation, Department of Statistics, Purdue University, West Lafayette, Indiana*, 1991.

2. Xiong, X. Absorption Probability Distribution of Random Paths from Finite Populations, *Technical Report 92-41C, Department of Statistics*, *Purdue University, West Lafayette, Indiana*, 1992.

3. Xiong X. Principle of Generalized Conditional PLR Sequential Test and Its applications, *Technical Report 93-15, Department of Statistics, Purdue University, West Lafayette, Indiana*, 1993.

4. Xiong X**.** A Class of Sequential Conditional Probability Ratio Tests. *Journal of American Statistical Association* 90 (432): 1463-1473, 1995.

5. Xiong X and Tan M. Fast Computation of Extended Operating Characteristics of Sequential Tests. *Computing Science and Statistics* 27: 279-183, 1995.

6. Xiong X. Absorption Probability Distribution of Random Paths from Finite Populations, *Sequential Analysis* 15 (1):1-19, 1996.

7. Tan M and Xiong X. Continuous and Group Sequential Conditional Probability Ratio Tests for Phase II Clinical Trials. *Statistics in Medicine* 15: 2037-2051, 1996.

8. Tan M, Xiong X, and Kutner MH. Clinical Trial Designs Based on Sequential Conditional Probability Ratio Tests and Reverse Stochastic Curtailing. *Biometrics* 54: 682-695, 1998.

9. Xiong X and Tan M. Sufficiency-Based Methods for Evaluating Sequential Tests and Estimations, *ASA Proceedings 1999, Biometrics Section*, 268-273, 1999.

10. Xiong X and Tan M. Evaluating Sequential Tests for a Class of Stochastic Processes. *Computing Science and Statistics* 33: 30-34, 2001.

11. Xiong X, Tan M, and Kutner MH. Computational Methods for Evaluating Sequential Tests and Post-test Estimations via Sufficiency Principle, *Statistica Sinica* 12(4):1027-1041, 2002.

12. Xiong X, Tan M and Boyett J. Sequential Conditional Probability Ratio Tests for Normalized Test Statistic on Information Time. *Biometrics* 59: 624-631, 2003.

13. Xiong X, Tan M, and Boyett J. SCPRT: A Sequential Procedure that Gives another Reason to Stop Clinical Trials Early. *Advance in Statistical Methods for Health Sciences* (in *Series in Statistics for Industry and Technology*, Birkhauser: Boston): 419-434, 2006.

14. Xiong X, Tan M, and Boyett J. A Sequential Procedure for Monitoring Clinical Trials against Historical Controls, *Statistics in Medicine* (in press); published online in *Wiley InterScience* July, 2006.