1 ExpDesign Studio

1.1 INTRODUCTION

ExpDesign Studio (ExpDesign) is an integrated environment for designing experiments or clinical trials. It is a powerful and user-friendly statistical software product that has seven integrated main components: classical design (CD), sequential design (SD), multistage design (MSD), dose-escalation design (DED), adaptive design (AD), adaptive trial monitoring (ATM), and dose-escalation trial monitoring (DTM) modules. In addition, the ExpDesign randomizor can generate random variates from a variety of distributions. The ExpDesign toolkit provides features for distributional calculation, confidence intervals, and function and data plotting (Figure 1.1).

Classical trials are the most commonly used in practice. ExpDesign provides nearly 150 methods for sample-size calculations in CD for different trial designs. It includes methods for single-, two-, and multiple-group designs, and for superiority, noninferiority, and equivalence designs with various endpoints. See the list of classical design methods in Appendix B.

Group sequential trials are advanced designs with multiple analyses. A group sequential trial is usually a cost-effective design compared to a classical design. SD covers a broad range of sequential trials with different endpoints and different types of stopping boundaries.

A multistage design is an exact method for group sequential trials with a binary response, whereas group sequential design uses an asymptotic approach. MSD provides three optimal designs among others: MinMax, MinExp, and MaxUtility, which minimize the maximum sample size, minimize the expected sample size, and maximize the utility index, respectively.

A dose-escalation trial in aggressive disease areas such as oncology has unique characteristics. Due to the toxicity of the testing drug, researchers are allowed to use fewer patients to obtain as much information as possible about the toxicity profile or maximum tolerable dose. By means of computer simulations, DED provides researchers with an efficient way to search for an optimal design for dose-escalation trials with a variety of criteria. It includes traditional escalation rules, restricted escalation rules, two-stage

Classical and Adaptive Clinical Trial Designs Using ExpDesign Studio™,
By Mark Chang

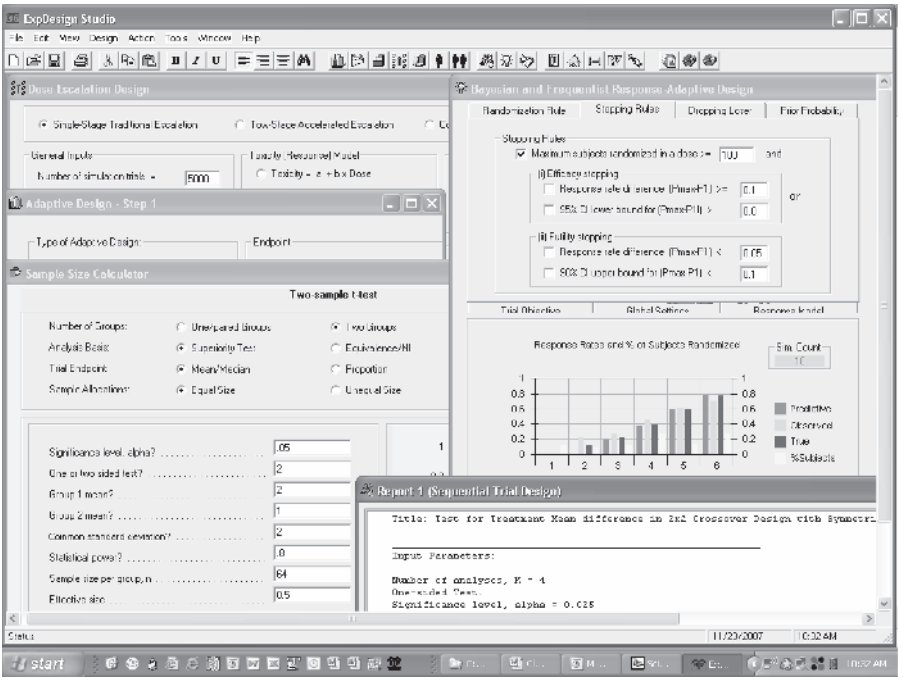


Figure 1.1 ExpDesign integrated environment.

escalation algorithms, and the Bayesian continual reassessment method (CRM).

AD in ExpDesign Studio allows you to design and simulate various adaptive trial, such as sample-size reestimation, dropping a loser, response-adaptive randomization, and biomarker-adaptive designs. You can use response-adaptive randomization to assign more patients to superior treatment groups or to drop a "loser" or inferior group. You may stop a trial prematurely to claim efficacy or futility based on the data observed. You may modify the sample size based on the treatment difference observed. All design reports are generated through an automation procedure that has built-in knowledge of statistical experts in a clinical trial.

ATM and DTM assist in monitoring an ongoing trial. They inform the user if the stopping boundary has been crossed and will also generate interim results such as conditional power, new sample size required, and dynamic randomization to instruct the user to make appropriate adaptations.

Indeed, ExpDesign Studio covers broad statistical tools needed to design a trial. To try ExpDesign, the user simply needs to know the functions of the icons on the toolbar. The black–white icons on the left-hand side of the toolbar are standard for all word processors. The first five icons of the second group of seven icons are used to launch five different types of designs: classical trial

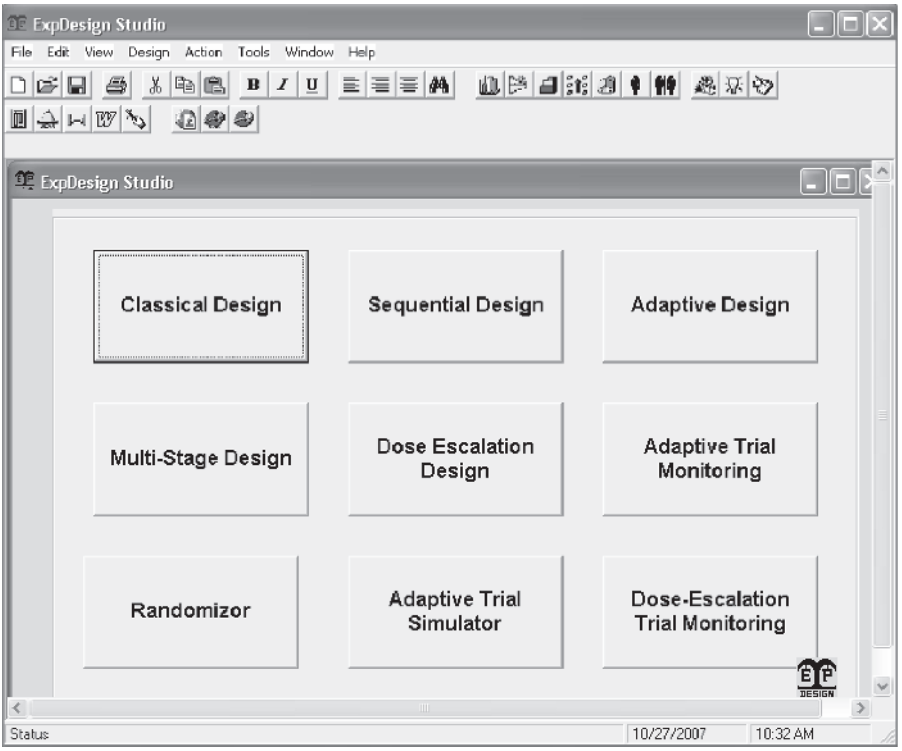


Figure 1.2 ExpDesign Studio startup window.

design, sequential trial design, multistage trial design, dose-escalation trial design, and adaptive design (see Figure 1.2). Alternatively, the user can click one of the nine buttons in the ExpDesign start window to start the corresponding design. The next set of three icons is for launching a design example, computing design parameters, and generating a design report. Following these are five color icons for the toolkits, including a graphic calculator, a distribution calculator, a confidence interval calculator, a word splitter, and TipDay. The mouse can be moved over any icon on the toolbar to see the Tiptext, which describes what the icon is for. We are now ready to design a trial.

1.2 HOW TO DESIGN A TRIAL USING EXPDESIGN STUDIO

1. Double-click on the ExpDesign Studio icon or click Start, the **Start** button. A menu will appear. Click on **Programs** in the **Start** button. The list of available programs will appear. Then click , ExpDesign Studio.

2. On the ExpDesign **Start** window (Figure 1.2), select one of the following tasks you want to do: classical, sequential, adaptive, multistage, dose-escalation design, adaptive trial monitoring, random number generation, adaptive trial simulation, or dose-escalation trial monitoring.

1.2.1 How to Design a Classical Trial

1. Click Classical Design or  to start a classical design.
2. Select options for **Number of Groups, Analysis Basis, Trial Endpoint**, and **Sample Allocations** in the design option panel.
3. Select a method from the list of methods available.
4. Enter appropriate values for your design (click Example for an example).
5. Click on Compute to calculate the sample size required.
6. Click the report icon  on the toolbar to view the design report.
7. Click Print to print the design form or click  to print the report.
8. You can click Copy Graph to copy the graph for the stopping boundaries and use **Paste-Special** to paste it to other applications.
9. Click  to save the design specification or report (see Figure 1.3).

1.2.2 How to Design a Group Sequential Trial

1. Click Sequential Design or  on the toolbar to start a group sequential design.
2. Select options for **Number of Groups, Analysis Basis, Trial Endpoint**, and **Potential Interim Claim** in the design option panel.
3. Select a method from the list of methods available.
4. Enter appropriate values for your design or click Example.
5. Click Compute to generate the design.
6. Click the report icon  on the toolbar to view the design report.

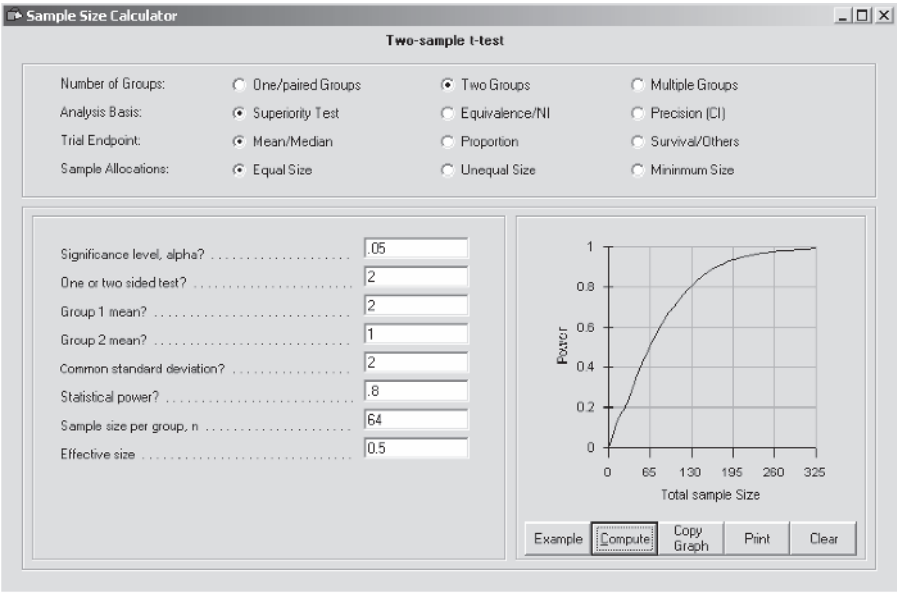


Figure 1.3 Classical design window.

7. Click Print to print the design form or click  to print the report.
8. You can click Copy Graph to copy the graph for the stopping boundaries and use **Paste-Special** to paste it to other applications.
9. Click Save to save the design specification or report (see Figure 1.4).

1.2.3 How to Design an Adaptive Trial

1. Click Adaptive Design or  on the toolbar; the **Adaptive Design–Step 1** window will appear (see Figure 1.5).
2. Select the **Sample-Size Reestimation** option in the **Type of Adaptive Design** panel.
3. Select the **Proportion** option in the **Endpoint** panel.
4. Enter appropriate values for the **Response Under Ha** in the **Hypotheses** panel, the noninferiority margin for the noninferiority trial, **One-Sided Alpha,** and **Power**.
5. Click Next; the **Adaptive Design–Step 2** window will appear.

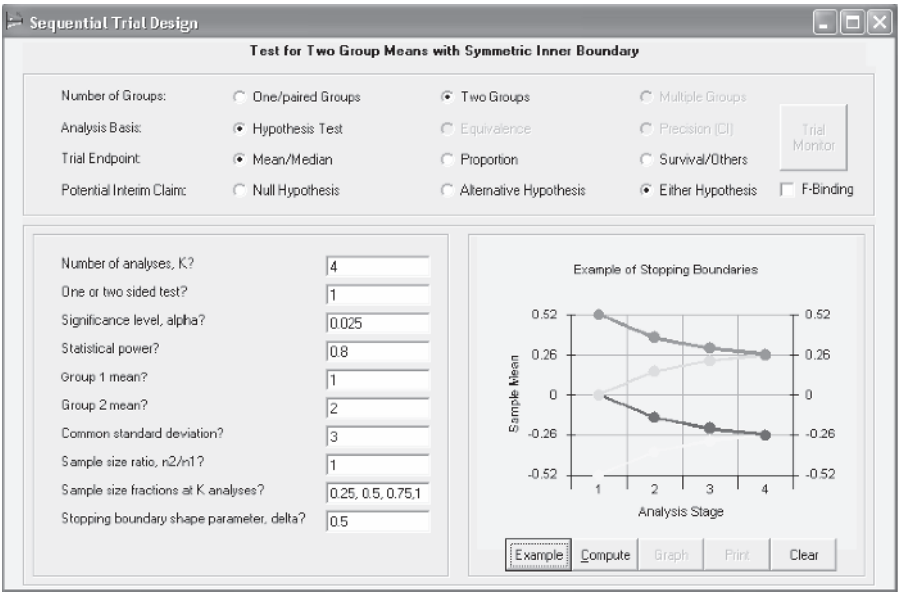


Figure 1.4 Group sequential design window.

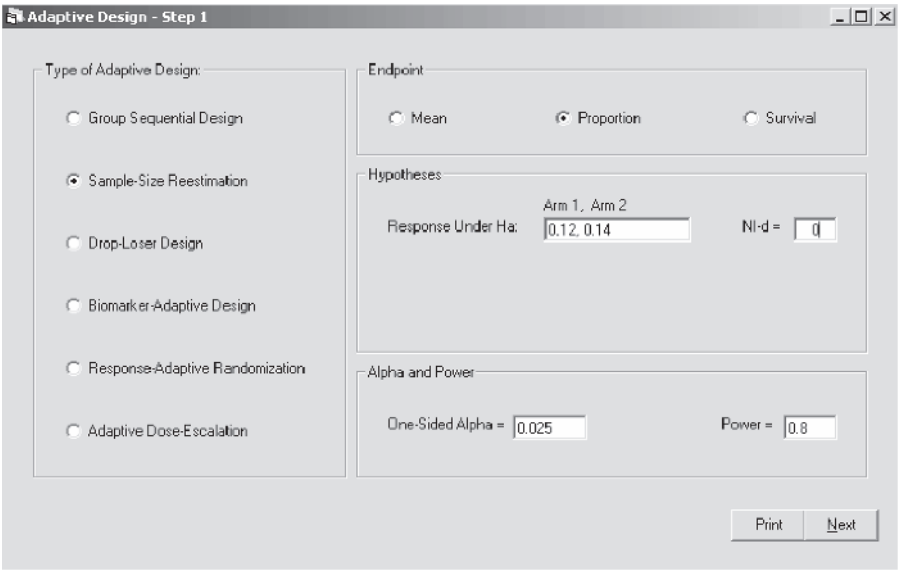


Figure 1.5 Sample size reestimation step 1 window.

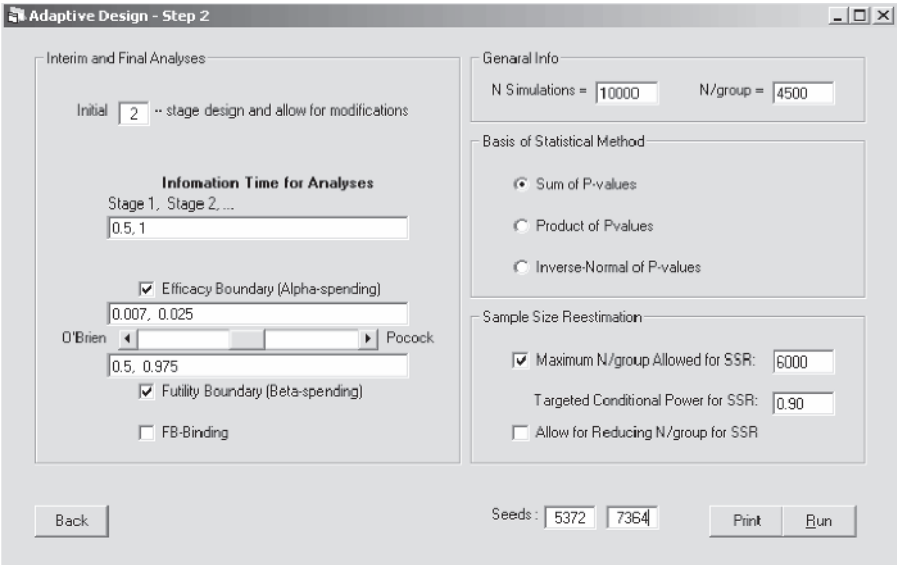


Figure 1.6 Sample size reestimation step 2 window.

In the **Adaptive Design–Step 2** window, do the following (Figure 1.6):

1. Enter values for the initial number of stages and **Information Time for Analyses**.
2. Choose stopping boundaries using the arrow near **O'Brien** or **Pocock**.
3. Enter values for **N Simulations** and **N/group**.
4. Select a statistical method in the panel.
5. Enter values for **Maximum N/group Allowed for SSR** and **Targeted Conditional Power for SSR**.
6. Click  to start the simulation.

After the simulation is completed, the window in Figure 1.7 will pop up to remind you to click the report icon  on the toolbar to view the report that is generated automatically for the adaptive design. Figure 1.8 is an example of the report for the adaptive design.

1.2.4 How to Run Adaptive Trial Simulations

1. Click  to set up adaptive trial simulations.
2. Follow the steps specified in the **Simulation Setup** panel.

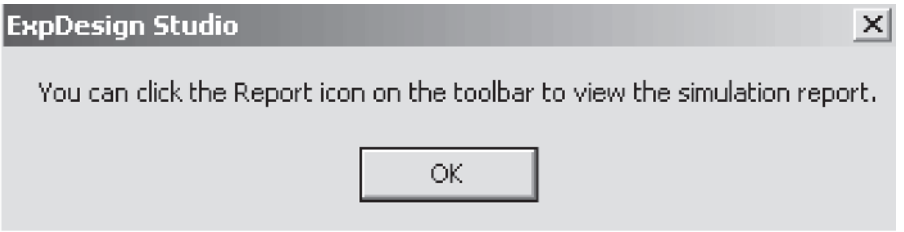


Figure 1.7 Pop-up message when calculation is completed.

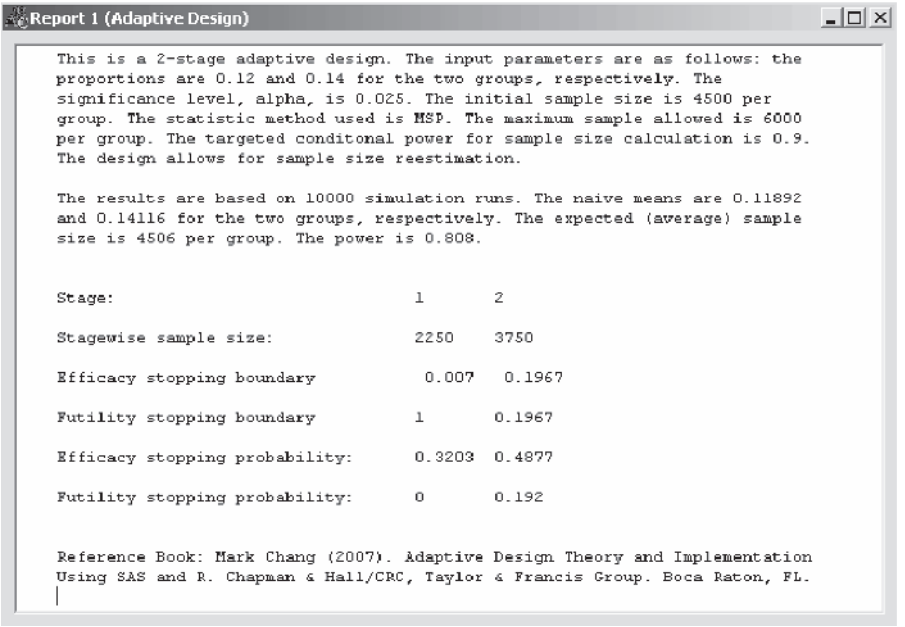


Figure 1.8 Report generated automatically by ExpDesign.

3. Specify parameters in each of the steps or click Example.
4. Click Run to generate the simulation results.
5. Click the report icon to view the design report.
6. Click Print to print the design form or click to print the report.
7. Click Save to save the design specification or report, whichever is highlighted (see Figure 1.9).

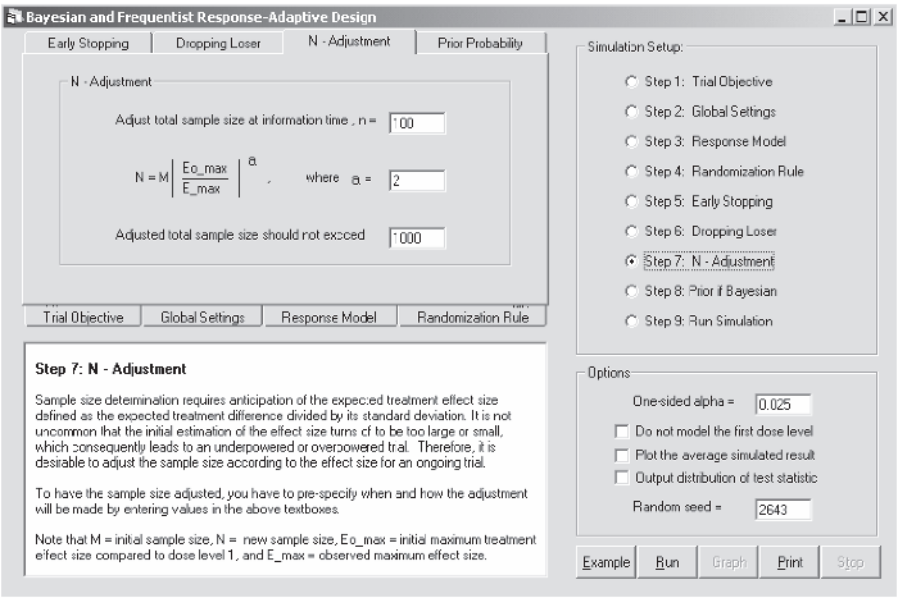
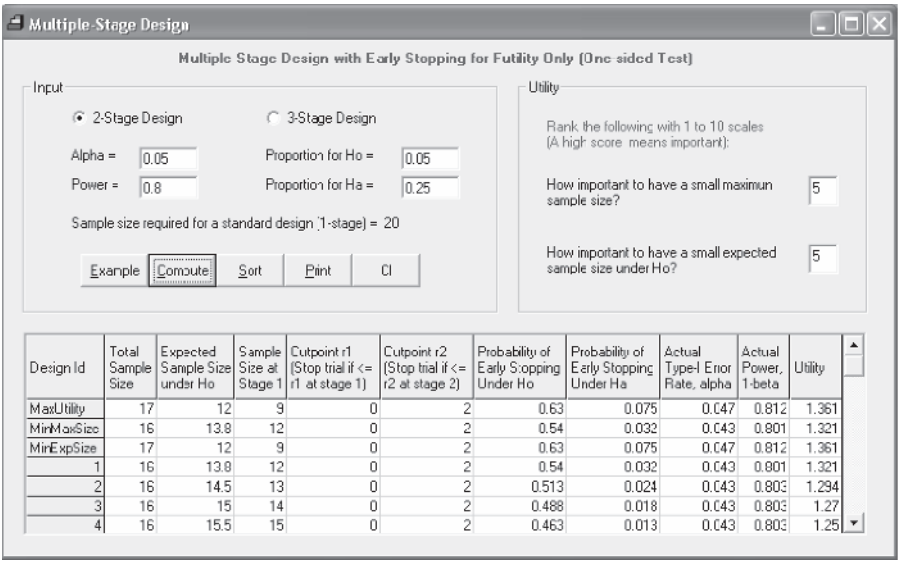


Figure 1.9 Trial simulation window.

1.2.5 How to Design a Multistage Trial

1. Click Multistage Design or  on the toolbar to start a multistage design.
2. Select **2-Stage Design** or **3-Stage Design** in the Multistage design window or open an existing design by clicking  on the toolbar.
3. Enter appropriate values for your design in the textboxes. You may click Example to see an input example.
4. Click Compute to generate the valid designs.
5. Click  on the toolbar to view the design report.
6. Click Print to print the design form or  to print a report.
7. Click  to save the design specification or report (see Figure 1.10).



Design Id	Total Sample Size	Expected Sample Size under Ho	Sample Size at Stage 1	Cutpoint r1 (Stop trial if <= r1 at stage 1)	Cutpoint r2 (Stop trial if <= r2 at stage 2)	Probability of Early Stopping Under Ho	Probability of Early Stopping Under Ha	Actual Type-I Error Rate, alpha	Actual Power, 1-beta	Utility
MaxUtility	17	12	9	0	2	0.63	0.075	0.047	0.812	1.361
MinMaxSize	16	13.8	12	0	2	0.54	0.032	0.043	0.801	1.321
MinExpSize	17	12	9	0	2	0.63	0.075	0.047	0.812	1.361
1	16	13.8	12	0	2	0.54	0.032	0.043	0.801	1.321
2	16	14.5	13	0	2	0.513	0.024	0.043	0.803	1.294
3	16	15	14	0	2	0.488	0.018	0.043	0.803	1.27
4	16	15.5	15	0	2	0.463	0.013	0.043	0.803	1.25

Figure 1.10 Multistage design window.

1.2.6 How to Design a Dose-Escalation Trial

1. Click Dose-Escalation Trial Monitoring or  on the toolbar to start a dose-escalation design.
2. Enter appropriate values for your design on the *Basic Spec.* panel. You may click Example to see an input example.
3. Select *Dose-Response Model, Escalation Scheme*, and *Dose Interval Spec.* or open an existing design by clicking  .
4. Click Compute to generate the simulation results.
5. Click  to view the design report.
6. Click Print to print the design form or  to print a report.
7. Click  to save the design specification or report, whichever is highlighted (see Figure 1.11).

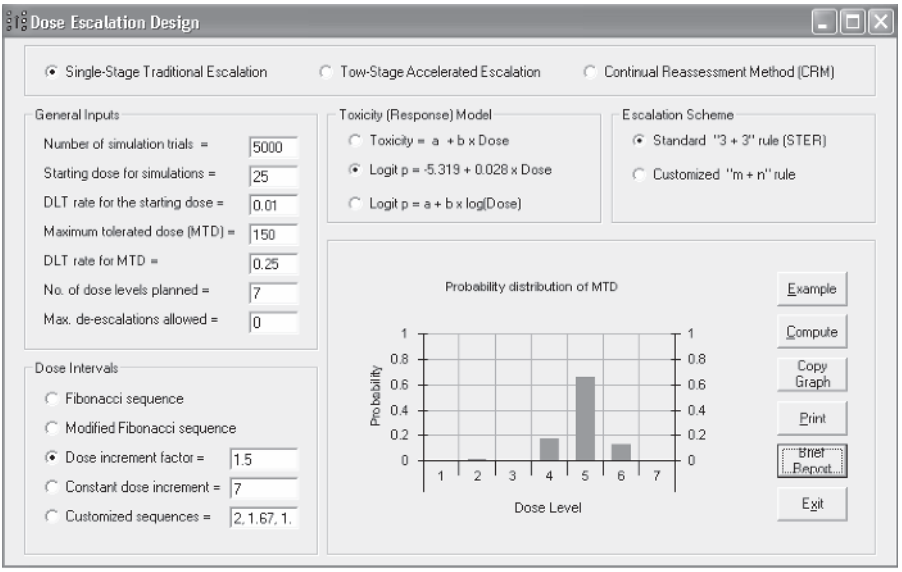


Figure 1.11 Traditional dose-escalation design window.

1.3 EXPDESIGN MENUS

File Menu The ExpDesign file menu is a standard menu similar to that in MS Word. The **Save** option can be used to save a report generated by ExpDesign or design specifications. The **Print** option can be used to print a report generated by ExpDesign.

Edit Menu The edit menu is a standard menu just like the one in MS Word. The hotkey combinations for **cut, copy**, and **paste** are <Ctrl>-X, <Ctrl>-C, and <Ctrl>-V, respectively.

View Menu The view menu is shown in Figure 1.12. The **Toolbar** option toggles between displaying and hiding the toolbar. If the option has a check mark beside it, the toolbar is on and displayed in the ExpDesign window. When you select **Toolbar**, the toolbar will disappear from the ExpDesign window. If the **Toolbar** option has no check mark beside it, the toolbar is off and is not displayed in the ExpDesign window. The **Status Bar** option toggles between displaying and hiding the status bar. It lies at the bottom of your ExpDesign window. The bar displays useful information during the design.

Figure 1.12 View menu.

Figure 1.13 Design menu.

The **MyExpDesign Studio.htm** option can be used to access the local Web page, which you can change as you like. To edit the page, you can use MS Word by right-clicking on **MyExpDesignStudio.htm** and selecting the **Edit** item from the pop-up menu. The **CTriSoft.com** option can be used to access the ExpDesign Web site, www.CTriSoft.net, where users can get technical support and product information. The **Statisticians.org** option can be used to access the relevant information to trial design and statistics.

Design Menu The design menu is shown in Figure 1.13. The option **ExpDesign Studio** can be used to display the start window for classical, sequential, multistage, dose-escalation trial, and adaptive designs; and for adaptive trial monitoring, dose-escalation monitoring, the randomizor, and the adaptive trial simulator. The options **Classic Trial Design, Sequential Trial Design, Multi-Stage Design, Dose Escalation Design, Adaptive Design, Adaptive Trial Monitor**, and **Randomizor** can be used for the corresponding task.

Action Menu The action menu has three items: **Example, Compute**, and **Report** (Figure 1.14). The **Example** option can be used to launch an example of a design. The **Compute** option can be used to generate a design after the appropriate inputs. The **Report** option can be used to view a design report.

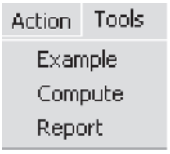


Figure 1.14 Action menu.

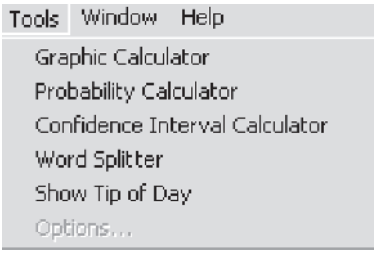


Figure 1.15 Tools menu.

Tools Menu In the tools menu (Figure 1.15) the **Graphic Calculator** option can be used to access the calculator to perform simple arithmetic and complex function calculations, and to plot curves. The **Probability Calculator** option can be used to obtain probabilities and percentiles for various continuous and discrete distributions. The **Confidence Interval Calculator** option can be used to obtain various confidence intervals.

Window and Help Menus The window and help menus are standard, just like those in MS Word.