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Preface

Acknowledgments

Welcome to East 6.2, a software package for the design, simulation and interim monitoring of clinical trials. East is the industry standard for designing adequate and well-controlled clinical trials in accordance with FDA and EMA guidances.

The current release of East (version 6.2) is powered by the Architect platform. It was developed by a team consisting of (in alphabetical order of last names): Gayatri Bartake, Sudipta Basu, Apurva Bhingare, Pushkar Borkar, Bristi Bose, Chandrashekhar Budhwant, V. P. Chandran, Aniruddha Deshmukh, Namita Deshmukh, Namrata Deshpande, Yogesh Dhanwate, Monika Ghatage, Vishal Gujar, Shashikiran Halvagal, Karen Han, Pravin Holkar, Abhijit Jadhav, Yannis Jemiai, Ashwini Joshi, Nilesh Kakade, Anthiyur Kannappan, Kapildev Koli, Yogita Kotkar, Niranjan Kshirsagar, Hrishikesh Kulkarni, Kaushal Kulkarni, Mandar Kulkarni, Mangesh Kulkarni, Shailesh Kulthe, Nilesh Lanke, Manisha Lohokare, Charles Liu, Lingyun Liu, Shashank Maratkar, Cyrus Mehta, Abdulla Mulla, Nabeela Muzammil, Seema Nair, Neelam Nakadi, Atul Paranjape, Vidyadhar Phadke, Ashvinikumar Pinjarkar, Shital Pokharkar, Vidyagouri Prayag, Misha Salganik, Makarand Salvi, Pralay Senchaudhuri, Brian Sharkey, Priyadarshan Shinde, Sheetal Solanki, Chitra Tirodkar, Amrut Vaze, Suryakant Walunj, Suchita Wageshwari, Ritika Yadav, Sanhita Yeolekar.

Other contributors who worked on previous releases of East: Ujwala Bamishte, Dhaval Bapat, Krisnaiah Byagari, Vibhavari Deo, Yogesh Deshpande, Pranab Ghosh, Ketan Godse, Aarati



Hasabnis, Jaydip Mukhopadhyay, Sandhya Paranjpe, Nabarun Saha, Abhijit Shelar.

Others who provided valuable assistance in this release are Asmita Ghatnekar, Ajay Sathe, Rhiannon Sheapare, and Tammy Sneddon.

A large number of people, other than those listed above, have helped us through the years with the various releases of East. We received valuable assistance from Sandro Pampallona, Mandar Kale, David Bristol, Yogesh Gajjar, Rajesh Mehta, Dhanashri Pathak, Vivek Pradhan, Vipul Suru, Nitin Patel, and others.

East draws on and extends the pioneering research of

Peter Armitage, Peter Bauer, Werner Brannath, David DeMets, Tom Fleming, Christopher Jennison, Kyungmann Kim, Gordon Lan, Hans-Helge Müller, Peter O'Brien, Sandro Pampallona, Stuart Pocock, Martin Posch, Helmut Schäfer, Daniel Scharfstein, Anastasios Tsiatis, and Bruce Turnbull.

Special credit should also be given to Sue-Jane Wang, James Hung and Robert O'Neill of the Center for Drug Evaluation at the FDA. These investigators have performed original research on the design of adaptive trials and have been instrumental in creating an atmosphere of scientific rigor for the regulatory submissions of such trials.

The textbooks, "Group Sequential Methods with Applications to Clinical Trials" by Christopher Jennison and Bruce Turnbull (Chapman and Hall/CRC, 2000), and "Statistical Monitoring of Clinical Trials: A Unified Approach" by Michael Proschan, Gordon Lan, and Janet Wittes (Springer, 2006) are excellent complements to the East software.

We express our gratitude to

David DeMets, Chris Jennison, Kyungmann Kim, Tony Lachenbruch, Anastasios Tsiatis and Bruce Turnbull

for agreeing to serve as members of the East Advisory Committee.

Preface

We thank all our beta testers for their input and obvious enthusiasm for the East software. They are acknowledged by name in Appendix **??**.

We owe a debt of gratitude to Marvin Zelen and to Swami Sarvagatananda, special people whose wisdom, encouragement and generosity have inspired Cytel for over two decades.

Finally, we dedicate this software package to our families and to the memory of our dearly departed Stephen Lagakos and Aneesh Patel.

Our Philosophy

We would like to share with you what drives and inspires us during the research and development stages of the East software.

Empower, do not Frustrate

We believe in making simple, easy-to-use software that empowers people.

We believe that statisticians have a strategic role to play within their organization and that by using professionally developed trial design software they will utilize their time better than if they write their own computer programs in SAS or R to create and explore complex trial designs. With the help of such software they can rapidly generate many alternative design options that accurately address the questions at hand and the goals of the project team, freeing time for strategic discussions about the choice of endpoints, population, and treatment regimens.

We believe that software should not frustrate the user's attempt to answer a question. The user experience ought to engage the statistician and inspire exploration, innovation, and the quest for the best design. To that end, we believe in the following set of principles:

Fewer, but Important and Useful Features It is better to implement fewer, but important and useful features, in an elegant and simple-to-use manner, than to provide a host of options that confuse more than they clarify.



As Steve Jobs put it: 'Innovation is not about saying "Yes" to everything. It's about saying "No" to all but the most crucial features.'

- Just because we Can, doesn't mean we Should Just because we can provide functionality in the software, doesn't mean we should.
- Simplify, Simplify, Simplify Find and offer simple solutions even for the most complex trial design problems.
- Don't Hurry, but continually Improve Release new solutions when they are ready to use and continually improve the commercial releases with new features, bug fixes, and better documentation.
- Provide the best Documentation and Support Our manuals are written like textbooks, to educate, clarify, and elevate the statistical knowledge of the user.
 Our support is provided by highly competent statisticians and software engineers, focusing on resolving the customer's issue, and being mindful of the speed and quality requirements. We believe that delivering *delightful customer support is essential to our company's lifeblood*.

Finally, we listen to our customers constantly and proactively through countless informal and formal interactions, software trainings, and user group meetings. This allows us to follow all the principles laid out above in the most effective manner.

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1 Installing East 6.2

1.1 System Requirements to run East 6.2

The minimum hardware/operating system requirements for East 6.2 are:

- A system running one of the following operating systems:
 - Windows XP (32 or 64 bit)
 - Windows 7 (32 or 64 bit)
- A minimum of 512 MB RAM (1 GB recommended)
- A hard disk with at least 300 MB of free disk space

1.2 Installation

To install East 6.2, please follow these steps:

- If any copy (including a beta or demo version) of East 6.2 is currently installed on your PC, please uninstall it or else the installation of the current version will not proceed correctly. To uninstall the earlier version of East 6.2, go to the Start Menu and select Programs→ East 6.2 → Uninstall East 6.2
- 2. Insert the East 6.2 CD into your CD-drive.
 - (a) If your Windows Autorun Default is already active, you'll see an installation screen similar to what is shown below. Follow the instructions that will appear on the

Chapter 1: Installing East 6.2

screen.



(b) If your Windows Autorun Default is not active, you won't see any installation screen. In that case, open your Windows Explorer, click on the CD Drive, and double-click on Setup. Then you will see the installation screen . Follow the instructions that will appear on the screen.

2 Getting Started

East has evolved over the past several years with MS $\text{Excel}^{(\mathbb{R})}$ as the user interface. The East on MS $\text{Excel}^{(\mathbb{R})}$ did not integrate directly with any other **Cytel** products. Under the **Architect** platform, East is expected to coexist and integrate seamlessly with other **Cytel** products such as SiZ, and Compass. Architect is a common platform designed to support various Cytel products. It provides a user-friendly, Windows-standard graphical environment, consisting of tabs, icons, and dialog boxes, with which you can design, simulate and analyze. Throughout the user manual, this product is referred to as East 6.

One major advantage of East 6 is the facility for creating multiple designs. This is achieved by giving multiple inputs of the parameters as either comma separated, or in a range such as (a:b:c) with a as the initial value, b as the last value and c as the step size. If you give multiple values for more than one parameter, East creates all possible combinations of the input parameters. This is an immense advancement over earlier versions of East, where you had to create one design at a time. Furthermore, one could not compare different types of designs (e.g., superiority vs. noninferiority designs). Similarly, graphical comparison of designs with different numbers of looks was difficult with earlier versions of East. All such comparisons are readily available in East 6.

We have also provided powerful data editors to create, view, and modify data. A wide variety of statistical tests are now a part of East 6, which enables you to conduct statistical analysis of interim data for continuous, discrete and time to event endpoints.

Simulations help to develop better insight into the operating characteristic of a design. In East 6, the simulation module has now been enhanced to allow fixed or random allocation to treatment and control, and different sample sizes. Such options were not possible with earlier versions of East.

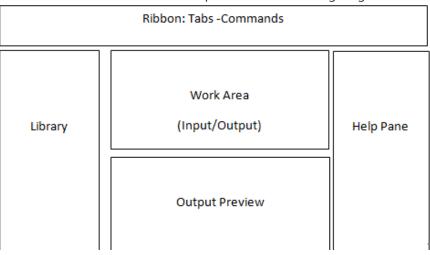
Chapter 2: Getting Started

Another new feature is the option to add assumptions for accruals and dropouts. Previously this was available for survival, but has been extended to continuous and discrete endpoints in East 6. Information about accrual rates, response lag, and dropouts can be given whether designing or simulating a trial. This makes more realistic, end-to-end simulation of a trial possible.

The purpose of this chapter is to familiarize you with the East 6 user interface.

2.1 Workflow in Architect

In this section, the structure of Architect platform is explained. The logical workflow in which the different parts of the interface co-ordinate with each other is discussed.



The basic structure of the interface items is depicted in the following diagram.

Besides the top **Ribbon**, there are mainly four main windows in East 6 namely, (starting from left), the **Library**, the **Input / Output** window, the **Output Preview** area and the **Help Pane**. Note that both the **Library** and the **Help Pane** can be auto-hidden temporarily or throughout the session, allowing the other windows to occupy larger area on the screen for display.



Initially, **Library** shows only the **Root** node. As you work with East, multiple designs, simulation scenarios, data sets and related analysis can be managed using this panel. Various nodes for outputs and plots are created in the **Library**, facilitating work on multiple scenarios at a time. The width of the **Library** window can be adjusted for better readability.

The central part of the interface, the Input / Output, is the main work area where you can-

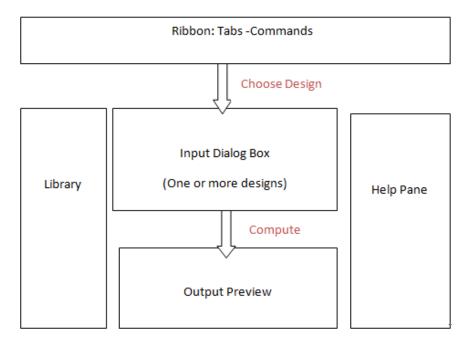
- Enter input parameters for design computation create and compare multiple designs, view plots
- Simulate a design under different scenarios
- Perform interim analysis on a group sequential design look by look and view the results, receive decisions such as stopping or continuing during the execution of a trial
- Open a data on which you want to perform analysis, enter new data, view outputs, prepare a report etc.

This is the area where the user interacts with the product most frequently.

The **Output Preview** area compiles several outputs together in a grid like structure where each row is either a design or simulation run. This area is in use only when working with Design or Simulations.

Chapter 2: Getting Started

When the **Compute** or **Simulate** button is clicked, all requested designs or simulation results are computed and are listed in rows in the **Output Preview** area:



By clicking different rows of interest while simultaneously holding the **Ctrl** key, either a single or multiple designs can be displayed in the **Output Summary** in vertical manner or



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	07	

side-by-side comparison can be done.

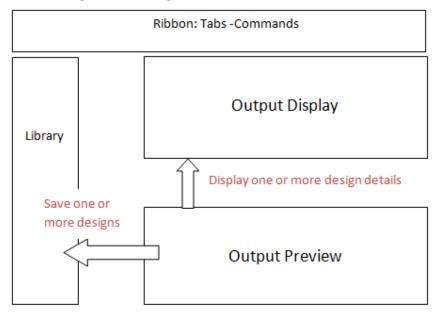
Note that the active window and the **Output Preview** can be minimized, maximized, or

resized. If you want to focus on the **Output Summary**, click the icon in the top-right corner of the main window. The Output will be maximized as shown below:

💟 = 📰 = 🐐 🚔		Output Summa
	Des2	
Mnemonic	MN-2S-DI	
Test Parameters		
Design Type	Superiority	
No. of Looks	3	
Test Type	2-Sided	
Specified α	0.05	
Power	0.9	
Model Parameters		
Input Method	Individual Means	
Diff. in Means ($\delta = \mu t - \mu c$)	0.3	
Mean Control (µc)	0	
Mean Treatment (µt1)	0.3	
Std. Deviation (σ)	1	
Test Statistic	Z	
Allocation Ratio (nt/nc)	1	
Boundary Parameters		
Efficacy Boundary	LD (OF)	
Spacing of Looks	Equal	
Sample Size		
Maximum	473	
Expected Under H0	471.064	
Expected Under H1	379.185	

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Any of the designs/simulations in the **Output Preview** area can be saved in the **Library**, as depicted in the following workflow diagram.



Double click any of these nodes and the detailed output of the design will be displayed. This will include all relevant input and output information. Right clicking any design node in the **Library** will allow you to perform various operations on the design such as interim monitoring and simulation.

The **Help Pane** displays the context sensitive help for the control currently under the focus. This help is available for all the controls in the **Input / Output** window. This pane also displays the design specific help which discusses the purpose of the selected test, the published literature referred while developing it and finally the user manual references to quickly look-up for more details in the East6 User Manual. This pane can be hidden or locked by clicking the pin symbol.



All the windows and features mentioned above are described in detail with the help of an illustration in the subsequent sections of this chapter.

2.2 A Quick Overview of User Interface

Almost all the functionalities of East 6 are invoked by selecting appropriate menu items and icons from the **Ribbon**. The interface consists of four windows as described in the previous section and four major menu items. These menu items are:



- Home. This menu contains typical file-related Windows sub-menus. The Help sub-menu provides access to this manual.
- Data Editor. This menu will be available once a data set is open, providing several sub-menus used to create, manage and transform data.
- Design. This menu provides a sub-menu for each of the study designs which can be created using East 6. The study designs are grouped according to nature of the response. The tasks like Simulations and Interim Monitoring are available for almost all the study designs under this menu.
- Analysis. This menu provides a sub-menu for each of the analysis procedure that can be carried out in East 6. The tests are grouped according to the nature of the response. There are also options for basic statistics and plots.

Chapter 2: Getting Started

2.3 Home Menu

The **Home** menu contains a variety of submenus:

	See Sec		
Home Data Editor Design Analysis			
🕒 📄 🛶 Import 🛛 🖆 💾	Help Pane		
New Open File Save Save Save Conversion As	Options 🔽 Library	Arrange Switch Help	
File	Settings View	Window Help	

2.3.1 File

•

Click this icon to create new case data or crossover data. A new workbook or log can also be created.

Click this icon to open a saved data set, workbook, or log file.

- Click this icon to import external files created by other programs.
- Export

Click this icon to export files in various formats.



Click this icon to save the current files or workbooks.



12

Click this icon to save a file or workbook with different name.

2.3.2 Importing workbooks from East5.4

East allows the conversion of workbooks previously created in East 5.4 (and above) to be imported into East 6 for further development. In order to open a workbook with the .es5 extension given by previous versions of East, it must first be converted to a file with the .cywx extension that will be recognized by East 6. This is easily accomplished through the Covert



Old Workbook utility. Click on the utility.

Old Workbook utility. Click on the coversion icon under Home menu to see the location of this

From the Windows **Start** menu under **All Programs**, select **Covert Old Workbook** located in the **Cytel Architect** folder:

<u>*6</u>



We can see the following window which accepts East5.4 workbook as input and outputs a workbook of East6. Click the **Browse** buttons to choose the East 5.4 file to be converted and the file to be saved with **.cywx** extension of East 6 version. To start the conversion click **Convert Workbook**:

🖶 East 5 to East 6 Conversion	_ _ ×
Select East 5 workbook to convert: (This version supports files from East 5.4 ar	nd above)
C:\My Cytel Files\East Workbooks\EastBook1.es5	Browse
Save converted East 6 workbook as:	
C:\My Cytel Files\East Workbooks\EastBook1.cywx	Browse
Conversion Log:	
	*
	· ·
Save Log	Convert Workbook

Once complete, the file can be opened as a workbook in East 6 through Home-> File-> Open.

Chapter 2: *Getting Started*

2.3.3 Settings



icon in the **Home** menu to adjust default values in East 6.

Options			х
Global Settings Design Defaults Simulation Defaults Chart Settings	Oisplay Precision General Select Category Critical Points Critical Points		
	Reset	ок	Cancel

The options provided in the **Display Precision** tab are used to set the decimal places of numerical quantities. The settings indicated here will be applicable to all tests in East 6 under the **Design** and **Analysis** menus.

The **General** tab has the provision of adjusting the paths for storing workbooks, files, and temporary files. These paths will remain throughout the current and future sessions even after East is closed. This is the place where we need to specify the installation directory of the R software in order to use the feature of R Integration in East6.



Options				x
	Common Group Sequen	tial		
Global Settings Design Defaults Simulation Defaults Chart Settings	Design Type Superiority Non-inferiority Equivalence Confidence Interval Type I Error (α): Power (1- β): Sample Size (n): Allocation Ratio (n _t /n _c): Do not round off sample			
			Reset OK	Cancel

The **Design Defaults** is where the user can change the settings for trial design:

Under the **Common** tab, default values can be set for input design parameters. Under the **Group Sequential** tab, defaults are set for boundary information. When a new design is started, input fields will contain these specified defaults.

Simulation Defaults is where we can change the settings for simulation:

Chapter 2: Getting Started

Options		х
	Simulation	
Clobal Settings Design Defaults Simulation Defaults Chart Settings	Number of Simulations: 10000 Refresh Frequency: 1000 -Random Number Seed O Clock O Fixed 100 - Output Options D Save summary statistics for every simulation run Suppress All Intermediate Output	
	Reset OK Cano	el



Options					х
Global Settings Design Defaults Simulation Defaults Chart Settings	Chart Settings Expected Sample Size Study Duration vs. Accrua Conditional Power Post-Hoc Power Confidence Intervals Stopping Boundaries Power vs. Treatment Effect Sample Size / Events vs. T IM Error Spending IM Stopping Boundaries Sample Size / Completers Power vs. Sample Size Error Spending	Fi	eries Y Labels	Scale Automatic Scaling Divisions	360 480 4*
				Reset OK	Cancel

The **Chart Settings** allows defaults to be set for the following quantities on East6 charts:

2.3.4 View

The **View** submenu consists of enabling or disabling the **Help** and **Library** panes by (un)checking the respective check boxes.



2.3.5 Window

The **Window** submenu contains an **Arrange** and **Switch** option. This provides the ability to view different standard arrangements of available windows (Design Input Output, Log, Details,

charts and plots) and to switch the focus from one window to another.



2.3.6 Help

The **Help** submenu provides the following ways to access the East6 documenatation:



- **User Manual**: Invoke the current East 6 user manual.
- **Tutorial**: Invoke the available East 6 tutorials.
- About East 6: Displays the current version and license information for the installed software.

Volume 2 Continuous Endpoints

- 3 Tutorial: Normal Endpoint 21
 4 Normal Superiority One-Sample 35
- 5 Normal Noninferiority Paired-Sample 59

3 Tutorial: Normal Endpoint

This tutorial introduces you to East on the Architect platform, using an example clinical trial to test difference of means.

3.1 Fixed Sample Design

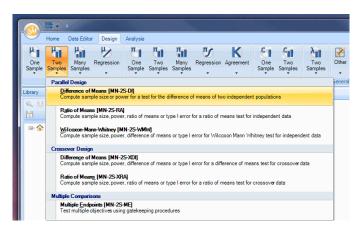
When you open East, you will see the following screen below.

👧 🔄 🖬 🕘 🛞 🗉		East 6 - [Log]	- C - X
Home Data Editor Design	n Analysis		_ 8 3
- ha - ha - ha		i Ai 🕅	
Two Many Regression Samples Samples	on One Two Many Regression Agreement One Two Sample Samples Samples	no Two Ofter des Samples	
Continuous	Discrete Count	Survival General	Help 4
	8 M		neip T
0	ytel Architect (1.0.0) 35 May 2014) ate: Wednesday 14 May 2014 ime: 09:59:30 AM.		
A Root	nstalled Product: East 6 (6.3)		
	icense: Custom		
51	ite Name: Cytel Pune, for user: Development Team	(serial 1d 200002)	
L1	icense туре: single		
N	amber of Available Packages: 12		
	vailable Packages:		
NJ		Expiry Date	
Ba		31 May 2014	
E.		31 May 2014	
E)	kact Inference	31 May 2014	
Gr	roup Sequential Designs	31 May 2014	
G	roup Sequential Designs for Survival Endpoints	31 May 2014	
M	ultiple Arm comparisons	31 May 2014	
R		31 May 2014	
R		31 May 2014	
5	ample Size Re-estimation	31 May 2014	
Si	ample Size Re-estimation for Survival Endpoints	31 May 2014	
R	version 3.0.2 (2013-09-25)		
Log Inputs / Output Preview		View - Ready	

By default, the Design tab in the ribbon will be active. The items on this tab are grouped under the following categories of endpoints: Continuous, Discrete, Count, Survival, and General. Click

Chapter 3: Tutorial: Normal Endpoint





The following input window will appear.

	1-Sided	Input Method: Individual Means Test Statistic: Z	
e <u>s</u> t Type: ype I <u>E</u> rror (α): o <u>w</u> er: ample Si <u>z</u> e (n):	0.025 O 0.9 O Computed O	μριμη Method: (Individual Means Lets Matste:: ∠	
llocation <u>R</u> atio: (n _t /n _c)] Ass <u>u</u> rance (Pro	1 bability of Success)		

By default, the radio button for **Sample Size (n)** is selected, indicating that it is the variable to be computed. The default values shown for **Type I Error** and **Power** are 0.025 and 0.9. Keep the same for this design. Since the default inputs provide all of the necessary input information, you are ready to compute sample size by clicking the **Compute** button. The



calculated result will appear in the **Output Preview** pane, as shown below.

•	ID	Design Type	No. of Looks	Test Type	Specified α	Power	nt/nc	Sample Size	Input Method	δ1	μς	Mean Treatment (Alt.)	σ	Test Statistic
5	Des 1	Superiority	1	1-Sided	0.025	0.9	1	467	Individual Means	0.3	0	0.3	1	Z

This single row of output contains relevant details of inputs and the computed result of total sample size (and total completers) of 467. Select this row, and click ut display a summary of the design details in the upper pane (known as **Output Summary**).

	Des 1
Mnemonic	MN-2S-DI
Test Parameters	
Design Type	Superiority
No. of Looks	1
Test Type	1–Sided
Specified α	0.025
Power	0.9
Model Parameters	
Input Method	Individual Means
Diff. in Means ($\delta = \mu t - \mu c$)	0.3
Mean Control (µc)	0
Mean Treatment (µt1)	0.3
Std. Deviation (σ)	1
Test Statistic	Z
Allocation Ratio (nt/nc)	1
Sample Size	
Maximum	467

The discussion so far gives you a quick feel of the software for computing sample size for a single look design. We will describe further features in an example for a group sequential design in the next section.

Chapter 3: Tutorial: Normal Endpoint

3.2 Group Sequential Design for a Normal Superiority Trial

3.2.1 Study Background

Drug X is a newly developed lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats. The performance of this drug needs to be compared with an already marketed drug Y for the same condition. In a randomized, double-blind, trial comparing the efficacy and safety of 1 year of treatment with X to Y (each at 120 mg for three times a day), obese adults are to be randomized to receive either X or Y combined with dietary intervention for a period of one year. The endpoint is weight loss (in pounds). You are to design a trial having 90% power to detect a mean difference of 9 lbs between X and Y, assuming 15 lbs and 6 lbs weight loss in each treatment arm, respectively, and a common standard deviation of 32 lbs. The design is required to be a 2-sided test at the 5% significance level.

From the design menu choose **Continuous: Two Samples**, and then **Parallel Design: Difference of Means**. Select **2–Sided** for **Test Type**, and enter 0.05 for **Type I Error**. Specify the **Mean Control** be 6, the **Mean Treatment** to be 15, and the common **Std. Deviation** to be 32. Next, change the **Number of Looks** to be 5. You will see a new tab, **Boundary Info**, added to the input dialog box.

le <u>s</u> t Type:	2-Sided	 <u>Input Method</u>: Individual Means 	5 🔻	Test Statistic: Z
Type I <u>E</u> rror (α):	0.05	Specify Mean Responses		
ype i <u>c</u> itor (u).		Mean Control (μ _c):	6	Std. De <u>v</u> iation (σ): 32
o <u>w</u> er:	0.9		15	
Sample Si <u>z</u> e (n):	Computed 💿	Mean T <u>r</u> eatment (µ _t):	15	
Allocation <u>R</u> atio:	1			
(n_{+}/n_{c})				

Click the **Boundary Info** tab, and you will see the following screen. On this tab, you can choose whether to specify stopping boundaries for efficacy, or futility, or both. For this trial,

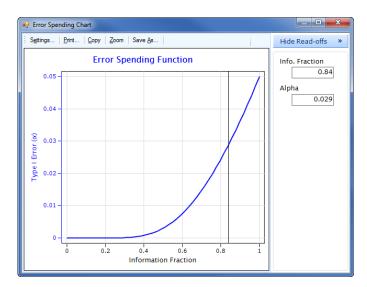


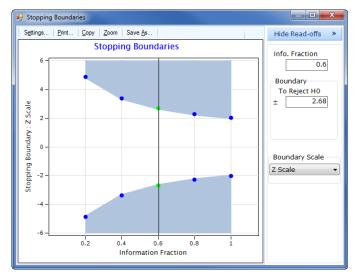
choose efficacy boundaries only, and leave all other default values. We will implement the Lan-Demets (O'Brien-Fleming) spending function, with equally spaced looks.

Efficacy					utility			
Bound	ary Family:	Spending	g Functions 🚽		Boundary Family:	None 🔻		
Spendi	ng Function	Lan-DeMe	ts 👻					
Parame	ter	OF	•					
		01						
Type I	Error (α):	0.05						
Spacing	of Looks	0	0		Efficacy Boundary:	Z Scale	- <i>1</i>	1
		⊙ Equal	O Unequ	Jal	Enreacy Boundary.	2 Scale		9
Look #	Info.	Cum. α	Efficacy	Boundary				
LOOK #	Fraction	Spent	Upper	Lower				
	0.200	0.000	4.877	-4.877	7			
1	0.200		3.357	-3.357	7			
1	0.200	0.001						
1 2 3		0.008	2.680	-2.680				
	0.400		2.680 2.290	-2.680				

Chapter 3: Tutorial: Normal Endpoint

charts.





Click **Compute**. East will show the results in the **Output Preview**.



The maximum combined sample size required under this design is 544. The expected sample sizes under H0 and H1 are 540 and 403, respectively. Click in the **Output Preview** toolbar to save this design to Wbk1 in the **Library**. Double-click on Des1 to generate the following output.

Design: Continuous Endpoint: Two-Sample Test - Parallel Design - Difference of Means

Std. Deviation (o) 32 1 0.2 109 1.104E-6 4.872 4.872 5.519E-7 5.519E-7 3.32E-4 1.146 Allocation Ratio (n/ng) 1 2 0.401 218 7.981E-4 3.354 -3.354 3.985E-4 0.01 2.11 <												
Design Type Superiority Number of Looks Control Treatment Name Total Number of Looks 5 Test Type 2Sidedin Size (n)	Test Parameters		😁 Sample	e Size informa	tion							
Junger of Locks Summer of Locks Arm Arm Initial Test Type 2-Sided Specified 0.05 544 Specified 0.05 201474 403249 Power 0.9 Model Parametrix 201775 201474 403249 Model Parameters Expected H1 201775 201474 403249 Macan Control (μ) 6 6 6 6 6 Macan Control (μ) 6 6 6 70027 540.43 Macan Control (μ) 6 6 6 700274 270.224 270.207 540.43 Macan Control (μ) 6 6 6 70027 540.43 5 Macan Control (μ) 6 6 6 8 6 100 10047 10	Design ID	Des2		C 1			-					
Number of Looks 5 Test Type 2:Sided Maximum 272 544 Specified a 0.05 Power 0.9 Model Parameters 270.207 540.43 Input Method 270.224 270.207 540.43 Maximum Information (i).0.133 30 5 Maximum Information (i).0.133 5 4 Statistic 2 7 Maximum Information (i).0.133 5 4 Maximum Information (i).0.133 5 4 Statistic 2 7 5 Maximum Information (i).0.133 5 4 4 Statistic 2 2 5 4 Maximum Information (i).0.133 5 5 1 0 Maximum Information (i).0.13 5 5 1 0 1 Other H1 9 5 4 1 0 1 0 2 1 0 2 1 0 2	Design Type	Superiority										
lest type 2/sided Maximum 272 272 544 Specified 0 0.05 0.05 Maximum 1775 201/474 403.249 Power 0.9 Model Parametry Expected H1 270.224 270.207 540.43 Maximum information (); 0, 133 Maximum information (); 0, 135 Stopping Boundaries: Look by Look Stopping Boundaries: Look by Look Model H1 Model H1 Model (); 0, 123 G Devideo (); 0, 123 Fraction (); 0, 133 Sample Size (n) Sample Size (n) Cumulative 0 Boundaries: Look by Look Under H0	Number of Looks	5	0				-					
Specified σ 0.05 Power Expected H1 201.775 201.474 403.249 403.249 Model Parameters Expected H0 270.207 200.201 504.03 Maximum Information (0,0.133 Maximum Information (0,0.133 - - Mean Control (μ ₂) 6 - - - - Mean Control (μ ₂) 6 - - - - - Model Parameters - - - - - - Maximum Information (0,0.133 - - - - - - Model Parameters -	Test Type	2-Sided					-					
Drover Model Parameters Expected H0 270.224 270.207 540.43 Model Parameters Test Statistic Z Maximum Information (1) 0.133 Image: Statistic (1) - 133 Image: Stat	Specified a	0.05					-					
Model Parameters Maximum Information (I) 0.133 Test Statistic Z Input Method Individual Means Maximum Information (I) 0.133 Mean Treatment (µ _{rt}) 6 5 = µ ₁ · µ ₂ Cumulative Inder H0 Boundaries: Look by Look Under H0 0 Under H1 9 Std Deviation (qir) 1 0 - 2 109 1.104E-6 4.872 4.872 5.519E-7 5.39E-4 1.148E- 2 2 Mozardner Ratio (n/n) 1 0.2 109 1.104E-6 4.872 4.872 5.519E-7 5.519E-7 3.32E-4 1.148E- 3.0559 326 0.008 2.682 -2.682 0.003 0.301 7.44	Power	0.9					_					
Teat Statistic Z Input Method Individual Means Outrol (μ) 6 Mean Control (μ) 15 Individual Fraction (n/m_max) Sample State (n) Vid Deviation (r) 1 0.2 109 1.104E-6 4.872 5.918E-7 5.519E-7 3.519E-7 3.22E-4 1.14 Boundary Parameters 3 0.599 3.26 0.008 2.682 2.682 0.003 0.031 0.44 8.45	Model Parameters		Expe				_					
Index Mean Control (μ, μ) 6 Mean Teatment (μ, μ) 15 5 = μ, - μ_0 Info. Max Treatment (μ, μ) 15 5 = μ, - μ_0 Info. Under H0 0 Under H1 9 Sto. Deviation (r) 32 1 Allocation Ratio (r/n, μ) 1 2 0.421 1 0.2 1002 109 2 1.104E-6 2 0.401 2 0.401 2 0.401 2.80 0.008 2.80 0.008 2.80 0.008 2.80 0.008 2.80 0.008 2.80 0.008 2.80 0.008 3 0.599 3 0.599 3 0.024 4 0.8 4 0.8 4 0.8 4.90 0.004 0.024 2.29		7		Maximum In	formation (I):0.	133						
Man Cantrol (µ) 6 Man Treatment (µ),1 15 5 = µ, - µ, Under H0 0 0, dr H1 9 Std. Deviation (x) 1 0, 21 0, 21 1 0, 22 100 1, 104E-6 4, 872 4, 872 4, 872 4, 519E-7 20, 0010 218 7, 981E-4 3, 354 30, 0599 326 0, 0024 2, 562 2, 0, 001 218 30, 0599 326 0, 0024 2, 562 0, 0031 0, 31 4 0, 8 4 0, 8 4 0, 8 4 0, 8 4 0, 8 0, 0024 2, 9 0, 0030 0, 004 4 0, 8 4 0, 8 0, 0024 2, 9 29 0, 008 0, 008 20, 0229 0, 008 0, 0008		Individual	Stoppi	ng Boundaries	s: Look by Lo	ok						
Boundaries Hight of the second sec	Mean Control (µ_)	6										
5 = μ, - μ_c Look Imode (n/m,mx) Sample Size (n) Cumulative Praction Cumulative Practin Praction Cumulativ	- 10-	15					Boun	darios	Bo			ility
Under H0 0 # Income Size (n) Spent Efficacy Z Upper Lows Upper Lows <th< td=""><td>δ = μ_t - μ_c</td><td></td><td>Look</td><td></td><td>Sample</td><td></td><td>Douin</td><td colspan="2" rowspan="2"></td><td colspan="2" rowspan="2">Under H0</td><td>er H1</td></th<>	δ = μ _t - μ _c		Look		Sample		Douin			Under H0		er H1
Under H1 9 Skill Deviation (r) 32 Allocation Ratio (n/n.) 1 0.2 109 1.104E-6 4.872 5.519E-7 5.519E-7 3.32E-4 1.146 2 0.401 218 7.981E-4 3.354 -3.354 3.985E-4 3.985E-4 0.2 1.09 Boundary Parameters 3 0.599 326 0.008 2.682 0.003 0.003 0.344 8.481 Spacing of Looks Equal 4 0.8 435 0.024 2.29 -2.09 0.008 0.001 7.455	Under H0	0	#		Size (n)		Effic					
Std. Devation (r) 32 1 0.2 109 1.104E-6 4.872 4.872 6.519E-7 5.519E-7 3.32E-4 1.146 Allocation Ratio (n/n.) 1 2 0.401 218 7.981E-4 3.354 -3.354 3.985E-4 3.985E-4 0.10 2.81 Boundary Parameters 3 0.699 326 0.008 2.682 0.003 0.034 8.483 Spacing of Looks Equal 4 0.8 435 0.024 2.29 0.008 0.301 7.455	Under H1	9					L	· ·		<u> </u>		Lower
Allocation (xin_0) 1 2 0.401 218 7.981E-4 3.354 -3.354 3.985E-4 3.985E-4 0.1 2.816 Boundary Parameters 3 0.599 326 0.008 2.682 2.003 0.003 0.344 8.484 Spacing of Looks Equal 4 0.8 435 0.024 2.29 -2.29 0.008 0.008 17.455	Std. Deviation (o)	32	1	0.2	100	1 1045 6						
Boundary Parameters 3 0.599 326 0.008 2.682 -2.682 0.003 0.003 0.344 8.483 Spacing of Looks Equal 4 0.8 435 0.024 2.29 -2.29 0.008 0.008 0.301 7.455	Allocation Ratio (n/n	1										
Spacing of Looks Equal 4 0.003 320 0.000 2.002 -0.002 0.003 0.004 0.004 0.004 0.005 0.004 0.005 0.005 0.004 0.005 0.005 0.004 0.005 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.004 0.005 0.004 0.004 0.005 0.004 0.004 0.005 0.004 0.004 0.005 0.004 0.004 0.004 0.005 0.004 0.004 0.005 0.004 0.004 0.005 0.004 0.004 0.005 0.004	Boundary Paramete	rs										
Efficacy Boundary LD (OF) 5 1 544 0.05 2.031 -2.031 0.013 0.013 0.154 4.003	Efficacy Boundary			0.8								7.455E-8 4.003E-8

Once you have finished examining the output, close this window, and re-start East before continuing.

3.2.2 Creating multiple designs easily

In East, it is easy to create multiple designs by inputting multiple parameter values. In the trial described above, suppose we want to generate designs for all combinations of the following parameter values: **Power** = 0.8, 0.9, and **Difference in Means** = 8.5, 9, 9.5, 10. The number of such combinations is $2 \times 4 = 8$.

East can create all 8 designs by a single specification in the input dialog box. Enter the following values as shown below. Remember that the common **Std. Deviation** is 32. From the **Input Method**, select the **Difference of Means** option. The values of **Power** have been entered as a list of comma-separated values, while **Difference in Means** has been entered as

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a colon-separated range of values: 8.5 to 10 in steps of 0.5.

Design Type: Su	periority 🔹	Number of Loo <u>k</u> s: 5
Design Parameters	Boundary Info	
Te <u>s</u> t Type:	2-Sided	Input Method: Difference of Means Iest Statistic: Z
Type I <u>E</u> rror (α): Power:	0.05	$ \underline{D} iff. in Means (\delta = \mu_t - \mu_c): \qquad \boxed{8.5:10:0.5} \qquad Std. Deviation (\sigma): \boxed{32} $
_	Computed \odot	
Allocation <u>R</u> atio: (n _t /n _c)	1	
Accurance (Prob	ability of Success)	

Now click compute. East computes all 8 designs, and displays them in the **Output Preview** as shown below. Click is to maximize the **Output Preview**.

Select the first 3 rows using the Ctrl key, and click *to display a summary of the design details in the upper pane, known as the Output Summary.*

	Des 1	Des2	Des 3
Mnemonic	MN-25-DI	MN-2S-DI	MN-2S-DI
Test Parameters			
Design Type	Superiority	Superiority	Superiority
No. of Looks	5	5	5
Test Type	2-Sided	2-Sided	2-Sided
Specified α	0.05	0.05	0.05
Power	0.8	0.8	0.801
Model Parameters			
Input Method	Difference of Means	Difference of Means	Difference of Means
Diff. in Means ($\delta = \mu t - \mu c$)	8.5	9	9.5
Std. Deviation (σ)	32	32	32
Test Statistic	Z	Z	Z
Allocation Ratio (nt/nc)	1	1	1
Boundary Parameters			
Efficacy Boundary	LD (OF)	LD (OF)	LD (OF)
Spacing of Looks	Equal	Equal	Equal
Sample Size			
Maximum	456	407	366
Expected Under H0	453.004	404.326	363.595
Expected Under H1	366.549	327.093	294.023

Select Des1 in the **Output Preview**, and click toolbar to save this design in the **Library**. We will use this design for simulation and interim monitoring, as described below. Now that you have saved Des1, delete all designs from the **Output Preview** before continuing, by selecting all designs with the Shift key, and clicking in the toolbar.



3.2.3 Simulation

Right-click Des1 in the **Library**, and select **Simulate**. Alternatively, you can select Des1 and click the **S** icon.

rial Typ	e: Supe	riority	-			Test Statistic: t 🔹
Fest Type	e: 2-Sid	led	-			
Sample S	ize (n):	456				Variance: Equal
1	Info Franking	Cum. c	x Spent	Effic	acy Z	A
Look #	Info. Fraction	Cum. o Upper	x Spent Lower	Effic	acy Z Lower	~
Look # 1	Info. Fraction					
		Upper	Lower	Upper	Lower	E E
	0.200	Upper 0.000	Lower	Upper 4.883	Lower -4.883	
1	0.200	Upper 0.000 0.000	Lower 0.000 0.000	Upper 4.883 3.361	Lower -4.883 -3.361	

We will carry out a simulation of Des1 to check whether it preserves the specified power. Click **Simulate**. East will execute by default 10000 simulations with the specified inputs. Close the intermediate window after examining the results. A row labeled as Sim1 will be added in the **Output Preview**.

Click the icon to save this simulation to the **Library**. A simulation sub-node will be added under Des1 node. Double clicking on the Sim1 node, will display the detailed

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simulation output in the work area.

Simulation: Continuous Endpoint: Two-Sample Test - Parallel Design - Difference of Means

Simulation Parameters	
Simulation ID	Sim1
Design Type	Superiority
Number of Looks	5
Test Type	2-Sided
Sample Size (n)	456
Variance	Equal
Test Statistic	t
Avg. Power at Termination	0.802
Response Generation F	Parameters
Generate Data Using	Individual Means
Mean Control (µ_)	0
Mean Treatment (µt)	8.5
SD Control (o)	32
SD Treatment (o _t)	32
Simulation Control Para	ameters
Starting Seed	Clock
Number of Simulations	10000

⊖Average	Sample Size
	A

Look #	Average Sample Size (n)
1	91
2	182
3	274
4	365
5	456
Average	366.996

⊖ Simulation Boundaries and Boundary Crossing Probabilities

		Bound	laries	Stoppi	ng For	Total Simulations	
Look #	Sample Size			Stoppi	ing FOI		
LOOK	(n)	Upper	Lower	Upper Efficacy	Lower Efficacy	Count	%
1	91	4.883	-4.883	2	0	2	0.020%
2	182	3.361	-3.361	609	0	609	6.090%
3	274	2.678	-2.678	2523	0	2523	25.230%
4	365	2.289	-2.289	2893	0	2893	28.930%
5	456	2.031	-2.031	1996	0	3973	39.730%
Total				8023	0	10000	
%				80.230%	0.000%		

 Simulation Seed and Elapsed Time

 Starting Seed:
 725323

 Total Number of Simulations:
 10000

 Elapsed Time:
 00:01:05

In 80.23% of the simulated trials, the null hypothesis was rejected. This value is very close to the specified power of 80%. The next section will explore interim monitoring with this design.

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3.2.4 Interim Monitoring

Right-click Des1 in the **Library** and select **Interim Monitoring**. Click the **Enter Interim Data** to open the **Test Statistic Calculator**. Suppose that after 91 subjects, at the first look, you have observed a mean difference of 8.5, with a standard error of 6.709.

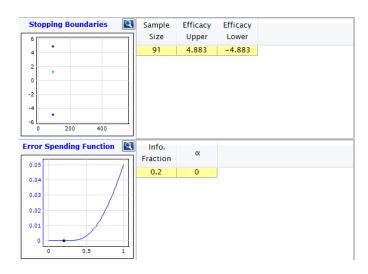
Test Statistic Calculator	×
Editing look #1	
□ Set Current Look as Last	
Cumulative Sample Size:	91
Input for Normal end point Estimate of δ : $\delta = (\mu, - \mu_r)$	8.5
Standard Error of Estimate of δ:	6.709
Output	
Test Statistic:	1.267
Recalc OK	Cancel

Click **OK** to update the IM Dashboard.

Look	Information	Cumulative	Test	8	Standard	Effic	cacy	95% R	CI for δ	Repeated	CP	Predictive
#	Fraction	Sample Size	Statistic	Ū	Error	Upper	Lower	Upper	Lower	p-value	Ci	Power
1	0.2	91	1.267	8.5	6.709	4.883	-4.883	41.257	-24.257	0.932	0.828	0.673
2												
3												
4												
5												

The Stopping Boundaries and Error Spending Function charts on the left:

Chapter 3: Tutorial: Normal Endpoint



The Conditional Power and Confidence Intervals charts on the right:



Suppose that after 182 subjects, at the second look, you have observed a mean difference of



16, with a standard error of 4.744. Click **Recalc**, and then **OK** to update the IM Dashboard. In this case, a boundary has been crossed, and the following window appears.

Click **Stop** to complete the trial. The IM Dashboard will be updated accordingly, and a table for **Final Inference** will be displayed as shown below.

Final Inference	
Final Outputs at Look #	2
Adj. p-value	0.001
Adj. Pt. Est. for δ	16
Adj. 95% CI for δ	
Upper Confidence Bound	25.298
Lower Confidence Bound	6.702
Post-Hoc Power	

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4 *Normal Superiority One-Sample*

To compare a new process or treatment to a well-established control, a single-sample study may suffice for preliminary information prior to a full-scale investigation. This single sample may either consist of a random sample of observations from a single treatment when the mean is to be compared to a specified constant or a random sample of paired differences or ratio between two treatments. The former is presented in Section (4.1) and the latter is discussed in Section (4.2) and Section (4.3).

4.1 Single Mean

• 4.1.1 Trial Design • 4.1.2 Simulation • 4.1.3 Interim Monitoring

• 4.1.4 Trial Design Using a t-Test (Single Look)

The problem of comparing the mean of the distribution of observations from a single random sample to a specified constant is considered. For example, when developing a new drug for treatment of a disease, there should be evidence of efficacy. For this single-sample problem, it is desired to compare the unknown mean μ to a fixed value μ_0 . The null hypothesis H_0 : $\mu = \mu_0$ is tested against the two-sided alternative hypothesis H_1 : $\mu \neq \mu_0$ or a one-sided alternative hypothesis H_1 : $\mu < \mu_0$ or H_1 : $\mu > \mu_0$. The power of the test is computed at a specified value of $\mu = \mu_1$ and standard deviation σ .

Let $\hat{\mu}_j$ denote the estimate of μ based on n_j observations, up to and including the *j*-th look, j = 1, ..., K, with a maximum of *K* looks. The test statistic at the *j*-th look is based on the value specified by the null hypothesis, namely

$$Z_j = n_j^{1/2} (\hat{\mu}_j - \mu_0) / \hat{\sigma}_j, \tag{4.1}$$

where $\hat{\sigma}_i^2$ is the sample variance based on n_j observations.

4.1.1 Trial Design

Consider the situation where treatment for a certain infectious disorder is expected to result in a decrease in the length of hospital stay. Suppose that hospital records were reviewed and it was determined that, based on this historical data, the average hospital stay is approximately 7 days. It is hoped that the new treatment can decrease this to less than 6 days. It is assumed that the standard deviation is $\sigma = 2.5$ days. The null hypothesis H_0 : $\mu = 7(= \mu_0)$ is tested against the alternative hypothesis H_1 : $\mu < 7$.

First, click **Continuous: One Sample** on the **Design** tab and then click **Single Arm Design: Single Mean** as shown below.

This will launch a new input window.

Single-Look Design

We want to determine the sample size required to have power of 90% when $\mu = 6(= \mu_1)$, using a test with a one-sided type-1 error rate of 0.05. Choose **Test Type** as **1–Sided**. Specify **Mean Response under Null (** μ_0 **)** as 7, **Mean Response under Alt. (** μ_1 **)** as 6 and **Std**. **Deviation** (σ) as 2.5. The upper pane should appear as below:

Design Paramet Test Type: Type I Error (α): Power: Sample Size (n):	1-Sided 0.05 0.9	• 0 0	Specify Mean Responses Mean Response under Null (μ_0) : 7 Mean Response under Alt. (μ_1) : 6	Test Statistic: Ζ Std. Deviation (σ):	v 2.5
---	------------------------	-------------	--	--	-----------------

Click Compute. This will calculate the sample size for this design and the output is shown as a



row in the **Output Preview**. The computed sample size is 54 subjects.

	🔝 🦻 🗟 🗙 🎪 🍓 🎭 Output Preview												
	ID	Design Type	No. of Looks	Test Type	Specified α	Power	Sample Size	σ	μ0	μΊ	Test Statistic		
۳	Des 1	Superiority	1	1-Sided	0.05	0.902	54	2.5	7	6	Z		

This design has default name Des 1. Select this design by clicking anywhere along the row and click in the **Output Preview** toolbar. Some of the design details will be displayed in the upper pane, labeled as **Output Summary**.

🗳 = 🛅 = 🍬 🏨		Output Summa
	Des 1	
Mnemonic	MN-1S-SM	
Test Parameters		
Design Type	Superiority	
No. of Looks	1	
Test Type	1-Sided	
Specified α	0.05	
Power	0.902	
Model Parameters		
Std. Deviation (σ)	2.5	
Mean Response under Null (µ0)	7	
Mean Response under Alt. (µ1)	6	
Test Statistic	Z	
Sample Size		
Maximum	54	

In the **Output Preview** toolbar select Des 1, click in the **Library**.

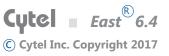
Five-Look Design

To allow the opportunity to stop early and proceed with a full-scale plan, five equally-spaced analyses are planned, using the Lan-DeMets (O'Brien-Fleming) stopping boundary. Create a new design by right-clicking Des 1 in the **Library**, and selecting **Edit Design**. In the Input, change the **Number of Looks** from 1 to 5, to generate a study with four interim looks and a final analysis. A new tab for **Boundary Info** should appear. Click this tab to reveal the

stopping boundary parameters. By default, the **Spacing of Looks** is set to **Equal**, which means that the interim analyses will be equally spaced in terms of the number of patients accrued between looks. The left side contains details for the **Efficacy** boundary, and the right side contains details for the **Futility** boundary. By default, there is an efficacy boundary (to reject H_0) selected, but no futility boundary (to reject H_1). The **Boundary Family** specified is of the **Spending Functions** type. The default **Spending Function** is the **Lan–DeMets** (Lan & DeMets, 1983), with **Parameter** as **OF** (O'Brien-Fleming), which generates boundaries that are very similar, though not identical, to the classical stopping boundaries of O'Brien and Fleming (1979). For a detailed description of the different spending functions and stopping boundaries available in East refer to Chapter **??**. The cumulative alpha spent and the boundary values are displayed below.

	out	eriority	 Numb 	of Looks: 5	Include Option
	Parameters	Boundary	Info		
		Lan-DeMe	Functions	Futility Boundary Family: None 🔹	
Spacing	of Looks	⊙ Equal	O Unequal	Efficacy Boundary: Z Scale 🔹 🗾	3
Look #	Info. Fraction	Cum. α Spent	Efficacy Boundary		^
1	0.200	0.000	-4.229		-
2	0.400	0.002	-2.888		=
3	0.600	0.011	-2.298		
4	0.800	0.028	-1.962		
5	1.000	0.050	-1.740		-

Click **Compute**. The maximum and expected sample sizes are highlighted in yellow in the **Output Preview**. Save this design in the current workbook by selecting the corresponding row in the **Output Preview** and clicking on the **Output Preview** toolbar. To compare Des 1 and Des 2, select both rows in **Output Preview** using the Ctrl key and click in the



	Des 1	Des2
Mnemonic	MN-1S-SM	MN-1S-SM
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	1	5
Test Type	1–Sided	1–Sided
Specified α	0.05	0.05
Power	0.902	0.903
Model Parameters		
Std. Deviation (σ)	2.5	2.5
Mean Response under Null (µ0)	7	7
Mean Response under Alt. (µ1)	6	6
Test Statistic	Z	Z
Boundary Parameters		
Spacing of Looks		Equal
Efficacy Boundary		LD (OF)
Sample Size		
Maximum	54	56
Expected Under H0		55.531
Expected Under H1		39.897

Output Preview toolbar. This will display both designs in the Output Summary pane.

Des 2 results in a maximum of 56 subjects in order to attain 90% power, with an expected sample size of 40 under the alternative hypothesis. In order to see the stopping probabilities, double-click Des 2 in the **Library**.

⊖ Stopping Boundaries: Look by Look

	Info.		Cumulative	Boundaries	Boundary Cross (Incren		
Look #	Fraction	Sample Size (n)	α		Under H0	Under H1	
"	(n/n_max)	5126 (11)	Spent	Efficacy Z	Efficacy	Efficacy	
					Emoucy	Linducy	
1	0.196	11	9.767E-6	-4.27	9.767E-6	0.002	
2	0.393	22	0.002	-2.918	0.002	0.147	
3	0.607	34	0.012	-2.279	0.01	0.376	
4	0.804	45	0.029	-1.958	0.017	0.25	
5	1	56	0.05	-1.741	0.021	0.128	

The clear advantage of this sequential design resides in the relatively high cumulative probability of stopping by the third look if the alternative is true, with a sample size of 34 patients, which is well below the requirements for a fixed sample study (54 patients). Close the Output window before continuing.

Examining stopping boundaries and spending functions

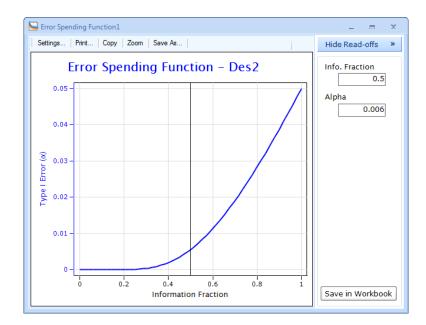
You can plot the boundary values of Des 2 by clicking Series on the Library toolbar, and then



clicking Stopping Boundaries. The following chart will appear:

You can choose different boundary scales from the drop down box located in the right hand side. The available boundary scales are Z scale, Score Scale, μ/σ Scale and *p*-value scale. To plot the error spending function for Des 2, select Des 2 in the Library, click in the





toolbar, and then click Error Spending. The following chart will appear:

The above spending function is according to Lan and DeMets (1983) with O'Brien-Fleming flavor and for one-sided tests has the following functional form:

$$\alpha(t) = 2 - 2\Phi\left(\frac{Z_{\alpha/2}}{\sqrt{t}}\right)$$

Observe that very little of the total type-1 error is spent early on, but more is spent rapidly as the information fraction increases, and reaches 0.05 at an information fraction of 1. Feel free to try other plots by clicking in the Library toolbar. Close all charts before continuing.

4.1.2 Simulation

Suppose we want to see the advantages of performing the interim analyses, as it relates to the chance of stopping prior to the final analysis. This examination can be conducted using

simulation. Select Des 2 in the **Library**, and click in the toolbar. Alternatively, right-click on Des 2 and select **Simulate**. A new Simulation window will appear. For example, suppose you wish to determine how quickly this trial could be terminated if the treatment difference was much greater than expected. For example, under the alternative hypothesis, $\mu = 4.5$. Click on the **Response Generation Info** tab, and specify: **Mean Response(** μ **)** = 4.5 and **Std. Deviation (** σ **)** = 2.5.

Simulation Parameters	Response	Generation Info	Simulation Control Info					
Specify Mean Response Mean Response (µ):	4.5	Std. Deviation (σ): 2.5					

Click **Simulate** to start the simulation. Once the simulation run has completed, East will add an additional row to the **Output Preview** labeled as Sim 1.

Select Sim 1 in the **Output Preview** and click . Now double-click on Sim 1 in the **Library**. The simulation output details will be displayed in the upper pane.

		Boundaries	Stanning For	Total			
Look #	Sample Size (n)	Efficacy	Stopping For	Simulations			
	(")	Lower	Efficacy	Count	%		
1	11	-4.27	2606	2606	26.060%		
2	22	-2.918	6886	6886	68.860%		
3	34	-2.279	504	504	5.040%		
4	45	-1.958	4	4	0.040%		
5	56	-1.741	0	0	0.000%		
Total			10000	10000			
%			100.000%				

⊖ Simulation Boundaries and Boundary Crossing Probabilities

Observe that 100% simulated trials rejected the null hypothesis, and about 26% of these simulations were able to reject the null at the first look after enrolling only 11 subjects. Your numbers might differ slightly due to a different starting seed.



4.1.3 Interim Monitoring

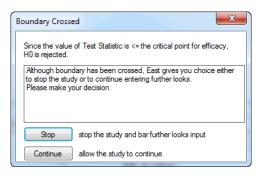
Suppose that the trial has commenced and Des 2 was implemented. Right-click Des 2 in the **Library**, and select **Interim Monitoring**.

Although we specified that there will be five equally spaced interim looks, the Lan-DeMets methodology implemented in East allows you to alter the number and spacing of these looks. Accordingly, suppose that an interim look was taken after enrolling 20 subjects and the sample mean, based on these 20 subjects, was 5.1 with a standard error of 0.592. Since $\mu_0 = 7$, based on equation (4.1) the value of the test statistic at the first look would be $Z_1 = (5.1 - 7)/0.592$ or -3.209.

Click **Enter Interim Data** on the toolbar. In the **Test Statistic Calculator**, enter the following values, and click **Recalc** and then**OK**.

Test Statistic Calculator	X
Editing look #1	
□ Set Current Look as Last	
Cumulative Sample Size:	20
Input for Normal end point	
Estimate of µ:	5.1
Standard Error of Estimate of µ:	0.592
Output	
μ – μ ₀	-1.9
Test Statistic:	-3.209
Recalc OK	Cancel

Since the stopping boundary is crossed, the following dialog box appears.



Click **Stop** to take you back to the interim monitoring dashboard. For final inference, East will display the following summary information on the dashboard.

Final Outputs at Look #	1
Adj. p-value	0.001
Adj. Pt. Est. for μ	5.1
Adj. 90% CI for µ	
Upper Confidence Bound	6.074
Lower Confidence Bound	4.126
Post-Hoc Power	

4.1.4 Trial Design Using a t-Test (Single Look)

The sample size obtained to correctly power Des 1 in Section (4.1.1) relied on using a Wald-type statistic for the hypothesis test, given by equation (4.1). Due to the assumption of normal distribution for the test statistic, we have ignored the fact that the variance σ is estimated from the sample. For large sample sizes this approximation is acceptable. However, in small samples with unknown standard deviation the test statistic

$$Z = n^{1/2} (\hat{\mu} - \mu_0) / \hat{\sigma}, \tag{4.2}$$

is distributed with student's t distribution with (n - 1) degrees of freedom. Here, $\hat{\sigma}^2$ denotes the sample variance based on n observations.

Consider the example in Section 4.1.1 where we would like to test the null hypothesis that the



average hospital stay is 7 days, H_0 : $\mu = 7(=\mu_0)$, against the alternative hypothesis that is less than 7 days, H_1 : $\mu < 7$. We will now design the same trial in a different manner, using the t distribution for the test statistic.

Right-click Des 1 in the **Library**, and select **Edit Design**. In the input window, change the **Test Stat.** from z to t. The entries for the other fields need not be changed.

Click **Compute**. East will add an additional row to the **Output Preview** labeled as Des 3. The required sample size is 55. Select the rows corresponding to Des 1 and Des 3 and click III This will display Des 1 and Des 3 in the **Output Summary**.

	Des 1	Des 3
Mnemonic	MN-1S-SM	MN-1S-SM
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	1	1
Test Type	1-Sided	1-Sided
Specified α	0.05	0.05
Power	0.902	0.9
Model Parameters		
Std. Deviation (σ)	2.5	2.5
Mean Response under Null (µ0)	7	7
Mean Response under Alt. (µ1)	6	6
Test Statistic	Z	t
Sample Size		
Maximum	54	55

Des 3, which uses the t distribution, requires that we commit a combined total of 55 patients to the study, just one more compared to Des 1, which uses the normal distribution. The extra patient is needed to compensate for the extra variability due to estimation of the var $[\hat{\delta}]$.

4.2 Mean of Paired Differences

4.2.1 Trial Design = 4.2.2 Simulation = 4.2.3 Interim Monitoring

4.2.4 Trial Design Using a t-Test (Single Look)

The paired t-test is used to compare the means of two normal distributions when each observation in the random sample from one distribution is matched with a unique observation from the other distribution. Let μ_c and μ_t denote the two means to be compared and let σ^2 denote the variance of the differences.

The null hypothesis H_0 : $\mu_c = \mu_t$ is tested against the two-sided alternative hypothesis H_1 : $\mu_c \neq \mu_t$ or a one-sided alternative hypothesis H_1 : $\mu_c < \mu_t$ or H_1 : $\mu_c > \mu_t$. Let $\delta = \mu_t - \mu_c$.

The null hypothesis can be expressed as H_0 : $\delta = 0$ and the alternative can be expressed as H_1 : $\delta \neq 0$, H_1 : $\delta > 0$, or H_1 : $\delta < 0$. The power of the test is computed at specified values of μ_c, μ_t , and σ .

Let $\hat{\mu}_{cj}$ and $\hat{\mu}_{tj}$ denote the estimates of μ_c and μ_t based on n_j observations, up to and including *j*-th look, $j = 1, \ldots, K$ where a maximum of *K* looks are to be made. The estimate of the difference at the *j*-th look is

 $\hat{\delta}_j = \hat{\mu}_{tj} - \hat{\mu}_{cj}$

and the test statistic at the j-th look is

$$Z_j = n_j^{1/2} \hat{\delta}_j / \hat{\sigma}_j, \tag{4.3}$$

where $\hat{\sigma}_{i}^{2}$ is the sample variance of n_{i} paired differences.

4.2.1 Trial Design

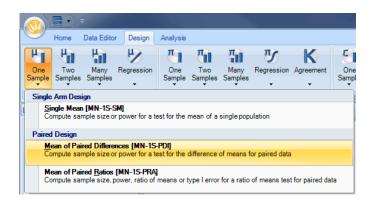
Consider the situation where subjects are treated once with placebo after pain is experimentally induced, and later treated with a new analgesic after pain is induced a second time. Pain is reported by the subjects using a 10 cm visual analog scale (0="no pain", ..., 10="extreme pain"). After treatment with placebo, the average is expected to be 6 cm. After treatment with the analgesic, the average is expected to be 4 cm. It is assumed that the common standard deviation is $\sigma = 5$ cm. The null hypothesis H_0 : $\delta = 0$ is tested against the alternative hypothesis H_1 : $\delta < 0$.

Start East afresh. First, Continuous: One Sample on the Design tab, and then click Paired

46



Design: Mean of Paired Differences



This will launch a new input window.

Single-Look Design

We want to determine the sample size required to have power of 90% when $\mu_c = 6$ and $\mu_t = 4$, using a test with a one-sided type-1 error rate of 0.05. Select **Test Type** as **1–Sided**, **Individual Means** for **Input Method**, and specify the **Mean Control** (μ_c) as 6 and **Mean Treatment** (μ_t) as 4. Enter **Std. Dev. of Paired Difference** (σ_0) as 5. The upper pane should appear as below:

C	Design: Continuo	ous Endpoint	One-Sample Test - Paired Design - N	lean of Paired Diffe	rences	88. 🕥	.00 💌
Design Type: Si Design Paramete	uperiority rs	▼ Numb	eer of Looks: 1 -				
Test Type: Type I Error (α): Power: Sample Size (n):	1-Sided 0.05 0.9 Computed	• • •	$\label{eq:linear} \begin{array}{l} \mbox{Individual Means} \\ \mbox{Specify Mean Responses} \\ \mbox{Mean Control } (\mu_{e}); \\ \mbox{Mean Treatment } (\mu_{t}): \end{array}$	• 6 4	Test Statistic: Z Std. Dev. of Paired Difference (σ_D) :	5	
Assurance (Pro	bability of Succe	255)				Cor	+ npute

Click Compute. This will calculate the sample size for this design and the output is shown as a

row in the **Output Preview**. The computed sample size is 54 subjects.

11 9 1	s × 🖉 🚔	ъ.				Output Preview						Profile 🕶 ⊄ 🏹 🖭		
ID	Design Type	No. of Looks	Test Type	Specified α	Power	Sample Size	Test Statistic	Input Method	μc	Mean Treatment (Alt.)	δ1	σD		
Des 1	Superiority	1	1-Sided	0.05	0.902	54	Z	Individual Means	6	4	-2	5		

This design has default name Des 1. Select this design by clicking anywhere along the row in the **Output Preview** and click . Some of the design details will be displayed in the upper pane, labeled as **Output Summary**.

Si • 📰 • 🍬 🚔 🦳	
	Des 1
Mnemonic	MN-1S-PDI
Test Parameters	
Design Type	Superiority
No. of Looks	1
Test Type	1–Sided
Specified α	0.05
Power	0.902
Model Parameters	
Test Statistic	Z
Input Method	Individual Means
Mean Control (µc)	6
Mean Treatment (µt)	4
Diff. of Means (µt - µc)	-2
Std. Deviation (σD)	5
Sample Size	
Maximum	54

In the **Output Preview** toolbar select Des 1, click **Library**.

to save this design to Wbk1 in the

Three-Look Design

For the above study, suppose we wish to take up to two equally spaced interim looks and one final look as we accrue data, using the Lan-DeMets (O'Brien-Fleming) stopping boundary. Create a new design by right-clicking Des 1 in the **Library**, and **Edit Design**. In the Input, change the **Number of Looks** from 1 to 3, to generate a study with two interim looks and a final analysis.

Click **Compute**. The maximum and expected sample sizes are highlighted in yellow in the **Output Preview**. Save this design in the current workbook by selecting the corresponding



row in **Output Preview** and clicking on the **Output Preview** toolbar. To compare Des 1 and Des 2, select both rows in **Output Preview** using the Ctrl key and click . Both designs will be displayed in the **Output Summary** pane.

	Des 1	Des2
Mnemonic	MN-1S-PDI	MN-1S-PDI
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	1	3
Test Type	1–Sided	1-Sided
Specified α	0.05	0.05
Power	0.902	0.902
Model Parameters		
Test Statistic	Z	Z
Input Method	Individual Means	Individual Means
Mean Control (µc)	6	6
Mean Treatment (µt)	4	4
Diff. of Means (µt - µc)	-2	-2
Std. Deviation (oD)	5	5
Boundary Parameters		
Efficacy Boundary		LD (OF)
Spacing of Looks		Equal
Sample Size		
Maximum	54	55
Expected Under H0		54.685
Expected Under H1		42.646

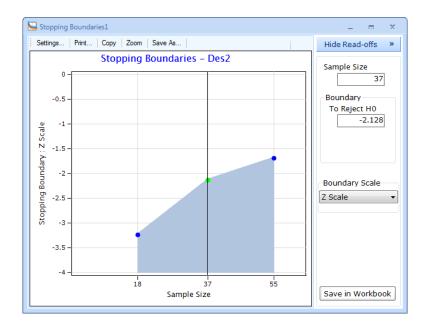
Des 2 results in a maximum of 55 subjects in order to attain 90% power, with an expected sample size of 43 under the alternative hypothesis. In the **Output Preview** toolbar select Des 2, click to save this design to Wbk1 in the **Library**. In order to see the stopping probabilities, double-click Des 2 in the **Library**.

Stopping Boundaries: Look by Look Stopping Boundary Crossing Probability (Incremental) (Incremental)								
Look #	Fraction	Sample Size (n)	α Spent		Under H0	Under H1		
	(n/n_max)	(,		Efficacy Z	Efficacy	Efficacy		
4	0.327	18	6.124E-4	-3.233	6.124E-4	0.062		
1	0.327	10	0.1Z4E-4	-3.233	0.1Z4E-4	0.062		
2	0.673	37	0.017	-2.128	0.016	0.558		
3	1	55	0.05	-1.696	0.033	0.282		

The clear advantage of this sequential design resides in the high cumulative probability of stopping by the third look if the alternative is true, with a sample size of 37 patients, which is well below the requirements for a fixed sample study (54 patients). Close the Output window

before continuing.

Select Des 2 and click **Select** on the Library toolbar. You can select one of many plots, including one for **Stopping Boundaries**:



Close this chart before continuing.

4.2.2 Simulation

Select Des 2 in the **Library**, and click in the toolbar. Click on the **Response Generation Info** tab, and make sure **Mean Treatment**(μ_t) = 4, **Mean Control**(μ_c) = 6 and **Std. Deviation** (σ) = 5. Click **Simulate**. Once the simulation run has completed, East will add an additional row to the **Output Preview** labeled as Sim 1.

Select Sim 1 in the **Output Preview** and click 🖄 . Now double-click on Sim 1 in the



Library. The simulation output details will be displayed.

Differences Simulation Parameters Average Sample Size Simulation ID Sim1 Design Type Superiority Number of Looks 3 Test Type 1-Sided Sample Size (n) 55 Test Statistic t Avg. Power at Termination 0 895 Response Generation Parameters Mean Control (µ_) 6 Mean Treatment (µ,) 4 Std. Deviation (op) 5 Simulation Control Parameters Starting Seed Clock

10000

Average Sample Size						
Look #	Average Sample Size (n)					
1	18					
2	37					
3	55					
Average	41.981					

Simulation: Continuous Endpoint: One-Sample Test - Paired Design - Mean of Paired

Simulation Boundaries and Boundary Crossing Probabilities

		Boundaries	Ctanning Fas	Total Simulations		
Look #	Sample Size (n)	Efficacy	Stopping For			
(11)		Lower	Efficacy	Count	%	
1	18	-3.233	950	950	9.500%	
2	37	-2.128	5280	5280	52.800%	
3	55	-1.696	2719	3770	37.700%	
Total			8949	10000		
%			89.490%			

Overall, close to 90% of simulations have rejected H_0 . The numbers on your screen might differ slightly due to a different seed.

Interim Monitoring 4.2.3

Number of Simulations

For an ongoing study we evaluate the test statistic at an interim stage to see whether we have enough evidence to reject H_0 . Right-click Des 2 in the Library, and select **Interim Monitoring**.

Although the design specified that there be three equally spaced interim looks, the Lan-DeMets methodology implemented in East allows you to alter the number and spacing of these looks. Suppose that an interim look was taken after enrolling 18 subjects and the sample mean, based on these subjects, was -2.2 with a standard error of 1.4. Then based on equation (4.3), the value of the test statistic at first look would be $Z_1 = (-2.2)/1.4$ or -1.571.

Click Enter Interim Data on the toolbar. In the Test Statistic Calculator, enter the following

values, and click	Recalc	and	then	OK
-------------------	--------	-----	------	----

Test Statistic Calculator
Editing look #1
□ Set Current Look as Last
Cumulative Sample Size: 18
Input for Normal end point
Estimate of δ: -2.2
δ = mean of paired difference
Standard Error of Estimate of δ: 1.4
Output
Test Statistic: -1.571
Recalc OK Cancel

The dashboard will be updated accordingly.

ter In	terim Data 🔀	CP 🗭 🛄 🛛	B 🚬 -						Interim	Monitoring: Des2					
ook	Information		Test	δ	Standard	Efficacy	Repeated	95% CI for δ	Repeat						
#	Fraction	Sample Size	Statistic	v	Error	enteacy	Upper	Lower	p-value						
1	0.327	18	-1.571	-2.2	1.4	-3.233	2.326	-Infinity	0.278						
2															
,															
Ste	opping Bound	laries 🛛 🖳	Sample						Conditio	nal Power 🛛 📱	Trmt.				
0.7			Size	Efficacy							Eff.	CP			
-0.5			18	-3.233					1		-2.22	0.911			
-1				01200					0.8		-1.99	0.867			
-1.5											-1.715	0.798			
									0.6		-1.439	0.711			
-2									0.4		-1.164	0.61			
-2.5											-0.888	0.501			
-3									0.2		-0.613	0.392	-		
3.5											-0.062	0.292	-		
-4 -	20	40 60							°	-1 0	0.03	0.181			
-								L					_		
rro	r Spending F	unction 🛛 🖳	Info.						Confiden	e Intervals 🛛 📱	Info.	RCI	RCI	Naive CI	Naiv
			Fraction	α				1	3.564		Fraction	Upper	Lower	Upper	Lov
0.05			0.327	0.001					2.97		0.327	2.326	-Infinity	0.103	-Infi
0.04									2.376	т					
									1.782						
0.03									0.594						
0.02									0	-					
									-0.594						
0.01									-1.188						
		·							-2.376	+	1				

As the observed value -1.571 has not crossed the critical boundary value of -3.233, the trial continues. Now, 18 additional subjects are enrolled, and a second interim analysis with 36

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subjects is conducted. Suppose that the observed difference is -2.3 with standard error as 0.8. Select the Look 2 row and click **Enter Interim Data**. Enter these values, and click **Recalc**, and then**OK**.

Test Statistic Calculator	
Editing look #2	
□ Set Current Look as Last	
Cumulative Sample Size: 36	
Input for Normal end point	
Estimate of δ: -2.3	
δ = mean of paired difference	
Standard Error of Estimate of δ: 0.8	
Output	
Test Statistic: -2.875	
	_
Recalc OK Cancel	

Since the stopping boundary is crossed, the following dialog box appears. Click on **Stop**.

Boundary Crosse	d 🛛 🔍
Since the value H0 is rejected.	of Test Statistic is <= the critical point for efficacy,
	lary has been crossed, East gives you choice either y or to continue entering further looks. ur decision.
Stop	stop the study and bar further looks input
Continue	allow the study to continue

For final inference, East will display the following summary information on the dashboard.

Final Inference						
Final Outputs at Look #	2					
Adj. p-value	0.002					
Adj. Pt. Est. for δ	-2.287					
Adj. 90% CI for δ						
Upper Confidence Bound	-0.959					
Lower Confidence Bound	-3.607					
Post-Hoc Power						

4.2.4 Trial Design Using a t-Test (Single Look)

The sample size obtained to correctly power the trial in Section (4.2.1) relied on using a Wald-type statistic for the hypothesis test, given by equation (4.3). However, we neglected the fact that the variance σ is estimated by assuming that the test statistic follows a standard normal distribution. For large sample sizes, asymptotic theory supports this approximation. In a single-look design, this test statistic is calculated as

$$Z = n^{1/2} \hat{\delta} / \hat{\sigma}, \tag{4.4}$$

where $\hat{\sigma}^2$ is the sample variance based on n observed paired differences. In the following calculations we take into consideration that Z follows a Student's t-distribution with (n-1) degrees of freedom.

Consider the example in Section 4.2.1 where we would like to test the null hypothesis that the analgesic does not reduce pain, H_0 : $\delta = 0$, against the alternative hypothesis that the new analgesic works to reduce pain, H_1 : $\delta < 0$. We will design this same trial using the t distribution for the test statistic.

Right-click Des 1 from the **Library**, and select **Edit Design**. Change the **Test Stat.** from **Z** to t. The entries for the other fields need not be changed, and click **Compute**. East will add an additional row to the **Output Preview** labeled as Des 3. Select the rows corresponding to



	Des 1	Des 3
Mnemonic	MN-1S-PDI	MN-1S-PDI
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	1	1
Test Type	1–Sided	1–Sided
Specified α	0.05	0.05
Power	0.902	0.9
Model Parameters		
Test Statistic	Z	t
Input Method	Individual Means	Individual Means
Mean Control (µc)	6	6
Mean Treatment (µt)	4	4
Diff. of Means (µt - µc)	-2	-2
Std. Deviation (σD)	5	5
Sample Size		
Maximum	54	55

Des 1 and Des 3. This will display Des 1 and Des 3 in the **Output Summary**.

Using the t distribution, we need one extra subject to compensate for the extra variability due to estimation of the var $[\hat{\delta}]$.

4.3 Ratio of Paired Means

The test for ratio of paired difference is used to compare the means of two log normal distributions when each observation in the random sample from one distribution is matched with a unique observation from the other distribution. Let μ_c and μ_t denote the two means to be compared and let σ_c^2 adn σ_t^2 are the respective variances.

The null hypothesis $H_0: \mu_c/\mu_t = 1$ is tested against the two-sided alternative hypothesis $H_1: \mu_c/\mu_t \neq 1$ or a one-sided alternative hypothesis $H_1: \mu_c/\mu_t < 1$ or $H_1: \mu_c/\mu_t > 1$. Let $\rho = \mu_t/\mu_c$. Then the null hypothesis can be expressed as $H_0: \rho = 1$ and the alternative can be expressed as $H_1: \rho \neq 1$, $H_1: \rho > 1$, or $H_1: \rho < 1$. The power of the test is computed at specified values of μ_c, μ_t , and σ . We assume that $\sigma_t/\mu_t = \sigma_c/\mu_c$ i.e., the coefficient of variation (CV) is the same under both control and treatment.

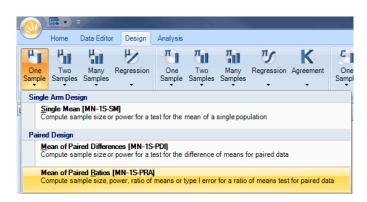
4.3.1 Trial Design

Start East afresh. Click Continuous: One Sample on the Design tab, and then click Paired

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Design: Mean of Paired Ratios as shown below.



This will launch a new window. The upper pane of this window displays several fields with default values. Select **Test Type** as **1–Sided**, and **Individual Means** for **Input Method**. Specify the **Mean Control** (μ_c) as 4 and **Mean Treatment** (μ_t) as 3.5. Enter **Std. Dev. of Log ratio** as 0.5. The upper pane should appear as below:

De	esign: Continuo	us Endp	oint: One-Sample Test - Paired Design - Mean of Paire	d Ratios	💀 85. 85. 🚱
Design Type: Superiorit Design Parameters	y 🔻				
Test Type: Type I Error (α): Power: Sample Size (n):	1-Sided 0.05 0.9 Computed	• 0 0	Input Method: Individual Means \checkmark Specify Mean Responses Mean Control (μ_c): 4 Mean Treatment (μ_t): 3,5	Test Statistic: Z Std. Dev. of Log ratio:	0.5
					Compute

Click **Compute**. This will calculate the sample size for this design and the output is shown as a row in the **Output Preview**. The computed sample size is 121 subjects (or pairs of observations).

This design has default name Des 1. In the **Output Preview** toolbar select Des 1, click is save this design to Wbk1 in the **Library**.



4.3.2 Trial Design Using a t-test

Right-click Des 1 in the **Library** and select **Edit Design**. In the input window, change the **Test Stat.** from z to t.

Click **Compute**. East will add an additional row to the **Output Preview** labeled as Des 2.

Select the rows corresponding to Des 1 and Des 2 using the Ctrl key and click . This will display Des 1 and Des 2 in the **Output Summary**.

	Des 1	Des2		
Mnemonic	MN-1S-PRA	MN-1S-PRA		
Test Parameters				
Design Type	Superiority	Superiority		
Test Type	1–Sided	1-Sided		
Specified α	0.05	0.05		
Power	0.902	0.901		
Model Parameters				
Mean Control (µc)	4	4		
Mean Treatment (µt)	3.5	3.5		
Std.Dev. of Log Ratio	0.5	0.5		
Input Method	Individual Means	Individual Means		
Test Statistic	Z	t		
Sample Size				
Maximum	121	122		

Des 2 uses the t distribution and requires that we commit a combined total of 122 patients to the study, one more compared to Des 1, which uses a normal distribution.

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5 *Normal Noninferiority Paired-Sample*

Two common applications of the paired sample design include: (1) comparison of two treatments where patients are matched on demographic and baseline characteristics, and (2) two observations made from the same patient under different experimental conditions. The type of endpoint for paired noninferiority design could be difference of means or ratio of means. The former is presented in Section 5.1 and the latter is discussed in Section 5.2. For paired sample noninferiority trials, East can be used only when no interim look is planned.

5.1 Mean of Paired Differences

5.1.1 Trial Design **5.1.2** Trial Design Using a t-Test (Single Look) **5.1.3** Simulation

Consider a randomized clinical trial comparing an experimental treatment, T, to a control treatment, C, on the basis of outcome variable, X, with means μ_t and μ_c , respectively, and with a standard deviation of paired difference as σ_D^2 . Here, the null hypothesis H_0 : $\mu_t - \mu_c \leq \delta_0$ is tested against the one-sided alternative hypothesis H_1 : $\mu_t - \mu_c > \delta_0$. Here δ_0 denotes the noninferiority margin and $\delta_0 < 0$. Let $\delta = \mu_t - \mu_c$. Then the null hypothesis can be expressed as H_0 : $\delta \leq \delta_0$ and the alternative can be expressed as H_1 : $\delta > \delta_0$.

Here we assume that the each paired observation on X from T and C are distributed according to a bivariate normal distribution with means as (μ_t, μ_c) , variances as (σ_t^2, σ_c^2) and correlation coefficient as ρ . Let us have N such paired observations from T and C and $\hat{\mu}_c$ and $\hat{\mu}_t$ denote the estimates of μ_c and μ_t based on these N pairs. Therefore, the estimate of the difference is $\hat{\delta} = \hat{\mu}_t - \hat{\mu}_c$. Denoting the standard error of $\hat{\delta}$ by $se(\hat{\delta})$, the test statistic can be defined as

$$Z = \frac{\delta - \delta_0}{se(\hat{\delta})} \tag{5.1}$$

Chapter 5: Normal Noninferiority Paired-Sample

The test statistic Z is distributed as a t distribution with (N-1) degrees of freedom. For large samples, the t-distribution can be approximated by the standard normal distribution. The power of the test is computed at specified values of μ_c , μ_t , and σ_D . East allows you to analyze using both normal and t distribution.

The advantage of the paired sample noninferiority design compared to the two independent sample noninferiority design lies in the smaller $se(\hat{\delta})$ in former case. The paired sample design is more powerful than the two independent sample design: to achieve the same level of power, the paired sample design requires fewer subjects.

5.1.1 Trial Design

Iezzi et. al. (2011) investigated the possibility of reducing radiation dose exposure while maintaining the image quality in a prospective, single center, intra-individual study. In this study, patients underwent two consecutive multidetector computed tomography angiography (MDCTA) scans 6 months apart, one with a standard acquisition protocol (C) and another using a low dose protocol (T). Image quality was rated as an ordinal number using a rating scale ranging from 1 to 5. Let μ_c and μ_t denote the average rating of image quality for standard acquisition and low dose protocol, respectively, and $\delta = \mu_t - \mu_c$ be the difference between two means. Based on the 30 samples included in the study, μ_c and μ_t were estimated as 3.67 and 3.12, respectively. The noninferiority margin for image quality considered was -1. Accordingly, we will design the study to test

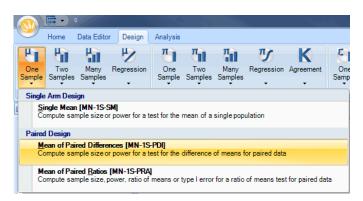
 $H_0: \delta \leq -1$ against $H_1: \delta > -1$

The standard deviation of paired difference was estimated as 0.683. We want to design a study with 90% power at $\mu_c = 3.67$ and $\mu_t = 3.12$ and that maintains overall one-sided type I error of 0.025.

First, click Continuous: One Sample on the Design tab and then click Paired Design: Mean

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of Paired Differences as shown below.



This will launch a new window. Select **Noninferiority** for **Design Type**, and **Individual Means** for **Input Method**. Specify the **Mean Control** (μ_c) as 3.67, **Mean Treatment** (μ_t) as 3.12, and the **Std. Dev. of Paired Difference** (σ_D) as 0.683. Finally, enter -1 for the **Noninferiority Margin** (δ_0). Leave all other entries with their default values. The upper pane should appear as below:

	Design: Contin	uous Er	ndpoint: One-Sample Test - Paired Design - Mean of Paired D	ifferences 🕜 🐯 💀 📼
Design Paramete		• N	Number of Looks: 1	Test Statistic' Z
Test Type: Type I Error (α): Power: Sample Size (n):	1-Sided 0.025 0.9 Computed	0 0 ⊙	$\begin{tabular}{ c c c c c }\hline \hline & \end{tabular} tab$	Std. Dev. of Paired 0.683 Difference (σ_{D}) :
				Compute

Click **Compute**. This will calculate the sample size for this design and the output is shown as a row in the **Output Preview** located in the lower pane of this window. The computed sample

Chapter 5: Normal Noninferiority Paired-Sample

size (25 subjects) is highlighted.

•	ID	Design Type	No. of Looks	Test Type	Specified α	Power	Sample Size	Test Statistic	Input Method	μς	Mean Treatment (Alt.)	δ1	δ0	σD
5	Des 1	Noninferiority	1	1-Sided	0.025	0.909	25	Z	Individual Means	3.67	3.12	-0.55	-1	0.683

This design has default name Des 1. You can select this design by clicking anywhere along the row in the **Output Preview**. Select this design and click in the **Output Preview** toolbar. Some of the design details will be displayed in the upper pane, labeled as **Output Summary**.

Si • 📰 • 🐐 🚔		Output Summa
	Des 1	
Mnemonic	MN-1S-PDI	
Test Parameters		
Design Type	Noninferiority	
No. of Looks	1	
Test Type	1-Sided	
Specified α	0.025	
Power	0.909	
Model Parameters		
Test Statistic	Z	
Input Method	Individual Means	
Mean Control (µc)	3.67	
Mean Treatment (µt)	3.12	
Diff. of Means (µt - µc)	-0.55	
Noninferiority Margin (δ0)	-1	
Std. Deviation (σD)	0.683	
Sample Size		
Maximum	25	

A total of 25 subjects must be enrolled in order to achieve the desired 90% power under the alternative hypothesis. In the **Output Preview** select Des 1 and click in the toolbar to save this design to Wbk1 in the **Library**.

The noninferiority margin of -1 considered above is the minimal margin. Since the observed difference is only little less than -0.5 we would like to calculate sample size for a range of noninferiority margins, say, -0.6, -0.7, -0.8, -0.9 and -1. This can be done easily in East. First select Des 1 in the Library, and click on the Library toolbar. In the Input, change the

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Noninferiority Margin (δ_0 **)** -0.6 : -1 : -0.1.

Specify Null Hypothesis	
Noninferiority Margin (δ_0):	-0.6:-1:-0.1

Click **Compute** to generate sample sizes for different noninferiority margins. This will add 5 new rows to the **Output Preview**. There will be a single row for each of the noninferiority margins.

🔟 🖻 🔚 🗙 🔬 🚔 🍓						Output Preview						Profile	7 🔺	
•	ID	Design Type	No. of Looks	Test Type	Specified α	Power	Sample Size	Test Statistic	Input Method	μς	Mean Treatment (Alt.)	δ1	δ0	σD
۳	Des 1	Noninferiority	1	1-Sided	0.025	0.909	25	z	Individual Means	3.67	3.12	-0.55	-1	0.683
۳	Des2	Noninferiority	1	1-Sided	0.025	0.9	1961	Z	Individual Means	3.67	3.12	-0.55	-0.6	0.683
6	Des 3	Noninferiority	1	1-Sided	0.025	0.9	218	Z	Individual Means	3.67	3.12	-0.55	-0.7	0.683
۳	Des4	Noninferiority	1	1-Sided	0.025	0.902	79	Z	Individual Means	3.67	3.12	-0.55	-0.8	0.683
۳	Des 5	Noninferiority	1	1-Sided	0.025	0.907	41	Z	Individual Means	3.67	3.12	-0.55	-0.9	0.683
4	Des6	Noninferiority	1	1-Sided	0.025	0.909	25	Z	Individual Means	3.67	3.12	-0.55	-1	0.683

The computed sample sizes are 1961, 218, 79, 41 and 25 with noninferiority margins -0.60, -0.7, -0.8, -0.9 and -1, respectively. To compare all 5 designs, select last 5 rows in **Output Preview**, and click **III**. The 5 designs will be displayed in the **Output Summary** pane.

	Des2	Des 3	Des4	Des 5	Des6
Mnemonic	MN-1S-PDI	MN-1S-PDI	MN-1S-PDI	MN-1S-PDI	MN-1S-PDI
Test Parameters					
Design Type	Noninferiority	Noninferiority	Noninferiority	Noninferiority	Noninferiority
No. of Looks	1	1	1	1	1
Test Type	1-Sided	1-Sided	1-Sided	1-Sided	1–Sided
Specified α	0.025	0.025	0.025	0.025	0.025
Power	0.9	0.9	0.902	0.907	0.909
Model Parameters					
Test Statistic	Z	Z	Z	Z	Z
Input Method	Individual Means				
Mean Control (µc)	3.67	3.67	3.67	3.67	3.67
Mean Treatment (µt)	3.12	3.12	3.12	3.12	3.12
Diff. of Means (µt - µc)	-0.55	-0.55	-0.55	-0.55	-0.55
Noninferiority Margin (δ0)	-0.6	-0.7	-0.8	-0.9	-1
Std. Deviation (σD)	0.683	0.683	0.683	0.683	0.683
Sample Size					
Maximum	1961	218	79	41	25

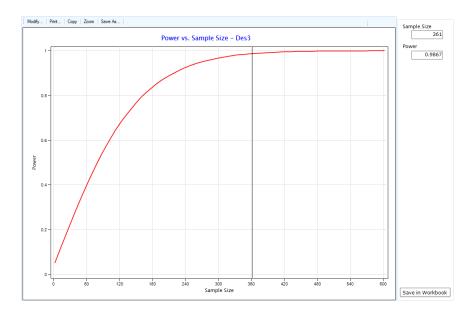
Suppose we have decided to go with Des 3 to test the noninferiority hypothesis with noninferiority margin of -0.7. This requires a total sample size of 218 to achieve 90% power. Select Des 3 in the **Output Preview** and click in the toolbar to save this design to

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Wbk1 in the Library. Before we proceed we would like to delete all designs from the **Output Preview**. Select all rows and then either click in the toolbar, or click **Delete** after right click. To delete the designs from the workbook in **Library** select the corresponding designs individually (one at a time) and then click **Delete** after right click. You can try deleting Des 1 from the Library.

Plotting

With Des 3 selected in the **Library**, click **Series** on the **Library** toolbar, and then click **Power vs Sample Size**. The resulting power curve for this design will appear.



You can move the vertical bar along the X axis. To find out power at any sample size, move the vertical bar to that sample size and the numerical value of sample size and power will be displayed on the right of the plot.You can export this chart in one of several image formats (e.g., Bitmap or JPEG) by clicking **Save As...** Close this chart before continuing. In a similar fashion one can see power vs delta plot by clicking **Save As...** and then **Power vs Treatment Effect**.

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You can obtain the tables associated with these plot by clicking \square , and then clicking the appropriate table. Close the plots before continuing.

5.1.2 Trial Design Using a t-Test (Single Look)

The sample size obtained to correctly power Des 3 relied on using a Wald-type statistic for the hypothesis test. Due to the assumption of a normal distribution for the test statistic, we have ignored the fact that the variance σ is estimated from the sample. For large sample sizes, this approximation is acceptable. However, in small samples with unknown standard deviation, the test statistic

 $Z = (\hat{\delta} - \delta_0) / se(\hat{\sigma})$

is distributed as Student's t distribution with (n - 1) degrees of freedom where n is the number of paired observations.

Select Des 3 from the **Library**, and click \ge . This will take you to the input window. Now change the **Test Statistic** from **z** to t. The entries for the other fields need not be changed.

Click **Compute**. East will add an additional row to the **Output Preview**. The required sample size is 220. This design uses the t distribution and it requires us to commit a combined total of 220 patients to the study, two more compared to Des 3 which uses the normal distribution. The extra couple of patients are needed to compensate for the extra variability due to estimation of the var $[\hat{\delta}]$.

5.1.3 Simulation

Select Des 3 in the **Library**, and click in the toolbar. Alternatively, right-click on Des 3 and select **Simulate**. A new Simulation window will appear. Click on the **Response Generation Info** tab, and specify: **Mean control** = 3.67, **Mean Treatment** = 3.12, and **Std**.

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Deviation of Paired Difference (σ_D **) =** 0.683.

Simulation Parameters	Response	Generation Info	Simulation Control Info			
Specify Mean Responses Mean Control (μ_c): Mean Treatment (μ_t):	3.67 3.12	Std. Dev. of Pair Difference (σ _D				

Leave all default values, and click **Simulate**. Once the simulation run has completed, East will add an additional row to the **Output Preview** labeled as Sim 1.

Select Sim 1 in the **Output Preview** and click *in the click Sim 1* in the **Library**, and the simulation output details will be displayed in the right pane under the **Simulation** tab.

Simulation: Continuous Endpoint: One-Sample Test - Paired Design - Mean of Paired Differences

Simulation Parameters							
Simulation ID	Sim1						
Design Type	Noninferiority						
Number of Looks	1						
Test Type	1-Sided						
Sample Size (n)	218						
Noninf. Margin (δ ₀)	-0.7						
Test Statistic	t						
Avg. Power at Termination	0.899						
Response Generation F	Parameters						
Mean Control (µ _o)	3.67						
Mean Treatment (µ _t)	3.12						
Std. Deviation (σ_D)	0.683						
Simulation Control Para	ameters						
Starting Seed	Clock						
Number of Simulations	10000						

∋Average Sample Size							
Look #	Average Sample Size (n)						
1	218						
Average	218						

⊖ Simulation Boundaries and Boundary Crossing Probabilities

		Boundaries	Changing Free	To	tal		
Look #	Sample Size (n)	Efficacy	cacy Stopping For Sir		ulations		
	(")	Upper	Efficacy	Count	%		
1	218	1.96	8986	10000	100.000%		
Total			8986	10000			
%			89.860%				

Notice that the percentage of rejections out of 10000 simulated trials is consistent with the design power of 90%. The exact result of the simulations may differ slightly, depending on the seed.

Now we wish to simulate from a point that belongs to H_0 to check whether the chosen design maintains type I error of 5%. Right-click Sim 1 in the **Library** and select **Edit Simulation**. Go to the **Response Generation Info** tab in the upper pane and specify: **Mean control** = 3.67,



Mean Treatment = 2.97, and **Std. Deviation of Paired Difference (** σ_D **) =** 0.683.

Simulation Parameters	Response	Generation Info	Simulation Control Info			
Specify Mean Responses Mean Control (μ_c): Mean Treatment (μ_t):	3.67 2.97	Std. Dev. of Pair Difference (σ _D				

Click **Simulate**. Once the simulation run has completed, East will add an additional row to the **Output Preview** labeled as Sim 2. Select Sim 2 in the **Output Preview** and click . Now double-click on Sim 2 in the **Library**. The simulation output details will be displayed.

Simulation: Continuous Endpoint: One-Sample Test - Paired Design - Mean of Paired Differences

Simulation Parameters								
Sim2								
Noninferiority								
1								
1-Sided								
218								
-0.7								
t								
0.023								
Parameters								
3.67								
2.97								
0.683								
ameters								
Fixed								
10000								

Look #	Average Sample Size (n)		
1	218	1	
Average	218]	
Simulatio	on Boundaries a	id Boundary C	rossing Probabil

	Boundaries		Stopping For	Total Simulations		
Look #	Sample Size (n)	Efficacy				
	Upper Effica			Count	%	
1	218	1.96	233	10000	100.000%	
Total			233	10000		
%			2.330%			

The upper efficacy stopping boundary was crossed close to the specified type I error of 2.5%. The exact result of the simulations may differ slightly, depending on the seed.

5.2 Ratio of Paired Means

Consider a randomized clinical trial comparing an experimental treatment, T, to a control treatment, C, on the basis of outcome variable, X, with means μ_t and μ_c , respectively, and let σ_t^2 and σ_c^2 denote the respective variances. The null hypothesis H_0 : $\mu_t/\mu_c \leq \rho_0$ is tested against the one-sided alternative hypothesis H_1 : $\mu_t/\mu_c > \rho_0$. Here, ρ_0 denotes the noninferiority margin and $\rho_0 < 1$. Let $\rho = \mu_t/\mu_c$. Then the null hypothesis can be expressed as H_0 : $\rho \leq \rho_0$ and the alternative can be expressed as H_1 : $\rho > \rho_0$.

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Let us have N such paired observations from T and C and (X_{it}, X_{ic}) denotes the *i*th pair of observations ($i = 1, \dots, N$). Then $\log X_{it} - \log X_{ic} = \log (X_{it}/X_{ic})$ denotes the logarithm of ratio of means for *i*th subject. We assume that the paired log-transformed observations on X from T and C, $(\log X_{it}, \log X_{ic})$ are bivariate normally distributed with common parameters. In other words, (X_{it}, X_{ic}) is distributed as bivariate log-normal distribution.

Denote $\log X_{it}$ by y_{it} , $\log X_{ic}$ by y_{ic} , and the corresponding difference by $\delta_{yi} = y_{it} - y_{ic}$. Assume that $\hat{\delta}_y$ denotes the sample mean for these paired differences with estimated standard error $se(\hat{\delta}_y)$. The test statistic can be defined as

$$Z = \frac{\hat{\delta}_y - \log \rho_0}{se(\hat{\delta}_y)},\tag{5.2}$$

The test statistic Z is distributed as a t distribution with (N - 1) degrees of freedom. For large samples, the t-distribution can be approximated by the standard normal distribution. East allows you to analyze using both normal and t distribution. The power of the test is computed at specified values of μ_c , μ_t , and σ .

5.2.1 Trial Design

We will use the same example cited in the previous section, but will transform the difference hypothesis into the ratio hypothesis. Let μ_c and μ_t denote the average rating of image quality for standard acquisition and low dose protocol, estimated as 3.67 and 3.12, respectively. Let $\rho = \mu_t/\mu_c$ be the ratio between two means. Considering a noninferiority margin of -0.7 for the test of difference, we can rewrite the hypothesis mentioned in previous section as

$$H_0: \rho \le 0.81$$
 against $H_1: \rho > 0.81$

We are considering a noninferirority margin of $0.81 (= \rho_0)$. For illustration we will assume the standard deviation of log ratio as 0.20. As before, we want to design a study with 90% power at $\mu_c = 3.67$ and $\mu_t = 3.12$, and maintains overall one-sided type I error of 0.025.

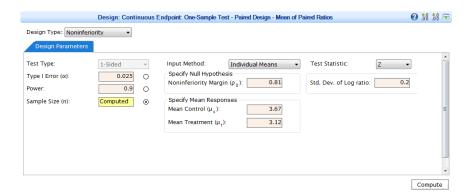
Start East afresh. Click Continuous: One Sample on the Design tab and then click Paired

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Home Data Editor Design Analysis 4 π C 4 One Many Two Many Regression Two Regression Agreen One Samples Samples Sample Samples Samples Samp Single Arm Design Single Mean [MN-1S-SM] Compute sample size or power for a test for the mean of a single population Paired Design Mean of Paired Differences [MN-1S-PDI] Compute sample size or power for a test for the difference of means for paired data Mean of Paired Ratios [MN-1S-PRA] Compute sample size, power, ratio of means or type I error for a ratio of means test for paired data

Design: Mean of Paired Ratios as shown below.

This will launch a new window. The upper pane of this window displays several fields with default values. Select **Noninferiority** for **Design Type**, and **Individual Means** for **Input Method**. Specify the **Mean Control** (μ_c) as 3.67, **Mean Treatment** (μ_t) as 3.12, and **Noninferiority margin** (ρ_0) as 0.81. Enter 0.20 for **Std. Dev. of Log Ratio**, and 0.025 for **Type I Error** (α). The upper pane now should appear as below:



Click **Compute**. This will calculate the sample size for this design and the output is shown as a row in the **Output Preview** located in the lower pane of this window. The computed sample

Chapter 5: Normal Noninferiority Paired-Sample

size (180 subjects) is highlighted in yellow.

M	9	s × 🔬 븕 🎙	•			Output Preview					Prof	
•	ID	Design Type	Test Type	Specified α	Power	Input Method	Sample Size	Test Statistic	μς	Mean Treatment (Alt.)	ρ0	Std Dev Log Ratio
۳	Des 1	Noninferiority	1-Sided	0.025	0.9	Individual Means	180	Z	3.67	3.12	0.81	0.2

This design has default name Des 1. You can select this design by clicking anywhere along the row in the **Output Preview**. Select this design and click in the **Output Preview** toolbar. Some of the design details will be displayed in the upper pane, labeled as **Output Summary**.

	Des 1
Mnemonic	MN-1S-PRA
Test Parameters	
Design Type	Noninferiority
Test Type	1–Sided
Specified α	0.025
Power	0.9
Model Parameters	
Mean Control (µc)	3.67
Mean Treatment (µt)	3.12
Noninferiority Margin (p0)	0.81
Std.Dev. of Log Ratio	0.2
Input Method	Individual Means
Test Statistic	Z
Sample Size	
Maximum	180

A total of 180 subjects must be enrolled in order to achieve the desired 90% power under the alternative hypothesis. In the **Output Preview** select Des 1 and click in the toolbar to save this design to Wbk1 in the **Library**.

Suppose you think enrolling 180 subjects is too much for your organization and you can go up to only 130 subjects. You want to evaluate the power of your study at sample size 130 but with the design parameters remain unaltered. In order to compute power with 130 subjects, first select the Des 1 in the Library, and click on the Library toolbar. In the Input dialog



box, first select the radiobutton for **Power**, and then enter 130 for **Sample Size**.

Design Type: Noninferiority -								
Design Parameters								
Test Type:	1-Sided	Ŧ						
Type I Error (α):	0.025	0						
Power:	Computed	۲						
Sample Size (n):	130	0						

Now click **Compute**. This will add another row labeled as Des 2 in **Output Preview** with computed power highlighted in yellow. The design attains a power of 78.7%. Now select both the rows in **Output Preview** by pressing the Ctrl key, and click in the **Output Preview** toolbar to see a summary of both designs in the **Output Summary**.

	Des 1	Des2
Mnemonic	MN-1S-PRA	MN-1S-PRA
Test Parameters		
Design Type	Noninferiority	Noninferiority
Test Type	1-Sided	1-Sided
Specified α	0.025	0.025
Power	0.9	0.787
Model Parameters		
Mean Control (µc)	3.67	3.67
Mean Treatment (µt)	3.12	3.12
Noninferiority Margin (ρ0)	0.81	0.81
Std.Dev. of Log Ratio	0.2	0.2
Input Method	Individual Means	Individual Means
Test Statistic	Z	Z
Sample Size		
Maximum	180	130

In the **Output Preview** select Des 2 and click in the toolbar to save this design to Wbk1 in the **Library**.

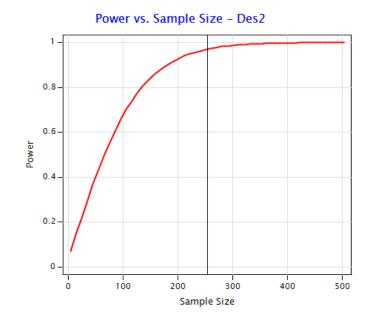
Plotting

With Des 2 selected in the **Library**, click **Series** on the **Library** toolbar, and then click **Power vs Sample Size**. The resulting power curve for this design will appear. You can move the

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Chapter 5: Normal Noninferiority Paired-Sample

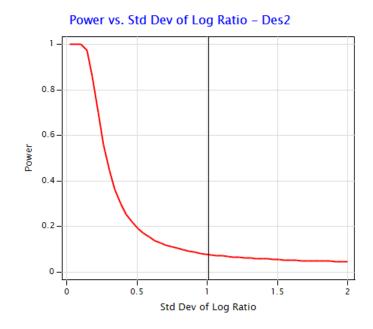
vertical bar along the X axis.



Suppose you would like to explore the relationship between power and standard deviation. In order to visualize this relationship, select Des 2 in the Library, click on the Library toolbar, and then click General (User Defined Plot). Select Std Dev of Log Ratio for



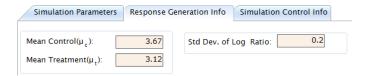
X-Axis. This will display the power vs. standard deviation plot.



Close the plot window before you continue.

5.2.2 Simulation

Select Des 2 in the **Library**, and click in the toolbar. Alternatively, right-click on Des 2 and select **Simulate**. A new Simulation window will appear. Click on the **Response Generation Info** tab, and specify: **Mean control** = 3.67, **Mean Treatment** = 3.12, and **Std Dev of Log Ratio** = 0.2.



Click **Simulate**. Once the simulation run has completed, East will add an additional row to the **Output Preview** labeled as Sim 1.

Select Sim 1 in the **Output Preview** and click . Now double-click on Sim 1 in the **Library**. The simulation output details will be displayed.

Simulation: Continuous Endpoint: One-Sample Test - Paired Design - Mean of Paired Ratios

Simulation Parameters	
Simulation ID	Sim1
Trial Type	Noninferiority
Test Type	1-Sided
Sample Size (n)	130
Test Statistic	t
Noninferiority Margin (p ₀)	0.81
Response Generation Parameter	S
Mean Response under Control (µ _c)	3.67
Mean Response under Treatment ($\mu_{t'}$	3.12
Simulation Std. Dev. of Log Ratio	0.2
Simulation Control Parameters	
Starting Seed	Clock
Number of Simulations	10000

Simulation Boundaries						
Critical Point: 1.96						
⊖Overall Simulation Results						

	Upper H0	Lower H0
No.of Rejections	7832	NA
%	78.32	NA

Starting Seed:6641254Total Number of Simulations:10000Elapsed Time:00:00:05

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6 Binomial Superiority One-Sample

This chapter deals with the design, simulation, and interim monitoring of two types of tests involving binomial response rates. In Section 6.1, we discuss group sequential designs in which an observed binomial response rate is compared to a fixed response rate, possibly derived from historical data. Section 6.2 deals with McNemar's test for comparing matched pairs of binomial responses in a group sequential setting.

6.1 Binomial One Sample

• 6.1.1 Trial Design • 6.1.2 Trial Simulation • 6.1.3 Interim Monitoring

In experimental situations, where the variable of interest has a binomial distribution, it may be of interest to determine whether the response rate π differs from a fixed value π_0 . Specifically we wish to test the null hypothesis H_0 : $\pi = \pi_0$ against the two sided alternative hypothesis H_1 : $\pi \neq \pi_0$ or against one sided alternatives of the form H_1 : $\pi > \pi_0$ or H_1 : $\pi < \pi_0$. The sample size, or power, is determined for a specified value of π which is consistent with the alternative hypothesis, denoted π_1 .

6.1.1 Trial Design

Consider the design of a single-arm oncology trial in which we wish to determine if the tumor response rate of a new cytotoxic agent is at least 15%. Thus, it is desired to test the null hypothesis H_0 : $\pi = 0.15$ against the one-sided alternative hypothesis H_1 : $\pi > 0.15$. We will design this trial with a one sided test that achieves 80% power at $\pi = \pi_1 = 0.25$ with a one-sided level 0.05 test.

Single-Look Design To begin, click Design tab, then Single Sample under Discrete group,

										East	Architect - [Log]
	Home	Data Editor	r Design	Analysis							
-	5	4	1	π	7	5	5	K			
One Sample	Two Samples	Many Samples	Regression •	One Sample	Two Samples	Many Samples	Regression •	Agreement •	Two Samples	Other	
	Co	ntinuous		Single	Arm Desi	gn					
	Single Proportion [PN-1S-SP] Compute sample size or power for a test for a single binomial proportion										
	Paired Design										
					cNemar's mpute sar			cNemar's test	for comparir	ng matche	ed pairs of binomial responses

and then click Single Proportion.

In the ensuing dialog box, choose the design parameters as shown below. We first consider a single-look design, so leave the default value for **Number of Looks** to 1. In the drop down menu, next to **Test Type** select 1–Sided. Enter 0.8 for **Power**. Enter 0.15 in the box next to **Prop. Response under Null (** π_0 **)** and 0.25 in the box next to **Prop. Response under Alt (** π_1 **)**. This dialog box also asks us to specify whether we wish to standardize the test statistic (for performing the hypothesis test of the null hypothesis H_0 : $\pi = 0.15$) with the null or the empirical variance. We will discuss the test statistic and the method of standardization in the next subsection. For the present, select the default radio button **Under Null Hypothesis**.

Design: Discrete Endpoint: One-Sample Test - Single Arm Design - Single Proportion	■ 8.0 100.
Design Type: Superiority Number of Looks: 1	Include Options
Design Parameters	
Test Type: I_Sided Specify Proportion Response Variance of Standardized - Test Statistic Type I Error (α): 0.05 O Prop. Response under Null (π_0): 0.15 O Under Null Hypothesis Power: 0.8 O Prop. Response under Alt (π_1): 0.25 O Empirical Estimate Sample Size (n): Computed O O Prop. O	
	- Compute

Now click **Compute**. The design is shown as a row in the Output Preview located in the lower pane of this window. The sample size required in order to achieve the desired 80% power is 91



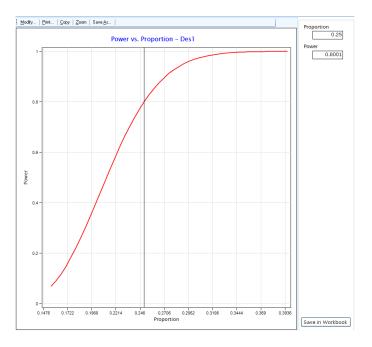
subjects.

U 9 🛃 X & 🚔 🎭								0	utput	Preview
	ID	Design Type	No. of Looks	Test Type	Specified α	Power	Sample Size	π0	π1	Variance
ⁿ 1	Des 1	Superiority	1	1–Sided	0.05	0.801			0.25	Under Null Hypothesis

You can select this design by clicking anywhere on the row in the **Output Preview**. Click icon to get the design output summary displayed in the upper pane. In the **Output Preview** toolbar, click icon to save this design Des1 to workbook Wbk1 in the **Library**. If you hover the cursor over the node Des1 in the Library, a tooltip will appear that summarizes the input parameters of the design.

Library #	💟 • 🗐 • 🍬 🚔	
Q. III Q □ - Ø S 4, □ × ■ A □	Mnemonic	Des 1 PN-1S-SP
Bring Koot	Test Parameters	
To Des1	Design Type No. of Looks	Superiority 1
Design Type = Superiority No. of Looks = 1 Test Type = 1-Sided	Test Type Specified α Power	1-Sided 0.05 0.801
Specified $\alpha = 0.05$ Power = 0.801 Sample Size = 91 Prop. Response under Null (π 0) = 0.15	Model Parameters Prop. Response under Null (π0) Prop. Response under Alt. (π1)	0.15
Prop. Response under Null (π 0) = 0.25 Prop. Response under Alt. (π 1) = 0.25 Variance of Standardized Test Statistic = Under Null Hypothe	Variance of Standardized Test Statistic is Sample Size Maximum	Under Null Hypothesis 91

With the design Des1 selected in the Library, click \square icon on the Library toolbar, and then click **Power vs. Treatment Effect (** δ **)**. The power curve for this design will be displayed. You can save this chart to the Library by clicking **Save in Workbook**. Alternatively, you can export the chart in one of several image formats (e.g., Bitmap or JPEG) by clicking **Save As...** For now,



you may close the chart before continuing.

Three-Look Design In order to reach an early decision and enter into comparative trials, let us plan to conduct this single-arm study as a group sequential trial with a maximum of 3 looks.

Create a new design by selecting Des1 in the **Library**, and clicking the icon on the **Library** toolbar. Change the **Number of Looks** from 1 to 3, to generate a study with two interim looks and a final analysis. A new tab **Boundary Info** will appear. Clicking on this tab will reveal the stopping boundary parameters. By default, the **Spacing of Looks** is set to **Equal**, which means that the interim analyses will be equally spaced in terms of the number of patients accrued between looks. The left side contains details for the **Efficacy** boundary, and the right side for the **Futility** boundary. By default, there is an efficacy boundary (to reject H0) selected, but no futility boundary (to reject H1). The **Boundary Family** specified is of the Spending Functions type. The default **Spending function** is the Lan-DeMets (Lan & DeMets, 1983), with **Parameter** OF (O'Brien-Fleming), which generates boundaries that are very similar,

though not identical, to the classical stopping boundaries of O'Brien and Fleming (1979). Technical details of these stopping boundaries are available in Appendix **??**.

Desigr	n Type: Sup	eriority	 Numbe 	r of Looks: 3 💌
Desigr	n Parameters	Boundar	/ Info	
Efficacy				Futility
Bounda	ary Family:	Spending	Functions -	Boundary Family: None -
Spendir	ng Function:	Lan-DeM	ets 👻	
Parameter: OF 🗸			•	
Type I I	Error (α):	0.05		
Spacing of Looks ⓒ Equal O Unequal			O Unequal	Efficacy Boundary: Z Scale 🔹 🔟 🔀
Look #	Info.	Cum. α	Efficacy	
LOOK #	Fraction	Spent	Boundary	
1	0.333	0.001	3.200	
2	0.667	0.016	2.141	
3	1.000	0.050	1.695	

Return to the design parameters by clicking **Design Parameters** tab. The dialog box requires us to make a selection in the section labeled **Variance of Standardized Test Statistic**. We are being asked to specify to East how we intend to standardize the test statistic when we actually perform the hypothesis tests at the various monitoring time points. There are two options: **Under Null Hypothesis** and **Empirical Estimate**. To understand the difference between these two options, let $\hat{\pi}_j$ denote the estimate of π based on n_j observations, up to and including the j th monitoring time point.

Under Null Hypothesis The test statistic to be used for the interim monitoring is

$$Z_j^{(N)} = \frac{\hat{\pi}_j - \pi_0}{\sqrt{\pi_0 (1 - \pi_0)/n_j}} .$$
(6.1)

Empirical The test statistic to be used for the interim monitoring is

$$Z_j^{(E)} = \frac{\hat{\pi}_j - \pi_0}{\sqrt{\hat{\pi}_j (1 - \hat{\pi}_j)/n_j}} .$$
(6.2)

The choice of variance should not make much of a difference to the type 1 error or power for

studies in which the sample size is large. In the present case however, it might matter. We shall therefore examine both the options. First, we select the **Under Null Hypothesis** radio button.

Click **Compute** button to generate output for Design Des2. With Des2 selected in the **Output Preview**, click icon to save Des2 to the **Library**. In order to see the stopping

probabilities, as well as other characteristics, select Des2 in the **Library**, and click icon. The cumulative boundary stopping probabilities are shown in the **Stopping Boundaries** table. We see that for Des2 the maximum sample size is 91 subjects, with 90 expected under the null hypothesis H_0 : $\pi = 0.15$ and 73 expected when the true value is $\pi = 0.25$.

Test Parameters						
Design ID:	Des2					
Design Type:	Superiority					
Number of Looks:	3					
Test Type:	1-Sided					
Specified a:	0.05					
Power:	0.801					
Model Parameters						
Prop. Response under Null	(π ₀): 0.15					
Prop. Response under Alt. (π ₁): 0.25					
Variance of Std. Test Stat.:	Under Null Hypothesis					
Boundary Parameters						
Spacing of Looks:	Equal					
Efficacy Boundary:	LD (OF)					

		-		· · · ·			
L		Info.	Sizo (n) a	Boundaries	Incr. Boundary Crossing Prob.		
	Look	Fraction (n/n_max)		α	Doundaries	Under H0	Under H1
	#				Efficacy Z	Efficacy	Efficacy
	1	0.33	30	6.412E-4	3.22	6.412E-4	0.082
[2	0.67	61	0.017	2.133	0.016	0.439
	3	1	91	0.05	1.696	0.033	0.28

Sample	Size	Information:

Stopping Boundaries: Look by Look

	Maximum	Expected H1	Expected H0
Sample Size (n)	91	72.823	90.48
Information	485.333	388.388	482.56

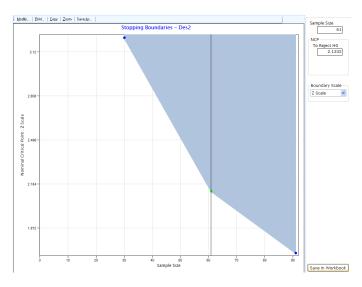
Close the Output window before continuing. The stopping boundary can be displayed by clicking on the **Series** icon on the **Library** toolbar, and then clicking **Stopping Boundaries**.

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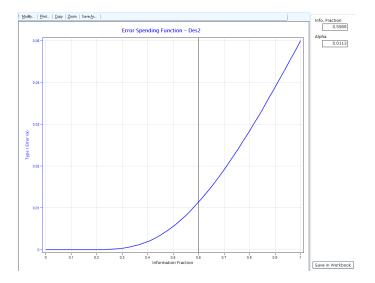
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The following chart will appear.



To examine the error spending function, click **Ser** icon on the **Library** toolbar, and then click



Error Spending. The following chart will appear.

To examine the impact of using the empirical variance to standardized test statistic, select Des2 in the Library, and click icon on the Library toolbar. In the Variance of Standardized Test Statistic box, now select Empirical Estimate.

Design Type: Superiority	Number of Looks: 3 -	
Test Type: 1-Sided Type I Error (α): 0.05 Power: 0.8 Ο Sample Size (n): Computed Ο	Specify Proportion Response Prop. Response under Null (π_0): 0.15 Prop. Response under Alt (π_1): 0.25	Variance of Standardized Test Statistic O Under Null Hypothesis O Empirical Estimate

Next, click **Compute**. With Des3 selected in the **Output Preview**, click icon. In the **Library**, select the nodes Des2 and Des3, by holding the Ctrl key, and then click icon.

	Wbk1:Des2	Wbk1:Des3
Mnemonic	PN-1S-SP	PN-1S-SP
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	3	3
Test Type	1–Sided	1–Sided
Specified α	0.05	0.05
Power	0.801	0.802
Model Parameters		
Prop. Response under Null (π0)	0.15	0.15
Prop. Response under Alt. (π1)	0.25	0.25
Variance of Standardized Test Statistic	Under Null Hypothesis	Empirical Estimate
Boundary Parameters		
Spacing of Looks	Equal	Equal
Efficacy Boundary	LD (OF)	LD (OF)
Sample Size		
Maximum	91	119
Expected Under H0	90.48	118.326
Expected Under H1	72.823	98.803

The upper pane will display the summary details of the two designs side-by-side:

The maximum sample size needed for 80% power is 119, and the expected sample size is 99 under the alternative hypothesis H_1 with $\pi_1 = 0.25$, if we intend to standardize the test statistic with the empirical variance. The corresponding maximum and expected sample sizes if the null variance is to be used for the standardization are 91 and 73, respectively. Thus, for this configuration of design parameters, it would appear preferable to specify in advance that the test statistic will be standardized by the null variance. Evidently, this is the option with the smaller maximum and expected sample size. These results, however, are based on the large sample theory developed in Appendix ??. Since the sample sizes in both Des2 and Des3 are fairly small, it would be advisable to verify that the power and type 1 error of both the plans are preserved by simulating these designs. We show how to simulate these plans in Section 6.1.2.

In some situations, the sample size is subject to external constraints. Then, the power can be computed for a specified maximum sample size. Suppose that in the above situation, using the observed estimates for the computation of the variance, the total sample size is constrained to be at most, 80 subjects. Select Des3 in the **Library** and click on the **Library** toolbar. Change the selections in the ensuing dialog box so that the trial is now

Design: Discrete Endpoint: One-Sample Test - Single Arm Design - Single Proportion Number of Looks: 3 🗸 Design Parameters Boundary Info Trial Type: Superiority Specify Proportion Response Variance of Standardized Test Statistic 0.15 Prop. Response under Null (π_0) : 1-Sided Test Type: O Under Null Hypothesis 0.25 Prop. Response under Alt $(\pi,)$: Type I Error (α): 0.05 Empirical Estimate Computed Power: \odot Sample Size (n): 80 0

designed to compute power for a maximum sample size of 80 subjects, as shown below.

Click **Compute** button to generate the output for Design Des4. With Des4 selected in the **Output Preview**, click icon. In the **Library**, select the nodes for Des2, Des3, and Des4 by holding the Ctrl key, and then click icon. The upper pane will display the summary details of the three designs side-by-side:

	Wbk1:Des2	Wbk1:Des3	Wbk1:Des4
Mnemonic	PN-1S-SP	PN-1S-SP	PN-1S-SP
Test Parameters			
Design Type	Superiority	Superiority	Superiority
No. of Looks	3	3	3
Test Type	1-Sided	1-Sided	1-Sided
Specified α	0.05	0.05	0.05
Power	0.801	0.802	0.655
Model Parameters			
Prop. Response under Null (π0)	0.15	0.15	0.15
Prop. Response under Alt. (π1)	0.25	0.25	0.25
Variance of Standardized Test Statistic	Under Null Hypothesis	Empirical Estimate	Empirical Estimate
Boundary Parameters			
Spacing of Looks	Equal	Equal	Equal
Efficacy Boundary	LD (OF)	LD (OF)	LD (OF)
Sample Size			
Maximum	91	119	80
Expected Under H0	90.48	118.326	79.548
Expected Under H1	72.823	98.803	70.711

From this, we can see that Des4 has only 65.5 % power.

6.1.2 Trial Simulation

In Section 6.1.1, we created group sequential designs with two different assumptions for the manner in which the test would be standardized at the interim monitoring stage. Under Des2, we assumed that the null variance, and hence the test statistic (6.1) would be used for the



interim monitoring. This plan required a maximum sample size of 91 subjects. Under Des3, we assumed that the empirical variance, and hence the test statistic (6.2) would be used for the interim monitoring. This plan required a maximum sample size of 119 subjects. Since the sample sizes for both plans are fairly small and the calculations involved the use of large sample theory, it would be wise to verify the operating characteristics of these two plans by simulation.

Select Des2 in the **Library**, and click the Sicon from **Library** toolbar. Alternatively, right-click on Des2 node and select **Simulate**. A new Simulation worksheet will appear.

	er of Looks: 3					
Simulation Parameters Response Ceneration Info Simulation Control Info Trial Type: Superiority Specify Proportion Response Test Type: 1-Sided Prop. Response under Null (π_0): 0.15 Sample Size (n): 91 91 0.15						Variance of Standardized Test Statistic ③ Under Null Hypothesis ③ Empirical Estimate
Look #	Info. Fraction	Cum. α Spent	Efficacy Z			
1	0.330	0.001	3.220			
2	0.670 1.000	0.017 0.050	2.133			
Resto	ore Original Desig	n				

Click **Simulate** to start the simulation. Once the simulation run has completed, East will add an additional row to the **Output Preview** labeled Sim1. Select Sim1 row in the **Output Preview**

and click *icon*. Note that some of the simulation output details will be displayed in the upper pane. Click *icon* to save it to the **Library**. Double-click on Sim1 node in the

Library. The simulation output details will be displayed.

Simulation ID:	Sim1
Design Type:	Superiority
Number of Looks:	3
Test Type:	1-Sided
Prop. Response under Null (r	r _o): 0.15
Variance:	Under Null Hypothesis
Avg. Power at Termination:	0.802
Response Generation Par	ameters
Proportion Response (π):	0.25
Simulation Control Parame	eters
Starting Seed:	Fixed
Number of Simulations:	10000

Simulation: Discrete Endpoint: One-Sample Test - Single Arm Design - Single Proportion

	Sample Size (n)	Boundaries	Early	Total	
Look #		Efficacy	Stopping For	Simul	ations
		Upper	Efficacy	Count	%
1	30	3.22	978	978	9.78
2	61	2.133	4824	4824	48.24
3	91	1.696	2217	4198	41.98
Total			8019	10000	
%			80.19		

Simulation Boundaries and Boundary Crossing Probabilities:



 Overall Simulation Results

 Starting Seed:
 68976527

 Total Number of Simulations:
 10000

 Elapsed Time:
 00:00:02

Upon running 10,000 simulations with $\pi = 0.25$ we obtain slightly over 80% power as shown above.

Next we run 10,000 simulations under H_0 by setting $\pi = 0.15$ in the choice of simulation parameters. Select Des2 in the **Library**, and click icon from **Library** toolbar. Under the **Response Generation Info** tab, change the **Proportion Response** to 0.15. Click **Simulate** to start the simulation. Once the simulation run has completed, East will add an additional row to the **Output Preview** labeled Sim2. Select Sim2 in the **Output Preview**. Click icon to save it to the **Library**. Double-click on Sim2 in the **Library**. The simulation output details will

88



be displayed.

Simulation ID:	Sim2
Design Type:	Superiority
Number of Looks:	3
Test Type:	1-Sided
Prop. Response under Null (m	r _o): 0.15
Variance:	Under Null Hypothesis
Avg. Power at Termination:	0.057
Response Generation Par	ameters
Proportion Response (π):	0.15
Simulation Control Parame	eters
Starting Seed:	Fixed
Number of Simulations:	10000

Simulation: Discrete Endpoint: One-Sample Test - Single Arm Design - Single Proportion

 Boundaries (n)
 Boundaries (Efficacy)
 Early (Stopping For Simulations)

 1
 30
 3.22
 222
 22
 0.22

Simulation Boundaries and Boundary Crossing Probabilities:

1	30	3.22	22	22	0.22
2	61	2.133	304	304	3.04
3	91	1.696	244	9674	96.74
Total			570	10000	
%			5.7		

Average Sample Size:

Look #	Average Sample Size (n)
1	30
2	61
3	91
Average	89.954

 Overall Simulation Results

 Starting Seed:
 68976527

 Total Number of Simulations:
 10000

 Elapsed Time:
 00:00:01

We observe that 6% of these simulations reject the null hypothesis thereby confirming that these boundaries do indeed preserve the type 1 error (up to Monte Carlo accuracy).

Finally we repeat the same set of simulations for Des3. Select Des3 in the Library, and click

icon from **Library** toolbar. Upon running 10,000 simulations with $\pi = 0.25$, we obtain

82% power.

Simulation Parameters		Simulati	on Boundar	ies and Bo	undary Cros	ssing Pro	babilit
Simulation ID: Design Type:	Sim3 Superiority	Look #	Sample Size	Boundaries Efficacy	Early Stopping For		tal ations
Number of Looks:	3		(n)	Upper	Efficacy	Count	%
Test Type:	1-Sided	1	40	3,185	247	247	2.4
Prop. Response under Null (m ₀)		2	79	2,147	4889	4889	48.8
Variance:	Empirical Estimate	3	119	1.694	3114	4864	48.64
Avg. Power at Termination:	0.825	Total			8250	10000	
Response Generation Parar	neters	%			82.5		
Proportion Response (π): Simulation Control Parameter	0.25	Average	Sample Siz	e:			
Starting Seed: Number of Simulations:	Fixed 10000	Look #	Average Sample S (n)				
)			
		2	2 79)			
			3 119	•			
		Average	97,493	2			

Simulation: Discrete Endpoint: One-Sample Test - Single Arm Design - Single Proportion

68976527

00:00:01

However, when we run the simulations under H_0 : $\pi = 0.15$, we obtain a type 1 error of about 3.23% instead of the specified 5% as shown below. While this ensures that the type 1 error is preserved, it also suggests that the use of the empirical variance rather than the null variance to standardize the test statistic might be problematic with small sample sizes.

Starting Seed:

Elapsed Time:

Total Number of Simulations: 10000

Simulation: Discrete Endpoint: One-Sample Test - Single Arm Design - Single Proportion

Simulation ID:	Sim4
Design Type:	Superiority
Number of Looks:	3
Test Type:	1-Sided
Prop. Response under Null (π	r _o):0.15
Variance:	Empirical Estimate
Avg. Power at Termination:	0.032
Response Generation Par	ameters
Proportion Response (π):	0.15
Simulation Control Parame	eters
Starting Seed:	Fixed
Number of Simulations:	10000

Simulati	on Boundar	ies and Bo	undary Cros	ssing Pro	babilitie
		Boundaries	Early	То	tal
Look #	Sample Size (n)	Efficacy	Stopping For	Simul	ations
	(0)	Upper	Efficacy	Count	%
1	40	3.185	0	0	0
2	79	2.147	108	108	1.08
3	119	1.694	215	9892	98.92
Total			323	10000	
%			3.23		

. .

. .

Average Sample Size:

Look #	Average Sample Size (n)
1	40
2	79
3	119
Average	118.568

Overall Simulation Results Starting Seed: 68976527 Total Number of Simulations: 10000 Elapsed Time: 00:00:01

Let us now investigate if the problem disappears with larger studies. Select Des3 in the **Library** and click on the **Library** toolbar. Change the value of **Prop. Response under Alt (** π_1 **)** from 0.25 to 0.18.

Design Type: Su	periority	▼ Numl	ber of Looks: 3 💌	
Design Parameter	rs Boundary I	nfo		
Test Type:	1-Sided		Specify Proportion Response	Variance of Standardized
Type I Error (α):	0.05		Prop. Response under Null (π_0): 0.15	Test Statistic O Under Null Hypothesis
Power:	0.8	0	Prop. Response under Alt (π_1) : 0.18	⊙ Empirical Estimate
Sample Size (n):	Computed	\odot		

Click **Compute** to generate the output for Des5. In the **Output Preview**, we see that Des5 requires a sample size of 1035 subjects. To verify whether the use of the empirical variance will indeed produce the correct type-1 error for this large trial, select Des5 in the **Output Preview** and click icon. In the **Library**, select Des5 and click icon from **Library** toolbar . First, run 10,000 trials with $\pi = 0.15$. On the **Response Generation Info** tab, change **Proportion Response** from 0.18 to 0.15. Next click **Simulate**. Observe that the type-1 error obtained by simulating Des5 is about 4.5%, an improvement over the corresponding type 1

error obtained by simulating Des3.

Simulation Parameters		Simulation	on Boundar	ies and Bo	oundary Cros	ssing Pro	ba
Simulation ID: Design Type:	Sim5 Superiority	Look #	Sample Size	Boundaries Efficacy	Early Stopping For		otal latio
Number of Looks:	3		(n)	Upper	Efficacy	Count	
Test Type:	1-Sided	1	345	3.2	6	6	
Prop. Response under Null (π	0	2	690	2.141	128	128	
Variance:	Empirical Estimate	3	1035	1.695	309	9866	9
Avg. Power at Termination:	0.044	Total			443	10000	
Response Generation Par	ameters	%			4.43		
Proportion Response (π): Simulation Control Parame	0.15 eters	Average	Sample Siz				
Starting Seed: Number of Simulations:	Clock 10000	Look #	Average sample S (n)				
		1	1 345	5			
		2	2 690)			
		1	3 1035	5			
		Average	1030.17	7			
		Overall	Simulation F	Results			
		Starting S		198915			
		Total Num	ber of Simulat	tions: 10000			

Simulation: Discrete Endpoint: One-Sample Test - Single Arm Design - Single Proportion

Next, verify that a sample size of 1035 suffices for producing 80% power by running 10,000



simulations with $\pi = 0.18$.

Simulation ID:	Sim6
Design Type:	Superiority
Number of Looks:	3
Test Type:	1-Sided
Prop. Response under Null (r	r _o):0.15
Variance:	Empirical Estimate
Avg. Power at Termination:	0.814
Response Generation Par	ameters
Proportion Response (π):	0.18
Simulation Control Parame	eters
Starting Seed:	Clock
Number of Simulations:	10000

Simulation: Discrete Endpoint: One-Sample Test - Single Arm Design - Single Proportion

	Sample Size	Boundaries	Early	To	tal
Look #	(n)	Efficacy	Stopping For	Simul	ations
	(0)	Upper	Efficacy	Count	%
1	345	3.2	242	242	2.42
2	690	2.141	4601	4601	46.01
3	1035	1.695	3300	5157	51.57
Total			8143	10000	
%			81.43		

Simulation Boundaries and Boundary Crossing Probabilities:

Average Sample Size:

Look #	Average Sample Size (n)
1	345
2	690
3	1035
Average	859.568

 Overall Simulation Results

 Starting Seed:
 2072502

 Total Number of Simulations:
 10000

 Elapsed Time:
 00:00:02

This example has demonstrated the importance of simulating a design to verify that it does indeed possess the operating characteristics that are claimed for it. Since these operating characteristics were derived by large-sample theory, they might not hold for small sample sizes, in which case, the sample size or type-1 error might have to be adjusted appropriately.

6.1.3 Interim Monitoring

Consider interim monitoring of Des3, the design that has 80% power when the empirical estimate of variance is used to standardize the test statistic. Select Des3 in the **Library**, and click icon from the Library toolbar. Alternatively, right-click on Des3 and select **Create IM Dashboard**. The interim monitoring dashboard contains various controls for monitoring the trial, and is divided into two sections. The top section contains several columns for displaying output values based on the interim inputs. The bottom section contains four charts, each with a corresponding table to its right. These charts provide graphical and numerical

descriptions of the progress of the clinical trial and are useful tools for decision making by a data monitoring committee.

	interim Data 🔀	CP 🚺 🛄 🕷	ð 🖳 -							Interim Monitoring: Des3							0.
ook	Information	Cumulative	Test	π	Standard	Efficacy	Repeated 9	5% CI for π	Repeat								
#		Sample Size	Statistic		Error		Upper	Lower	p-value								
1																	
23																	
<i>.</i>																	
ct	the Look #1 r	ow for which	data entry	is desired	and click t	ie "Enter In	terim Data"	button on th	e toolbar.								
	Stopping Bou	ndaries	Sai	mple						Conditional Power	2	Prop.	CP				
-				ize Effi	cacy				. In			0.15	0.05				
										1		0.16	0.089				
										0.8		0.172	0.157				
										0.6		0.185	0.246				
0			- 1									0.197	0.353				
										0.4	- 11	0.209	0.468				
										0.2		0.221	0.581				
												0.234	0.685				
										0		0.246	0.774				
		0							L	0.15 0.2	0.25	0.25	0.8				
-				1fo.						Confidence Intervals		Info.	RCI	RCI	Naive CI	Naive CI	
E	rror Spending															Lower	
E	rror Spending	Function			x												
-		Function		ction	α							Fraction	Upper	Lower	Upper	Lower	
0.05	1	Function			ox							Fraction	Upper	Lower	Upper	Lower	
0.05	4	Function			α							Fraction	Upper	Lower	Upper	Lower	
0.05	4	Function			α							Fraction	Upper	Lower	Upper	Lower	
0.05 0.04 0.03		Function			α					0		Fraction	Upper	Lower	Upper	Lower	
0.05		Function			α					0		Fraction	Upper	Lower	Upper	Lower	
0.03		Function			α					0		Fraction	Upper	Lower	Upper	Lower	
0.05 0.04 0.03		Function			α					0		Fraction	Upper	Lower	Upper	Lower	

At the first interim look, when 40 subjects have enrolled, suppose that the observed response rate is 0.35. Click **Enter Interim Data** icon to invoke the **Test Statistic Calculator**. In the box next to **Cumulative Sample Size** enter 40. Enter 0.35 in the box next to **Estimate of** π . In the

94



Test Statistic Calculator	
Editing Look #1	
Set Current Look as Last	
Cumulative Sample Size:	40
Input for Binomial end point	
Estimate of π:	0.35
Standard Error of Estimate of $\boldsymbol{\pi}:$	0.07542
Output	
π - π ₀	0.2
Test Statistic:	2.652
Recalc OK	Cancel

box next to **Standard Error of Estimate of** π enter 0.07542. Next click **Recalc**.

Observe that upon pressing the **Recalc** button, the test statistic calculator automatically computes the value of the test statistic as 2.652.

Clicking **OK** results in the following output.

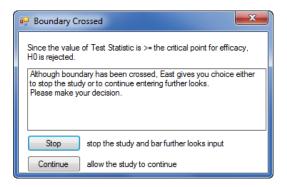
nter Ir	nterim Data 🗙	CP 📝 🛄 I	8 🔛 -							Interim Monitoring: Des3						
ook	Information		Test	π	Standard	Efficacy	Repeated 95% CI for $\boldsymbol{\pi}$		Repeated							
#		Sample Size	Statistic		Error		Upper	Lower	p-value							
1	0.336	40	2.652	0.35	0.075	3.185	1	0.11	0.095							
23																
lact	the Look #2 r	ow for which	data entry i	s desired a	and click th	a "Enter In	terim Data"	button on the	a toolbar							
	Stopping Bou		Sam	nla		ie citerin	Com Data 1	outton on the	e toondal.	Conditional Power	3	Prop.	CP			
4 -			Siz		acy						ň	0.15	0.514			
3.5			40	3.1	85					1		0.17	0.685			
3	:									1.8		0.195	0.836			
2.5										1.6		0.219 0.244	0.925			
1.5										.4		0.268	0.989			
1			_							1.2		0.293	0.997			
0.5												0.317	0.999			
۰.	50									0	1	0.342	1			
0	50	100	150							0.15 0.2 0.25 0.3 0.35		0.35	1			
Er	ror Spending	Function	🖳 Inf		x					Confidence Intervals	٩	Info.	RCI	RCI	Naive CI	Naive
0.05			Fract	ion	^					1.4		Fraction	Upper	Lower	Upper	Lowe
0.04			0.3	36 0.0	01					1.2		0.336	1	0.11	1	0.22
										1						
0.03										0.8						
0.02										0.6	11					
0.01										0.4	11					
		/								0.2	11					
										0						
٥	0	0.5								0 0.5 1	11					

Since our test statistic, 2.652, is smaller than the stopping boundary, 3.185, the trial continues.

At the second interim monitoring time point, after 80 subjects have enrolled, suppose that the estimate of $\hat{\pi}$ based on all data up to that point is 0.30. Click on the second row in the table in the upper section. Then click **Enter Interim Data** icon. In the box next to **Cumulative Sample Size** enter 80. Enter 0.30 in the box next to **Estimate of** π . In the box next to **Standard Error of Estimate of** π enter 0.05123. Next click **Recalc**. Upon clicking **OK** we observe that the



stopping boundary is crossed and the following message is displayed.



We can conclude that $\pi > 0.15$ and terminate the trial. Clicking **Stop** yields the following output.

nter li	nterim Data 🗙	CP 🚺 🛄 I	8 🔛 -							Interim Monitoring: Des3								.00
ook	Information		Test	π	Standard	Efficacy	Repeated S	95% CI for π	Repeated									
ø	Fraction	Sample Size	Statistic		Error	Efficacy	Upper	Lower	p-value									
1	0.336	40	2.652	0.35	0.075	3.185	1	0.11	0.095									
2	0.672	80	2.928	0.3	0.051	2.13	1	0.191	0.01									
	the Look #2 Stopping Bou	ow for which ndaries	data entry is	le.	and click t	he "Enter In	terim Data"	button on the	e toolbar.	Final Infere	ince							
4			Size	- EII	icacy					Final Outputs at Look #			2					
3.5			40	3.	185					Adj. p-value		0.0						
3	~	~	80	2	.13					Adj. Pt. Est. for π		0.2	299					
2.5									- H-	Adj. 90% CI for π Jpper Confidence Bound		0.						
2										ower Confidence Bound		0.3						
1.5									-	Post-Hoc Power		0.4	1.1.4					
0.5 0	50 Tror Spending	100 Function	150							Confidence Intervals	Q	Info.	RCI	RCI	Naive CI	Naive CI	Adj. Cl	
_			Fractio		α							Fraction	Upper	Lower	Upper	Lower	Upper	
0.05			0.33		001					1.4		0.336	1	0.11	1	0.226		
0.04		/	0.67		017					1.2		0.672	1	0.191	1	0.216	0.384	÷
0.03										0.8								

6.2 McNemar's Test

McNemar's Test is used in experimental situations where paired comparisons are observed. In a typical application, two binary response measurements are made on each subject – perhaps from two different treatments, or from two different time points. For example, in a

comparative clinical trial, subjects are matched on baseline demographics and disease characteristics and then randomized with one subject in the pair receiving the experimental treatment and the other subject receiving the control. Another example is the cross over clinical trial in which each subject receives both treatments. By random assignment, some subjects receive the experimental treatment followed by the control while others receive the control followed by the experimental treatment. Let π_c and π_t denote the response probabilities for the control and experimental treatments, respectively. The probability parameters for McNemar's test are displayed in Table 6.1.

	Experim	Total									
Control	No Response	Response	Probability								
No Response	π_{00}	π_{01}	$1-\pi_c$								
Response	π_{10}	π_{11}	π_c								
Total Probability	$1 - \pi_t$	π_t	1								

Table 6.1. A 2 x 2 Table of Probabilities for McNemar's Test

The null hypothesis

$$H_0: \pi_c = \pi_t$$

is tested against the alternative hypothesis

$$H_1: \pi_c \neq \pi_t$$

for the two sided testing problem or the alternative hypothesis

$$H_1$$
: $\pi_c > \pi_t$

(or H_1 : $\pi_c < \pi$) for the one-sided testing problem. Since $\pi_t = \pi_c$ if and only if $\pi_{01} = \pi_{10}$, the null hypothesis is also expressed as

$$H_0: \pi_{01} = \pi_{10}$$
,

and is tested against corresponding one and two sided alternatives. The power of this test depends on two quantities:



1. The difference between the two discordant probabilities (which is also the difference between the response rates of the two treatments)

 $\delta = \pi_{01} - \pi_{10} = \pi_t - \pi_c \; ;$

2. The sum of the two discordant probabilities

 $\xi = \pi_{10} + \pi_{01} \; .$

East accepts these two parameters as inputs at the design stage.

We next specify the test statistic to be used during the interim monitoring stage. Suppose we intend to execute McNemar's test a maximum of K times in a group sequential setting. Let the **c**umulative data up to and including the j th interim look consist of N(j) matched pairs arranged in the form of the following 2×2 contingency table of counts:

Table 6.2: 2×2 Contingency Table of Counts of Matched Pairs at Look j

	Experim	ental	Total
Control	No Response	Response	Probability
No Response	$n_{00}(j)$	$n_{01}(j)$	$r_0(j)$
Response	$n_{10}(j)$	$n_{11}(j)$	$r_1(j)$
Total Probability	$c_0(j)$	$c_1(j)$	N(j)

For a = 0, 1 and b = 0, 1 define

$$\hat{\pi}_{ab}(j) = \frac{n_{ab}(j)}{N(j)} \tag{6.3}$$

Then the sequentially computed McNemar test statistic at look j is

$$Z_j = \frac{\hat{\delta}_j}{\mathsf{se}(\hat{\delta}_j)} \tag{6.4}$$

where

$$\hat{\delta}_j = \hat{\pi}_{01}(j) - \hat{\pi}_{10}(j) \tag{6.5}$$

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and

$$\operatorname{se}(\hat{\delta}_j) = \frac{\sqrt{[n_{00}(j) + n_{11}(j)][n_{01}(j) + n_{10}(j)] + 4n_{01}(j)n_{10}(j)}}{N(j)\sqrt{N(j)}}.$$
(6.6)

Note that the standard error (6.6) is equal to

$$\operatorname{se}(\hat{\delta}_j) = \frac{\sqrt{\hat{\xi}_j - \hat{\delta}_j^2}}{\sqrt{N(j)}}.$$
(6.7)

The above statistic was defined in the non-sequential setting by Fleiss (1981, page 117). We now show how to use East to design and monitor a clinical trial based on McNemar's test.

6.2.1 Trial Design

Consider a trial in which we wish to determine whether a transdermal delivery system (TDS) can be improved with a new adhesive. Subjects are to wear the old TDS (control) and new TDS (experimental) in the same area of the body for one week each. A response is said to occur if the TDS remains on for the entire one week observation period. From historical data, it is known that control has a response rate of 85% ($\pi_c = 0.85$). It is hoped that the new adhesive will increase this to 95% ($\pi_t = 0.95$). Furthermore, of the 15% of the subjects who did not respond on the control, it is hoped that 87% will respond on the experimental system. That is, $\pi_{01} = 0.87 \times 0.15 = 0.13$. Based on these data, we can fill in all the entries of Table 6.1 as displayed in Table 6.2.

	Experim	ental	Total						
Control	No Response	Response	Probability						
No Response	0.02	0.13	0.15						
Response	0.03	0.82	0.85						
Total Probability	0.05	0.95	1						

Table 6.3: McNemar Probabilities for the TDS Trial

Although it is expected that the new adhesive will increase the adherence rate, the comparison is posed as a two-sided testing problem, testing H_0 : $\pi_c = \pi_t$ against H_1 : $\pi_c \neq \pi_t$ at the 0.05



level. We wish to determine the sample size to have 90% power for the values displayed in Table 6.3. To design this trial, click **Design** tab, then **Single Sample** on the **Discrete** group, and then click **McNemar's Test for Matched Pairs**.



Single-Look Design First, consider a study with no interim analyses, and 90% power for two sided test at $\alpha = 0.05$. Choose the design parameters as shown below. We first consider a single-look design, so leave the default value for **Number of Looks** to 1. Enter 0.9 for **Power**. As shown in Table 6.2, we must specify $\delta_1 = \pi_t - \pi_c = 0.1$ and $\xi = \pi_{01} + \pi_{10} = 0.16$.

		Design: Disc	rete Endpoint: On	e-Sample Test - Pa	aired Design - McNernar's
Design Type: Superiority	Number of Looks: 1	•			
Design Parameters					
Test Type: 2-Sided		Probabilities (δ_1) : $(\delta_1 = \pi_t - \pi_c)$	0.1		
Type I Error (α): 0.05 Power: 0.9	O Prop. of Disc	ordant Pairs (ξ): (ξ = $\pi_{01} + \pi_{10}$)	0.16		
Sample Size (n): Computed	 Probability A 	llocation: Row = C	ontrol, Column =	Treatment	
		No Response	Response	Total	
	No Response	ε π ₀₀	π ₀₁	1-π _c	-
	Response	π ₁₀	π ₁₁	π	
	Total	1 - π _t	π	1]

Click **Compute**. The design Des1 is shown as a row in the Output Preview located in the lower

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pane of this window. A total of 158 subjects is required to have 90% power.

	9	b 🗙 🖉 븕							
	ID	Design Type	No. of Looks	Test Type	Specified α	Power	Sample Size	δ1	ξ
n I	Des 1	Superiority	1	2-Sided	0.05	0.901	158	0.1	0.16

You can select this design by clicking anywhere on the row in the **Output Preview**. Click on icon to get the output summary displayed in the upper pane. In the **Output Preview** toolbar, click the sicon to save this design Des1 to workbook Wbk1 in the **Library**. If you hover the cursor over Des1 in the Library, a tooltip will appear that summarizes the input parameters of the design.

Library 7	💟 = 🗊 = 🍬 🚔 🎂	
🔍 📗 🖳 - 📰 - 🦻 (S 🍓 💾 🗙		Wbk1:Des1
🦲 🍂 🗒	Mnemonic	PN-1S-McN
	Test Parameters	
🖃 🏠 Root	Design Type	Superiority
🖻 🧰 Wbk1	No. of Looks	1
Toes1	Test Type	2-Sided
Design Type = Superiority	Specified α	0.05
No. of Looks = 1	Power	0.901
Test Type = 2-Sided	Model Parameters	
Specified $\alpha = 0.05$	Difference in Probabilities (δ1)	0.1
Power = 0.901	Prop. of Discordant Pairs (ξ)	0.16
Sample Size = 158	Sample Size	
Difference in Probabilities $(\delta 1) = 0.1$	Maximum	158
Prop. of Discordant Pairs $(\xi) = 0.16$		

Five-Look Design Now consider the same design with a maximum of 5 looks, using the default Lan-DeMets (O'Brien-Fleming) spending function. Create a new design by selecting Des1 in the **Library**, and clicking icon on the **Library** toolbar. Change the **Number of Looks** from 1 to 5, to generate a study with four interim looks and a final analysis. A new tab **Boundary Info** will appear. Clicking on this tab will reveal the stopping boundary parameters. By default, the **Spacing of Looks** is set to **Equal**, which means that the interim analyses will be equally spaced in terms of the number of patients accrued between looks. The left side contains details for the **Efficacy** boundary, and the right side for the **Futility** boundary. By default, there is an efficacy boundary (to reject H0) selected, but no futility boundary (to reject



H1). The **Boundary Family** specified is of the Spending Functions type. The default **Spending function** is the Lan-DeMets (Lan & DeMets, 1983), with **Parameter** OF (O'Brien-Fleming), which generates boundaries that are very similar, though not identical, to the classical stopping boundaries of O'Brien and Fleming (1979). Technical details of these stopping boundaries are available in Appendix **??**.

Desigr	n Type: Su	periority	▼ Nun	nber of Lo	ooks:	5 🔻		
Desigr	n Parameter	s Boundary	/ Info					
Spendir Parame	ary Family: ng Function		Functions	•	Futilit Bour	ty ndary Family:	None	T
	of Looks	⊙ Equal	O Unequ	al	Effic	acy Boundary:	Z Scale •	
Look #	Info. Fraction	Cum. α Spent	Efficacy Upper	Boundary Lowe				
1	0.200	0.000	4.877	-4.87	7			
2	0.400	0.001	3.357	-3.35	7			
3	0.600	0.008	2.680	-2.68	0			
4	0.800	0.024	2.290	-2.29	0			
5	1.000	0.050	2.031	-2.03	1			

Click **Compute** to generate output for Des2. With Des2 selected in the **Output Preview**, click the icon to save Des2 to the **Library**. In the **Library**, select the nodes for both Des1 and Des2, by holding the Ctrl key, and then click the icon. The upper pane will display the

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	Wbk1:Des1	Wbk1:Des2
Mnemonic	PN-1S-McN	PN-1S-McN
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	1	5
Test Type	2-Sided	2-Sided
Specified α	0.05	0.05
Power	0.901	0.901
Model Parameters		
Difference in Probabilities (δ1)	0.1	0.1
Prop. of Discordant Pairs (ξ)	0.16	0.16
Boundary Parameters		
Spacing of Looks		Equal
Efficacy Boundary		LD (OF)
Sample Size		
Maximum	158	162
Expected Under H0		160.935
Expected Under H1		119.965

output summary of the two designs side-by-side:

There has been a slight inflation in the maximum sample size, from 158 to 162. However, the expected sample size is 120 subjects if the alternative hypothesis of $\delta_1 = 0.10$ and $\xi = 0.16$ holds. The stopping boundary, spending function, and Power vs. Sample Size charts can all be displayed by clicking on the appropriate icons from the **Library** toolbar.

6.2.2 Interim Monitoring

Consider interim monitoring of Des2. Select Des2 in the **Library**, and click **III** icon from the Library toolbar. Alternatively, right-click on Des2 and select **Create IM Dashboard**. A new IM



worksheet will appear.

nter l	nterim Data 🗙	CP 🚺 🔢 🕯	8 🔛 -						Interi	m Monitoring	Des2					
ook	Information	Cumulative	Test	δ	Standard	Effi	cacy	Repeated 9	95% CI for δ	Repeat						
#	Fraction	Sample Size	Statistic	•	Error	Upper	Lower	Upper	Lower	p-value						
1																
2																
3 4																
5																
_																
	the Look #1 s	our for which	data anto: i	e docirod o	nd alials als	e "Ceter le	terim Date	hutten en t	he teelher							
		e Look #1 row for which data entry is desired and click the "Enter Interim Data" butto ping Boundaries Sample Efficacy Efficacy Size Upper Lower	button on t		itional Pow		1									
S	topping Bound	laries 📔							Cond	itional Pow	er 🔍		CP			
Γ			Size	Upper	Lower				1			Size				
									0.8			0	0.05			
									0.6			0.01	0.062			
0										/		0.035	0.193			
									0.4			0.047	0.315			
									0.2			0.059	0.465			
									0	-		0.071	0.623			
	0								0	0.05	0.1	0.084	0.765			
Erro	or Spending F	unction	Info.						Confid	ence Interv	als 🔍		RCI	RCI	Naive CI	Naive
	or opending t		Fraction	α					com	chec meri		Fraction	Upper	Lower	Upper	Lowe
0.05			riaction						_			Haction	opper	Lower	opper	LOWE
0.04																
0.03																
0.05									0							
0.02																
0.02																

Suppose, that the results are to be analyzed after results are available for every 32 subjects. After the first 32 subjects were enrolled, one subject responded on the control arm and did not respond on the treatment arm; four subjects responded on the treatment arm but did not respond on the control arm; 10 subjects did not respond on either treatment; 17 subjects responded on both the arms. This information is sufficient to complete all the entries in Table 6.3 and hence to evaluate the test statistic value.

Click **Enter Interim Data** icon to invoke the **Test Statistic Calculator**. In the box next to **Cumulative Sample Size** enter 32. Enter the values in the table as shown below and click

Chapter 6: Binomial Superiority One-Sample

Recalc.

Test Statistic Calculator			×							
Editing Look #1										
Set Current Loo	□ Set Current Look as <u>L</u> ast									
Cumulative Sam	ple Size:		32							
-Input for Binomi	al end point									
Row =	= Control, Colu	mn = Treatment								
	No Response	Response	Total							
No Response	10	4	14							
Response	1	17	18							
Total	11	21	32							
- Output										
<u>T</u> est Statistic:			1.34							
<u>R</u> ecalc	<u>O</u> K	<u>C</u> ance	2							

Clicking **OK** results in the following entry in the first look row.

Enter I	nterim Data 🗙	CP 🚺 📗 🛛	ð 🖳 -						Interi	m Monitoring
Look	Information	rmation Cumulative Test action Sample Size Statistic	δ	Standard	Standard Efficacy		acy Repeated 95% CI for δ			
#	Fraction		Statistic	0	Error	Upper	Lower	Upper	Lower	p-value
1	0.198	32	1.342	0.094	0.07	4.909	-4.909	0.437	-0.249	0.902
2										
3										
4										
5										

As you can see the value of the test statistic, 1.342, is within the stopping boundaries, (4.909,-4.909). Thus, the trial continues.

The second interim analysis was performed after data were available for 64 subjects. A total of two subjects responded on the control arm and failed to respond on the treatment arm; seven subjects responded on the treatment arm and failed to respond on the control arm; 20 subjects responded on neither arm; 35 subjects responded on both the arms.

Click on the second row in the table in the upper section. Then click **Enter Interim Data** icon.



Enter the appropriate values in the table as shown below and click **Recalc**.

Test Statistic Calculator			X						
Editing Look #2									
□ Set Current Look as Last									
Cumulative Sam	ple Size:		64						
-Input for Binomi	al end point —								
Row =	Control, Colu	mn = Treatmen	ıt						
	No Response	Response	Total						
No Response	20	7	27						
Response	2	35	37						
Total	22	42	64						
Output									
Test Statistic:			1.67						
Recalc	ОК	Car	ncel						

Then click **OK**. This results in the following screen.

Enter I	nterim Data 🗙	CP 🚺 🔟 🕯	ð 🖳 -						Interi	im Monitoring	j: De
Look		Cumulative	Test		Standard	Effi	cacy	Repeated 9	5% CI for δ	Repeat	
#	Fraction	Sample Size	Statistic	δ	Error	Upper	Lower	Upper	Lower	p-value	
1	0.198	32	1.342	0.094	0.07	4.909	-4.909	0.437	-0.249	0.902	
2	0.395	64	1.667	0.078	0.047	3.38	-3.38	0.237	-0.08	0.434	
3											
4											
5											

At the third interim analysis, after 96 subjects were enrolled, a total of two subjects responded on the control arm and failed to respond on the treatment arm; 13 subjects responded on the treatment arm and failed to respond on the control arm; 32 subjects did not respond on either arm; 49 subjects responded on both the arms.

Click on the third row in the table in the upper section. Then click **Enter Interim Data** icon.

Chapter 6: *Binomial Superiority One-Sample*

Enter the appropriate values in the table as shown below and click **Recalc**.

Test Statistic Calculator			×						
-Editing Look #3									
Set Current Look	as Last								
Cumulative Sample Size: 96									
Input for Binomia	Input for Binomial end point								
Row =	Row = Control, Column = Treatment								
l i	No Response	Response	Total						
No Response	32	13	45						
Response	2	49	51						
Total	34	62	96						
Output Test Statistic:	Output								
Recalc	ОК	Can	icel						

Then click **OK**. This results in the following message box.

🖳 Boundary Ci	rossed 📃 📉
Since the value H0 is rejected.	of Test Statistic is >= the critical point for efficacy,
	dary has been crossed, East gives you choice either dy or to continue entering further looks. our decision.
Stop	stop the study and bar further looks input
Continue	allow the study to continue



				Eas	t 6 - [Interi	m Monitor	ing:Wbk1:E	Des2:Interin	Monitoring	1							- 0
🥗 Home Data Editor Design Analysi	ia -																-
	Two Many le Samples Samples	Regression Agreen	ent One Sample	•	Two Samples	Dither •											
Continuous rary 🗘	Discr Enter Interim Dat			ount	Survival G	eneral			lator	im Monitoring: Des	,						.88
		ion Cumulative	Test		Standard	Eff	icacv	Reneated	95% CI for 8								.00
Root	# Fractio			δ	Error	Upper	Lower	Upper	Lower	p-value							
B W6k1	1 0.198	32	1.342	0.094	0.07	4.909	-4.909	0.437	-0.249	0.902							
- 🛅 Des1	2 0.395		1.667	0.078	0.047	3.38	-3.38	0.237	-0.08	0.434							
Des2 IM Interim Monitoring	3 0.593	96	2.84	0.115	0.04	2.699	-2.699	0.223	0.006	0.038							
	Stopping B	oundaries	Sample	Efficace						Final Inf	erence						
	Stopping B	100 2	Size 32 64 96	Efficaci Upper 4,909 3,38 2,699	-4.909 -3.38	•			An Upper Co Lower Co	Final Infi utputs at Look # Adj. p-value Adj. Pt. Est. for 8 0 onfidence Bound onfidence Bound Post-Hoc Power	erence		3 0.005 0.114 0.193 0.035				
	Error Spendi	100 2	Size 32 64 96	Upper 4.909 3.38 2.699	-4.909 -3.38	•			An Upper Co Lower Co	atputs at Look # Adj. p-value Adj. Pt. Est. for δ dj. 95% CI for δ onfidence Bound onfidence Bound	erence	Info. Fraction	0.005 0.114 0.193 0.035 RCI	RCI		Naive CI Lower	
	6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	100 2	Size 32 64 96 10 10 10 10 10 10 10 10 10 10 10 10 10	Upper 4.909 3.38 2.699 α α	-4.909 -3.38	•			An Upper Co Lower Co Confid	utputs at Look # Adj. p-value idj. Pt. Est. for δ dj. 95% CI for δ onfidence Bound pofidence Bound Post-Hoc Power		Fraction 0.198	0.005 0.114 0.193 0.035 RCI Upper 0.437	Lower -0.249	Upper 0.231	Lower -0.043	
	Error Spendi	100 2	Size 32 64 96 10 10 10 10 10 10 10 10 10 10 10 10 10	Upper 4.909 3.38 2.699 α α 0 0.001	-4.909 -3.38	•			Confid	utputs at Look # Adj. p-value idj. Pt. Est. for δ dj. 95% CI for δ onfidence Bound pofidence Bound Post-Hoc Power		Fraction 0.198 0.395	0.005 0.114 0.193 0.035 RCI Upper 0.437 0.237	-0.249 -0.08	Upper 0.231 0.17	Lower -0.043 -0.014	Upp
	6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	100 2	Size 32 64 96 10 10 10 10 10 10 10 10 10 10 10 10 10	Upper 4.909 3.38 2.699 α α	-4.909 -3.38	•			2 Au Upper C Lower Co Confie 0.4 0.2 0 0.4 0.2	utputs at Look # Adj. p-value idj. Pt. Est. for δ dj. 95% CI for δ onfidence Bound pofidence Bound Post-Hoc Power		Fraction 0.198	0.005 0.114 0.193 0.035 RCI Upper 0.437	Lower -0.249	Upper 0.231	Lower -0.043	Adj. Uppi
Los 🅐 Intel 🔹 Culture Preview Millipaneter	Error Spendi	100 2 ng Function	Size 32 64 96 10 10 10 10 10 10 10 10 10 10 10 10 10	Upper 4.909 3.38 2.699 α α 0 0.001	-4.909 -3.38	•			2 Au Upper C Lower Co Confie 0.4 0.2 0 0.4 0.2	Adj. p-value Adj. p-value Adj. p-value Adj. p-text. for Adj. P. text. for Buildence Bound Infidence Bound Infidence Bound Post-Hoc Power Bence Intervals		Fraction 0.198 0.395 0.593	0.005 0.114 0.193 0.035 RCI Upper 0.437 0.237	Lower -0.249 -0.08 0.006	Upper 0.231 0.17	Lower -0.043 -0.014 0.036	Upp

Clicking on Stop yields the following Interim Monitoring output.

We reject the null hypothesis that $\delta = 0$, based on these data.

6.2.3 Simulation

Des2 can be simulated to examine the properties for different values of the parameters. First, we verify the results under the alternative hypothesis at which the power is to be controlled, namely $\delta_1 = 0.10$ and $\xi = 0.16$.

Select Des2 in the **Library**, and click Sicon from **Library** toolbar. Alternatively, right-click

Chapter 6: Binomial Superiority One-Sample

Numbe	er of Loo <u>k</u> s: 5	-				
Simula	tion Parameters	Response Gene	eration Info Si	imulation Contro	l Info	
<u>T</u> rial Type	: Superi	ority				
Test Type	2-Sid	od	~			
iest type	2-510	eu	•			
Sample Si	<u>z</u> e (n):	162				
			x Spent	Effic	acy Z	
Sample Si Look #	<u>z</u> e (n):		x Spent Lower	Effic	acy Z Lower	
		Cum. c			-	
	Info. Fraction	Cum. o Upper	Lower	Upper	Lower	E
Look #	Info. Fraction	Cum. c Upper 0.000	Lower	Upper 4.909	Lower -4.909	E
Look #	0.198 0.401	Cum. c Upper 0.000 0.000	Lower 0.000 0.000	Upper 4.909 3.351	Lower -4.909 -3.351	E

on Des2 and select Simulate. A new Simulation worksheet will appear.

Click **Simulate** to start the simulation. Once the simulation run has completed, East will add an additional row to the **Output Preview** labeled Sim1. Select Sim1 in the **Output Preview**. If you click icon, you will see some of the simulation output details displayed in the upper pane. Click icon to save it to the **Library**. Double-click on Sim1 in the **Library**. The simulation output details will be displayed as shown below. The results confirm that the power



is at about 90%.

Sim1						
Superiority						
5						
2-Sided						
0.904						
rameters						
1):0.1						
: 0.16						
Simulation Control Parameters						
Fixed						
10000						

Simulation: Discrete Endpoint: One-Sample Test - Paired Design - McNemar's

Look #	Sample Size		idaries cacy	Ea Stoppi		Total Simulations		
LOOK #	(n)	Upper	Lower	Upper Efficacy	Lower Efficacy	Count	%	
1	32	4.909	-4.909	0	0	0	0	
2	65	3.351	-3.351	175	0	175	1.75	
3	97	2.684	-2.684	3593	0	3593	35.93	
4	130	2.285	-2.285	3607	0	3607	36.07	
5	162	2.032	-2.032	1660	0	2625	26.25	
Total				9035	0	10000		
%				90.35	0			

Simulation Boundaries and Boundary Crossing Probabilities:

Average Sample Size:

Look #	Average Sample Size (n)
1	32
2	65
3	97
4	130
5	162
Average	125.406

Overall Simulation Results Starting Seed: 85535015 Total Number of Simulations: 10000 Elapsed Time: 00:00:01

To confirm the results under the null hypothesis, set $\delta_1 = 0$ in the **Response Generation Info** tab in the simulation worksheet and then click textbfSimulate. The results, which confirm that

Chapter 6: Binomial Superiority One-Sample

the type-1 error rate is approximately 5%, are given below.

Simulation: Discrete Endpoint: One-Sample Test - Paired Design - McNemar's

Simulation Parameters						
Simulation ID:	Sim2					
Design Type:	Superiority					
Number of Looks:	5					
Test Type:	2-Sided					
Avg. Power at Termination:	0.044					
Response Generation Par	rameters					
Difference in Probabilities (δ_1): 0					
Prop. of Discordant Pairs (ξ): 0.16						
Simulation Control Parameters						
Starting Seed:	Fixed					
Number of Simulations:	10000					

			Idaries		arly	Total Simulations		
Look #	Sample Size	Eth	Efficacy		Stopping For		ations	
	(n)	Upper	Lower	Upper Efficacy	Lower Efficacy	Count	%	
1	32	4.909	-4.909	0	0	0	0	
2	65	3.351	-3.351	1	0	1	0.01	
3	97	2.684	-2.684	19	21	40	0.4	
4	130	2.285	-2.285	80	90	170	1.7	
5	162	2.032	-2.032	117	107	9789	97.89	
Total				217	218	10000		
%				2.17	2.18			

Simulation Boundaries and Boundary Crossing Probabilities:

Average Sample Size:

Look #	Average Sample Size (n)
1	32
2	65
3	97
4	130
5	162
Average	161.186

Overall Simulation Results Starting Seed: 85773537 Total Number of Simulations: 10000 Elapsed Time: 00:00:01

While it is often difficult to specify the absolute difference of the discordant probabilities, δ_1 , it is even more difficult to specify the sum of the discordant probabilities, ξ . Simulation can be used to examine the effects of misspecification of ξ . Run the simulations again, now with



 δ_1 =0.10 and ξ =0.2. The results are given below.

Sim3
Superiority
5
2-Sided
0.809
rameters
₁):0.1
: 0.2
neters
Fixed
10000

Simulation: Discrete Endpoint: One-Sample Test - Paired Design - McNemar's

	0 1 0		Idaries	Ea		Total Simulations		
Look #	Sample Size (n)	Upper	cacy Lower	Stoppin Upper Efficacy	Lower Efficacy	Count	ations %	
1	32	4.909	-4.909	0	0	0	0	
2	65	3.351	-3.351	203	0	203	2.03	
3	97	2.684	-2.684	2428	0	2428	24.28	
4	130	2.285	-2.285	3485	0	3485	34.85	
5	162	2.032	-2.032	1978	0	3884	38.84	
Total				8094	0	10000		
%				80.94	0			

Simulation Boundaries and Boundary Crossing Probabilities:

Average Sample Size:

Look #	Average Sample Size (n)
1	32
2	65
3	97
4	130
5	162
Average	133.097

 Starting Seed:
 86003123

 Total Number of Simulations:
 10000

 Elapsed Time:
 00:00:01

Notice that this provides a power of approximately 81%. Larger values of ξ would further decrease the power. However, values of $\xi > 0.2$ with $\delta_1 = 0.1$ would be inconsistent with the initial assumption of $\pi_c = 0.85$ and $\pi_t = 0.95$. Additional simulations for various values of δ and ξ can provide information regarding the consequences of misspecification of the input parameters.

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7 Dose Escalation

This chapter deals with the design, simulation, and interim monitoring of Phase 1 oncology trials. A brief overview of the designs is given below; more technical details are available in the Appendix.

One of the primary goals of Phase I trials in oncology is to find the maximum tolerated dose (MTD). Currently, the vast majority of such trials have employed traditional dose escalation methods such as the 3+3 design. The 3+3 design starts by allocating three patients typically to the lowest dose level, and then adaptively moves up and down in subsequent cohorts until either the MTD is obtained, or the trial is stopped for excessive toxicity. In addition to the 3+3, East also provides the Continual Reassessment Method (CRM), the modified Toxicity Probability Interval (mTPI) method, and the Bayesian logistic regression model (BLRM). Compared to the 3+3, these modern methods may offer a number of advantages, which can be explored systematically via simulation and interim monitoring.

The CRM (Goodman et al., 1995; O'Quigley et al., 1990) is a Bayesian model-based method that uses all available information from all doses to guide dose assignment. One first specifies a target toxicity, a one-parameter dose response curve and corresponding prior distribution. The posterior mean, and predictions for the probability of toxicity at each dose, is updated as the trial progresses. The next recommended dose is the one whose toxicity probability is closest to the target toxicity.

The mTPI method (Ji et al., 2010) is Bayesian like the CRM, but rule-based like the 3+3. In this way, the mTPI represents a useful compromise between the other methods. An independent beta distribution is assumed for the probability of toxicity at each dose. A set of decision intervals are specified, and subsequent dosing decisions (up, down, or stay) are determined by computing the normalized posterior probability in each interval at the current dose. The normalized probability for each interval is known as the unit probability mass (UPM).

A more advanced version of the CRM is the BLRM (Neuenschwander et al., 2008), which assumes a two-parameter logistic dose response curve. In addition to a target toxicity, one specifies a set of decision intervals and associated losses for guiding dosing decisions. As data accumulate, the posterior expected loss (or *Bayes risk*), at each dose is calculated, and the next recommended dose is the one with the lowest expected loss.

7.1 3+3

7.1.1 Simulation 7.1.2 Interim Monitoring

7.1.1 Simulation

Click Discrete: One Sample on the Design tab, and then click Dose Escalation Design: 3+3.

Design	Analysis
egression	One Sample Two Samples Many Samples Regression Samples Agreement Sample One Sample Two Samples Other
	Single Arm Design
	Single Proportion [PN-1S-SP] Compute sample size or power for a test for a single binomial proportion Simon's Two Stage Design [PN-1S-SI] Compute sample size for Simon's two stage design
	Paired Design
	McNema's [PN-15-McN] Compute sample size or power for McNemar's test for comparing matched pairs of binomial responses
	Dose Escalation Design
	3-3 [PN-15-3-3] Identify maximum tolerated dose using 3+3
	Continual Reassessment Method [PN-15-CRM] Identify maximum tolerated dose using CRM
	Mgdfried Toxicity Probability Interval [PN-15-mTP] Identify maximum tolerated dose using mTPI
	Bayesian Logistic Regression Model [PN-15-BLRM] Identify maximum tolerated dose using BLRM

In the upper pane of this window is the Input dialog box, which is separated into three tabs: Simulation Parameters, Response Generation Info, and Simulation Control Info. First, you



may specify the Max. Number of Doses as 7.

In the **Simulation Parameters** tab, enter 30 as the **Max. Sample Size**. For the 3+3 design, the **Cohort Size** is fixed at 3. For the **Starting Dose**, select the **Lowest Dose**.

There are two flavors of 3+3 offered: L and H. The key difference between the 3+3 H method and 3+3 L method is: If we have observed 2 DLTs out of 6 patients at the current dose, the 3+3 H method will declare the current dose as MTD, while the 3+3 L method will recommend de-escalation.

Select 3+3 H. The **Decision Rules** table gives a compact summary of the algorithm implemented here.

Max. Number of Doses:	7			
Simulation Paramete	rs Response Generation Inf	o Simulation	Control Inf	0
Max. Sample Size:	30	Decision Rules	;	
Cohort Size:	3	○ 3+3 L	⊙ 3+3 H	
Starting Dose:	Lowest Dose 🔹	#Subjects	#DLTs	Decision
		3	0	Escalate
		3	1	Stay
		3	>=2	De-escalate
		6	0	MTD
		6	1	MTD or Escalate
		6	2	MTD
		6	>2	De-escalate

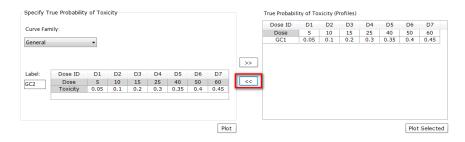
In the Response Generation Info tab, you can specify a set of true dose response curves from

which to simulate.

poon, i	rue Probabilit	of Toxi	city							True Probabi	lity of To	xicity (P	rofiles)				
	- 11									Dose ID	D1	D2	D3	D4	D5	D6	D7
Curve Fan	niiy:									Dose	5	10	15	25	40	50	60
General		-								GC1	0.05	0.1	0.2	0.3	0.35	0.4	0.45
.abel: GC2	Dose ID Dose Toxicity	D1 5	D2 10	D3 15	D4 25	D5 40	D6 50	D7 60	<<								

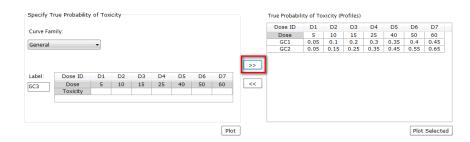
The grid on the right displays the set of dose response profiles from which East will simulate. In the row titled *Dose*, you can specify the dose levels (e.g., in mg). In the row titled *GC1*, you can edit the true probabilities of toxicity at each dose. You can also rename the profile by directly editing that cell. For now, leave all entries at their default values.

There are two ways to add profiles. The first way involves copying an existing profile on the right grid to the left grid. Select the row for GC1, and click the leftward pointing arrow to paste the GC1 profile onto the left grid.



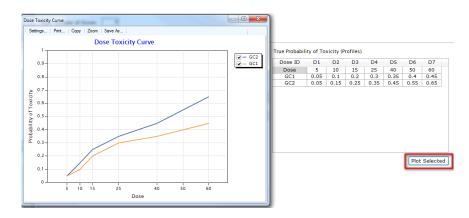
Edit the profile GC2 with the following probabilities (0.05, 0.15, 0.25, 0.35, 0.45, 0.55, 0.65), and





click the rightward pointing arrow to add this profile to the right grid.

Select both rows GC1 and GC2 in the right grid, and click **Plot Selected**. The dose toxicity curves will be plotted on the same chart.



The second way to add a new profile is to generate from a parametric curve family. For example, click on the menu **Curve Family** and select **Emax**. You may construct a

four-parameter Emax curve by adjusting its parameters as below.

Curve Fan Emax	nily:	• P	arameto E(Max 0.75	ED50	Hi 0	1
Label:	Dose ID	D1	D2	D3	D4	D5	D6	D7
EM1	Dose	5	10	15	25	40	50	60
	Toxicity	0.118	0.175	0.223	0.3	0.383	0.425	0.459

You can click **Plot** to generate the dose toxicity curve for this single profile in the left grid. For now, let us ignore the Emax curve, and continue with the two general curves.

In the **Simulation Control Info** tab, check the boxes corresponding to **Save summary statistics** and **Save subject-level data**. These options will provides access to several charts derived from these more detailed levels of simulated data. If you wish to display subject-level plots for more than one simulation, you can increase the number. For now, leave this at 1 to save computation time.

Simulation: Discrete Endpoint: One Sam	ple Test - Dose Escalation Design - 3 + 3	¥
Max. Number of Doses: 7 Simulation Parameters Response Generation Info	Simulation Control Info	
Number of Simulations: 1000 Refresh Frequency: 100 Random Number Seed O Clock O Fixed 100	Output Options Output Type: Case Data Save summary statistics for every simulation run Save subject-level data for 1 simulation runs Note: Max. 100,000 records will be saved.	
Suppress All Intermediate Output Pause after Refresh Stop At End	Simulate	

Click Simulate. East will simulate data generated from the two profiles you specified, and apply the 3+3 design to each simulation data set. Once completed, the two simulations will appear as two rows in the **Output Preview** pane below.

N	Edit	🛃 🗙 😹 🍓 😽 Output Preview						Output Preview						1	<u>.</u>
	ID 🔺	Max. Sample Size	No. of Doses	Cohort Size	Starting Dose	Curve Family	Median Sample Size	Mean Sample Size	Median No. of DLTs	Mean No. of DLTs	Median Prop. of DLTs	Mean Prop. of DLTs	Median MTD	Mean MTD	N
9	Sim1	30	7	3	Lowest Dose	General	18	17.124	3	3.177	0.185	0.192	15	21.325	
9	Sim2	30	7	3	Lowest Dose	General	15	15.402	3	3.204	0.208	0.215	15	16.795	

Select both rows in the **Output Preview** and click the 📕 icon in the toolbar. The two simulations will be displayed side by side in the **Output Summary**.

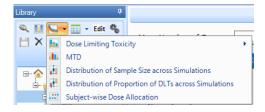
🙀 = 🛅 = 🍫 🚔		Output Summary
	Sim1	Sim2
Mnemonic	PN-15-3+3	PN-15-3+3
Design		
Max. Sample Size	30	30
Cohort Size	3	3
Starting Dose	Lowest Dose	Lowest Dose
Response Generation		
Curve Family	General	General
Summary Statistics		
Median Sample Size	18	15
Mean Sample Size	17.124	15.402
Median No. of DLTs	3	3
Mean No. of DLTs	3.177	3.204
Median Prop. of DLTs	0.185	0.208
Mean Prop. of DLTs	0.192	0.215
MTD Analysis		
Median MTD	15	15
Mean MTD	21.325	16.795
Mode of MTD	15	15
Mode (%)	31.6	34.8
% of Overdosing	0.8	0.9
% of Underdosing	1.3	0
Other Parameters		
No. of Doses	7	7

In the **Output Preview** toolbar, click the 📩 icon to save both simulations to the **Library**.

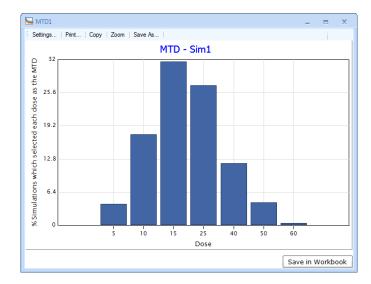
4 🚔 🛗 🌯 🔽 - 🗐 -🔍 📗 💟 + 📰 + Edit 🍓 💾 🗙 📒 🔬 🛗 Simulation: Discrete Endpoint: One Sample - East Dose Escalation - 3 + 3 🖃 🏫 Root Summary Statistics Design 🔓 🥌 Wbk1 Simulation ID Sim1 Mean SD Median Maximum Sample Size 30 SummaryStat 17.124 5.392 18 Cohort Size 3 Sample Size 1 212 Starting Dose Lowest - TI Sim2 Proportion of DLT 0.192 Dose 0.066 0.185 --- El SummaryStat Number of Doses 7 Decision Rules Target Analysis Decision Subjects Toxicity Mean SD Median Escalate 0 Estimated MTD 21.325 11.745 15 Stay Allocation 0 6 >=2 De-escalate 1.291 0.806 0 MTD Proportion of DLT 0.215 0 134 0.333 Escalate 6 1 MTD De-escalate 97 % of Simulations Declaring MTD Simulation Control Information % Simulations Declaring MTD Below Lowest Dose 0.8 Clock Starting Seed % of Simulations Declaring MTD Above Highest Dose 1.3 Number of Simulations 1000 % of Simulations unable to Declare MTD due to Inadequate Sample Size 0.9 Dose-wise Summary True Toxicity Average DLT Allocation Average Allocation ID Doses Frequency D1 0.05 1000 3 4 3 8 D2 10 975 4.04 0.1 D3 15 902 4.68 0.953 D4 25 634 4.954 1.434

Double-click Sim1 in the Library to display the simulation output details.

With Sim1 selected in the Library, click the Plots icon to access a wide range of available plots.







Below is an example of the MTD plot:

Close each plot after viewing, or save them by clicking **Save in Workbook**. To save your simulations and charts to disk, right-click Wbk1 in the **Library** and then **Save As...**.



Once you have saved the workbook, you may like to clean up your library by selecting Wbk1 in the **Library** and clicking the Delete icon. The same action can be performed for Sim1 and Sim2

in the Output Preview.

7.1.2 Interim Monitoring

Right-click one of the Simulation nodes with 3+3 in the Library, and select **Interim Monitoring**. This will open an empty interim monitoring dashboard.

Enter Interi	m Data 🗙 🕴	🖳 Final Infere	ence	
Cohort	Dose	and the second		Recommended
#	Assigned	#Subjects	#DLTs	Dose
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
	Cohort # 1 r			is desired and click cations #DLTs
	Ó			

Click Enter Interim Data to open a window in which to enter data for the first cohort: in



particular, the **Dose Assigned** and the **DLTs Observed**. Click **OK** to continue.

Enter Interim Data
Editing Cohort #1
Dose Assigned: 5
#Subjects Allocated: 3
#DLTs Observed: 0
OK Cancel

The dashboard will be updated accordingly, and the next **Recommended Dose** is 10.

Enter Interi	Enter Interim Data 🔀 🖳 👻 Final Inference								
Cohort #	Dose Assigned	#Subjects	#DLTs	Recommended Dose					
1	5	3	0	10					
2									
3									
4									
5									
6									
7									
8									
9									
10									

Click Enter Interim Data again, with 10 selected as Dose Assigned, enter 2 for DLTs

.

Observed, and click **OK**.

Enter Interim Data						
Editing Cohort #2]					
Dose Assigned:	10 •					
#Subjects Allocated:	3					
#DLTs Observed:	2					
OK Cancel						

East now recommends de-escalation to 5.

Enter Interi	m Data 🔀 💧	🖳 🝷 Final Infe	erence	
Cohort #	Dose Assigned	#Subjects	#DLTs	Recommended Dose
1	5	3	0	10
2	10	3	2	5
3				
4				
5				
6				
7				
8				
9				
10				

Click Enter Interim Data, with 5 selected as Dose Assigned, enter 2 for DLTs Observed, and

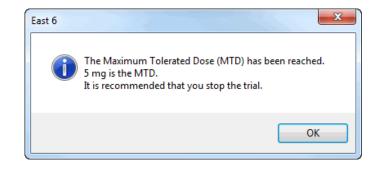
<<< Contents * Index >>>

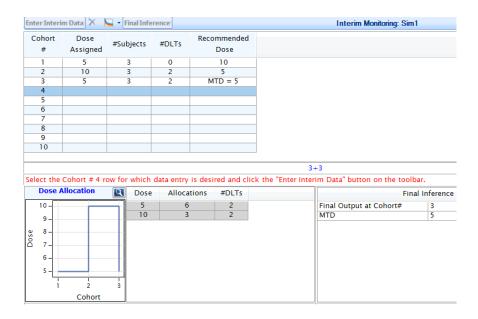


click **OK**.

En	iter Interim Data	
	Editing Cohort #3	
	Dose Assigned:	5 •
	#Subjects Allocated:	3
	#DLTs Observed:	2
		DK Cancel

East recommends that you stop the trial.





Click Final Inference to generate a table for final inference.

7.2 Continual Reassessment Method (CRM)

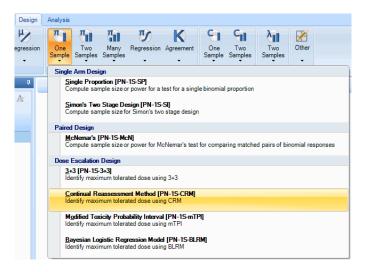
7.2.1 Simulation 7.2.2 Interim Monitoring

7.2.1 Simulation

Click Discrete: One Sample on the Design tab, and then click Dose Escalation Design:

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Continual Reassessment Method.



In the upper pane of this window is the Input dialog box, which is separated into four tabs: Simulation Parameters, Stopping Rules, Response Generation Info, and Simulation Control Info.

Iax. Number of Doses: 7 Simulation Parameters Stopping Rules	Response Generation Info Simulation Control Info		
Max. Sample Size: 30 Cohort Size: 3 Starting Dose: Lowest Dose] Start With 3+3 Design:	Target Probability of Toxicity (P _T): 0.3 Toxicity Probability Upper Limit (UL): 0.3 ■ Assign the dose whose toxicity probability is closest to P _T , and below UL. ▲ Additional Options	Model Type: Logistic c: Prior - <th>-7</th>	-7

In the **Simulation Parameters** tab, enter 30 as the **Maximum Sample Size**, and 3 for **Cohort Size**. For the **Starting Dose**, select the **Lowest Dose**. If you were to check the box **Start with 3+3 Design**, then you would be simulating from the 3+3 design first, before switching to the

CRM, either upon reaching the MTD, or upon observing the first DLT. For this tutorial, however, leave the box unchecked.

Enter 0.25 for the **Target Probability of Toxicity**, and 0.3 for the **Target Probability Upper Limit**. This will ensure that the next dose assignment is that whose toxicity probability is closest to 0.25, and below 0.3.

Target Probability of Toxicity (P_T):	0.25
Toxicity Probability Upper Limit (UL):	0.3
Assign the dose whose toxicity probabi closest to P_{T} , and below UL.	lity is
Additional Options	

If you were to click **Additional Options...**, a new window will appear, which provides two options corresponding to the original CRM procedure: (1) Allow skipping of untried doses while escalating, and (2) Allow dose escalation even if previous subject experienced DLT.

Additional Options	23
□ Allow Skipping untried Doses while Escalating	
Allow Dose Escalation even if Previous Subject Experienced	DLT
ОК	

As was recommended in later variations of CRM, in the interests of promoting safety, leave these two options unchecked. This means that no doses will be skipped while escalating, and no dose escalation will occur when the most recent subject experienced a DLT.

For **Model Type**, select **Power**, with a Gamma($\alpha = 1, \beta = 1$) prior for θ . Other model types available include the **Logistic** and the **Hyperbolic Tangent**. Finally, for the prior probabilities of toxicity of all doses (known as the *skeleton*), enter: 0.05, 0.1, 0.2, 0.3, 0.35, 0.4,

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and 0.45.

Model Type: Power		•	
Prior			
Distribution: Gamma	Probabilit	y of Toxicity	
θ α(shape): 1	Dose ID	Probability of Toxicity	
β(rate): 1	D1	0.050	
p(rate).	D2	0.100	
	D3	0.200	
	D4	0.300	
	D5	0.350	
	D6	0.400	
	D7	0.450	

In the **Stopping Rules** tab, you may specify various rules for stopping the trial. Enter the following inputs as below.

Simulation Parameters Stopping Rules Response Generation Info Simulation Control Info
Threshold
Overdosing Rule: Prob.(P ₁ > P _T I data) > 0.8 Max. Allocation Rule: Number of Subjects Allocated to a Dose >= 9
Underdosing Rule: Prob.($P_h > P_T$ data) > 0.9
P _T : Target Probability of Toxicity
P _h : True Toxicity Probability at Highest Dose
P ₁ : True Toxicity Probability at Lowest Dose
Minimum Number of Subjects to be Observed on a Dose: 6

The **Overdosing Rule** states that if the posterior probability of overdosing (toxicity at the lowest dose is greater than target toxicity) exceeds 0.8, then the trial will be stopped. The **Underdosing Rule** states that if the posterior probability of underdosing (toxicity at the highest dose is lower than target toxicity) exceeds 0.9, then the trial will be stopped. A minimum of 6 subjects will need to be observed on a dose before either of these two rules is activated. A further stopping rule is based on the **Max. Allocation Rule**: As soon as 9 subjects are allocated to any single dose, the trial will be stopped.

In the **Response Generation Info** tab, you can specify a set of true dose response curves from which to simulate. Leave the default profile as shown below. If you wish to edit or add

	Frue Probability									True Probabil	·						
urve Fa	mile									Dose ID	D1	D2	D3	D4	D5	D6	D7
avera	inny.									Dose	5	10	15	25	40	50	60
eneral		-								GC1	0.05	0.1	0.2	0.3	0.35	0.4	0.45
									>>								
abel:	Dose ID	D1	D2	D3	D4	D5	D6	D7									
C2	Dose	5	10	15	25	40	50	60	<<								
	Toxicity																
																_	
								Plot								Plot	Selected

additional profiles (dose response curves), see the corresponding section for the 3+3 design.

In the **Simulation Control Info** tab, check the boxes corresponding to **Save summary statistics** and **Save subject-level data**. These options will provides access to several charts derived from these more detailed levels of simulated data. If you wish to display subject-level plots for more than one simulation, you can increase the number. For now, leave this at 1 to save computation time.

Simulation Parameters Stopping Rules R	esponse Generation Info Simulation Control Info
Number of Simulations: 1000 Refresh Frequency: 100 Random Number Seed O O Clock Fixed O Fixed 100 Suppress All Intermediate Output Pause after Refresh	Output Options Output Type: Case Data Save summary statistics for every simulation run Save subject-level data for Note: Max. 100,000 records will be saved.
Stop At End	
	Simulat

Click **Simulate** to simulate the CRM design. In the **Output Preview** toolbar, click the icon to save the simulation to the **Library**. Double-click the simulation node in the **Library** to display the simulation output details. Click the Plots icon in the **Library** to access a wide range of available plots.



7.2.2 Interim Monitoring

Right-click the Simulation node with CRM in the Library, and select **Interim Monitoring**. This will open an empty interim monitoring dashboard.

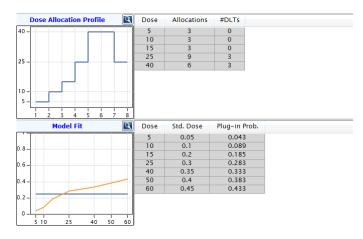
Click **Enter Interim Data** to open a window in which to enter data for the first cohort: in particular, the **Dose Assigned** and the **DLTs Observed**. Click **OK** to continue.

Enter Interim Data	
Editing Cohort #1]
Dose Assigned:	5 •
#Subjects Allocated:	3
#DLTs Observed:	0
	DK Cancel

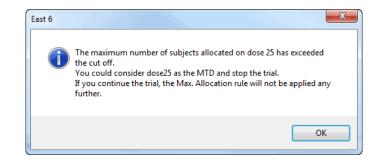
Continue in this manner by clicking **Enter Interim Data**, entering the following doses, and the corresponding number of DLTs: 0 DLTs at dose 10, 0 DLTs at dose 15, 1 DLT at dose 25, 1 DLT at dose 40, 2 DLTs at dose 40, 1 DLT and dose 25, and finally 1 DLT at dose 25.

Enter Interi	nter Interim Data 🔀 🛄 💀 💟 👻 📰 👻 Final Inference						
Cohort #	Dose Assigned	#Subjects	#DLTs	Recommended Dose	Posterior Mean(⊖)		
1	5	3	0	10	1.493		
2	10	3	0	15	1.773		
3	15	3	0	25	2.074		
4	25	3	1	40	1.509		
5	40	3	1	40	1.375		
6	40	3	2	25	1.105		
7	25	3	1	25	1.072		
8	25	3	1	25	1.049		

After each cohort, East will update the Interim Monitoring Dashboard.



At this point, East recommends that you stop the trial.



Click Final Inference to generate a table for final inference.

Final Inference					
Final Output at Cohort#	8				
MTD	25 (under max. allocation)				
Fitted MTD	21.662				

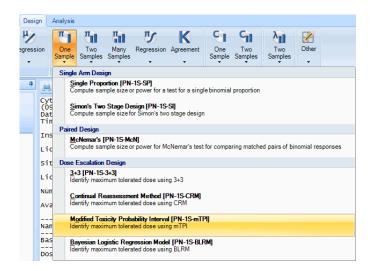


7.3 modified Toxicity Probability Interval (mTPI)

7.3.1 Simulation 7.3.2 Interim Monitoring

7.3.1 Simulation

Click **Discrete: One Sample** on the Design tab, and then click **Dose Escalation Design: Modified Toxicity Probability Interval**.



In the upper pane of this window is the Input dialog box, which is separated into four tabs: Simulation Parameters, Stopping Rules, Response Generation Info, and Simulation Control Info.

Chapter 7: Dose Escalation

ax. Number of Doses:	7					
Simulation Parameters	Stopping Rules R	esponse Generation Info	Simulation C	ontrol Info		
Max. Sample Size:	30	Target Probability of	Toxicity (P_)	0.3	Prior	
		raiget frobability of	ioxicity (i t).	0.5	P, ~ Beta (a, b)	
ohort Size:	3	Toxicity Intervals	Lower Limit	Upper Limit		
tarting Dose:	Lowest Dose -	Under dosing	0.000	0.250	P _i : True Toxicity Probability at Dose	1
	concac boac	Proper dosing	0.250	0.350	a (Prior Toxicity):	
Start With 3+3 Design:		Over dosing	0.350	1.000	a (mor roxieity).	1
					b (Prior Non-Toxicity):	1

In the **Simulation Parameters** tab, enter 30 as the **Maximum Sample Size**, and 3 for **Cohort Size**. For the **Starting Dose**, select the **Lowest Dose**. If you were to check the box **Start with 3+3 Design**, then you would be simulating from the 3+3 design first, before switching to the mTPI, either upon reaching the MTD, or upon observing the first DLT. For this tutorial, however, leave the box unchecked.

Enter 0.25 for the **Target Probability of Toxicity**, 0.2 for the upper limit of the **Under dosing** interval, and 0.3 for the upper limit of **Proper dosing** interval.

Target Probability of	0.25	
Toxicity Intervals	Lower Limit	Upper Limit
Under dosing	0.000	0.2
Proper dosing	0.200	0.3
Over dosing	0.300	1

These entries imply that toxicity probabilities within this interval [0.2 to 0.3] can be regarded as equivalent to the target toxicity (0.25) as far as dosing decisions are concerned. Finally, we will



assume a uniform Beta(a = 1, b = 1) prior distribution for all doses.

Prior								
P _i ~ Beta (a, b)								
P_i : True Toxicity Probability at	Dose i							
a (Prior Toxicity):	1							
b (Prior Non-Toxicity):	1							

In the **Stopping Rules** tab, enter the following inputs as below.

Simulation Parameters	Stopping Rules	Response Generati	on Info S	imulation Control I	Info
Dose Exclusion Rule					
Т	hreshold				
$Prob.(P_1 > P_T data) >$	0.95				
P ₁ : True Toxicity Probabi	ility at Lowest Do	se			
P _T : Target Probability of	Toxicity				
Minimum Number of Sub	ojects to be Obse	rved on a Dose:	3		
Note: If the lowest dose is e	excluded then al	doses are excluded	l and trial is	stopped due to ex	cessive toxicity.

For the mTPI design, the stopping rule is based on dose exclusion rules. This states that if there is greater than a 0.95 posterior probability that toxicity for a given dose is greater than the target toxicity, that dose and all higher doses will be excluded in subsequent cohorts. When this dose exclusion rule applies to the lowest dose, then all doses are excluded, and hence the trial will be stopped for excessive toxicity. Furthermore, the dose exclusion rule is not activated until at least 3 subjects are observed on a dose.

In the **Response Generation Info** tab, you can specify a set of true dose response curves from which to simulate. Leave the default profile as shown below. If you wish to edit or add

Chapter 7: Dose Escalation

	Frue Probability	101 101	icity							True Probabil	ity of 10	KICITY (P	romes)				
urve Fa	milu									Dose ID	D1	D2	D3	D4	D5	D6	D7
rve Fa	mily:									Dose	5	10	15	25	40	50	60
eneral		-								GC1	0.05	0.1	0.2	0.3	0.35	0.4	0.45
									>>								
abel:	Dose ID	D1	D2	D3	D4	D5	D6	D7									
C2	Dose	5	10	15	25	40	50	60	<<								
	Toxicity																
								Plot								Plot	: Selected

additional profiles (dose response curves), see the corresponding section for the 3+3 design.

In the **Simulation Control Info** tab, check the boxes corresponding to **Save summary statistics** and **Save subject-level data**. These options will provides access to several charts derived from these more detailed levels of simulated data. If you wish to display subject-level plots for more than one simulation, you can increase the number. For now, leave this at 1 to save computation time.

Simulation Parameters Stopping Rules	Response Generation Info Simulation Control Info
Number of Simulations: 1000 Refresh Frequency: 100 Random Number Seed O Clock O Fixed 100	Output Options Output Type: Case Data Save summary statistics for every simulation run Save subject-level data for 1 simulation runs Note: Max. 100,000 records will be saved.
Suppress All Intermediate Output Pause after Refresh Stop At End	
	Simulat

Click **Simulate** to simulate the mTPI design. In the **Output Preview** toolbar, click the icon to save the simulation to the **Library**. Double-click the simulation node in the **Library** to display the simulation output details. Click the Plots icon in the **Library** to access a wide range of available plots.



7.3.2 Interim Monitoring

Right-click one of the Simulation nodes with mTPI in the Library, and select **Interim Monitoring**. This will open an empty interim monitoring dashboard.

Enter Interi	nter Interim Data 🗙 🔝 💀 💟 🗂 Trial Monitoring Table 🛛 Final Inference												
Cohort #	Dose Assigned	#Subjects	#DLTs	Decision	Recommended Dose								
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													

Click on **Trial Monitoring Table** to generate a table to guide dosing decisions for this trial. For example, if the cumulative number of patients treated at the current dose is 8, and the cumulative number of toxicities at this dose is 3, then the mTPI method recommends a Stay decision. Close this table before continuing.

												Nu	mbe	r of	pati	ents	trea	ted	at c	urre	nt de	ose
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	s	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	s	s	s	S	s	s	s	E	E	E	E	E	E	E	E	E	E	E	Ε
3			DU	DU	D	s	s	s	s	s	s	s	s	s	s	E	E	E	E	E	E	E
4				DU	DU	DU	D	D	s	s	s	s	s	s	s	s	s	s	s	s	E	E
5					DU	DU	DU	DU	DU	D	s	S	s	s	S	S	s	S	S	S	s	S
6						DU	DU	DU	DU	DU	DU	D	S	s	s	s	s	S	s	s	S	s
7							DU	D	s	s	s	s	s	s	s	s						
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	s	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	s	S	s
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
12												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
13													DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
14														DU	DU	DU	DU	DU	DU	DU	DU	DU
15															DU	DU	DU	DU	DU	DU	DU	DU

Click Enter Interim Data to open a window in which to enter data for the first cohort: in

Chapter 7: Dose Escalation

Enter Interim Data
Editing Cohort #1
Dose Assigned: 5 🔹
#DLTs Observed: 0
OK Cancel

particular, the **Dose Assigned** and the **DLTs Observed**. Click **OK** to continue.

The dashboard will be updated accordingly. The decision for the next cohort is based on the highest Unit Probability Mass (UPM): the posterior probability for each toxicity interval divided by the length of the interval. The underdosing interval corresponds to an E (Escalate) decision, the proper dosing interval corresponds to an S (Stay) decision, and the overdosing interval corresponds to a D (De-escalate) decision. In this case, the UMP for underdosing is highest.

5 2.734	1.379	0.275

Thus, the recommendation is to escalate to dose 10.

Enter Interi	m Data 🗙 📗	I 🖈 🖳 - I	🚺 🔻 Trial M	onitoring Table	Final Inference
Cohort #	Dose Assigned	#Subjects	#DLTs	Decision	Recommended Dose
1	5	3	0	E	10
2					

Continue in this manner by entering data for each subsequent cohort, and observe how the



Enter Interi	Enter Interim Data 🔀 🌃 🔊 도 📰 👻 Trial Monitoring Table 🛛 Final Inference											
Cohort #	Dose Assigned	#Subjects	#DLTs	Decision	Recommended Dose							
1	5	3	0	E	10							
2	10	3	0	E	15							
3	15	3	0	E	25							
4	25	3	2	D	15							
5	15	3	2	S	15							
6	15	3	1	S	15							
7	15	3	2	S	15							
8	15	3	0	S	15							
9												
10												

interim monitoring dashboard updates. One example is given below.

Suppose we wished to end the study after 8 cohorts (24 patients). Click **Final Inference** to end the study and generate a table of final inference. Here, the MTD is 15, while the fitted MTD is 13.269, estimated from the interpolated isotonic estimates.

Fit	nal Inference
Final Output at Cohort#	8
MTD	15
Fitted MTD	13.269

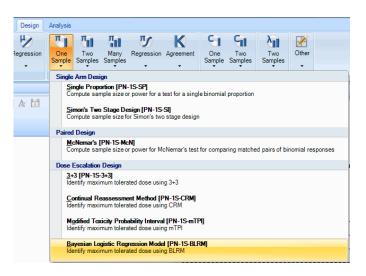
7.4 Bayesian logistic regression model (BLRM)

7.4.1 Simulation

Click Discrete: One Sample on the Design tab, and then click Dose Escalation Design:

Chapter 7: Dose Escalation

Bayesian Logistic Regression Model.



In the upper pane of this window is the Input dialog box, which is separated into four tabs: Simulation Parameters, Stopping Rules, Response Generation Info, and Simulation Control Info.

Simula	tion: Discrete Endpoint	One Sample 1	fest - Dose Esc	alation Desi	ign - BLRM	0	8 :88 📼
Max. Number of Doses: 7							
Simulation Parameters Stopping Rules Respo	nse Generation Info	Simulation C	ontrol Info				
Max. Sample Size: 30	Target Probability of T		0.3		Distribution: Bivariate Lognormal		
Cohort Size: 3	Dose Selection Meth				Prior		
Starting Dose: Lowest Dose +	• Bayes Risk	O EWOC			In (α) In (β)		
Start With 3+3 H -					Mean: -0.85 0.265	_	
a start with 3+3 H	Toxicity Intervals	Lower Limit	Upper Limit	Losses	Variance: 1.28 1.98 Correlation:	0	
	Under dosing	0.000	0.200	1			
	Targeted toxicity	0.200	0.350	0			
	Excessive toxicity	0.350	0.600	1	Posterior Sampling Methods		
	Unacceptable toxicity	0.600	1.000	2			
	Reference Dose (d*):	25					
							nulate

In the **Simulation Parameters** tab, enter 30 as the **Maximum Sample Size**, and 3 for **Cohort Size**. For the **Starting Dose**, select the **Lowest Dose**. If you were to check the box **Start with**



3+3 Design, then you would be simulating from the 3+3 design first, before switching to the BLRM, either upon reaching the MTD, or upon observing the first DLT. For this tutorial, however, leave the box unchecked.

The next step is to choose a **Dose Selection Method**: either by **Bayes Risk** or by **EWOC**. For the next cohort, the Bayes risk method selects the dose that minimizes the posterior expected loss, aka Bayes risk. In contrast, the escalation with overdose control (EWOC) method selects the dose that maximizes the posterior probability of targeted toxicity, for all doses where the posterior probability of overdosing (either excessive or unacceptable toxicity) is less than the user-specified threshold. In this example, we will use the EWOC method.

O Bayes Risk	● EWOC							
Toxicity Intervals	Lower Limit	Upper Limit						
Under dosing	0.000	0.200						
Targeted toxicity	0.200	0.350						
Excessive toxicity	0.350	0.600						
Unacceptable toxicity	0.600	1.000						

A bivariate normal distribution with corresponding means, variances, and correlation, can be specified for the $\ln(\alpha)$ and $\ln(\beta)$ parameters of the two-parameter logistic.

Prior		. (0)	
	In (α)	In (β)	
Mean:	-0.85	0.265	
Variance:	1.28	1.98	Correlation: 0

Click Posterior Sampling Methods to select from one of two methods: Metropolis Hastings,

Chapter 7: Dose Escalation

or direct Monte Carlo. For this tutorial, click **OK** to select **Metropolis Hastings**.

Posterior Sampling Methods		
 Metropolis Hastings 	O Direct	
	In (α)	In (β)
Starting Values:	-0.85	0.265
Random Walk (σ):	2	
Steady state simulations:	1000 Burn-in:	500
C	Cancel	

In the **Stopping Rules** tab, you can specify up to two rules for stopping the trial. Check the appropriate boxes and enter values as below.

Simulation Parameters	Stopping Rules	Response Generation Info	Simulation Control Info		
☑ Target Rule: Prob.(Targ	ated toxicity) >	Threshold	Max Allocation Rule:	Number of Subjects Allocated to a Dose >=	12
Minimum Number of Sub			E Max, Anocation Rule.	Number of Subjects Anocated to a Dose >=	12

The **Target Rule** will stop the trial when the posterior probability of being in the Target toxicity interval exceeds 0.8. A minimum of 6 subjects should be observed before this rule is activated. The **Max. Allocation Rule** will stop the trial if at least 12 subjects are allocated to any dose.

In the **Response Generation Info** tab, you can specify a set of true dose response curves from which to simulate. Leave the default profile as shown below. If you wish to edit or add



										Dose ID	D1	D2	D3	D4	D5	D6	D7
Curve Fa	mily:									Dose	5	10	15	25	40	50	60
General		•								GC1	0.05	0.1	0.2	0.3	0.35	0.4	0.45
Label: GC2	Dose ID Dose Toxicity	D1 5	D2 10	D3 15	D4 25	D5 40	D6 50	D7 60	<<								
								Plo									Selected

additional profiles (dose response curves), see the corresponding section for the 3+3 design.

In the **Simulation Control Info** tab, check the boxes corresponding to **Save summary statistics**, **Save subject-level data**, and **Save final posterior samples**. These options will provides access to several charts derived from these more detailed levels of simulated data. If you wish to display subject-level plots, or posterior distribution plots, for more than one simulation, you can increase the number. For now, leave both of these at 1 to save computation time.

Simulation Parameters Stopping Rules	Response Generation Info Simulation Control Info	
Number of Simulations: 1000 Refresh Frequency: 100 Random Number Seed O Clock O Fixed 100 Suppress All Intermediate Output Pause after Refresh Stop At End	Output Options Output Type: Case Data Save summary statistics for every simulation run Save subject-level data for 1 simulation runs Save final posterior samples for 1 simulation runs Note: Max. 100,000 records will be saved.	
	Si	imulate

Click **Simulate** to simulate the BLRM design. In the **Output Preview** toolbar, click the icon to save the simulation to the **Library**. Double-click the simulation node in the **Library** to display the simulation output details. Click the Plots icon in the **Library** to access a wide range of available plots.

Chapter 7: Dose Escalation

7.4.2 Interim Monitoring

Right-click the Simulation node with BLRM in the Library, and select **Interim Monitoring**. This will open an empty interim monitoring dashboard.

nter Interi	m Data 🗙 👖	Interim Monitoring: Sim1						
Cohort #	Dose Assigned	#Subjects	#DLTs	Recommended Dose	Posterior Mean(In(α))	Post. SD of In(α)	Posterior Mean(β)	Post. SD of p
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								

Click **Enter Interim Data** to open a window in which to enter data for the first cohort: in particular, the **Dose Assigned** and the **DLTs Observed**. Click **OK** to continue.

Enter Interim Data	
Editing Cohort #1	
Dose Assigned:	5 •
#Subjects Allocated:	3
#DLTs Observed:	0
]
0	K Cancel

The dashboard will be updated accordingly. The decision for the next cohort is based on the dose with the highest posterior probability of targeted toxicity, with less than the

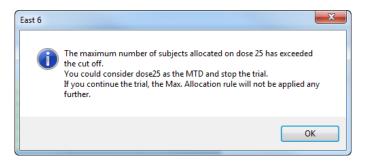


Cohort Dose Recommended #Subjects #DLTs Assigned # Dose 1 5 3 0 15 2 3 4 5 6 7 8 9 10

Continue in this manner by entering data for each subsequent cohort, and observe how the interim monitoring dashboard updates. One example is given below.

Cohort #	Dose Assigned	#Subjects	#DLTs	Recommended Dose
1	5	3	0	15
2	15	3	0	15
3	15	3	0	25
4	25	3	0	25
5	25	3	1	25
6	25	3	1	25
7				
8				
9				
10				

At this point, East will display the following message:



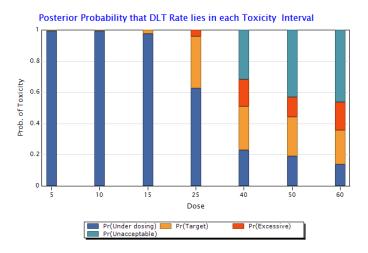
Click OK to continue, and then click Final Inference Interim Monitoring toolbar. The following

user-specified threshold (0.25) probability of overdosing. In this case, this is dose 15.

final inference table will be displayed.

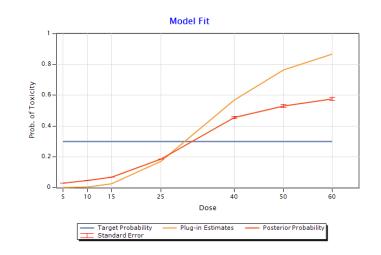
Final Inference							
Final Output at Cohort#	7						
MTD	25 (under max. allocation)						
Fitted MTD	30.12						

Dose 25 happens to have the highest posterior probability of being in the target toxicity interval, with little probability of being in the overdosing (excessive or unacceptable) intervals.



The **Model Fit** plot has also been updated. One curve is the two-parameter logistic function described by plug-in (posterior mean) estimates. The other curve interpolates between the posterior mean of the toxicity probability at each dose. In both cases, the target probability lies

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quite close to the predicted toxicity probability at dose 25, with the fitted MTD at around 30.

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8 Count Data One-Sample

This chapter deals with the design of tests involving count or Poisson response rates. Here, independent outcomes or events under examination can be counted in terms of whole numbers, and typically are considered rare. In other words, a basic assumption of the Poisson distribution is that the probability of an event occurring is proportional to the length of time under consideration. The longer the time interval, the more likely the event will occur. Therefore, in this context interest lies in the rate of occurrence of a particular event during a specified period. Section 8.1 focuses on designs in which an observed Poisson response rate is compared to a fixed response rate, possibly derived from historical data.

8.1 Single Poisson Rate

Data following a Poisson distribution are non-negative integers, and the probability that an outcome occurs exactly *k* times can be calculated as:

 $P(k) = \frac{e^{-\lambda}\lambda^k}{k!}, k = 0, 1, 2, \dots$ where λ is the average rate of occurrence.

When comparing a new protocol or treatment to a well-established control, a preliminary single-sample study may result in valuable information prior to a full-scale investigation. In experimental situations it may be of interest to determine whether the response rate λ differs from a fixed value λ_0 . Specifically we wish to test the null hypothesis H_0 : $\lambda = \lambda_0$ against the two sided alternative hypothesis H_1 : $\lambda \neq \lambda_0$ or against one sided alternatives of the form H_1 : $\lambda > \lambda_0$ or H_1 : $\lambda < \lambda_0$. The sample size, or power, is determined for a specified value of λ which is consistent with the alternative hypothesis, denoted λ_1 .

Chapter 8: Count Data One-Sample

8.1.1 Trial Design

Consider the design of a single-arm clinical trial in which we wish to determine if the positive response rate of a new acute pain therapy is at least 30% per single treatment cycle. Thus, it is desired to test the null hypothesis H_0 : $\lambda = 0.2$ against the one-sided alternative hypothesis H_1 : $\lambda \ge 0.3$. The trial will be designed such that a one sided $\alpha = 0.05$ test achieves 80% power at $\lambda = \lambda_1 = 0.3$.

In the **Design** tab under the **Count** group choose **One Sample** and then **Single Poisson Rate**.

	16-	⇒ 14 1						-		Eas	st 6		
9	Home	Data Edito	r Design	Analysis									
H	- 6	5	1	Π	7	-	5	K	61	9		R	
One	Two Sample	Many s Samples	Regression	One	Two Samples	Many	Regression	Agreement	One	Two Samples	Two Samples	Other	
- Julip		a Jampica T	•	T	- The second sec	- Jumpica	•	•	- The second sec	- Valinpica	- Valipica	-	
	C	ontinuous				Discr	ete		Poiss	m			
Library		₽	Log						Si	ngle <u>P</u> oisso	on Rate [PO-	-15-SR]	
			Log						Co	mpute sam	ple size, pow	er or type	e Ierror for single Poisson rate
2	1 🔛 -	II • I	a 🖪						<u> </u>				6

This will launch the following input window:

Γest T <u>y</u> pe: Γγpe I <u>E</u> rror (α):	1-Sided	•	Specify Rate Rate under Null (λ_0): 0.1 Eollow-Up Time (D):	1
o <u>w</u> er:	0.9	õ	Rate under \underline{A} It. (λ_1): 0.2	

Enter the following design parameters:

Test Type: 1 sided Type 1 Error (α): 0.05 Power: 0.8 Sample Size (n): Computed (select radio button) Rate under Null (λ_0): 0.2 Rate under Alt. (λ_1): 0.3



Follow-up Time (D): 1

	Des	gn: Count Data: One-Sample Test - Poisson Rate	88. 88. 🕥
Design Parameters Test Τ <u>γ</u> pe: Type I <u>E</u> rror (α): Po <u>w</u> er:	0.8	Specify Rate Specify Followup Time Rate under Alt. (\(\lambda_1\)): 0.3]
Sample Si <u>z</u> e (n):	Computed	Ð 	

Click Compute. The design is shown as a row in the Output Preview window:

J	📕 Edit	🛓 🗙 🏄	# %						Output Preview	Profile + 📝 🌹	
	ID	Test Type	Specified α	Power	D	Sample Size	λ0	λ1			
C	Des 1	1-Sided	0.05	0.809	1	155	0.2	0.3			

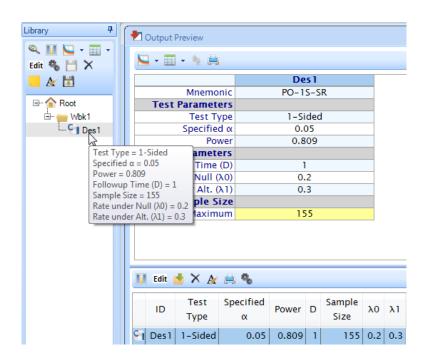
The sample size required in order to achieve the desired 80% power is 194 subjects. As is standard in East, this design has the default name **Des 1**. To see a summary of the output of this design, click anywhere in the row and then click the **I** icon in the Output Preview toolbar. The design details will be displayed in the upper pane, labeled **Output Summary**.

	Des 1
Mnemonic	PO-1S-SR
Test Parameters	
Test Type	1–Sided
Specified α	0.05
Power	0.809
Model Parameters	
Follow-Up Time (D)	1
Rate under Null (λ0)	0.2
Rate under Alt. (λ1)	0.3
Sample Size	
Maximum	155

In the **Output Preview** toolbar, click icon to save this design **Des1** to workbook **Wbk1** in the **Library**. An alternative method to view design details is to hover the cursor over the node **Des1** in the **Library**. A tooltip will appear that summarizes the input parameters of the

Chapter 8: Count Data One-Sample

design.



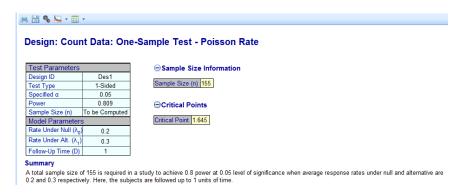
With the design **Des1** selected in the Library, click **Series** icon on the Library toolbar, and then click **Power vs. Sample Size**. The power curve for this design will be displayed. You can save this chart to the Library by clicking **Save inWorkbook**. Alternatively, you can export the chart in one of several image formats (e.g., Bitmap or JPEG) by clicking **Save As...** or **Export** into a



Sample Size Chart1 _ Y Settings... | Print... | Copy | Zoom | Save As... | Hide Read-offs Power vs. Sample Size - Des1 Sample Size 225.522 0.9 Power 0.899 0.72 0.54 0.36 0.18 100 200 300 600 400 500 Sample Size Save in Workbook

PowerPoint presentation.

Close the Power vs. Sample Size chart. To view a summary of all characteristics of this design, select **Des1** in the **Library**, and click icon.



In addition to the **Power vs. Sample** size chart and table, East also provides the efficacy boundary in the **Stopping Boundaries** chart and table.

Chapter 8: Count Data One-Sample

Alternatively, East allows the computation of either the **Type-1 error** (α) or **Power** for a given sample size. Using the **Design Input/Output** window as described above, simply enter the desired sample size and click **Compute** to calculate the resulting power of the test.

9 Count Data Two-Samples

Often in experiments based on count data, the aim is to compare independent samples from two populations in terms of the rate of occurrence of a particular outcome. In medical research, outcomes such as the number of times a patient responds to a therapy, develops a certain side effect, or requires specialized care, are of interest. Or perhaps a therapy is being evaluated to determine the number of times it must be applied until an acceptable response rate is observed. East supports the design of clinical trials in which this comparison is based on the ratio of rates, assuming a Poisson or Negative Binomial distribution. These two cases are presented in Sections 9.1 and 9.2, respectively.

9.1 Poisson - Ratio of Rates

9.1.1 Trial Design

Let λ_c and λ_t denote the Poisson rates for the control and treatment arms, respectively, and let $\rho_1 = \lambda_t / \lambda_c$. We want to test the null hypothesis that $\rho_1 = 1$ against one or two-sided alternatives. The sample size, or power, is determined to be consistent with the alternative hypothesis, that is $H_1 : \lambda_t \neq \lambda_c$, $H_1 : \lambda_t > \lambda_c$, or $H_1 : \lambda_t < \lambda_c$.

9.1.1 Trial Design

Suppose investigators are preparing design objectives for a prospective randomized trial of a standard treatment (control arm) vs. a new combination of medications (therapy arm) to present at a clinical trials workshop. The endpoint of interest is the number of abnormal ECGs (electrocardiogram) within seven days. The investigators were interested in comparing the therapy arm to the control arm with a two sided test conducted at the 0.025 level of

Chapter 9: Count Data Two-Samples

significance. It can be assumed that the rate of abnormal ECGs in the control arm is 30%, thus $\lambda_t = \lambda_c = 0.3$ under H_0 . The investigators wish to determine the sample size to attain power of 80% if there is a 25% decline in the event rate, that is $\lambda_t/\lambda_c = 0.75$. It is important to note that the power of the test depends on λ_c and λ_t , not just the ratio, so different values of the pair (λ_c , λ_t) with the same ratio will yield different solutions.

We will now design a study that compares the control arm to the combination therapy arm. In the **Design** tab under the **Count** group choose **Two Samples** and then **Poisson - Ratio of Rates**.

			-							Ea	st 6			
	Home	Data Editor	Design	Analysis										
9	-		۲	-	7	T	5	K	9	GI	N	R		
One Sample	Two Samples	Many Samples	Regression •	One Sample	Two Samples	Many Samples	Regression •	Agreement •	One Sample	Two Samples	Two Samples	Other		
	Co	ntinuous				Discr	ete		Co	Poissor	1			
Library	🔍 - 1	+ e	🛃 Desig	n Input Ou	itput						io of Rates [I npute sample		rer or type I error for ratio of Poisson rates	G

This will launch the following input window:

	Design	: Count	Data: Two-Samples Test - Poisson - Ratio of R	lates	5. 86. 🕤	8 📼
Design Parameters Test Type:	1-Sided	•	Specify Rate $R_{\underline{a}}$ te for Control (λ_c): 0.1	Specify Follow-Up Time Follow-Up Control (D _c):	1	•
Type I <u>E</u> rror (α): Po <u>w</u> er:	0.025	0 0	Specify Alternative Hypothesis Rate for Treat <u>m</u> ent (λ_{t}): 0.2	Follow-Up Treatment (D t)	1	E
Sample Si <u>z</u> e (n): Allocation <u>R</u> atio: (n,/n,)	Computed 1	۲	Ratio of Rates (ρ_1): $\rho_1 = (\lambda_t / \lambda_c)$:			
<			m		Сотр	• •

Enter the following design parameters:

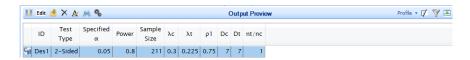
Test Type: 2-sided Type 1 Error (α): 0.05 Power: 0.8 Sample Size (n): Computed (select radio button) Allocation Ratio (n_t/n_c): 1



Rate for Control (λ_c) : 0.3 Rate for Treatment (λ_t) : 0.225 (will be automatically calculated) Ratio of Rates $\rho_1 = (\lambda_t/\lambda_c)$: 0.75 Follow-up Control (D_c) : 7 Follow-up Treatment (D_t) : 7

	Design: Coun	t Data: Two-Samples Test - Poisson - Ratio of	Rates	📼 88. 88. 🕥
Design Parameter Test Type: Type I Error (α): Power: Sample Size (n): Allocation <u>Ratio</u> : (n_t/n_c)	2-Sided ▼ 0.05 ○ 0.8 ○ Computed ⊙ 1	$\label{eq:specify-rate} \begin{array}{ c c c } \hline Specify Rate \\ Rate for Control (\lambda_c): 0.3 \\ \hline Specify Alternative Hypothesis \\ Rate for Treatment (\lambda_t): 0.225 \\ Ratio of Rates (\rho_1): 0.75 \\ \rho_1 = (\lambda_t \ / \ \lambda_c): \end{array}$	Specify Follow-Up Time Eollow-Up Control (D _e): Follow-Up Ireatment (D _e)	7 2
•		III		
				Compute

The Allocation Ratio $(n_t : n_c)$ describes the ratio of patients to each arm. For example, an allocation ratio of 3:1 indicates that 75% of the patients are randomized to the treatment arm as opposed to 25% to the control. Here we assume the same number of patients in both arms. Click **Compute**. The design is shown as a row in the **Output Preview** window:



The sample size required in order to achieve the desired 80% power is 211 subjects. As is standard in East, this design has the default name **Des 1**. To see a summary of the output of this design, click anywhere in the row and then click the **I** icon in the Output Preview

Chapter 9: Count Data Two-Samples

🛃 Output Preview	
💟 - 🛅 - 🍬 🚔	
	Des 1
Mnemonic	PO-2S-RR
Test Parameters	
Test Type	2-Sided
Specified α	0.05
Power	0.8
Model Parameters	
Follow-Up Control (Dc)	7
Follow-Up Treatment (Dt)	7
Allocation Ratio (nt/nc)	1
Rate for Control (λc)	0.3
Rate for Treatment (\lambda t)	0.225
Ratio of Rates (p1)	0.75
Sample Size	
Maximum	211

toolbar. The design details will be displayed in the upper pane, labeled **Output Summary**.

In the **Output Preview** toolbar, click icon to save this design **Des1** to workbook **Wbk1** in the **Library**. An alternative method to view design details is to hover the cursor over the node **Des1** in the **Library**. A tooltip will appear that summarizes the input parameters of the

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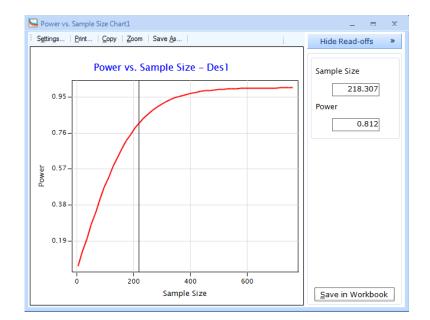


design.

Library	#	🛃 Output Preview				
Edit 🌯 💾 🗙		🔽 = 🖽 = 🍬 🛔	4			
- A 🗒				Des 1		
			Mnemonic	PO-2S-RR		
🖃 🏠 Root		Test Pa	rameters			
🖻 💼 Wbk1			Test Type	2-Sided		
Gil Dest		2	pecified α	0.05		
5	2		Power	0.8		
		e = 2-Sided	rameters			
	Specified		ontrol (Dc)	7		
	Power = (tment (Dt)	7		
	Sample S	ize = 211 Control (λc) = 0.3	tio (nt/nc)	1		
		reatment (λ t) = 0.225	ontrol (λc)	0.3		
		lates $(\rho 1) = 0.75$	tment (λt)	0.225		
		Control (Dc) = 7	Rates (p1)	0.75		
	Followup	Treatment (Dt) = 7	nple Size			
	Allocatio	n Ratio (nt/nc) = 1	Maximum	211		

With the design **Des1** selected in the Library, click **Ser** icon on the Library toolbar, and then click **Power vs. Sample Size**. The power curve for this design will be displayed. You can save this chart to the Library by clicking **Save inWorkbook**. Alternatively, you can export the chart in one of several image formats (e.g., Bitmap or JPEG) by clicking **Save As...** or **Export** into a

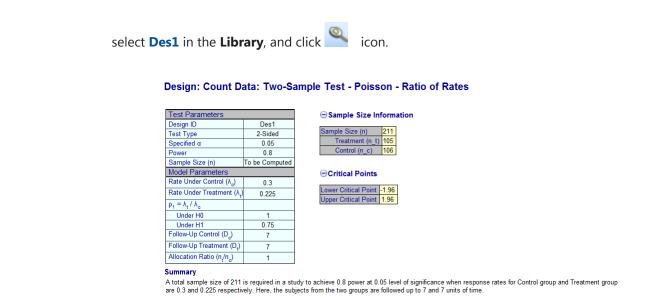
Chapter 9: Count Data Two-Samples



PowerPoint presentation.

Close the Power vs. Sample Size chart. To view all computed characteristics of this design,





In addition to the **Power vs. Sample** size chart and table, East also provides the efficacy boundary in the **Stopping Boundaries** chart and table.

Alternatively, East allows the computation of either the **Type-1 error** (α) or **Power** for a given sample size. Using the **Design Input Output** window as described above, simply enter the desired sample size and click **Compute** to calculate the resulting power of the test.

9.2 Negative Binomial Ratio of Rates

In experiments where the data follows a binomial distribution, the number of successful outcomes for a fixed number of trials is of importance when determining the sample size to adequately power a study. Suppose instead that it is of interest to observe a fixed number of successful outcomes (or failures), but the overall number of trials necessary to achieve this is unknown. In this case, the data is said to follow a Negative Binomial Distribution. There are two underlying parameters of interest. As with the Poisson distribution, λ denotes the average rate of response for a given outcome. In addition, a **shape** parameter γ specifies the desired

Chapter 9: Count Data Two-Samples

number of observed "successes". As with the Poisson distribution, the Negative Binomial distribution can be useful when designing a trial where one must wait for a particular event. Here, we are waiting for a specific number of successful outcomes to occur. A Poisson regression analysis assumes a common rate of events for all subjects within a stratum, as well as equal mean and variance (equidispersion). With over dispersed count data, estimates of standard error from these models can be invalid, leading to difficulties in planning a clinical trial. Increased variability resulting from over dispersed data requires a larger sample size in order to maintain power. To address this issue of allowing variability between patients, East provides valid sample size and power calculations for count data using a negative binomial model, resulting in a better evaluation of study design and increased likelihood of trial success.

9.2.1 Trial Design

Suppose that a hypothetical manufacturer of robotic prostheses, those that require several components to fully function, has an order to produce a large quantity of artificial limbs. According to historical data, about 20% of the current limbs fail the rigorous quality control test and therefore cannot be shipped to patients. For each order, the manufacturer must produce more than requested; in fact they must continue to produce the limbs until the desired quantity passes quality control. Given that there is a high cost in producing these prosthetic limbs, it is of great interest reduce the number of those that fail the test.

The company plans to introduce a new feature to the current model, the goal being the probability of failure is reduced to 10%. It is safe to assume that the enhancement will not cause a decline in the original success rate. In this scenario, we wish to test the null hypothesis H_0 : $\lambda_c = \lambda_t = 0.2$ against the one sided alternative of the form H_1 : $\lambda_c > \lambda_t$. Quality control investigators wish to conduct a one-sided test at the $\alpha = 0.05$ significance level to determine the sample size required obtain 90% power to observe a 50% decline in the event rate, i.e. $\lambda_t/\lambda_c = 0.5$. It is important to note that the power of the test depends on λ_c and λ_t , not just the ratio, so different values of the pair (λ_c , λ_t) with the same ratio will have different solutions. The same holds true for the shape parameter. Different values of (γ_c , γ_t) will result in different sample sizes or power calculations. East allows user specific shape parameters for both the treatment and control groups, however for this example assume that the desired



number of successful outcomes for both groups is 10.

The following illustrates the design of a two-arm study comparing the control arm, which the current model of the prosthesis, to the treatment arm, which is the enhanced model. In the **Design** tab under the **Count** group choose **Two Samples** and then **Negative Binomial** - **Ratio of Rates**.

	•	⊽	-	East 6												
	Home	Data Edite	or Design	Analysis												
One Sample	Two Samples	Many Samples	Regression	One Sample	Two Samples	Many Samples	Negression	K Agreement	One Sample	Two Samples	Two Samples	Other				
	Co	ontinuous				Discre	ete		Co	o Poisson						
Library	E-	\sim	Log							Ratio of Rates (PO-2S-RR) Compute sample size, power or type I error for ratio of Poisson rates						
											Negative Binomial					
			(09 Apr 2) Date: Sati	014)						Ratio of Rates [NB-2S-RR] Compute sample size, power or type I error for ratio of Negative Binomial rates						

This will launch the following input window:

	Design: Cou	nt Data	: Two-Samples Test - Negative Binomial - Ratio	of Rates	80. 88. 🕥
Design Parameters					
Test T <u>y</u> pe: Type I <u>E</u> rror (α):	1-Sided	•	Specify Rate R <u>a</u> te for Control (λ _c): 0.2	Specify Shape Parameter Shape Control (Y c):	1
Po <u>w</u> er: Sample Size (n):	0.9 Computed	0 0	Specify Alternative Hypothesis Rate for Treatment (λ_t) : 0.1	Shape <u>T</u> reatment (γ _t):	1
Allocation <u>R</u> atio: (n ₊ /n _c)	1	U	Ratio of Rates (Θ_1): 0.5 $\Theta_1 = (\lambda_t / \lambda_c)$:		
<		_	Specify Follow-Up Time		•

Enter the following design parameters:

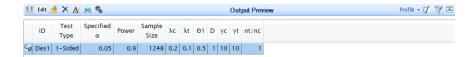
Test Type: 1 sided Type 1 Error (α): 0.05 Power: 0.9 Sample Size (n): Computed (select radio button) Allocation Ratio (n_t/n_c): 1 Rate for Control (λ_c): 0.2 Rate for Treatment (λ_t): 0.1

Chapter 9: Count Data Two-Samples

Ratio of Rates $\rho = (\lambda_t / \lambda_c)$: 0.5 Follow-up Time (*D*): 1 Shape Control (γ_c): 10 Shape Treatment (γ_t): 10

	Design: Count Data: Two-Samples Test - Negative Binomial - Ratio of Rates			💿 😚 😚 💽
Design Parameters Test Type : Type I Error (a): Power: Sample Size (n): Allocation Batio: (n _t /n _c)	1-Sided • 0.05 ○ 0.9 ○ Computed • 1 ●	Specify Rate Rate for Control (λ_c): 0.2 Specify Alternative Hypothesis Rate for Treatment (λ_c): 0.1 Ratig of Rates (Θ_1): 0.5 $\Theta_1 = (\lambda_c / \lambda_c)$: Specify Follow-Up Time Eollow-Up Time (D): 1	Specify Shape Parameter Shape Control (y c):	
•		ш		Compute

The Allocation Ratio $(n_t : n_c)$ describes the ratio of patients to each arm. For example, an allocation ratio of 3:1 indicates that 75% of the patients are randomized to the treatment arm as opposed to 25% to the control. Here we assume the same number of patients in both arms. Click **Compute**. The design is shown as a row in the **Output Preview** window:



The sample size required in order to achieve the desired 90% power is 1248 subjects. As is standard in East, this design has the default name **Des 1**. To see a summary of the output of this design, click anywhere in the row and then click the **I** icon in the Output Preview



🛃 Output Preview 🛛 = 🖽 = 🍬 🚔 Des 1 Mnemonic NB-2S-RR Test Parameters 1-Sided Test Type 0.05 Specified α Power 0.9 **Model Parameters** Follow-Up Time (D) 1 Shape Control (yc) 10 Shape Treatment (yt) 10 Allocation Ratio (nt/nc) 1 Rate for Control (\lambda c) 0.2 Rate for Treatment (\lambda t) 0.1 Ratio of Rates (O1) 0.5 Sample Size Maximum 1248

toolbar. The design details will be displayed in the upper pane, labeled Output Summary.

In the **Output Preview** toolbar, click icon to save this design **Des1** to workbook **Wbk1** in the **Library**. An alternative method to view design details is to hover the cursor over the node **Des1** in the **Library**. A tooltip will appear that summarizes the input parameters of the

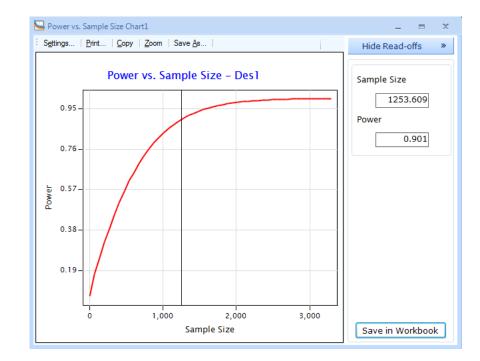
Chapter 9: Count Data Two-Samples

Library **д** 🛃 Output Preview 🔍 📗 💟 - 🎞 🖣 🕶 📰 📼 🍬 🚔 Edit 🧠 💾 🗙 Des 1 🚽 🛃 🐱 Mnemonic NB-2S-RR ⊡- Root □- Wbk1 □- Gi Des1 **Test Parameters** Test Type 1-Sided Specified α 0.05 Power 0.9 meters Test Type = 1-Sided Specified $\alpha = 0.05$ Time (D) 1 Power = 0.9 trol (yc) 10 Sample Size = 1248 hent (yt) 10 Rate for Control (λc) = 0.2 (nt/nc) 1 Rate for Treatment (λt) = 0.1 trol (λc) 0.2 Ratio of Rates (O1) = 0.5 hent (λt) 0.1 Followup Time (D) = 1 tes (O1) 0.5 Shape Control (yc) = 10 Shape Treatment (γ t) = 10 le Size Allocation Ratio (nt/nc) = 1aximum 1248

With the design **Des1** selected in the Library, click **Series** icon on the Library toolbar, and then click **Power vs. Sample Size**. The power curve for this design will be displayed. You can save this chart to the Library by clicking **Save inWorkbook**. Alternatively, you can export the chart in one of several image formats (e.g., Bitmap or JPEG) by clicking **Save As...** or **Export** into a

design.

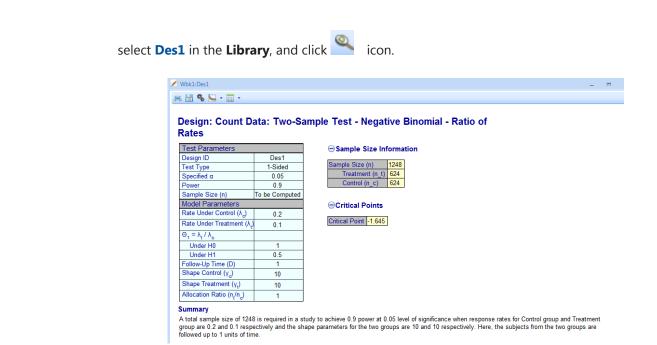




PowerPoint presentation.

Close the Power vs. Sample Size chart. To view all computed characteristics of this design,

Chapter 9: Count Data Two-Samples



In addition to the **Power vs. Sample** size chart and table, East also provides the efficacy boundary in the **Stopping Boundaries** chart and table.

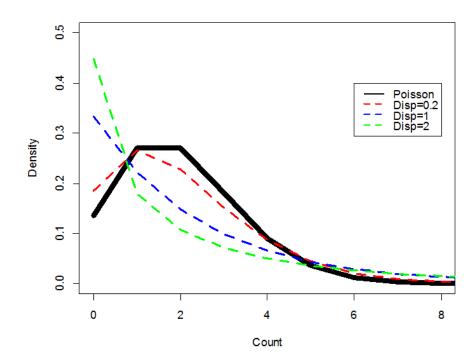
For a specific desired sample size, East allows the computation of either the **Type-1 error** (α) or **Power** for a test. Using the **Design Input Output** window and methods as described above, simply enter the desired sample size and click **Compute** to calculate the resulting power of the test.

In addition to this example, consider the following illustration of the benefit of using the negative binomial model in clinical trials. In real life settings, the variance of count data observed between patients is typically higher than the observed mean. The negative binomial model accommodates between subject heterogeneity according to a Gamma distribution. For example:

```
Poisson: Y \sim Poisson(\lambda)
```

Negative Binomial: $Y_i \sim Poisson(\lambda k_i)$ where $k_i \sim Gamma(k)$

In the case of no overdispersion (k = 0) the negative binomial model reduces to the Poisson model. In the figure below, the Poisson and negative binomial models are displayed under various values of the dispersion parameter.



Assuming the above parameterization, the variance of the negative binomial model is $\lambda + k\lambda^2$. The inflation in variance is thus linear by the factor $1 + k * \lambda$ and dependent on the mean. Depending on the distributional assumption used and its impact on the variance, sample size and power can vary widely.

In multiple sclerosis (MS) patients, magnetic resonance imaging (MRI) is used as a marker of efficacy by means of serial counts of lesions appearing on the brain. Exacerbations rates as a primary endpoint are frequently used in MS as well as in chronic obstructive pulmonary disease (COPD) and asthma (*Keene et al. 2007*). Poisson regression could be considered, however this model would not address variability between patients, resulting in over

Chapter 9: Count Data Two-Samples

dispersion. The negative binomial model offers an alternative approach.

TRISTAN (*Keene et al. 2007*) was a double-blind, randomized study for COPD comparing the effects of the salmeterol/fluticasone propionate combination product (SFC) to salmeterol alone, fluticasone proprionate alone and placebo. Although the primary end-point was pre-bronchodilator FEV1, the number of exacerbations was an important secondary endpoint.

Suppose we are to design a new trial to be observed over a period of 1 to 2 years. The primary objective is the reduction of the rate of exacerbations, defined as a worsening of COPD symptoms that require treatment with antibiotics, cortisone or both, with the combination product SFC versus placebo. Based on the TRISTAN results, we aim to reduce the incidence of events by 33%. Suppose the exacerbation rate is 1.5 per year, and can expect to detect a rate of 1.0 in the combination group. Assume a 2-sided test with a 5% significance level and 90% power. Using a Poisson model, a total of 214 patients are needed to be enrolled in the study.

For the TRISTAN data, the estimate of the overdispersion parameter was 0.46 (95% CI: 0.34-0.60). Using a negative binomial model with overdispersion of 0.33, 0.66, 1 and 2, the



	Design: Cour	nt Data	: Two-Samples Test - Negative Binomial - Ratio) of Rates	8	.00 .0	ŏĿ
Design Parameters							
Test Type:	2-Sided	•	Specify Rate Rate for Control (λ_c): 1.5	Specify Shape Parameter Shape Control (Y c): 0.66			[
Type I <u>E</u> rror (α):		0	Specify Alternative Hypothesis	Shape Treatment (Y,): 0.66			
o <u>w</u> er:	0.9	0	Rate for Treat <u>m</u> ent (λ_t): 1		_		
Sample Si <u>z</u> e (n):	Computed	۲	Ratio of Rates (0,): 0.667				
Allocation <u>R</u> atio:	1		$\Theta_1 = (\lambda_t / \lambda_c)$:				
(n _t /n _c)			Specify Follow-Up Time				
			Eollow-Up Time (D):				

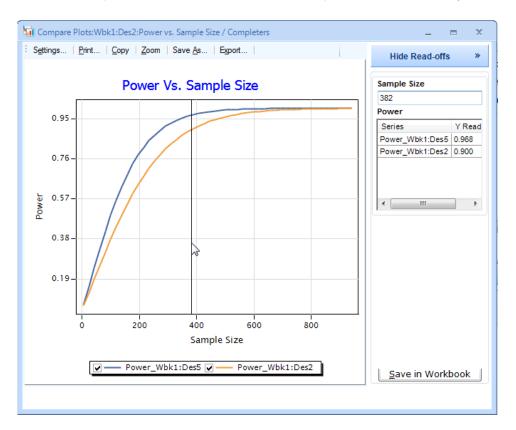
increase in sample size ranged from 299 to 726, respectively.

	Des 1	Des2	Des 3	Des4
Mnemonic	NB-2S-RR	NB-2S-RR	NB-2S-RR	NB-2S-RR
Test Parameters				
Test Type	2–Sided	2-Sided	2-Sided	2-Sided
Specified α	0.05	0.05	0.05	0.05
Power	0.902	0.9	0.901	0.901
Model Parameters				
Follow-Up Time (D)	1	1	1	1
Shape Control (yc)	0.33	0.66	1	2
Shape Treatment (yt)	0.33	0.66	1	2
Allocation Ratio (nt/nc)	1	1	1	1
Rate for Control (λc)	1.5	1.5	1.5	1.5
Rate for Treatment (\lambda t)	1	1	1	1
Ratio of Rates (O1)	0.667	0.667	0.667	0.667
Sample Size				
Maximum	299	382	470	726

Exacerbation rates are calculated as number of exacerbations divided by the length of time in treatment in years. EAST can be used to illustrate the impact of a one versus two year study by changing the follow-up duration.

Using a shape parameter of 0.66 for 382 patients, power is increased from 90% to 97% when follow-up time is doubled (see below). Alternatively, 277 patients observed for two years

Chapter 9: Count Data Two-Samples



would results in 90% power, which is the same as with 382 patients observed one year.

	💷 🦻 📥 X 🛓 🐁 🛛 Output Preview											
	ID	Test Type	Specified α	Power	Sample Size	λc	λt	<u></u> 01	D	γc	γt	nt/nc
GI		2-Sided	0.05	0.9		1.5		0.667			0.66	1
କା		2-Sided	0.05	0.902	277		1	0.667		0.66		1

Negative binomial models are increasing in popularity for medical research, and as the industry standard for trial design, East continues to evolve by incorporating sample size

methods for count data. These models allow the count to vary around the mean for groups of patients instead of the population means. Additionally, increased variability does lead to a larger test population; consequently the balance between power, sample size and duration of observation needs to be evaluated.

Reference: Oliver N. Keene, Mark R. K. Jones, Peter W. Lane, Julie Anderson (2007). Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study. Pharmaceutical statistics, 6, 89-97

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 12 Non-Inferiority Trials Given Accrual Duration and Accrual Rates 273
 13 Superiority Trials Given Accrual Duration and Study Duration 293
- 14 Non Inferiority Trials Given Accrual Duration and Study Duration 315

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10 *Tutorial: Survival Endpoint*

This tutorial introduces you to East 6, using examples for designing a clinical trial to compare survival in two groups. It is suggested that you go through the tutorial while you are at the computer, with East 6 running in it.

10.1 A Quick Feel of the Software

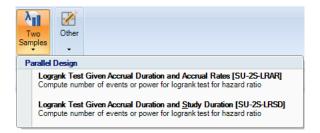
P Page State	(<u>)</u>		East 6 - [Log]	- s ×
arrow Arrow Main Main Image: State	One Two Man Serrole Samples Serrol	y Regression es Barroles Samples Sampl	Two Two Other e Samples Samples	_ # 1
VelCome to East 6 VelCome to East 6 <t< th=""><th>Library 4</th><th>Faa</th><th>😲 Welcome to East 6 X</th><th>Help 5</th></t<>	Library 4	Faa	😲 Welcome to East 6 X	Help 5
sample size Re-estimation Normal 31 Aug 2013	<	cycel architect (1.0.0) cycel architect (1.0.0) time: 0512210 pm.	Copen Tutorial Cost Number of Construction Cost Number of Number of Construction Cost Number of Numer of Number of Number of Number of Number of Nu	
		Sample Size Re-estimation Normal 31 Aug 2013		View a Beady

When you open East 6, the screen will look as shown below.

This is the **Welcome** screen of East 6 which enables us to open the tutorial file, select any design and open any existing workbook. Close this screen by clicking the Cancel button.

In the tabs bar at the top of the ribbon, Design tab is already selected. Each tab has its own ribbon. All the commands buttons under Design tab are displayed in its ribbon, with

suggestive icons. These commands have been grouped under the categories of Continuous, Discrete, Count, Survival and General. For this tutorial, let us explore the command **Two Samples** under **Survival** category. In East, we use the terms 'time to event' and 'survival' interchangeably. Click on **Two Samples**. You will see a list of action items, which are dialog box launchers.



Click on **Logrank Test Given Accrual Duration and Study Duration**. You will get the following dialog box in the work area.

Design: Survival End	dpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Study Duration	🕑 .88 .88 📼 Help
Design Type: Superiority Nu Design Parameters Accrual/Dropout Info	imber of Looks: 1 -	Log Rank Test Given Accrual Duration and Study
Test Type: 1-Sided Type I Error (a): 9002 Pogger: 0.9 Sample Sige (n): Computed No. of Egents: Computed Allocation Batio: 1 (n_1/n_2) 1	♥ of Hazard Reces: ▲ (nput Method: Hazard Rates ● Hazard Ratio (Optional) Alternative ● Hazard Ratio 0,1/A,1 0.5 ● Log Hazard Ratio 0,1/A,1 0.693 Period Starting at: Hoard Rate Hazard Rate, 0.003 1 0.0000 0.035 0.017 Variance of Log Hazard Ratio © Null ○ Alternative	Duration Duration East enables us to design and analyza design analyz

This dialog box is for computing Sample Size (n) and Number of Events. All the default input specifications under the tab Design Parameters are on display: Design Type=Superiority, Number of Looks=1, Test Type=1-Sided, Type-1 Error (α)=0.025, Power (1- β)=0.9, Allocation Ratio (n_t/n_c)=1, # of Hazard Pieces=1, Input Method=Hazard Rates, Hazard Ratio (λ_t/λ_c)=0.5, Log Hazard Ratio In(λ_t/λ_c)=-0.693, Hazard Rate (Control)=0.0347, Hazard Rate (Treatment)=0.0173, and Variance of Log-Hazard Ratio=Null. There are two radio buttons in this dialog box, one at the side of Power (1- β) box and the second at the side of the combined

boxes for Sample Size (n) and Number of Events. By default, the latter radio button is selected indicating that the items against this radio button are to be computed using all other inputs. Similarly, if the first radio button is selected, then Power will be computed using all other inputs.

Now click on the tab Accrual/Dropout and you will see the following dialog box.

Accrual Info			Piecewise	e Dropout Infor	mation	
Accrual Duration:	22 S <u>t</u> udy D	uration:	38 # of Piece	s: 0 🔻	Input <u>M</u> ethod:	Hazard Rates 🔹
# of Accrual <u>P</u> erio	ds: 1 🔻		Period #	Starting At	Hazard Rate (Control)	Hazard Rate (Treatment)
Period #	At Cum. % Accrued					
1 22	.000 100.000					

The default specifications in this dialog box are: Subjects are followed=Until End of Study, Accrual Duration=22, Study Duration=38, # of Accrual Periods=1, and no Dropouts. Now accept all the default specifications that are displayed for this single look design and be ready to compute the Sample Size (n) and the Number of Events for the design. Click Compute.

At the end of the computation, you will see the results appearing at the bottom of the screen, in the Output Preview pane, as shown below.

•	ID	Desi Typ	-	No. of Looks	Test Type	Specifie α	ed I	Power	nt/n	Sampl Size		Expected SS (H0)	Expected SS (H1)	Maxin Ever		Exp. Eve (H0)	nts	Exp. Even (H1)	ts
۸I	Des 1	Superi	ority	1	1-Sided	0.02	25	0.902		1 18	32	182	182		88		88	1	88
C	omm. (Dur			Accrual ion (H0)				zard Rat (Alt.)		Study Juration		Exp. Study Juration (H0	Exp. S Duratio		Var	(Log HR)	Aco	No. of rual Perioc	ds
		22		22	2	22			0.5	38		30.75	8 3	37.959		Null			1

This single row of output preview contains relevant details of all the inputs and the computed results for events and accruals. The maximum value for events is 88 and the committed accrual is 182 subjects. Since this is a fixed-look design, the expected events are same as the maximum required. Click anywhere in this row, and then click on the *icon* to get a

	Des 1
Mnemonic	SU-2S-LRSD
Test Parameters	
Design Type	Superiority
No. of Looks	1
Test Type	1–Sided
Specified a	0.025
Power	0.902
Model Parameters	
Hazard Ratio (Alt.)	0.5
Var (Log HR)	Null
Allocation Ratio (nt/nc)	1
Accrual & Dropout Parameters	
Subjects are Followed	Until End of Study
No. of Accrual Periods	1
No. of Dropout Pieces	0
Sample Size	
Maximum	182
Expected Under H0	182
Expected Under H1	182
Events	
Maximum	88
Expected Under H0	88
Expected Under H1	88
Study Duration	
Maximum	38
Expected Under H0	30.758
Expected Under H1	37.959
Accrual Duration	
Maximum	22
Expected Under H0	22
Expected Under H1	22

detailed display in the upper pane of the screen as shown below.

The contents of this output, displayed in the upper pane, are the same as what is contained in the output preview row for Design1 shown in the lower pane, but the upper pane display is easier to read and comprehend. The title of the upper pane display is **Output Summary**. This



is because, you can choose more than one design in the Output Preview pane and the display in the upper pane will show the details of all the selected designs in juxtaposed columns.

The discussion so far gives you a quick feel of the software for computing the required events and sample size for a single look survival design. We have not discussed about all the icons in the output preview pane or the library pane or the hidden Help pane in the screen. We will describe them taking an example for a group sequential design in the next section.

10.2 Group Sequential Design for a Survival Superiority Trial

- 10.2.1 Background Information on the study 10.2.2 Creating the design in East 10.2.3 Design Outputs
- **10.2.4 East icons explained 10.2.5 Saving created designs 10.2.6 Displaying Detailed Output**
- 10.2.7 Comparing Multiple Designs 10.2.8 Events vs. Time plot 10.2.9 Simulation
- 10.2.10 Interim Monitoring

10.2.1 Background Information on the study

The randomized aldactone evaluation study (RALES) was a double-blind multicenter clinical trial of aldeosterone-recepter blocker vs. placebo published in New England Journal of Medicine (vol 341, 10, pages 709-717, 1999). This trial was open to patients with severe heart failure due to systolic left ventricular dysfunction. The Primary endpoint was all-causes mortality. The anticipated accrual rate was 960 patients/year. The mortality rate for the placebo group was 38%. The investigators wanted 90% power to detect a 17% reduction in the mortality hazard rate for the Aldactone group (from 0.38 to 0.3154) with $\alpha = 0.05$, 2-sided test. Six DMC meetings were planned. The dropout rate in both the groups is expected to be 5% each year. The patient accrual period is planned to be 1.7 years and the total study duration to be 6 years.

10.2.2 Creating the design in East

For our purpose, let us create our own design from the basic details of this study. Now start

afresh East. On the Design tab, click on **Two Samples** under **Survival** category. You will see a list of action items, which are dialog box launchers.



Click on the second option **Logrank Test Given Accrual Duration and Study Duration**. You will get the following dialog box in the work area.

Design: Survival End	oint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Study Duration	😧 🕺 🐭 🐨 Help 🕴
Design Type: Superiority Nur Design Parameters Accrual / Dropout Info	nber of Looks: 1 •	Log Rank Test Given Accrual Duration and Study Duration
Test Type: 3-Sided Type I: Error (x): 0.905 Poyer: 0.90 Sample Size (n): Computed No. of Egress: Computed Allocation gato: 1	e of <u>Hazard</u> Races: <u>1</u> • [rput Method <u>Hazard Rates</u> • D Ha <u>zard</u> Rates (Optional) O Ha <u>zard</u> Ratio (Do ₁ , Λ ₂ ,) 0 Log Ha <u>zard</u> Ratio (n ₀ , Λ ₂) 0 Log Ha <u>zard</u> Ratio (n ₀ , Λ ₂) 0.05 0.05 0.017 0.000 0.035 0.017 Variance of Log Ha <u>zard</u> Rate 0 <u>Mull</u> ○ Alternative	East results us to East results us to subdies where time to event is the endpoint of interest. In contrast, in contrast to studies involving nomai and binomial endpoints, the statistical power study is determined, not by the number of subjects accrued, but rather by the number of events observed. One usually accrues a larger

All the specifications you see in this dialog box are default values, which you will have to modify for the study under consideration.

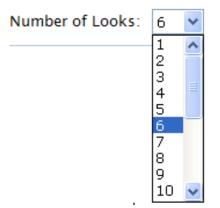
Now, let the Design Type be Superiority.

Design Type:	Superiority 🔹
	Superiority
1	Noninferiority

Next, enter 6 in the Number of Looks box. You can see the range of choices for the number of



looks is from 1 to 20.



Immediately after this selection, you will see a new tab **Boundary Info** added to the input dialog box. We will look into this tab, after you complete the filling of current tab **Design Parameters**.

Next, choose 2-Sided in the Test Type box.

Te <u>s</u> t Type:	2-Sided	*
	1-Sided	
	2-Sided	
	2-Sided (Asymmetric)	

Next, enter 0.05 in the Type-1 Error (α) box, and 0.9 in the Power box.

Type I <u>E</u> rror (α):	0.05	
Po <u>w</u> er:	0.9	0

Next enter the specifications for survival parameters. Keep **# of Hazard Pieces** as 1. Click on the check box against Hazard Ratio and choose Hazard Rates as the Input Method. Enter 0.83 as the Hazard Ratio and 0.38 as the Hazard Rate (Control). East computes and displays the Hazard Rate (Treatment) as 0.3154. Keep the default choice of Null for Variance of Log-Hazard

Ratio. Now the dialog box will look as shown below.

	ard Pieces:	1 V	Input Method: Haza	rd Rates 🔹 🔻
⊡⊻i Ha <u>z</u> ar	d Ratio (Opt	lional)		Alternative
⊙ Hazar <u>o</u>	<u>d</u> Ratio	(λ_t / λ_c)		0.83
O Log Ha	azard Ratio	$ln(\lambda_t^{}/\lambda_c^{})$		-0.186
Period #	Starting At	Hazard Rate (Control)	Hazard Rate (Treatment: Alt.)	
1	0.000	0.38	0.3154	
Variance	of Log Haz	ard Ratio		
⊙ <u>N</u> ull	2	O Alternati <u>v</u> e		

Next click the tab **Accrual/Dropout Info**. Keep the specification 'Until End of Study' for **Subjects are followed**. Enter 1.7 as **Accrual Duration** and 6 as **Study Duration**. Keep **# of Accrual Periods** as 1. Change the **# of Pieces** for dropouts to 1. Choose 'Prob. of Dropout' as the **Input Method** for entering information on dropouts. Enter 0.05 as probability of dropout at end of 1 year for both the groups. Now the dialog box will appear as shown below.

Accrual Info Accrual <u>D</u> ura	ition:	1.7 S <u>t</u> udy Du	ration: 6	Piecewise I # of P <u>i</u> eces:	Prob. of Dropout		
of Accrual	Periods: 1	-		Period #	By	Prob. of Dropout (Control)	Prob. of Dropout (Treatment)
Period #	At	Cum. % Accrued		1	1.000	0.05	0.05
1	1.700	100.000					

Now click on the **Boundary Info** tab. In the dialog box of this tab, you can specify stopping boundaries for efficacy or futility or both. For this trial, let us consider only Efficacy boundaries only. Choose 'Spending Functions' as the Efficacy Boundary Family.

Boundary Family:	Spending Functions 🛛 👻
	None
	Spending Functions
	Haybittle Peto (p-value)
	Wang-Tsiatis

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Choose 'Lan-DeMets' in the Spending Function box.

Spending Function:	Lan-DeMets	*
	Rho Family Gamma Family	
	Lan-DeMets Interpolated	
	· · ·	

Choose 'OF' in the Parameter box.

OF	*
OF	
PK	

Next, click the radio button near 'Equal' for Spacing of Looks.

Choose 'Z Scale' in the Efficacy Boundary Scale box.

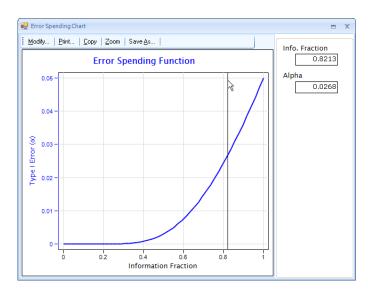
Z Scale 🔷 💊
Z Scale
Score Scale
In(HR) Scale HR Scale
HR Scale
p-value Scale

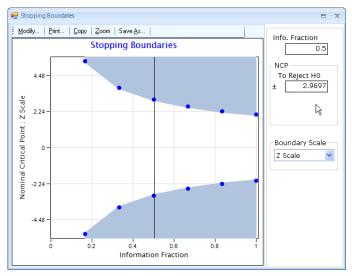
In the table below of look-wise details, the columns - Info Fraction, Cumulative Alpha Spent, and the upper and lower efficacy boundaries are computed and displayed as shown here. Scroll a little bit to see the sixth look details.

Look #	Info.	Cum.α	Efficacy Boundary			
LOOK #	Fraction	Spent	Upper	Lower		
1	0.167	0.0000	5.3666	-5.3666		
2	0.333	0.0002	3.7103	-3.7103		
3	0.500	0.0031	2.9697	-2.9697		
4	0.667	0.0121	2.5387	-2.5387		
5	0.833	0.0282	2.2522	-2.2522		

The two icons *and* and *represent buttons for Error Spending Function chart and* Stopping Boundaries chart respectively. Click these two buttons one by one to see the

following charts.







10.2.3 Design Outputs

Now you have completed specifying all the inputs required for a group sequential trial design and you are ready to compute the required events and sample size or accruals for the trial. Click on the **Compute** button. After the computation is over, East will show in the Output Preview pane the following results:

	ID	Design Type	No. of Looks	Test Type	Specified α	Power	nt/nc	Spacing of Looks	Efficacy Boundar		Expected SS (H0)	Expect SS (H1		Exp. Events (H0)	Exp. Events (H1)
۸II	Des 1	Superiority	6	2-Sided	0.05	0.9	1	Equal	LD (O) 1646	1645.996	1645.9	986 1243	1233.984	903.595
Co	mm. Ao (Dur.)	cr. Exp. A Duratio	ccrual on (H0)	Exp. Acc Duration		ard Ratio (Alt.)	Stu Dura		Study ion (H0)	Exp. Stud Duration (H	Var (L	og HR)	No. of Accrual Periods		
		1.7	1.7		1.7	0.8	3	6	5.354	3.7	25	Null	۱		

This single row of output preview contains relevant details of all the inputs and the computed results for events and accruals. The maximum required Events is computed as 1243 and the Committed Accrual to be 1646 subjects. The expected Events under H0 and H1 are estimated to be 1234 and 904 respectively. The expected Study Duration under H0 and H1 are 5.354 and 3.725 respectively.

Click anywhere in this Output Preview row and then click on 🛄 icon to get a summary in

the upper pane of the screen as shown below.

	Des1
Mnemonic	SU-2S-LRSD
Test Parameters	
Design Type	Superiority
No. of Looks	6
Test Type	2–Sided
Specified α	0.05
Power	0.9
Model Parameters	
Hazard Ratio (Alt.)	0.83
Var (Log HR)	Null
Allocation Ratio (nt/nc)	1
Boundary Parameters	
Spacing of Looks	Equal
Efficacy Boundary	LD (OF)
Accrual & Dropout Parameters	
Subjects are Followed	Until End of Study
No. of Accrual Periods	1
No. of Dropout Pieces	1
Sample Size	
Maximum	1646
Expected Under HO	1645.996
Expected Under H1	1645.986
Events	
Maximum	1243
Expected Under HO	1233.984
Expected Under H1	903.595
Study Duration	
Maximum	6
Expected Under HO	5.354
Expected Under H1	3.725
Accrual Duration	
Maximum	1.7
Expected Under HO	1.7
Expected Under H1	1.7

10.2.4 East icons explained



In the 'Output Preview' pane, you see the following icons in the upper row.



The functions of the above icons are as indicated below. The tooltips also will indicate their functions.

Output Summary(The output summary of selected design(s) will appear in the upper pane)



- Save in Workbook (Save one or more selected designs in a workbook)
- Delete (Delete one or more selected designs)
- Rename (Rename Design names)
- Print (Print selected designs)
- Display Precision (Local Settings)
- Filter (Filter and select designs according to specified conditions)

Show/Hide Columns (Show/Hide Columns of the designs in the Output Preview panel)

The following icons can be seen at the right end of Output Preview pane and Output Summary or Input/Output window respectively. Their functions are:

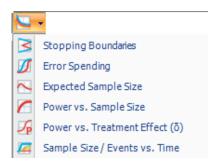
X

- Maximize Output Preview Pane
- Minimize Output Preview Pane

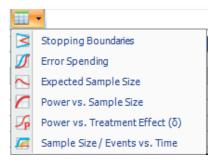
You may also notice a row of icons at the top of Output Summary window as shown below.



The first icon is for Plot (Plots of a selected design will appear in a pop-up window).



The second icon is for Show Tables (The data for different plots can be displayed in tabular form in pop-up windows).



If you have multiple designs in the output summary window, the third icon becomes active



and can be used to move the order of those columns in the Output Summary.



The fourth icon is to print the Output Summary window.

As an example, if you click Power vs. Sample Size under Plot icon, you will get the following

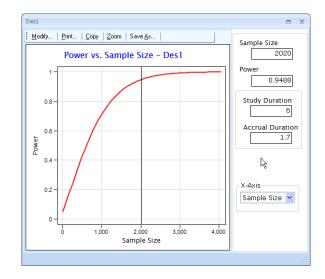


chart.

If you want to see the data underlying the above chart, click Show Table icon and click Power



From	То	Step Size		
4	3034.668	61.85	Tabulate	
Sample Size	Des1			
4	0.053			1
65.85	0.099			
127.701	0.146			
189.551	0.194			-
251.401	0.243			
313.252	0.291			
375.102	0.338			
436.953	0.384			
498.803	0.428			
560.653	0.471			
622.504	0.511			
684.354	0.55			
746.204	0.586			
808.055	0.621			

vs. Sample Size. You will see the following table in a pop-up window.

You can customize the format of the above table and also save it as case data in a workbook. You may experiment with all the above icon / buttons to understand their functions.

10.2.5 Saving created Designs in the library and hard disk

In the Output Preview pane, select one or more design rows and click the 🖄 icon,

The selected design(s) will then get added as a node(s) in the current workbook, as shown

below.



The above action only adds the design to the workbook node in the library and it is not saved in the hard disk. For saving in the hard disk, you may either save the entire workbook or only the design by right-clicking on the desired item and choosing save or save as options.

Here in the library also, you see rows of icons.

Library	1						₽
۹.			- 1	- 1	×	S	
IM I	а,	н	×		A		

Some of these icons you have already seen. The functions of other icons are:



IM

Details (Details of a selected design will appear on the upper pane in the work area)

- Output Settings (Output Settings can be changed here)
- Simulate (Start the simulation process for any selected design node)

Interim Monitoring (Start the Interim Monitoring process for any selected design)

Displaying Detailed Output 10.2.6

Select the design from the Library and click the sign or Right-click on the Des1 node in



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the library and click Details.



You will see the detailed output of the design displayed in the Work area.

Sample Size Information

Design: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Study Duration

Test Parameters	
Design ID	Des2
Design Type	Superiority
Number of Looks	6
Test Type	2-Sided
Specified a	0.05
Power	0.9
Model Parameters	
$HR = \lambda_t / \lambda_c$	
Under H0	1
Under H1	0.83
$\delta = \ln(HR)$	-0.186
Var (Log HR)	Null
Allocation Ratio (n _t /n _c)	1
Boundary Paramete	rs
Spacing of Looks	Equal
Efficacy Boundary	LD (OF)
Accrual/Dropout Pa	rameters
Accrual Duration	1.7
Max Study Duration	6
Dropout	Yes

	Control Arm	Treatment Arm	Total
Sample Size (n)			
Maximum	822	824	1646
Expected H1	822.993	822.993	1645.986
Expected H0	822.998	822.998	1645.996
Events (s)			
Maximum	643	600	1243
Expected H1	510.541	457.198	903.595
Expected H0	618.84	618.84	1233.984
Dropouts (d)			
Maximum	87	98	185
Expected H1	64.004	70.207	134.211
Expected H0	83.39	83.39	166.781
Max	imum Informa	tion (I):310.75	

Accrual and Study Duration

	Accrual Duration	Study Duration
Maximum	1.7	5.99
Expected H1	1.7	3.725
Expected H0	1.7	5.354

⊖ Stopping Boundaries: Look by Look

	Info.		Cumulative	Bound	laries		
Look #	Fraction	Events (s)	α	Efficacy Z			
"	(s/s_max)	(3)	Spent	Upper	Lower		
1	0.167	207	7.926E-8	5.369	-5.369		
2	0.333	414	2.057E-4	3.712	-3.712		
3	0.5	622	0.003	2.968	-2.968		
4	0.667	829	0.012	2.538	-2.538		
5	0.833	1036	0.028	2.252	-2.252		
6	1	1243	0.05	2.045	-2.045		



Look	Info.	Sample	Events	Dropouts	Pipeline	Analysis	Boundary Cross (Incren	sing Probability nental)
#	Fraction (s/s max)	Size (n)	(s)	(d)	(n-s-d)	Time	Effic	acy
	(3/3_110X)						Upper	Lower
1	0.167	1112	207	28	877	1.148	3.963E-8	3.963E-8
2	0.333	1628	414	56	1158	1.681	1.028E-4	1.028E-4
3	0.5	1646	622	84	940	2.201	0.001	0.001
4	0.667	1646	829	112	705	2.867	0.005	0.005
5	0.833	1646	1036	140	470	3.807	0.008	0.008
6	1	1646	1243	168	235	5.413	0.011	0.011

─Events, Sample Size, Dropouts, Pipeline and Analysis Times: Look by Look (Under H0)

─Events, Sample Size, Dropouts, Pipeline and Analysis Times: Look by Look (Under H1)

Look	Info.	Sample	Events	Dropouts	Pipeline	Analysis	Boundary Cross (Increm	
#	Fraction (s/s max)	Size (n)	(s)	(d)	(n-s-d)	Time	Effic	acy
	(3/3_max)						Upper	Lower
1	0.167	1160	207	31	922	1.198	9.783E-12	2.808E-5
2	0.333	1646	414	62	1170	1.753	1.026E-8	0.035
3	0.5	1646	622	92	932	2.326	5.886E-8	0.226
4	0.667	1646	829	123	694	3.067	7.835E-8	0.303
5	0.833	1646	1036	154	456	4.125	5.829E-8	0.218
6	1	1646	1243	185	218	5.99	3.309E-8	0.119

Survival Information : Hazard Rates

Accrual Information

Dropout Information : %Prob. of Dropout

Note: Period 1 hazard rates apply after time 1.

Variable Follow-Up Design: All subjects are followed until failure, drop out or end of study.

10.2.7 Comparing Multiple Designs

Click on Des1 row and then click Edit icon 🕺 . You will get the input dialog box in the upper pane. Change the Power value to 0.8 and then click Compute.

You will see now Des2 is created and a row added to Output Preview pane as shown below.

	ID 🔺	Design Type		Test Type	Specified α	Power	nt/nc	Spacing of Looks	Efficacy Boundary		Expected SS (H0)			Exp. Events (H0)	Exp. Events (H1)
À1	Des 1	Superiority	6	2-Sided	0.05	0.9	1	Equal	LD (OF)	1646	1645.996	1645.986	1243	1233.984	903.595
y11	Des2	Superiority	6	2-Sided	0.05	0.8	1	Equal	LD (OF)	1233	1232.997	1232.995	931	924.247	736.316

Click on Des1 row and then keeping Ctrl key pressed, click on Des2 row. Now both the rows will be selected. Next, click the Output Summary icon \blacksquare .

Now you will see the output details of these two designs displayed in the upper pane

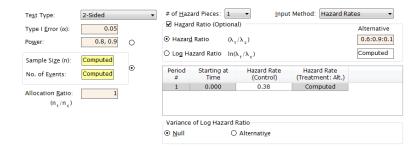


Compare Designs in juxtaposed columns, as shown below.

	Des 1	Des2
Mnemonic	SU-2S-LRSD	SU-2S-LRSD
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	6	6
Test Type	2-Sided	2-Sided
Specified α	0.05	0.05
Power	0.9	0.8
Model Parameters		
Hazard Ratio (Alt.)	0.83	0.83
Var (Log HR)	Null	Null
Allocation Ratio (nt/nc)	1	1
Boundary Parameters		
Spacing of Looks	Equal	Equal
Efficacy Boundary	LD (OF)	LD (OF)
Accrual & Dropout Parameters		
Subjects are Followed	Until End of Study	Until End of Study
No. of Accrual Periods	1	1
No. of Dropout Pieces	1	1
Sample Size		
Maximum	1646	1233
Expected Under H0	1645.996	1232.997
Expected Under H1	1645.986	1232.995
Events		
Maximum	1243	931
Expected Under H0	1233.984	924.247
Expected Under H1	903.595	736.316
Study Duration		
Maximum	6	6
Expected Under H0	5.354	5.352
Expected Under H1	3.725	4.203
Accrual Duration		
Maximum	1.7	1.7
Expected Under H0	1.7	1.7
Expected Under H1	1.7	1.7

In a similar way, East allows the user to easily create multiple designs by specifying a range of values for certain parameters in the design window. For example, in a survival trial the **Logrank Test given Accrual Duration and Study Duration** design allows the input of multiple key parameters at once to simultaneously create a number of different designs. For example, suppose in a multi-look study the user wants to generate designs for all combinations of the following parameter values: Power = 0.8 and 0.9, and **Hazard Ratio - Alternative** = 0.6, 0.7, 0.8 and 0.9. The number of combinations is $2 \times 4 = 8$. East creates all permutations using only a

single specification under the **Design Parameters** tab in the design window. As shown below, the values for **Power** are entered as a list of comma separated values, while the alternative hazard ratios are entered as a colon separated range of values, 0.6 to 0.9 in steps of 0.1.



East computes all 8 designs and displays them in the **Output Preview** window:

	ID	Design Type	No. of Looks	Test Type	Specified α	Power	nt/nc	Spacing of Looks	Efficacy Boundary	Sample Size	Expected SS (H0)	Expected SS (H1)	Maximum Events	Exp. Events (H0)	Exp. Events (H1)
۸ _{II}	Des 3	Superiority	6	2-Sided	0.05	0.801	1	Equal	LD (OF)	177	176.998	176.999	124	123.101	98.054
yII	Des4	Superiority	6	2-Sided	0.05	0.8	1	Equal	LD (OF)	349	348.998	348.999	254	252.158	200.903
۸II	Des 5	Superiority	6	2-Sided	0.05	0.8	1	Equal	LD (OF)	866	865.997	865.997	649	644.291	513.311
۱Ľ	Des6	Superiority	6	2-Sided	0.05	0.8	1	Equal	LD (OF)	3789	3788.999	3788.985	2910	2888.9	2301.893
yII	Des7	Superiority	6	2-Sided	0.05	0.901	1	Equal	LD (OF)	237	236.997	236.998	166	164.797	120.548
y ^{II}	Des 8	Superiority	6	2-Sided	0.05	0.901	1	Equal	LD (OF)	468	467.997	467.996	340	337.535	246.997
y.	Des9	Superiority	6	2-Sided	0.05	0.9	1	Equal	LD (OF)	1157	1156.996	1156.99	867	860.714	630.127
yII	Des10	Superiority	6	2-Sided	0.05	0.9	1	Equal	LD (OF)	5063	5062.998	5062.957	3888	3859.809	2826.252

East provides the capability to analyze multiple designs in ways that make comparisons between the designs visually simple and efficient. To illustrate this, a selection of a few of the above designs can be viewed simultaneously in both the **Output Summary** section as well as in the various tables and plots. The following is a subsection of the designs computed from the above example with differing values for number of looks, power and hazard ratio. Designs



	Des 3	Des 5	Des7	Des10
Mnemonic	SU-2S-LRSD	SU-2S-LRSD	SU-2S-LRSD	SU-2S-LRSD
Test Parameters				
Design Type	Superiority	Superiority	Superiority	Superiority
No. of Looks	6	6	6	6
Test Type	2-Sided	2-Sided	2-Sided	2-Sided
Specified α	0.05	0.05	0.05	0.05
Power	0.801	0.8	0.901	0.9
Model Parameters				
Hazard Ratio (Alt.)	0.6	0.8	0.6	0.9
Var (Log HR)	Null	Null	Null	Null
Allocation Ratio (nt/nc)	1	1	1	1
Boundary Parameters				
Spacing of Looks	Equal	Equal	Equal	Equal
Efficacy Boundary	LD (OF)	LD (OF)	LD (OF)	LD (OF)
ccrual & Dropout Parameters				
Subjects are Followed	Until End of Study			
No. of Accrual Periods	1	1	1	1
No. of Dropout Pieces	1	1	1	1
Sample Size				
Maximum	177	866	237	5063
Expected Under H0	176.998	865.997	236.997	5062.998
Expected Under H1	176.999	865.997	236.998	5062.957
Events				
Maximum	124	649	166	3888
Expected Under H0	123.101	644.291	164.797	3859.809
Expected Under H1	98.054	513.311	120.548	2826.252
Study Duration				
Maximum	6	6	6	6
Expected Under H0	4.534	5.253	4.532	5.597
Expected Under H1	4.257	4.214	3.786	3.703
Accrual Duration				
Maximum	1.7	1.7	1.7	1.7
Expected Under H0	1.7	1.7	1.7	1.7
Expected Under H1	1.7	1.7	1.7	1.7

are displayed side by side, allowing details to be easily compared:

In addition East allows multiple designs to be viewed simultaneously either graphically or in tabular format: Notice that all the four designs in the Output Summary window are selected. Following figures compare these four designs in different formats.

			S	topping Bo	undaries				0.0
oundary So Des3	ales : Z Sca	ale	•					Setting	js
Look #	Info.	Events	Cum. α	Bour	ndaries	Samp	le Size	Analys	is 7
	Fraction		Spent	Efficacy	Boundary				
				Upper	Lower	Under H0	Under H1	Under H0	ιE
1	0.169	21	0	5.322	-5.322	116	130	1.113	
2	0.331	41	0	3.727	-3.727	168	177	1.605	
3	0.5	62	0.003	2.969	-2.969	177	177	2.077	
4	0.669	83	0.012	2.532	-2.532	177	177	2.663	
5	0.831	103	0.028	2.258	-2.258	177	177	3.406	-
									F.
Des5									
Look #	Info. Fraction	Events	Cum. α	Bour	ndaries	Samp	le Size	Analys	is 7
	Fraction		Spent	Efficacy	Boundary				
				Upper	Lower	Under H0	Under H1	Under H0	E
1	0.166	108	0	5 371	-5 371	583	613	1 143	

Stopping Boundaries (table)

Expected Sample Size (table)

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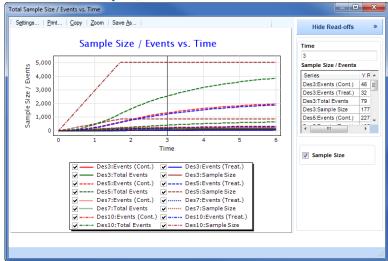


			E	xpected Ev	ents Vs. Effect Size (In(δ))	0.0 00.
Range for Eff	ect Siz		p Size	Output	s 🔻	
-0.5108	0.51	08 0.0	209	Tabulate]	
Effect Size (n(δ))	Des3	Des 5	Des7	Des10	
-0.511		98.0543	274.1463	120 548	731.0397	
-0.49				123.7632		
-0.469		102.1151		126.996	824,7602	
-0.448				130.2205		
-0.427				133,4095		
-0.407					1021.3545	
-0.386			345.8192		1086.5691	
-0.365		111.1467	362.1425	142.4828	1145.0984	
-0.344		112.6736	380.1161	145.2542	1195.5042	
-0.323		114.09	399.8297	147.8607	1239.3112	
-0.302		115.3919	421.2725	150.2848	1281.3259	
-0.281		116.5778	444.2846	152.5131	1328.9859	
-0.261		117.6478	468.5196	154.5372	1390.5158	
-0.24		118.6039	493.4314	156.3533	1472.5567	
-0.219		119.4494	518.2999	157.9623	1578.9906	
-0.198		120.1892	542.2995	159.3689	1712.4001	
-0.177		120.829	564.602	160.5817	1877.5152	
-0.156		121.375	584.4919	161.6116	2084.006	
-0.136		121.834	601.4662	162.4716	2345.0551	
-0.115		122.2126	615.2911	163.1753	2666.8597	
-0.094		122.5171	626.0035	163.7364	3028.8096	



Power vs. Sample Size (plot)

Sample Size / Events vs. Time (plot)





This capability allows the user to explore a greater space of possibilities when determining the best choice of study design.

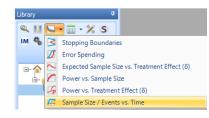
10.2.8 Events vs. Time plot

For survival studies, East provides a variety of charts and plots to visually validate and analyze the design. For example, the **Sample Size / Events vs. Time** plot allows the user to see the rate of increase in the number of events (control and treatment) over time (accrual duration, study duration). An additional feature of this particular chart is that a user can easily update key input parameters to determine how multiple different scenarios can directly impact a study. This provides significant benefits during the design phase, as the user can quickly examine how a variety of input values affect a study before the potentially lengthy task of simulation is employed.

To illustrate this feature what follows is the example from the RALES study. For study details, refer to subsection **Background Information on the study** of this tutorial.

Currently there are ten designs in the **Output Preview** area. Select Des1 from them and save it to the current workbook. You may delete the remaining ones at this point.

To view the **Sample Size / Events vs. Time** plot, select the corresponding node in the **Library** and under the **Charts** icon choose **Sample Size / Events vs. Time**:





Survival parameters for this design can be edited directly through this chart by clicking the **Modify** button. The **Modify Survival Design** window is then displayed for the user to update



design parameters:

		Hazar	d Rates				
liece	Starting At	Control	Treatment	Hazard Ratio			
1	0.000	0.380	0.315	0.830			

To illustrate the benefit of the modification feature, suppose at design time there is potential flexibility in the accrual and duration times for the study. To see how this may affect the number of subsequent events, modify the design to change the **Accrual Duration** to 3 and **Study Duration** to 4. Re-create the plot to view the effect of these new values on the shape and magnitude of the curves by clicking **OK**:



Similar steps can be taken to observe the effect of changing other parameter values on the number of events necessary to adequately power a study.



10.2.9 Simulation

In the library, right-click on the node **Des1** and click **Simulate**. You will be presented with the following Simulation sheet.

Numb	er of Loo <u>k</u> s: 6	w				
Simula	tion Parameters	Response Gene	eration Info A	ccrual/Dropout I	nfo Simulation Control Info	
<u>T</u> rial Type	e: Supe	riority	Ŧ			
Test Type	e: 2-Sid	ed	w			Test Statistic: Logrank 💌
Ma <u>x</u> . # of	f Events:	1243				
Fix at Eac	h Look: Total	No. of Events	-			
Fi <u>x</u> at Eac	h Look: Total			Effic	arv Z	A
Fi <u>x</u> at Eac	h Look: Total	No. of Events Cum. o Upper		Effic	acy Z	ŕ
		Cum. d	x Spent			
Look #	Info. Fraction	Cum. o Upper	x Spent Lower	Upper	Lower	
Look #	Info. Fraction	Cum. d Upper 0.000	x Spent Lower 0.000	Upper 5.369	Lower -5.369	
Look # 1 2	0.167 0.333	Cum. c Upper 0.000 0.000	x Spent Lower 0.000 0.000	Upper 5.369 3.712	Lower -5.369 -3.712	

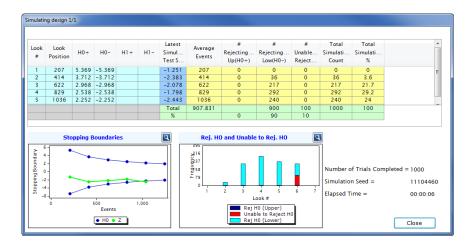
This sheet has four tabs - Simulation Parameters, Response Generation Info, Accrual/Dropout Info, and Simulation Control Info. Additionally, you can click **Include Options** and add some more tabs like Randomization Info or Stratification Info tab and so on. The first three tabs essentially contain the details of the parameters of the design. In the Simulation Control Info tab, you can specify the number of simulations to carry out and specify the file for storing simulation data. Let us first carry out 1000 simulations to check whether the design can reach the specified power of 90%. The Response Generation Info tab, by default, shows the hazard rates for control and treatment. We will use these values in our simulation.

Survival Information										
# of Hazard Pieces 1 Imput Method: Hazard Rates										
□ Hazard Ratio										
_ Hazaro	l Ratio									
		Hazaro	d Rates	Uses and Datis						
D Hazard Piece	Starting At	Hazard	l Rates Treatment	Hazard Ratio						

In the Simulation Control tab, specify the number of simulations as 1000.

	Output Options
Number of Simulations: 1000	Output Type: Case Data 👻
Refresh Frequency: 100	\Box Sa $\underline{v}e$ summary statistics for every simulation run
Random Number Seed	Save subject-level data for simulation runs
⊙ Cloc <u>k</u>	Note: Max. 100,000 records will be saved.
O <u>F</u> ixed 100	
Suppress All Intermediate Output	
<u>P</u> ause after Refresh	
☑ <u>S</u> top At End	

Let us keep the values in other tabs as they are and click **Simulate**. The progress of simulation process will appear in a temporary window as shown below.



This is the intermediate window showing the complete picture of simulations. Close this window after viewing it. You can see the complete simulation output in the details view. A new row, with the ID as Sim1, will be added in Output Preview.

-	ID	Design Type	No. of Looks	Test Type	Specified α	Power	nt/nc	Spacing of Looks	Efficacy Boundary	Sample Size	Expected SS (H0)	Expected SS (H1)	Maximum Events	Exp. Events (H0)	Exp. Events (H1)
y ¹	Des	Superiority	6	2-Sided	0.05	0.9	1	Equal	LD (OF)	1646	1645.996	1645.986	1243	1233.984	903.595
ý,	Sim	Superiority	6	2-Sided		0.9		User Specified	User Specified	1646			1243		

Click on Sim1 row and click the Output Summary icon 🛄 . You will see Simulation Output

summary appearing in the upper pane. It shows that the simulated power as 0.90, indicating that in 900 out of 1000 simulations the boundary was crossed.

	Wbk1:Des1:Sim1				
Mnemonic	SU-2S-LRSD				
Test Parameters					
Design Type	Superiority				
Test Type	2-Sided				
Test Statistic	Logrank				
Power	0.9				
No. of Looks	6				
Model Parameters					
No. of Hazard Pieces	1				
Boundary Parameters					
Efficacy Boundary	User Specified				
Spacing of Looks	User Specified				
Accrual & Dropout Parameters					
Followup Duration	Until End of Study				
No. of Accrual Periods	1				
Sample Size					
Maximum	1646				
Events					
Maximum	1243				
Simulation Results (Overall)					
Average Study Duration	3.741				
Average Sample Size	1645.967				
Average Events	907.831				

You can save Sim1 as a node in the workbook. If you right-click on this node and then click Details, you will see the complete details of simulation appearing in the work area. Here is a

part of it.

Simulation Parameters	
Simulation ID	Sim1
Design Type	Superiority
Number of Looks	6
Test Type	2-Sided
Sample Size (n)	1646
Fix at Each Look	Total No. of Events
Test Statistic	Logrank
Average Events	907.831
Total Accrual Duration	1.7
Avg. Power at Termination	0.9
Simulation Control Para	ameters
Starting Seed	Clock
Number of Simulations	1000

Simulation: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Study Duration

Look #	Average	Avera	ge Events	Average	e Dropouts	Average	Average
LOOK #	Sample Size	Control	Treatment	Control	Treatment	Look Time	Follow up
1	1161.186	112.317	94.683	15.162	15.501	1.199	0.514
2	1644.098	223.105	190.895	30.077	31.235	1.755	0.727
3	1646	332.552	289.448	45.083	47.01	2.326	1.09
4	1646	436.799	392.201	59.967	63.001	3.069	1.454
5	1646	538.154	497.846	75.235	78.8	4.129	1.82
6	1646	636.921	606.079	90.102	94.479	5.981	2.182
Average	1645.967	480.572	427.259	65.096	69.339	3.741	1.593

Simulation Boundaries and Boundary Crossing Probabilities

Look #	Events		daries cacy	Stoppi	ng For	Total Simulations		
LOOK	LVCIII	Upper	Lower	Upper Efficacy	Lower Efficacy	Count	%	
1	207	5.369	-5.369	0	0	0	0.000%	
2	414	3.712	-3.712	0	36	36	3.600%	
3	622	2.968	-2.968	0	217	217	21.700%	
4	829	2.538	-2.538	0	292	292	29.200%	
5	1036	2.252	-2.252	0	240	240	24.000%	
6	1243	2.045	-2.045	0	115	215	21.500%	
Total				0	900	1000		
%				0.000%	90.000%			

10.2.10 Interim Monitoring

Click Des1 node under workbook wbk1 and click the icon. Alternatively, you can right-click the Des1 node and select the item **Interim Monitoring**. In either case, you will see



ner I	nterim Data 🗙	+= 4/ IM								Interim	Monitoring	Dest					
	Information		Test	δ	Standard	Effi	cacy	95% R	CI for δ	Repeated	CP	Predicti					
#	Fraction	Events	Statistic	Ŭ	Error	Upper	Lower	Upper	Lower	p-value		Power	r				
1										[]							
2 3																	
4																	
5																	
6																	
elect	the Look # 1	row for which		is desire	d and click ti	ne "Enter Ir				$n(\lambda_t / \lambda_c) = -$	0.186						
5	Stopping Bou	ndaries	Eve			icacy				Condition	l Power	٩		CP			
Γ					Upper Lo	ower				1			Size				
													-0.188	0.905			
										0.8			-0.169	0.834			
										0.6			-0.122	0.563			
0													-0.099	0.403			
										0.4	\mathbf{X}		-0.076	0.258			
										0.2			-0.052	0.148			
												~ 11	-0.029	0.079			
										0			0.002	0.05			
		0								-0.15	-0.1 -0.0	15 0					
En	ror Spending	Function	Infe	o.	α					Confidence	Intervals	2	Info.	RCI	RCI	Naive CI	Naive
0.05			Fract	ion	u						_		Fraction	Upper	Lower	Upper	Low
0.05																	
0.04		- /															
0.03																	
0.02																	
0.01		1															
		/															

the IM dashboard appearing as shown below.

In the top row, you see a few icons. For now, we will discuss only the first icon EnterInterim Data which represents Test Statistic Calculator. Using this calculator, you will enter the details of interim look data analysis results into the IM dashboard.

Suppose we have the following data used by the Data Monitoring Committee during the first 5 looks of interim monitoring.

Date	Total Deaths	$\hat{\delta}$	$SE(\hat{\delta})$	Z-Statistic
Aug 96	125	-0.283	0.179	-1.581
Mar 97	299	-0.195	0.116	-1.681
Aug 97	423	-0.248	0.097	-2.557
Mar 98	545	-0.259	0.086	-3.012
Aug 98	670	-0.290	0.077	-3.766

The first look was taken at 125 events and the analysis of the data showed the value of δ =

-0.283 and SE(δ)=0.179. First, click the blank row in the IM Dashboard and then click the **ExterInterim Data** icon. Now you can enter the first analysis results into the TS calculator and click Recalc. The Test Statistic value will be computed and the TS calculator will appear as shown below.

Test Statistic Calculator	x
Editing Look #1	
□ Set Current Look as Last	
Cumulative Events:	125
Input for Survival end point Estimate of δ:	-0.283
$\delta = \ln(\lambda_t / \lambda_c)$	-0.205
Standard Error of Estimate of δ:	0.179
- Output	
Test Statistic:	-1.581
Recalc OK	Cancel

Now click on the button 'OK' to get the first look details into IM Dashboard. The following message will appear that some required computations are being carried out.

Í	Computing Look Information
	Provincian
	Processing
Į	

After the computations are over, the output for the first look will appear in the IM Dashboard



as shown below.

Look	Information	Cumulative	Test	δ	Standard	Effi	cacy	95% R	CI for δ	Repeated	СР	Predictive Power
#	Fraction	Events	Statistic	Ŭ	Error	Upper	Lower	Upper	Lower	p-value		
1	0.101	125	-1.581	-0.283	0.179	6.971	-6.971	0.965	-1.531	1	0.999	0.853
2												
3												
4												
5												
6												

For the first look at total number of events, 125, the Information Fraction works out to be 0.101. The efficacy boundaries for this information fraction are newly computed. The Repeated 95% Confidence Interval limits and Repeated p-value are computed and displayed. You may also see that the charts at the bottom of the IM Dashboard have been updated with relevant details appearing on the side.

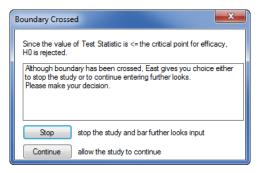
•	125 6.97			Size	CP			
		-6.971	1	-0.285	0.999			
			0.8	-0.256	0.996			
				-0.22	0.982			
			0.6	-0.185	0.936			
				-0.15	0.826			
•			0.4	-0.115	0.64			
			0.2	-0.079	0.412			
				-0.044	0.213			
•			0	0.003	0.088			
500 1,000 1,500			-0.3 -0.2 -0.1 0	0.003	0.004			
rror Spending Function	Info.		Confidence Intervals	Info.	RCI	RCI	Naive CI	Nai
	Fraction			Fraction	Upper	Lower	Upper	Lo
5	0.101 0		1.28	0,101	0,965	-1.531	0.068	-0
. / -	0.101 0		0.96	0.101	0.905	-1.551	0.008	-0
4 / 1			0.64	11				
			0.32	ill –				
			0.32					
2			0.64	11				
			-0.96					
1			1.28					

In a similar way, enter the interim analysis results for the next 3 looks in the IM Dashboard. Now the IM Dashboard will look like this:

Look	Information	Cumulative	Test	δ	Standard	Effi	cacy	95% R	CI for δ	Repeat	CP	Predictive	
#	Fraction	Events	Statistic	Ŭ	Ŭ	Error	Upper	Lower	Upper	Lower	p-value	Ci	Power
1	0.101	125	-1.581	-0.283	0.179	6.971	-6.971	0.965	-1.531	1	0.999	0.853	
2	0.241	299	-1.681	-0.195	0.116	4.423	-4.423	0.318	-0.708	0.66	0.95	0.795	
3	0.34	423	-2.557	-0.248	0.097	3.672	-3.672	0.108	-0.604	0.212	0.999	0.962	
4	0.438	545	-3.012	-0.259	0.086	3.206	-3.206	0.017	-0.535	0.069	1	0.993	
5													
6													

Now again click on the fifth row in IM Dashboard, enter the fifth look results into the Test Statistic Calculator and click OK. This time, the boundary is crossed. A message window

appears as shown below.



Click Stop and you will see the details of all the looks in the IM Dashboard as shown below.

Look	Information	Cumulative	Test	5	Standard	Effic	cacy	95% RC	CI for δ	Repeated	СР	Predictive
#	Fraction	Events	Statistic	0	Error Upper		Lower	Upper	Lower	p-value CP		Power
1	0.101	125	-1.581	-0.283	0.179	6.971	-6.971	0.965	-1.531	1	0.999	0.853
2	0.241	299	1.681	0.195	0.116	4.423	-4.423	0.708	-0.318	0.66	0.95	0.795
3	0.34	423	-2.557	-0.248	0.097	3.672	-3.672	0.108	-0.604	0.212	0.999	0.962
4	0.438	545	-3.012	-0.259	0.086	3.206	-3.206	0.017	-0.535	0.069	1	0.993
5	0.539	670	-3.766	-0.29	0.077	2.872	-2.872	-0.069	-0.511	0.008	NA	NA

The final Adjusted Inference output also appears as displayed below.

Final In	ference
Final Outputs at Look #	5
Adj. p-value	0.001
Adj. Pt. Est. for δ	-0.266
Adj. 95% CI for δ	
Upper Confidence Bound	-0.104
Lower Confidence Bound	-0.424
Post-Hoc Power	

One important point to note here is that this study got over almost about 2 years ahead of planned schedule, because of the very favorable interim analysis results.

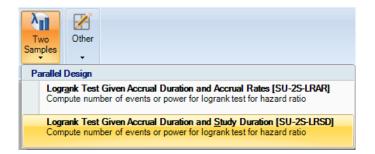
This completes the Interim Monitoring exercise in this trial.

10.3 User Defined R Function



East allows you to customize simulations by inserting user-defined R functions for one or more of the following tasks: generate response, compute test statistic, randomize subjects, generate arrival times, and generate dropout information. The R functionality for arrivals and dropouts will be available only if you have entered such information at the design stage. Although the R functions are also available for all normal and binomial endpoints, we will illustrate this functionality for a time-to-event endpoint. Specifically, we will use an R function to generate Weibull survival responses.

Start East afresh. On the **Design** tab, click **Survival: Two Samples** and then **Logrank Test Given Accrual Duration and Study Duration**.



Choose the design parameters as shown below. In particular, select a one sided test with

type-1 error of $\alpha = 0.025$.

Γ	ign: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Giv	ren Accrual Duration and Study Durati
Design Type: Superiority	nber of Loo <u>k</u> s: 1 🔹	
Design Parameters Accrual/Dropout In		
Test Type: 1-Sided Type I Error (α): 0.025 Power: 0.9	# of Hazard Pieces: 1 Input Method: Hazard Rater Hazard Ratio (Optional) Hazard Ratio ($\Lambda_{\chi}/\Lambda_{c}$)	Alternative
Sample Size (n): Computed No. of Events: Computed	○ Log Hazard Ratio $In(\lambda_t / \lambda_c)$ Period Starting Hazard Rate Hazard Rate # At (Control) (Treatment: Alt.)	-0.693
Allocation <u>R</u> atio: 1 (n _t /n _c)	1 0.000 0.035 0.017	
	Variance of Log Hazard Ratio O Null O Alternative	

Click **Compute** and save this design (Des1) to the **Library**. Right-click Des1 in the **Library** and click **Simulate**. In the **Simulation Control Info** tab, check the box for **Suppress All Intermediate Input**. Type 10000 for **Number of Simulations** and select **Clock** for **Random Number Seed**.

Simulation Parameters Response Generation Info	Accrual/Dropout Info Simulation Control Info
Number of Simulations: 10000 Refresh Frequency: 1000 Random Number Seed O Clock O Fixed 100	Output Options Output Type: Case Data Save summary statistics for every simulation run Save subject-level data for simulation runs Note: Max. 100,000 records will be saved.

In the top right-hand corner for the input window, click **Include Options**, and then click **User Defined R Function**.

	Include Options					
	Site Info					
	Randomization Info					
~	User Defined R Function					
	Stratification Info					

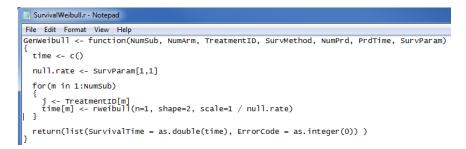


Go to the **User Defined R Function** tab. For now, leave the box **Initialize R simulation** (optional) unchecked. This optional task can be used to load required libraries, set seeds for simulations, and initialize global variables.

Select the row for **Generate Response**, click **Browse...**, and navigate to the folder containing your R file. Select the file and click **Open**. The path should now be displayed under **File Name**.

Simulation Parame	ters Response Generation Info	Accrual/Dropout Info	User Defined R Function	Simulation
Tasks		File Name		Fun
Generate Response	C:\Program Files (x86)\Cytel\Cyte	el Architect\East 6.3\R Sa	mples\SurvivalWeibull.r	
Compute Test Sta				
Randomize Subje				0
Generate Arrival				•
٠				Þ
🗆 Initialize R Simu	Ilation (Optional)	Bro	wse View	Clear

Click **View** to open a notepad application to view your R file. In this example, we are generating survival responses for both control and treatment arms from a Weibull with shape parameter = 2 (i.e. exponential), with the same hazard rate in both arms. This sample file is available in the folder named **R** Samples under installation directory of East 6.



Copy the function name (in this case GenWeibull) and paste it into the cell for Function Name.

Save and close the R file, and click **Simulate**.

Tasks	File Name	Function Name
	C:\Program Files (x86)\Cytel\Cytel A	GenWeibull
Compute Test Sta		
Randomize Subje		
Generate Arrival		

Return to the tab for **User Defined R Function**, select the **Generate Response** row, and click **View**. In the R function, change the shape parameter = 1, to generate responses from a Weibull distribution with increasing hazards. Save and close the R file, and click **Simulate**. You may have to save this file on some other location.

	SurvivalWeibull.r - Notepad					
F	ile Edit Format View Help					
ب ور }	enWeibull <- function(NumSub, NumArm, TreatmentID, SurvMethod, NumPrd, PrdTime, SurvParam) time <- c()					
	null.rate <- SurvParam[1,1]					
#	<pre>for(m in 1:NumSub) { j <- TreatmentID[m] time[m] <- rweibull(n=1, shape=1, scale=1 / null.rate) time[m] <- rweibull(n=1, shape=1, scale=1 / SurvParam[1, j+1]) }</pre>					
}	<pre>return(list(SurvivalTime = as.double(time), ErrorCode = as.integer(0)))</pre>					

Select both simulations (Sim1 and Sim2) from the Output Preview, and on the toolbar, click



to display in the **Output Summary**.

	Sim1	Sim2
Mnemonic	SU-2S-LRSD	SU-2S-LRSD
Test Parameters		
Design Type	Superiority	Superiority
Test Type	1–Sided	1–Sided
Test Statistic	Logrank	Logrank
Power	0.026	0.027
No. of Looks	1	1
Model Parameters		
No. of Hazard Pieces	1	1
Accrual & Dropout Parameters		
Followup Duration	Until End of Study	Until End of Study
No. of Accrual Periods	1	1
Sample Size		
Maximum	182	182
Events		
Maximum	88	88
Simulation Results (Overall)		
Average Study Duration	34.637	30.681
Average Sample Size	182	182
Average Events	88	88

Notice that the type-1 error appears to be controlled in both cases. When we simulated from the exponential (Sim2), the average study duration (30.7 months) was close to what was calculated at Des1 for the expected study duration under the null. However, when we simulated from the Weibull with decreasing hazards (Sim1), the average study duration increased to 34.6 months.

The ability to use custom R functions for many simulation tasks allows considerable flexibility in performing sensitivity analyses and assessment of key operating characteristics.

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11 Superiority Trials with Variable Follow-Up

This chapter will illustrate through a worked example how to design, monitor and simulate a two-sample superiority trial with a time-to-event trial endpoint. Each subject who has not dropped out or experienced the event is followed until the trial ends. This implies that a subject who is enrolled earlier could potentially be followed for a longer time than a subject who is enrolled later on in the trial. In East we refer to such designs as **variable follow-up designs**.

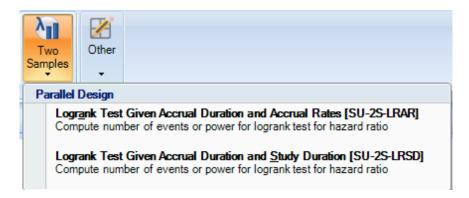
11.1 The RALES Clinical Trial: Initial Design

The RALES trial (Pitt et al., 1999) was a double blind study of aldosterone-receptor blocker spironolactone at a daily dose of 25 mg in combination with standard doses of an ACE inhibitor (treatment arm) versus standard therapy of an ACE inhibitor (control arm) in patients who had severe heart failure as a result of systolic left ventricular dysfunction. The primary endpoint was death from any cause. Six equally-spaced looks at the data using the Lan-DeMets-O'Brien-Fleming spending function were planned. The trial was designed to detect a hazard ratio of 0.83 with 90% power at a two-sided 0.05 level of significance. The hazard rate of the control arm was estimated to be 0.38/year. The trial was expected to enroll 960 patients/year.

We begin by using East to design RALES under these basic assumptions. Open East, click **Design** tab and then **Two Samples** button in **Survival** group. You will see the following

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screen.



Note that there are two choices available in the above list; Logrank Test Given Accrual Duration and Accrual Rates and Logrank Test Given Accrual Duration and Study Duration. The option Logrank Test Given Accrual Duration and Study Duration is explained later in Chapter 13. Now click Logrank Test Given Accrual Duration and Accrual Rates and you will get the following input dialog box.

	Des	ign: Survi	val Endpoin	t: Two-Sample Te	st - Parallel Desig	n - Logrank Given Accrual Duration and Accrual Rate
Design Type: Su	uperiority - Num	ber of Loo	ks: 1 🔻			
Design Paramete	rs Accrual/Dropout Info					
Test Type:	1-Sided •		ard Pieces: rd Ratio (Op		Input Method:	
Type I Error (α):	0.025	O Hazar				Alternative 0.5
Power:	0.9			(λ_t / λ_c)		-0.693
No. of Events:	Computed	U Log H	azard Ratio	$\ln(\lambda_t/\lambda_c)$		-0.693
Allocation Ratio: (n,/n,)	1	Period #	Starting At	Hazard Rate (Control)	Hazard Ra (Treatment:	
		1	0.000	0.035	0.017	
		• Variano	e of Log Haz	O Alternative		
		() Null		O Alternative		

In the above dialog box, enter 6 for **Number of Looks** and keep the default choices of **Design Type: Superiority**, **Test Type:** 2–**Sided**, **Type I Error** (α): 0.05, **Power**: 0.9, and the **Allocation Ratio:** 1.



Further, keep the default choices of **# of Hazard Pieces** as 1 and the **Input Method:** as **Hazard Rates**. Click the check box against **Hazard Ratio** and enter the **Hazard Ratio** as 0.83. Enter **Hazard Rate (Control)** as 0.38. You will see the **Hazard Rate (Treatment:Alt)** computed as 0.3154. Also, keep the **Variance of Log Hazard Ratio** to be used as under **Null**. Now the **Design Parameters** tab of the input dialog will appear as shown below.

Design Paramete	rs Boundary Info Accru	al/Dropout	Info			
Te <u>s</u> t Type: Type I <u>E</u> rror (α): Po <u>w</u> er: N <u>o</u> , of Events:	2-Sided ▼ 0.05 0.9 Computed	⊡ Ha <u>z</u> a ⊙ Hazar	zard Pieces: rd Ratio (Opt <u>d</u> Ratio azard Ratio		Input Method: Hazard	Alternative
Allocation <u>R</u> atio: (n _t /n _c)	1	Period # 1	Starting At 0.000	Hazard Rate (Control) 0.38	Hazard Rate (Treatment: Alt.) 0.315	
		-Variance ⊙ <u>N</u> ull	e of Log Haza	ard Ratio O Alternati <u>v</u> e		

Now click on the tab **Boundary Info**. You will see the following input dialog box.

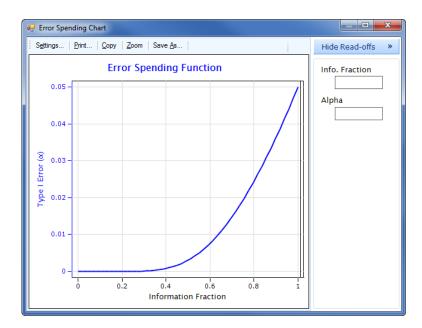
Desig	n Parameter	s Boundary	Info Accru	ual/Drop	out Info				
Efficacy					Futility				
Bounda	ary Family:	Spending	Spending Functions -		Boundary	Family:	None	•	
Spendi	ng Function	: Lan-DeMe	ets 🔻						
Parameter:									
Parameter.		OF	•						
Type I	Error (α):	0.05							
Spacing) of Looks	⊙ Egual	⊖ <u>U</u> nequ	ıal	Efficacy I	oundary:	Z Scale 🔹		
	Info.	Cum. α	Efficacy	Boundan	у				<u>^</u>
Look #	Fraction	Spent	Upper	Low	er				
1	0.167	0.000	5.367	-5.36	67				E
2	0.333	0.000	3.710	-3.7	10				
3	0.500	0.003	2.970	-2.97	70				
4	0.667	0.012	2.539	-2.53	39				
5	0.833	0.028	2.252	-2.25	52				-

Keep all the default specifications for the boundaries to be used in the design. You can look at

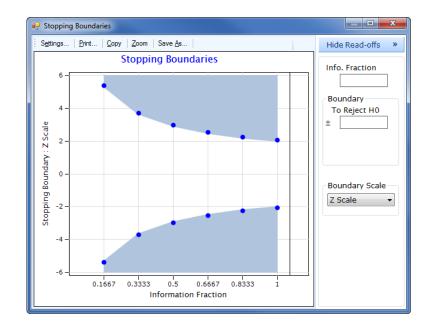
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the Error Spending Chart by clicking on the icon \blacksquare







If you click on the boundary chart icon *kill*, you will see the boundary chart as displayed below.

Now click **Accrual/Dropout Info** tab. Keep the default choice **Until End of Study** for the input **Subjects are followed:**. Keep the **# of Accrual Periods** as 1 and enter 960/year as the accrual rate. For this example, assume no dropouts. The dialog box will look as shown below.

Design Parameters Boundary Info Accrual/Dropout Info Subjects are followed: Until End of Study	
Accrual Info # of Accrual Periods:	Piecewise Dropout Information # of Pieces: 0 • Input Method: Hazard Rates •
Period # Starting At Accrual Rate 1 0.000 960.000	Period # Starting At Hazard Rate (Control) Hazard Rate (Treatment)
Accrual	
Min. Comtd. Sugg. Max. O Duration: 1.295 2.268 3.241	
⊙ Subjects: 1243 2177 3111	

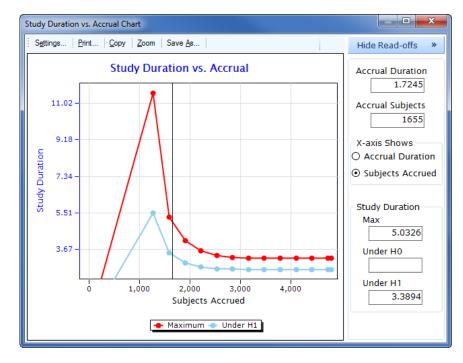
Under Accrual tab and in column titled Comtd. (commited), you see two radio buttons

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Durations and **Subjects** with the latter selected by default. The selected item will appear as the x-axis item in the **Study Duration vs. Accrual** chart, which you can get by clicking on the icon displayed on the side. Against **Durations** and **Subjects** you see two rows of three cells each. The first and third cells will show the min and max values for the row item and the middle cell, mid value between min and max values.

From the results displayed, you see that any sample size in the range 1243 to 3111 will suffice to attain the desired 90% power and selects 2177, the mid-point of the allowable range, as the default sample size. Depending on the needs of the study, you may wish to use a different sample size within the allowable range. The choice of sample size generally depends on how long you wish the study to last. The larger you make the patient accrual the shorter will be the total study duration, consisting of accrual time plus follow up time. To understand the essence of this trade-off, bring up the **Study Duration vs. Accrual** chart by clicking on the icon





Based on this chart, a sample size of 1660 subjects is selected. Enter 1660 for Committed Accrual (subjects). Click on Compute and see the results in the new plan created under Output Preview. This sample size ensures that the maximum study duration will be slightly more than 4.9 years. Additionally, under the alternative hypothesis, the expected study

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	Des 1		
Mnemonic	SU-2S-LRAR		
Test Parameters			
Design Type	Superiority		
No. of Looks	6		
Test Type	2–Sided		
Specified α	0.05		
Power	0.9		
Model Parameters			
Hazard Ratio (Alt.)	0.83		
Var (Log HR)	Null		
Allocation Ratio (nt/nc)	1		
Boundary Parameters			
Spacing of Looks	Equal		
Efficacy Boundary	LD (OF)		
Accrual & Dropout Parameters			
Accrual Rate	960		
Subjects are Followed	Until End of Study		
No. of Accrual Periods	1		
No. of Dropout Pieces	0		
Sample Size			
Maximum	1660		
Expected Under H0	1659.987		
Expected Under H1	1659.985		
Events			
Maximum	1243		
Expected Under H0	1233.984		
Expected Under H1	903.595		
Study Duration			
Maximum	4.905		
Expected Under H0	4.506		
Expected Under H1	3.337		
11.1 The RALES Clinical TAkes Inter Design on			

Maximum

-

1.729

.

duration will be only about 3.3 years.



11.2 Incorporating Drop-Outs

The investigators expect 5% of the patients in both the groups to drop out each year. To incorporate this drop-out rate into the design, in the **Piecewise Constant Dropout Rates** tab, select 1 for the number of pieces and change the Input Method from **Hazard Rates** to **Dropout Rates**. Then enter 5% dropouts at 1 year for both the groups.

Piecewise	Dropout Info	ormation	
# of P <u>i</u> ece	5: 1 🔻	Input <u>M</u> ethod:	Prob. of Dropout
Period #	Ву	Prob. of Dropout (Control)	Prob. of Dropout (Treatment)
1	1.000	0.05	0.05

We could have entered a hazard rate γ for dropping out instead. By solving $1 - \exp(-\gamma) = 0.05$ we find $\gamma = -\ln(0.95) = 0.051$. This calculation is handled by East

To make Plan1 and Plan2 comparable change the sample size of Plan2 to 1660 by typing this value into the **Committed Accrual (Subjects)** cell. Click on **Compute** and see the

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	Des 1	Des2
Mnemonic	SU-2S-LRAR	SU-2S-LRAR
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	6	6
Test Type	2–Sided	2–Sided
Specified α	0.05	0.05
Power	0.9	0.9
Model Parameters		
Hazard Ratio (Alt.)	0.83	0.83
Var (Log HR)	Null	Null
Allocation Ratio (nt/nc)	1	1
Boundary Parameters		
Spacing of Looks	Equal	Equal
Efficacy Boundary	LD (OF)	LD (OF)
Accrual & Dropout Parameters		
Accrual Rate	960	960
Subjects are Followed	Until End of Study	Until End of Study
No. of Accrual Periods	1	1
No. of Dropout Pieces	0	1
Sample Size		
Maximum	1660	1660
Expected Under H0	1659.987	1659.992
Expected Under H1	1659.985	1659.986
Events		
Maximum	1243	1243
Expected Under H0	1233.984	1233.984
Expected Under H1	903.595	903.595
Study Duration		
Maximum	4.905	5.87
Expected Under H0	4.506	5.258
Expected Under H1	3.337	3.687
Accrual Duration		
Maximum	1.729	1.729
Expected Under H0	1.729	1.729
Expected Under H1	1.729	1.729

results in the new plan created under **Output Preview**.

A comparison of the first and second plans reveals that, because of the drop-outs, the maximum study duration will be prolonged from 4.9 years under Plan1 to 5.9 years under Plan2. The expected study duration will likewise be prolonged from 3.3 years to 3.7 years under the alternative hypothesis, and from 4.5 years to 5.3 years under the null hypothesis.

11.3 Incorporating Non-Constant Accrual Rates



In many clinical trials, the enrollment rate is low in the beginning and reaches its maximum expected level a few months later when all the sites enrolling patients have been recruited. Suppose that patients are expected to enroll at an average rate of 400/year for the first six months and at an average rate of 960/year thereafter. Now in **Accrual Info** tab, specify that there are two accrual periods and enter the accrual rate for each period in the dialog box as shown below.

Accrual Info)			
# of Accrua	l <u>P</u> eriods: 2	•		
Period #	Starting At	Accrual Rate		
1	0	400.000		
2	0.5	960.000		
Accrual				
	Min.	Comtd. Su	ugg. Max.	
O Duration	1.779	2.021	3.618	
⊙ Su <u>bj</u> ects:	1428	1660	3193	

Once again change the sample size to 1660 to make Plan3 comparable to the other two plans.

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	Des 1	Des2	Des 3
Mnemonic	SU-2S-LRAR	SU-2S-LRAR	SU-2S-LRAR
Test Parameters			
Design Type	Superiority	Superiority	Superiority
No. of Looks	6	6	6
Test Type	2-Sided	2-Sided	2-Sided
Specified a	0.05	0.05	0.05
Power	0.9	0.9	0.9
Model Parameters			
Hazard Ratio (Alt.)	0.83	0.83	0.83
Var (Log HR)	Null	Null	Null
Allocation Ratio (nt/nc)	1	1	1
Boundary Parameters			
Spacing of Looks	Equal	Equal	Equal
Efficacy Boundary	LD (OF)	LD (OF)	LD (OF)
crual & Dropout Parameters			
Accrual Rate	960	960	Multiple
Subjects are Followed	Until End of Study	Until End of Study	Until End of Study
No. of Accrual Periods	1 ,	1	2
No. of Dropout Pieces	0	1	1
Sample Size			
Maximum	1660	1660	1660
Expected Under H0	1659.987	1659.992	1659.99
Expected Under H1	1659.985	1659.986	1659.985
Events			
Maximum	1243	1243	1243
Expected Under H0	1233.984	1233.984	1233.984
Expected Under H1	903.595	903.595	903.595
Study Duration			
Maximum	4.905	5.87	6.15
Expected Under H0	4.506	5.258	5.538
Expected Under H1	3.337	3.687	3.966
Accrual Duration			
Maximum	1.729	1.729	2.021
Expected Under H0	1.729	1.729	2.021
Expected Under H1	1.729	1.729	2.021

Click on **Compute** to complete the design.

Notice that the enrollment period has increased from 1.7 years to 2 years. Likewise, the maximum study duration and the expected study durations under H_0 and H_1 have also increased relative to Plans 1 and 2. Now the maximum study duration is 6.15 years.

11.4 Incorporating Piecewise Constant Hazards

Prior studies had suggested that the survival curves might not follow an exponential distribution. Suppose it is believed that the hazard rate for failure on the control arm decreases after the first 12 months from 0.38 to 0.35. We will assume that the hazard ratio is

# of <u>H</u> az Hazard F	ard Pieces: Ratio	2 •	Input Method: H	lazard Rates 🔹
⊙ Hazar <u>(</u>	<u>l</u> Ratio	(λ_t/λ_c)		Alternative 0.83
O Log Ha	azard Ratio	$ln(\lambda_t^{}/\lambda_c^{})$		-0.186
Period #	Starting At	Hazard Rate (Control)	Hazard Rate (Treatment: A	
1	0.000	0.38	0.3154	
	1.000	0.35	0.2905	

still 0.83. We can enter the appropriate piecewise hazard rates into East as follows.

Change the sample size to 1660 for comparability with the previous plans. Click on **Compute** and see the results of the plan in the **Output Preview**.

	Des 1	Des2	Des 3	Des4		
Mnemonic	SU-2S-LRAR	SU-2S-LRAR	SU-2S-LRAR	SU-2S-LRAR		
Test Parameters						
Design Type	Superiority	Superiority	Superiority	Superiority		
No. of Looks	6	6	6	6		
Test Type	2-Sided	2-Sided	2-Sided	2-Sided		
Specified α	0.05	0.05	0.05	0.05		
Power	0.9	0.9	0.9	0.9		
Model Parameters						
Hazard Ratio (Alt.)	0.83	0.83	0.83	0.83		
Var (Log HR)	Null	Null	Null	Null		
Allocation Ratio (nt/nc)	1	1	1	1		
Boundary Parameters						
Spacing of Looks	Equal	Equal	Equal	Equal		
Efficacy Boundary	LD (OF)	LD (OF)	LD (OF)	LD (OF)		
crual & Dropout Parameters						
Accrual Rate	960	960	Multiple	Multiple		
Subjects are Followed	Until End of Study					
No. of Accrual Periods	1	1	2	2		
No. of Dropout Pieces	0	1	1	1		
Sample Size						
Maximum	1660	1660	1660	1660		
Expected Under H0	1659.987	1659.992	1659.99	1659.991		
Expected Under H1	1659.985	1659.986	1659.985	1659.985		
Events						
Maximum	1243	1243	1243	1243		
Expected Under H0	1233.984	1233.984	1233.984	1233.984		
Expected Under H1	903.595	903.595	903.595	903.595		
Study Duration						
Maximum	4.905	5.87	6.15	6.555		
Expected Under H0	4.506	5.258	5.538	5.868		
Expected Under H1	3.337	3.687	3.966	4.136		
Accrual Duration						
Maximum	1.729	1.729	2.021	2.021		
Expected Under H0	1.729	1.729	2.021	2.021		
Expected Under H1	1.729	1.729	2.021	2.021		

We observe that the impact of changing from a constant hazard rate to a piecewise constant

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hazard rate is substantial. The maximum study duration has increased from 6.15 years for Plan3 to 6.56 years for Plan4.

11.5 Simulating a Trial with Proportional Hazards

11.5.1 Simulation Worksheet 11.5.2 Simulating Under *H*₁ **11.5.3 Simulating...**

It would be useful to verify the operating characteristics of the various plans created in the previous section by simulation. The new survival simulation capabilities in East permit this. Let us use these capabilities to simulate Plan4. Save this design in the workbook. Right-click on this design node and select the menu item **Simulate**. You'll see the following **Survival Simulation** worksheet.

			Simulation: Su	rvival Endpoint:	Two-Sample Test - Parallel Design - Lo	grank Given Accrual Duration and Accrual Rates
Numbe	er of Looks: 6	v				
Simulat	tion Parameters	Response Gene	eration Info A	ccrual/Dropout I	info Simulation Control Info	
Trial Type	s: Supe	riority	Ŧ			
Test Type	2-Sid	ed	*			Test Statistic: Logrank
Max # of	Events:	1243				
Max. # of		1243				
		1243 No. of Events	•			
Fix at Eacl	h Look: Total	No. of Events	• x Spent	Effic	acy Z	·
Fix at Eacl		No. of Events		Effic	acy Z Lower	
	h Look: Total	No. of Events Cum. o	x Spent			×
Fix at Eacl	h Look: Total	No. of Events Cum. o Upper	x Spent Lower	Upper	Lower	
Fix at Eacl Look # 1	h Look: Total	No. of Events Cum. o Upper 0.000	x Spent Lower 0.000	Upper 5.369	Lower -5.369	
Fix at Eacl Look # 1 2	h Look: Total	No. of Events Cum. o Upper 0.000 0.000	x Spent Lower 0.000 0.000	Upper 5.369 3.712	Lower -5.369 -3.712	

11.5.1 Components of the Simulation Worksheet

This simulation worksheet consists four tabs - Simulation Parameters, Response Generation Info, Accrual/Dropout Info, and Simulation Control Info. The Simulation Parameters tab displays all the parameters of the simulation. If desired, you may modify one or more of these parameter values before carrying out simulation. The second tab Response



Generation Info will appear as shown below.

Simula	tion Parameters	Response Ger	neration Info	Info Simulation Control Info	
# of Haza	ard Pieces 2	 Input M 	Aethod: Hazar	d Rates 🔹	
🗆 Hazard	Ratio				
Piece	Starting At				
Piece	Starting At	Control	Treatment	Hazard Ratio	
1	0.000	0.380	0.315	0.830	
2	1.000	0.350	0.291	0.830	

In this tab, you may modify values of response parameters before carrying out simulation. The third tab **Accrual/Dropout Info** will display information relating to accrual and dropouts.

Simulatio		Response Gener	ation Info	Accrual/Dropout	Info Simula	tion Contro	l Info	
Sample Si <u>z</u> e	e 🗌	1660			Distri <u>b</u> ution	of Accrual	Time: Uniform	
Subjects an	e <u>f</u> ollowed: Un	til End of Study	•					
Accrual Info)				Piecewise	Dropout Inf	ormation	
					# of Pieces	1 -	Input <u>M</u> ethod:	Prob. of Dropout 🔻
	I <u>P</u> eriods: 2	 Input <u>M</u>etho 	d: Accrual R	lates 🝷	Period #	By	Prob. of Dropout (Control)	Prob. of Dropout (Treatment)
Period #	Starting At	Accrual Rate			1	1.000	0.05	0.05
1	0	400.000						
2	0.5	960.000						
L					Note: Per	iod 1 hazar	d rates apply after ti	me 1.

As in the case of other tabs, you may modify one or more values appearing in this tab before simulation is carried out.

In the **Simulation Control Info**, you may specify the simulation parameters like number of simulations required and the desired simulation seed etc.

Simulation Parameters Response Generation Info	Accrual/Dropout Info Simulation Control Info
Number of Simulations: 10000 Refresh Frequency: 1000 Random Number Seed O O Clock Fixed Image: Suppress All Intermediate Output Pause after Refresh Stop At End	Output Options Output Type: Case Data Save summary statistics for every simulation run Save subject-level data for simulation runs Note: Max. 100,000 records will be saved.

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Also optionally, you may bring out one more tab Randomization Info by clicking on Include Options. In the Randomization Info, you may alter the allocation ratio of the design before carrying out simulation.

Simulation Parameters	Response Generation Info	Accrual/Dropout Info	Randomization Info	Simulation Control Info
Randomization Method:	Complete Randomized Design	-		
Allocation Ratio (n_t/n_c) :	1			

Keeping all the default parameter values same as in the different tabs, click **Simulate**. You can see the progress of the simulation process summarized as shown in the following screen shot.

.ook #	Look Position	H0+	H0-	H1+	H1-	Latest Simul Test S	Average Events	# Rejecting Up(H0+)	# Rejecting Low(H0-)	# Unable Reject	Total Simulati Count	Total Simulati %	
1	207	5.369	-5.369			-0.337	207	0	0	0	0	0	
2	414	3.712	-3.712			-1.104	414	0	347	0	347	3.47	
3	622		-2.968			-1.008	622	0	2270	0	2270	22.7	
4	829		-2.538			-2.031	829	0	2970	0	2970	29.7	
5	1036	2.252	-2.252			-2.389	1036	0	2215	0	2215	22.15	
						Total %	904.458	0	8969 89.69	1031	10000	100	
	Sto	opping E	Boundari	es		٩	Rej. H	D and Unable	to Rej. HO	Q			
	2		500 Events		1,000	•	4,100 3,280 2,560 1,540 0 1	Rej I	4 5 ook # H0 (Upper) le to Reject HI	6 7	Number o Simulation Elapsed Ti	n Seed =	pleted = 10000 2066997(00:00:49

At the end of simulation, the simulation results appear in a row in the **Output Preview** as shown below.

ID 🔻	Design Type	No. of Looks	Test Type	Specified α	Power	nt/nc	Spacing of Looks	Efficacy Boundary	Accrual Rate	Sample Size	Expected SS (H0)	Expected SS (H1)	Maximum Events	Average Study Duration	Average Events
Sim1	Superiority	6	2-Sided		0.897	1	User Specified	User Specified	Multiple	1660			1243	4.136	904.458

The output summary can be seen by clicking on the icon 🧾 after selecting the simulation



row in the Output Preview.

	Sim1
Mnemonic	SU-2S-LRAR
Test Parameters	
Design Type	Superiority
Test Type	2–Sided
Test Statistic	Logrank
Power	0.897
No. of Looks	6
Model Parameters	
No. of Hazard Pieces	2
Allocation Ratio (nt/nc)	1
Boundary Parameters	
Efficacy Boundary	User Specified
Spacing of Looks	User Specified
Accrual & Dropout Parameters	
Followup Duration	Until End of Study
Accrual Rate	Multiple
No. of Accrual Periods	2
Sample Size	
Maximum	1660
Events	
Maximum	1243
Simulation Results (Overall)	
Average Study Duration	4.136
Average Sample Size	1659.83
Average Events	904.458

Now save the simulation results to the workbook by selecting the simulation results row and then clicking on . On this newly added workbook node for simulation, right-click and

select **Details**. You will see the complete details simulation appearing on the output pane.

Simulation: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Accrual Rates

Simulation ID	Sim1
Design Type	Superiority
Number of Looks	6
Test Type	2-Sided
Sample Size (n)	1660
Fix at Each Look	Total No. of Events
Test Statistic	Logrank
Average Events	904.458
Total Accrual Duration	2.0208
Avg. Power at Termination	0.897
Randomization Parame	eters
Method	Complete Randomized Des
Allocation Ratio (n/n_)	1
Simulation Control Para	ameters
Starting Seed	Clock
Number of Simulations	10000

Look #	Average	Averag	ge Events	Average	e Dropouts	Average	Average
LOOK #	Sample Size	Control	Treatment	Control	Treatment	Look Time	Follow up
1	1137.766	111.911	95.089	15.066	15.532	1.476	0.525
2	1654.066	222.799	191.201	30.401	31.511	2.051	0.73
3	1660	332.382	289.618	45.931	48.045	2.641	1.104
4	1660	436.983	392.017	61.799	65.188	3.429	1.492
5	1660	538.567	497.433	77.752	82.34	4.556	1.883
6	1660	637.458	605.542	93.69	99.92	6.531	2.272
Average	1659.83	479.254	425.205	67.282	72.059	4,136	1.637

		Boundaries Efficacy		Stoppi	ng For	Total Simulations		
Look #	Events	Upper	Lower	Upper Efficacy	Lower Efficacy	Count	%	
1	207	5.369	-5.369	0	0	0	0.000%	
2	414	3.712	-3.712	0	347	347	3.470%	
3	622	2.968	-2.968	0	2270	2270	22.700%	
4	829	2.538	-2.538	0	2970	2970	29.700%	
5	1036	2.252	-2.252	0	2215	2215	22.150%	
6	1243	2.045	-2.045	0	1167	2198	21.980%	
Total				0	8969	10000		
%				0.000%	89.690%			

⊖ Simulation Boundaries and Boundary Crossing Probabilities

Simulating Under H₁ 11.5.2

We illustrate by running 1000 simulations for the current design with a fixed number of events at each look. Select a look time definition based on the number of events and click on the Simulate button. You will see a new row added in the Output Preview. Select this row and save it to Library node. If you double-click this node, you will see the following detailed



output. (The actual values may differ, depending on the starting seed used).

Simulation: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Accrual Rates

mulation ID:	Sim2			E	Boundaries		Early	1	Т	otal		
Design Type:	Superiority	Look #	Events	<u> </u>	Efficacy		pping F	For		lations		
Number of Looks: Test Type:	6 2-Sided	LOOK #	⊂vents	Upp		, Uppe	r Lo	ower	Count	%		
Fix at Each Look:	Z-Sided Total No. of Events					Emcad	y Effic	icacy				
Fest Statistic:	Logrank	1	207	5.368				0	0	0		
Average Events:	901.004	2	414	3.71				32	32	3.2		
Fotal Accrual Duration:	2.0208	3	622 829	2.968				232	232	23.2		
Avg. Power at Terminatio	n:0.911	4	1036	2.538				310 208	310 208	20.8		
Simulation Control Pa	rameters	6	1036	2.25				129	208	20.8		
Starting Seed:	Clock	Total	1243	2.044	10 12.044			125	1000	21.0		
Number of Simulations:	1000	10tai				0		1.1	1000			
		Average	· · ·		Dropouts ar		ïmes:					
		Look #		erage ble Size	Averag Control	e Events Treatme		Av Cont	erage Dri	pouts reatment	Average Look Time	Average Follow up
		-		6.227	111.737	Ireatme 95.26		Cont 15		reatment 15.426	1.4765	0.5256
				3.936	222.491	95.20		30.6		31.365	2.0503	0.5256
				1660	332.3264	289.673		45.92		47.9587	2.6428	1.1053
		4		1660	437.3967	391.603		61.99		65.375	3.4323	1.494
		6		1660	538.7418	497.258		78.44		82.5399	4.5669	1.8863
		(1660	637.6147	605.385		93.94		00.2248	6.5446	2.2754
		Average	165	9.935	477.596	423.40	8	67.0	91	71.981	4.1226	1.6333
		Accrual/I Sample S	Starting At 0 1 Dropout ize: are Follow put Metho	Control 0.38 0.35 Parame 1660 ed: Until id: Accr	End of Study ual Rates	0.83						
		No. of Dro Dropout In Period # 1 Overall : Average S Starting S Total Nurr Elapsed T	At Co At Co 1 Simulation tudy Dura eed: ber of Sin	od: Dropp ntrol Tre 5 on Resi tion:	atment 5 ults 4.123 426374642							

Let us examine these 1000 simulations more closely.

The column labeled **Events** in the first table, displays the number of events after which each interim look was taken. The column labeled **Avg**. **Look Time** in the second table, displays the average calendar times at which each interim look was taken. Thus, the first interim look (taken after observing 207 events) occurred after an average elapse of about 1.5 years; the second interim look (taken after observing 414 events) occurred after an average elapse of about 2.1 years; etc. The remaining columns of the simulation output are self-explanatory. The columns labeled **Early Stopping For** show that 911 of the 1000 simulations crossed the

lower stopping boundary, thus confirming (up to Monte Carlo accuracy) that this design has 90% power. The detailed output tables also show how the events, drop-outs, accruals, and average follow-up times were observed at each interim analysis.

11.5.3 Simulating Under H_0

To simulate under the null hypothesis we must go to the **Response Generation Info** tab. In this pane change the hazard rate for the treatment arm to 0.38 for the first piece and to 0.35 for the second piece of the hazard function.

Survival Information								
# of Hazard Pieces 2 Input Method: Hazard Rates								
🗆 Hazard	□ Hazard Ratio							
Piece	Starting At	Hazaro	d Rates	Hazard Ratio				
Piece	Starting At	Control	Treatment					
1	0.000	0.380	0.38	1.000				
2	1.000	0.350	0.35	1.000				

This change implies that we will be simulating under the null hypothesis. Click on the **Simulate** button. A new row in Output Preview will be added now. Select this row and add to the library node. By double-clicking on this node, you will see the detailed simulation



output as shown below. The results are displayed below.

Αv

Simulation: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Accrual Rates . .

....

Simulation Parameters	5	Simulati	on Boun	daries and	Boundary	Crossi	ng Prop	abilities:	
Simulation ID: Design Type:	Sim3 Superiority	Look #	Events		ndaries icacy		arly ing For		tal lations
Number of Looks: Test Type:	6 2-Sided	LOOK #	Events	Upper	Lower	Upper Efficacy	Lower Efficacy	Count	%
Fix at Each Look:	Total No. of Events	1	207	5.3688	-5.3688	0	0	0	0
Test Statistic:	Logrank	2	414	3.712	-3.712	0	0	0	0
Average Events: Total Accrual Duration:	1230.994 2.0208	3	622	2.9683	-2.9683	3	4	7	0.7
Avg. Power at Termination		4	829	2.5382	-2.5382	5	6	11	1.1
Avg. Power at Termination	1.0.051	5	1036	2.252	-2.252	6	9	15	1.5
Simulation Control Par	ameters	6	1243	2.0448	-2.0448	9	9	967	96.7
Starting Seed:	Clock	Total				23	28	1000	
Number of Simulations:	1000	%				2.3	2.8		

rerage Sa	ample Size, I	Dropouts an	d Look Time	s:			
Look #	Average	Average	e Events	Average	Dropouts	Average	Average
LOOK #	Sample Size	Control	Treatment	Control	Treatment	Look Time	Follow up
1	1089.595	103.372	103.628	13.924	14.346	1.4264	0.502
2	1614.547	207.072	206.929	28.183	28.46	1.9763	0.6816
3	1660	311.296	310.704	42.797	43.352	2.5136	1.0074
4	1660	414.5136	414.4864	57.8016	58.3162	3.2203	1.3596
5	1660	518.001	517.999	73.0183	73.5682	4.225	1.7154
6	1660	621.8925	621.1075	88.1303	88.7301	5.9331	2.0706
Average	1660	615 994	615	87.22	87.842	5.8538	2 0502

Response Generation Parameters

No. of Ha	azard Pie	ces:2					
Input Me	thod:	Hazard Rates					
Piece #	Starting At	Control	Treatment	н			

2	1	0.35	0.3	5	1
Accrual	/Dropo	ut Para	meters		
Sample :	Size:	16	60		
Subjects	are Foll	wed: Ur	ntil End o	fStu	ıdy
Accrual	input Mel	hod: Ad	crual Ra	tes	
Dariad f	Ctartin	At Ac.	crual Rate		
1		0	400		
2	0.	5	960	1	
				_	
No. of Dr	opout Pi	eces:1			
Dropout	Input Me	hod: Dr	opout Ra	tes	
Period #	At (Control	Treatmen	t	
1	1	5	5		
Overall	Simula	tion Re	esults		

verage Study Duration: 5.854 tarting Seed: 427433290 Starting Seed: arting Seed. 42743 tal Number of Simulations: 1000

Out of 1000 simulated trials only 23 crossed the upper stopping boundary and 28 crossed the lower stopping boundary thus confirming (up to Monte Carlo accuracy) that the type-1 error is preserved for this design.

11.6 Simulating a Trial with Non-Proportional Hazards

11.6.1 Single-Look Design = 11.6.2 Single-Look Design = 11.6.3 Group Seq. Design

A new agent is to be tested against placebo in a large cardiovascular study with the endpoint being time to stroke, MI or death. The control arm has a 12-month event-free rate of 97%. We

wish to design the study to detect a hazard ratio of 0.75 with 90% power, using a two-sided test conducted at the 0.05 level. An important design consideration is that treatment differences are expected to emerge only after one year of therapy. Subjects will enroll at the rate of 1000/month and be followed to the end of the study. The dropout rate is expected to be 10% per year for both treatment arms. Finally, the study should be designed for maximum study duration of 50 months.

The usual design options in East are not directly applicable to this trial because they require the hazard ratio to be constant under the alternative hypothesis. Here, however, we are required to power the trial to detect a hazard ratio of 0.75 that only emerges after patients have been on the study for 12 months. The simulation capabilities of East can help us with the design.

11.6.1 Single-Look Design with Proportional Hazards

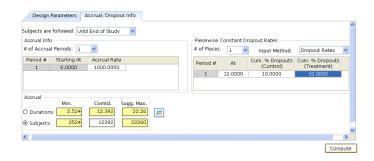
We begin by creating a single-look design powered to detect hazard ratio of 0.75, ignoring the fact that the two survival curves separate out only after 12 months. Open a new survival design worksheet by clicking on **Design->Time to Event->Logrank Test Given Accrual Duration** and Accrual Rates. In the resulting **Design Parameters** tab, enter the parameters values as shown below.

	Design: Surv	ival Endpoint: Two-S	Sample Test - Paralle	l Design - Logrank Giv	en Accrual Duration and Accrual
Design Type: Superiority	 Number 	er of Looks: 1 💌			
Design Parameters Accru	al/Dropout Info				
	05	# of Hazard Pieces: 27 Hazard Ratio (Opi 20 Hazard Ratio C Ratio of % Surviva 21 Period 21 12.0000	tional) (λ _τ /;	-	% Survival Alternative 0.75 1.0076
		Variance of Log Haz	ard Ratio		

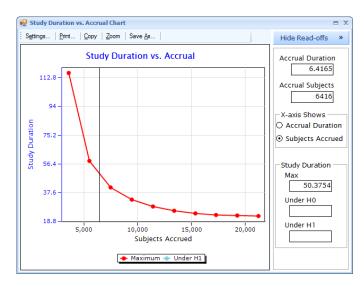
Click on the tab **Accrual/Dropout** Info and enter the values as shown below, excluding



the Accrual tab.

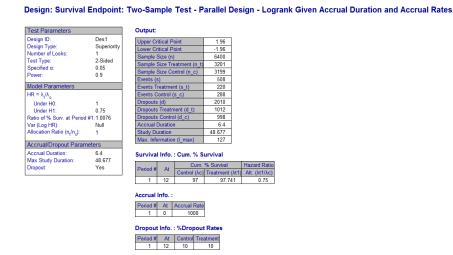


East informs you in the Accrual tab, that any sample size in the range 2524 to 22260 will suffice to attain the desired 90% power. However, the study will end sooner if we enroll more patients. Recall that we wish the trial to last no more than 50 months, inclusive of accrual and follow-up. The **Accrual-Duration** chart can provide guidance on sample size selection. This chart reveals that if 6400 subjects are enrolled, the expected maximum duration of a trial is close to 50 months.



Now change the **Comtd**. number of subjects to 6400 and click on **Compute** to complete the

design. A new row is added for this design in the Output Preview. Select this row and add it to a library node under a workbook. Now you double-click on this node, you will see the detailed output as shown below.



We can verify the operating characteristics of Plan1 by simulation. With the cursor on Plan1 node, Click on Simulation icon from the library menu bar. You'll be taken to the survival simulation worksheet. In the Simulation Control Info tab, specify the number of simulations to be 1000. Now click on Simulate button. This will generate 1000 simulations from the survival curves specified in the design. Each simulation will consist of survival data on 6400 subjects entering the trial uniformly at the rate of 1000/month. Events (failures) will be tracked and the simulated trial will be terminated when the total number of events equals 508. Subjects surviving past this termination time point will have their survival times censored. The resulting survival data will be summarized in terms of the logrank test statistic. Each simulation records two important quantities:

- the calendar time at which the last of the specified 508 events arrived;
- whether or not the logrank test statistic rejected the null hypothesis.

We would expect that, on average, the 508 events will occur in about 48.7 months and about 90% of the simulations will reject the null hypothesis. The simulation summary is shown in the



following screen shot.

Sim1
SU-2S-LRAR
Superiority
2–Sided
Logrank
0.891
1
1
Until End of Study
1000
1
6400
508
48.7946

Indeed we observe that the average study duration for this set of 1000 simulations was 48.8 months, and that 891 of the 1000 simulated trials crossed the critical value and rejected H_0 and hence the power attained is 0.891. This serves as an independent verification of the operating characteristics of Plan1, up to Monte Carlo accuracy.

11.6.2 Single-Look Design with Non-Proportional Hazards

Were it not for the fact that the hazard ratio of 0.75 only emerges after 12 months of therapy, Plan1 would meet the goals of this study. However, the impact of the late separation of the survival curves must be taken into consideration. This is accomplished, once again, by simulation. Click the Edit Simulation icon while the cursor is on the last simulation node. In the resulting simulation sheet click on Response Generation Info tab. In this tab, specify that the hazard rates for the control and treatment arms are identical and equal to 0.0025 for the first 12 months and the hazard ratio is 0.75 thereafter. This is done by making appropriate entries

in this tab as shown below.

Simula	tion Parameters	Response Gene	ration Info	Accrual/Drop	out Info	Simulation Control Info
⊙ Using H	Hazard Rates					
O Using (Cum.%Survival					
# of Haza	rd Pieces 2	*				
Piece	Starting At	Hazard Rates		Hazard	Batio	
Piece	starting Ac	Control	Treatme	nt	Rauo	
1	0.000	0.0025	0.0025	1.00	0	
2	12.000	0.0025	0.0019	0.75	0	
						Simulate
						Sindiace

Click on the **Simulate** button. This will generate 1000 simulations from survival curves specified in the **Survival Parameters Pane**. As before, each simulation will consist of survival data on 6400 subjects entering the trial uniformly at the rate of 1000/month. Events (failures) will be tracked and the simulated trial will be terminated when the total number of

events equals 508. The summary output of this simulation run as shown below.

	Wbk2:Des1:Sim2
Mnemonic	SU-2S-LRAR
Test Parameters	
Design Type	Superiority
Test Type	2–Sided
Test Statistic	Logrank
Power	0.565
No. of Looks	1
Model Parameters	
No. of Hazard Pieces	2
Accrual & Dropout Parameters	
Followup Duration	Until End of Study
Accrual Rate	1000
No. of Accrual Periods	1
Sample Size	
Maximum	6400
Events	
Maximum	508
Study Duration	
Maximum	46.9637

This time only 565 of the 1000 trials were able to reject H_0 . The drop in power is of course due to the fact that the two survival curves do not separate out until 12 months have elapsed. Thus events that arise within the first 12 months arrive at the same rate for both arms and are not very informative about treatment differences.

We need to increase the power of the study to 90%. This can be accomplished in one of two ways:

- 1. Prolonging the study duration until a sufficient number of events are obtained to achieve 90% power.
- 2. Increasing the sample size.

The first approach cannot be used because the study duration is not permitted to exceed 50 months. The simulations have shown that the study duration is already almost 50 months, and it has only achieved 56.5% power. Thus we must resort to increasing the sample size.

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Chapter 11: Superiority Trials with Variable Follow-Up

Now if we increase the sample size while keeping the total number of events fixed at 508, the average study duration will drop. The power, however, may not increase. In fact it might even decrease since a larger fraction of the 508 events will arise in the first 12 months, before the two survival curves have separated. To see this, increase the sample size from 6400 to 10000 in the **Accrual/Dropout Info** tab. Then click on **Simulate** button. From this simulation run, you will get the output summary as shown below.

	Wbk2:Des1:Sim3
Mnemonic	SU-2S-LRAR
Test Parameters	
Design Type	Superiority
Test Type	2–Sided
Test Statistic	Logrank
Power	0.297
No. of Looks	1
Model Parameters	
No. of Hazard Pieces	2
Accrual & Dropout Parameters	
Followup Duration	Until End of Study
Accrual Rate	1000
No. of Accrual Periods	1
Sample Size	
Maximum	10000
Events	
Maximum	508
Study Duration	
Maximum	29.7351

Notice that the average study duration has dropped to 29.7 months. But the power has dropped also. This time only 297 of the 1000 simulations could reject the null hypothesis.

To increase power we must increase sample size while keeping the study duration fixed at about 50 months. This is accomplished by selecting the **Look Time** option from the drop-down box in the **Fix at Each Look** section of the **Survival Parameters Pane** and choosing a 50 month Total Study Durn., while keeping the sample size increase from 6400



to 10000.				
Nu	mber of Looks:	1 ~	-	
Sim	ulation Parame	ters F	Response	Generation Info
Trial T	ype:	Superi	ority	~
Test T	ype:	2-Side	d	~
Study	Duration:		50	
Fix at I	Each Look:	Look T	ime	*

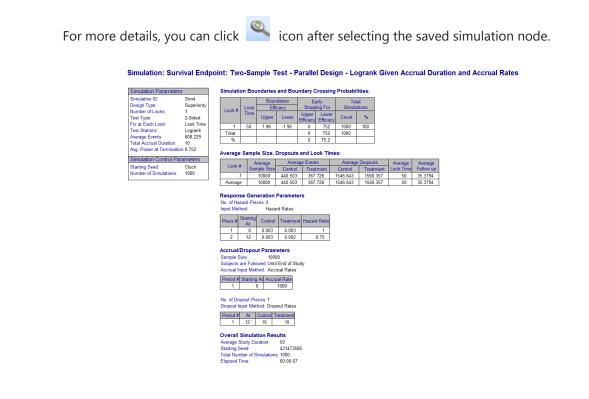
We will now run 1000 simulations in each of which 10000 subjects are enrolled at the rate of 1000/year. Each simulated trial will be terminated at the end of 50 months of calendar time and a logrank test statistic will be derived from the data.Click on the **Simulate** button. Add

the simulation run output to library node and see the following output summary.

	Wbk2:Des1:Sim4
Mnemonic	SU-2S-LRAR
Test Parameters	
Design Type	Superiority
Test Type	2–Sided
Test Statistic	Logrank
Power	0.752
No. of Looks	1
Model Parameters	
No. of Hazard Pieces	2
Accrual & Dropout Parameters	
Followup Duration	Until End of Study
Accrual Rate	1000
No. of Accrual Periods	1
Sample Size	
Maximum	10000
Events	
Maximum	808.229
Study Duration	
Maximum	50

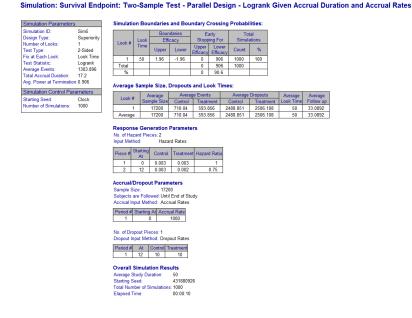
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Now you can see, the power of the study has increased to 75.2%. On average 808 events occurred during the 50 months that the study remained open. Since we require 90% power, the sample size must be increased even further. This can be done by trial and error over several simulation experiments. Eventually we discover that a sample size of 17200 patients

will provide about 90% power with an average of 1304 events.



It is evident from these simulations that the proportional hazards assumption is simply not appropriate if the survival curves separate out late. In the present example the proportional hazards assumption would have led to a sample size of 6400 whereas the sample size actually needed was 17200.

11.6.3 Group Sequential Design with Non-Proportional Hazards

The single-look design discussed in the previous section required a sample size of 17200 subjects. A group sequential design, monitored by an independent data monitoring committee, is usually more efficient for large studies of this type. Such a trial can be designed with efficacy stopping boundaries or with efficacy and futility stopping boundaries. Consider first a design with five equally spaced efficacy boundaries. Go back to the library, click on Des1

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node, and then click on Solution in the resulting design input dialog window, change the entry in the Number of Looks cell from 1 to 5. Click on Compute button and save the plan as Des2 in the library. Select Des1 and Des2 nodes and then click on solution to see the following details for both the plans.

	Wbk2:Des1	Wbk2:Des2
Mnemonic	SU-2S-LRAR	SU-2S-LRAR
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	1	5
Test Type	2-Sided	2-Sided
Specified α	0.05	0.05
Power	0.9	0.9002
Model Parameters		
Hazard Ratio (Alt.)	0.75	0.75
Var (Log HR)	Null	Null
Allocation Ratio (nt/nc)	1	1
Boundary Parameters		
Spacing of Looks		Equal
Efficacy Boundary		LD (OF)
Accrual & Dropout Parameters		
Accrual Rate	1000	1000
Subjects are Followed	Until End of Study	Until End of Study
No. of Accrual Periods	1	1
No. of Dropout Pieces	1	1
Sample Size		
Maximum	6400	12555
Expected Under H0	6400	12554.9964
Expected Under H1	6400	12554.1223
Events		
Maximum	508	520
Expected Under H0	508	516.5858
Expected Under H1	508	385.5073
Accrual Duration		
Maximum	6.4	12.555
Expected Under H0	6.4	12.555
Expected Under H1	6.4	12.5541
Study Duration		
Maximum	48.677	27.2317
Expected Under H0	41.817	24.2646
Expected Under H1	48.677	21.4502

Des2 reveals that a group sequential design, with five equally spaced looks, taken after observing 104, 208, 312, 416 and 520 events, respectively, utilizing the default Lan-DeMets-O'Brien-Fleming (LD (OF)) spending function, achieves 90% power with a

maximum sample size of 12555 and a maximum study duration of 27.232 months. The expected study duration under H_1 is 21.451 months. However, these operating characteristics are based on the assumption that the hazard ratio is constant and equals 0.75. Since in fact the hazard ratio is 0.75 only after 12 months of treatment, the actual power of this design is unlikely to be 90%. We can use simulation to determine the actual power. With the cursor in any cell of Des2 node, select **S** from the menu bar. You will be taken to the simulation worksheet. In the **Response Generation Info** tab, make the changes in the hazard rates as shown below.

Number of Looks: 5						
Simula	Simulation Parameters Response Generation Info Accrual/Dropout Info					
		Survival Info	rmation			
O Using	Hazard Rates					
O Using	% Survival Rates					
# of Haza	# of Hazard Pieces 2 🔹					
Piece	Piece Starting At Hazard Rates Hazard Ratio					
Piece	Piece Starting At Control Treatment Hazard Ratio					
1	0.000	0.0025	0.0025	1.000		
2	12.000	0.0025	0.0019	0.750		

After changing the number of simulations as 1000 in the **Simulation Control Info**, click on the **Simulate** button to run 1000 simulations of Des2 with data being generated from the survival distributions that were specified in the **Response Generation Info** tab. The

results of this simulation run are as shown below.

	Wbk2:Des2:Sim6
Mnemonic	SU-2S-LRAR
Test Parameters	
Design Type	Superiority
Test Type	2–Sided
Test Statistic	Logrank
Power	0.187
No. of Looks	5
Model Parameters	
No. of Hazard Pieces	2
Boundary Parameters	
Efficacy Boundary	User Specified
Spacing of Looks	User Specified
Accrual & Dropout Parameters	
Followup Duration	Until End of Study
Accrual Rate	1000
No. of Accrual Periods	1
Sample Size	
Maximum	12555
Events	
Maximum	520
Study Duration	
Maximum	25.2768

Only 187 of the 1000 simulated trials were able to reject the null hypothesis indicating that the study is grossly underpowered. We can improve on this performance by extending the total study duration so that additional events may be observed. To increase study duration, go to the **Simulation Parameters** tab and select the **Look Time** option under **Fix at Each Look**. We had specified at the outset that the total study duration should not exceed 50 months. Let us therefore fix the total study duration at 50 months and space each interim look

10 months apart by editing the **Study Duration**.

Simulat	ion Parameters	Response Gene	eration Info	
Trial Type	Sup	Superiority 🔽		
Test Type	: 2-Si	2-Sided		
Study Dur	ation:	50		
Fix at Eacl	Fix at Each Look: Look Time			
Look #	Analysis Time	Effica	acy Z	
LOOK #	Analysis fille	Upper	Lower	
1	10.0000	4.8769	-4.8769	
2	20.0000	3.3570	-3.3570	
3	30.0000	2.6803	-2.6803	
4	40.0000	2.2898	-2.2898	
5	50.0000	2.0310	-2.0310	

We are now ready to simulate a 5-look group sequential trial in which the LD (OF) stopping boundaries are applied and the looks are spaced 10 months apart. Each simulated trial will enroll 12555 subjects at the rate of 1000/month. The simulation data will be generated from survival distributions in which the hazard rates of both arms are 0.0025 for the first 12 months and the hazard ratio is 0.75 thereafter. To generate 1000 simulations of this design click on the Simulate button. These simulations do indeed show a substantial increase in power, from



18.7% previously to 79.9% .

	Wbk2:Des2:Sim6	Wbk2:Des2:Sim7
Mnemonic	SU-2S-LRAR	SU-2S-LRAR
Test Parameters		
Design Type	Superiority	Superiority
Test Type	2–Sided	2–Sided
Test Statistic	Logrank	Logrank
Power	0.187	0.799
No. of Looks	5	5
Model Parameters		
No. of Hazard Pieces	2	2
Boundary Parameters		
Efficacy Boundary	User Specified	User Specified
Spacing of Looks	User Specified	User Specified
Accrual & Dropout Parameters		
Followup Duration	Until End of Study	Until End of Study
Accrual Rate	1000	1000
No. of Accrual Periods	1	1
Sample Size		
Maximum	12555	12555
Events		
Maximum	520	879.219
Study Duration		
Maximum	25.2768	50

The design specifications stated, however, that the trial should have 90% power. In order to achieve this amount of power we will have to increase the sample size. By trial and error, upon increasing the sample size to 18200 on the **Simulation Parameters** tab we observe that

	Wbk2:Des2:Sim6	Wbk2:Des2:Sim7	Wbk2:Des2:Sim8
Mnemonic	SU-2S-LRAR	SU-2S-LRAR	SU-2S-LRAR
Test Parameters			
Design Type	Superiority	Superiority	Superiority
Test Type	2–Sided	2–Sided	2-Sided
Test Statistic	Logrank	Logrank	Logrank
Power	0.187	0.799	0.904
No. of Looks	5	5	5
Model Parameters			
No. of Hazard Pieces	2	2	2
Boundary Parameters			
Efficacy Boundary	User Specified	User Specified	User Specified
Spacing of Looks	User Specified	User Specified	User Specified
Accrual & Dropout Parameters			
Followup Duration	Until End of Study	Until End of Study	Until End of Study
Accrual Rate	1000	1000	1000
No. of Accrual Periods	1	1	1
Sample Size			
Maximum	12555	12555	18300
Events			
Maximum	520	879.219	1169.605
Study Duration			
Maximum	25.2768	50	50

the power has increased to 90 % (up to Monte Carlo accuracy).



11.7 Simulating a Trial with Stratification variables

The data presented in Appendix I of Kalbfleisch and Prentice (1980) on lung cancer patients were used as a basis for this example. We will design a trial to compare two treatments (Standard and Test) in a target patient group where patients had some prior therapy. The response variable is the survival time in days of lung cancer patients. First, we will create a design for 3 looks, to compare the two treatment groups. Next, using this design, we will carry out simulation with stratification variables. Three covariates in the data are used here as stratum variables: a) type of cancer cell (small, adeno, large, squamous,), b) age in years (<=50, >50), and c) performance status score (<=50, >50 and <=70, >70).

The input data for base design are as follows: Trial type:superiority; test type:2-sided; type I error:0.05; power:0.90; allocation ratio:1; hazard rate (control):0.009211; hazard rate (treatment):0.004114; number of looks:3; Boundary family:spending functions; spending function:Lan-DeMets (OF); subjects are followed:until end of study; subjects accrual rate:12 per day.

The input data for stratified simulation are as given below: The number of stratum variables=3 (cell type; age group; performance status score).

11.7.1 Creating the design

First we will create a design using the input data. Open East, click **Design** tab and then **Time to Event** button in **Survival** group. Now click **Logrank Test: Given Accrual Duration and Accrual Rates**. In the resulting screen, enter the input data in the dialog boxes under the different tabs. Finally click on **Compute** button. Now the dialog boxes under the different tabs will appear as shown below.

The Design Parameters tab is shown below, where you can see the computed value of No.of

Table 11.4: Input data for stratified simulation			
Cell type	Proportion	Hazard ratio	
small	0.28	Baseline	
adeno	0.13	2.127	
large	0.25	0.528	
squamous	0.34	0.413	
Age group	Proportion	Hazard ratio	
\leq 50 years	0.28	Baseline	
> 50 years	0.72	0.438	
Performance status score group	Proportion	Hazard ratio	
<u>≤</u> 50	0.43	Baseline	
> 50 and \leq 70	0.37	0.164	
> 70	0.20	0.159	

Events.

Design: Su	rvival Endpoint: Two-Sample Test - Parallel Design - Logrank Give	n Accrual Duration and Accrual Rates
Design Type: Superiority 💌 Num	ber of Looks: 3 💌	
Design Parameters Boundary Info Accrua	al/Dropout Info	
Test Type: 2-Sided Type I Error (a): 0.05 Power: 0.9 No. of Events: 66 Allocation Ratio: 1 (n_{χ}/n_{χ})	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Alternative Image: Constraint of the second se
	Variance of Log Hazard Ratio	

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Design Parameters Boundary Info Accrual/Dropout Info Efficacy Futility • Boundary Family: Spending Functions Boundary Family: None • Lan-DeMets • Spending Function: Parameter: OF • Type I Error (α): 0.05 -Spacing of Looks Efficacy Boundary: Z Scale • **1** O Equal O Unequal Efficacy Boundary Info. Cum. α Look # Fraction Spent Upper Lower 0.3333 3.7103 -3.7103 0.0002 0.6667 0.0121 2.5114 -2.5114 1.0000 0.0500 1.9930 -1.9930

The **Boundary Info** will appear as shown below, where all the input data are seen.

The Accrual/Dropout Info tab containing the input data will be as shown below.

Design Parameters Boundary Info Accrual/Dropout Info	
Subjects are followed: Until End of Study	Piecewise Constant Dropout Rates
# of Accrual Periods: 1 Period # Starting At Accrual Rate	# of Pieces: 0 Input Method: Hazard Rates
1 0.0000 12.0000	Period # Starting At (Control) (Treatment)
Accrual Min. Comtd. Sugg. Max.	
O Duration: 5.5 24 42.5	
Subjects: 66 288 510	

After the design is completed and saved in a workbook, select the design node and click on

the **output summary** icon to see the following output display.

	Wbk3:Des1
Mnemonic	SU-2S-LRAR
Test Parameters	
Design Type	Superiority
No. of Looks	3
Test Type	2–Sided
Specified α	0.05
Power	0.9023
Model Parameters	
Hazard Ratio (Alt.)	0.4466
Var (Log HR)	Null
Allocation Ratio (nt/nc)	1
Boundary Parameters	
Spacing of Looks	Equal
Efficacy Boundary	LD (OF)
Accrual & Dropout Parameters	
Accrual Rate	12
Subjects are Followed	Until End of Study
No. of Accrual Periods	1
No. of Dropout Pieces	0
Sample Size	
Maximum	288
Expected Under H0	287.9915
Expected Under H1	288
Events	
Maximum	66
Expected Under H0	65.7293
Expected Under H1	52.8227
Accrual Duration	
Maximum	24
Expected Under H0	23.9993
Expected Under H1	24
Study Duration	
Maximum	52.0169
Expected Under H0	40.3527
Expected Under H1	43.2957

11.7.2 Running Stratified Simulation

After selecting the design node, click on **Simulate** icon. You will see simulation screen with the dialog boxes under different tabs. Click on **Include Options** and select **Stratification Info**.

The dialog box under **Simulation Parameters** will be as shown below. Keep the default test statistic **LogRank** and the default choice of **Use Stratified Statistic**.

Trial Type	: Su	periority	*				
Test Type	2-5	ided	*			Test Statistic	: Logrank 💌
Max. # of	Events:	66					🖬 Use Stratified Statistic
Fix at Eac	h Look: Tot	al No. of Events	•				
		Cum.	x Spent	Effic	acy Z		
Look #	Info Creation						
Look #	Info. Fraction	Upper	Lower	Upper	Lower		
Look #	Info. Fraction 0.3333	Upper 0.0001	Lower 0.0001	Upper 3.7103	Lower -3.7103		
Look #							

After entering the stratification input information, the dialog box under **Stratification Info** will appear as shown below.

Simulatio	n Parame	ers Stra	tification I	nfo Res	ponse Gen	eration Ir	nfo Accr	ual/[propout Info	Simulation Control Info		
Number of S	tratum Va	riables: 3	• A	llocate Fr	actions to	Strata: 💿	Marginally	c	Individually			
Stratum	m # of Marginal Stratum Total Number of Strata: 24											
Variable	Levels	Distribut	on:						Stratum Spec	cific Information:		
Cell type	4 💌	Cell	type	Age	group	Perf	Status		Stratum ID	Label	Fraction	-
		Level	Fraction	Level	Fraction	Level	Fraction		SID01	small <=50 yrs Perf_1	0.034	1
Age group	2 🔻	small	0.28	<=50	0.28	Perf_1	0.43	_	SID02	small <=50 yrs Perf_2	0.029	4
PerfStatus	3 -	adeno	0.13	> 50	0.72	Perf_2	0.37		SID03 SID04	small <=50 yrs Perf_3 small > 50 yrs Perf_1	0.016	1
Chocacas	b	large	0.25			Perf_3	0.2		SID04	small > 50 yrs Perf_2	0.087	4
		squa	0.34						SID05	small > 50 yrs Perf_3	0.073	1
									SID00	adeno <=50 yrs Perf_1	0.016	
									SID08	adeno <=50 vrs Perf_2	0.013	
									SID09	adeno <=50 yrs Perf_3	0.007	•

After entering adding response related input information, the dialog box under Response

Generation Info will display details as shown in the following screen shots.

Simulation Parame	eters Stra	rs Stratification Info Response Gener		nerati	ion Info	Accrual/Drop	oout Info	Simu	ilation Control I	nfo
							Sun	vival Ir	formation —	
O User Specified Ha	O User Specified Hazard Rates				Stratum I	D: SID01:sm	all <=50	yrs F	Perf_1	
Model Based Hazard Rates Model: Hazard Rate ~ (Treatment + Cell type + Age group + PerfStat			C		Hazard Rates Cum. % Survival					
-Model Parameters				٦١٢	Piece	Starting At		Hazard	Rates	Hazard Ratio
Baseline Hazard Ra	te:	0.009			Piece	Starting At	Contr	ol	Treatment	Hazai u Katio
Variables: 9	pecify Haz	ard Ratio:			1	0.0000	0.009	92	0.0041	0.4466
Treatment		Treatment								
Cell type Age group	Level	Fraction	Hazard Ratio							
PerfStatus			Baseline							
	Treatment	0.500	0.447							

Variables:	Specify Hazard Ratio:									
Treatment)								
Cell type	Level	Fraction	Hazard Ratio							
Age group PerfStatus	small	0.280	Baseline							
	adeno	0.130	2.127							
	large	0.250	0.528							
	squamous	0.340	0.413							

Variables:	Specify Hazard Ratio:									
Treatment		Age group								
Cell type Age group	Level	Fraction	Hazard Ratio							
PerfStatus	<=50 yrs	0.280	Baseline	ſ						
	> 50 yrs	0.720	0.438							
1 1										

Variables:	Specify Haz	ard Ratio:	
Treatment		PerfStatu	s
Cell type Age group	Level	Fraction	Hazard Ratio
PerfStatus	Perf_1	0.430	Baseline
	Perf_2	0.370	0.164
	Perf_3	0.200	0.159



The Accrual/Dropout Info dialog box will appear as shown below.

Simulation Parameters	Stratification Info	Response Genera	ation Info	Accrua	al/Dropout Ir	nfo Simulation C	Control Info	
ample Size:	288		Distrib	ution	of Accrual Ti	me: Uniform		
ubjects are followed: Unti	I End of Study]						
Accrual Info			Piece	wise (Constant Dro	pout Rates		
			# of P	eces:	0 🔻	Input Method:	Hazard Rates	_
# of Accrual Periods: 1	 Input Method: 	Accrual Rates 💌	Perio	1# 9	starting At	Hazard Rate (Control)	Hazard Rate (Treatment)	
Period # Starting At	Accrual Rate					(,	(_
1 0.0000	12.0000		1					

In the **Simulation Control Info** tab, specify number of simulations as 1000 and select the choices under output options to save simulation data. The dialog box will appear as shown below.

Simulation Parameters	Stratification Info	Response Generation	Info Accrual/E	Propout Info	Simulation Control Info
Number of Simulations:	1000				
Refresh Frequency:	100				
Random Number Seed	Output Options			1	
Olock	Save summary	statistics for every simu	ulation run		
O Fixed 100	☑ Save subject-le	vel data for 10	simulation runs		
	Note: Max. 100,00	00 records will be saved	ι.		
Suppress All Intermedia	te Output				
Pause after Refresh					

After clicking on **Simulate** button, the results will appear in the Output Preview row. Click on it and save it in the workbook. Select this simulation node and click on **Output Summary** icon

to see the following	stratification	simulation	output summary.	

Wbk3:Des1:Sim1
SU-2S-LRAR
Superiority
2-Sided
Stratified Logrank
0.856
3
User Specified
User Specified
Until End of Study
12
1
288
66
172.4444
3
24
Marginally
Model based

The stratified simulation results show that the attained power 0.856 is slightly less than the design specified power of 0.90.

12 *Non-Inferiority Trials Given Accrual Duration and Accrual Rates*

This chapter will illustrate through a worked example how to design, monitor and simulate a two-sample non-inferiority trial with a time-to-event trial endpoint, when the accrual duration and accrual rates are fixed.

12.1 Establishing the Non-Inferiority Margin

The first step in designing a non-inferiority trial is to establish a suitable non-inferiority margin. This is typically done by performing a meta-analysis on past clinical trials of the active control versus placebo. Regulatory agencies then require the sponsor of the clinical trial to demonstrate that a fixed percentage of the active control effect (usually 50%) is retained by the new treatment. A further complication arises because the active control effect can only be estimated with error. We illustrate below with an example provided by reviewers at the FDA.

Rothman et al. (2003) have discussed a clinical trial to establish the non-inferiority of the test drug Xeloda (treatment *t*) relative to the active control (treatment *c*) consisting of 5-fluorouracil with leucovarin (5FU+LV) for metastatic colorectal cancer. In order to establish a suitable non-inferiority margin for this trial it is necessary to first establish the effect of 5FU+LV relative to the reference therapy of 5FU alone (treatment *p*, here regarded as placebo). To establish this effect the FDA conducted a ten-study random effects meta-analysis (FDA Medical-Statistical review for Xeloda, NDA 20-896, April 2001) of randomized comparisons of 5-FU alone versus 5-FU+LV. Letting λ_t , λ_c and λ_p denote the constant hazard rates for the new treatment, the active control and the placebo, respectively, the FDA meta-analysis established that

$$\ln\left(\widehat{\lambda_p/\lambda_c}\right) = 0.234$$

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with standard error

$$\operatorname{se}[\ln{(\widehat{\lambda}_p/\widehat{\lambda_c})}] = 0.075$$
.

Thus with 100γ % confidence the active control effect lies inside the interval

$$[0.234 - 0.075\Phi^{-1}(\frac{1+\gamma}{2}), 0.234 + 0.075\Phi^{-1}(\frac{1+\gamma}{2})]$$
(12.1)

The new study is required to demonstrate that some fraction (usually 50%) of the active control effect is retained. Rothman et al. (2003) state that the claim of non-inferiority for the new treatment relative to the active control can be demonstrated if the upper limit of a two-sided $100(1 - \alpha)$ % confidence interval for $\ln(\lambda_t/\lambda_c)$ is less than a pre-specified fraction of the lower limit of a two-sided 100γ % confidence interval for the active control effect established by the meta-analysis. This is known as the "two confidence intervals procedure". Specifically in order to claim non-inferiority in the current trial it is necessary to show that

$$\ln\left(\widehat{\lambda_t/\lambda_c}\right) + \Phi^{-1}(1-\alpha/2)\mathsf{se}[\ln\left(\widehat{\lambda_t/\lambda_c}\right)] < (1-f_0)\{\ln\left(\widehat{\lambda_p/\lambda_c}\right) - \Phi^{-1}(\frac{1+\gamma}{2})\mathsf{se}[\ln\left(\widehat{\lambda_p/\lambda_c}\right)]\}.$$
(12.2)

We may re-write the non-inferiority condition (12.2) in terms of a one-sided Wald test of the form $\widehat{}$

$$\frac{\ln\left(\widehat{\lambda_t}/\widehat{\lambda_c}\right) - \delta_0}{\mathsf{se}[\ln\left(\widehat{\lambda_t}/\widehat{\lambda_c}\right)]} < \Phi^{-1}(1 - \alpha/2) , \qquad (12.3)$$

where

$$\delta_0 = (1 - f_0) \{ \ln\left(\widehat{\lambda_p/\lambda_c}\right) - \Phi^{-1}\left(\frac{1+\gamma}{2}\right) \operatorname{se}[\ln\left(\widehat{\lambda_p/\lambda_c}\right)] \}$$
(12.4)

is the non-inferiority margin.

The choice $f_0 = 1$ implies that the entire active control effect must be retained in the new trial and amounts to running a superiority trial. At the other end of the spectrum, the choice $f_0 = 0$ implies that none of the active control effect need be retained; i.e., the new treatment is only required to demonstrate effectiveness relative to placebo. The usual choice is $f_0 = 0.5$, implying that the new treatment is required to retain at least 50% of the active control effect. The usual choice for α is $\alpha = 0.05$. A conservative choice for the coefficient γ is $\gamma = (1 - \alpha) = 0.95$. Rothman et al. (2003) refer to this method of establishing the non-inferiority margin as the "two 95 percent two-sided confidence interval procedure" or the



"95-95 rule". In general this approach leads to rather tight margins unless the active control effect is substantial. Rothman et al. (2003) have also proposed more lenient margins that vary with the amount of power desired. Fleming (2007), however, argues for the stricter 95-95 rule on the grounds that it offers greater protection against an ineffective medical compound being approved in the event that the results of the previous trials used to establish the active control effect are of questionable relevance to the current setting. Accordingly we evaluate (12.4) with $\gamma = 0.95$, $f_0 = 0.5$, $\ln(\widehat{\lambda_p/\lambda_c}) = 0.234$ and se $[\ln(\widehat{\lambda_p/\lambda_c})] = 0.075$ thereby obtaining the non-inferiority margin to be $\delta_0 = 0.044$ for the log hazard ratio and $\exp(0.044) = 1.045$ for the hazard ratio.

12.2 Design of Metastatic Colorectal Cancer Trial

12.2.1 Single-Look Design 12.2.2 Early Stopping for Futility

In this section we will use East to design a single-look non-inferiority trial comparing the test drug Xeloda (treament t) to the active control 5FU+LV (treatment c) for the treatment of metastatic colorectal cancer. On the basis of a meta-analysis of ten previous studies of the active control versus placebo (Rothman et al., 2003), a non-inferiority margin of 1.045 for λ_t/λ_c has been established. Thus we are interested in testing the null hypothesis of inferiority H_0 : $\lambda_t/\lambda_c \ge 1.045$ versus the one-sided alternative hypothesis that $\lambda_t/\lambda_c < 1.045$. Subjects are expected to enroll at the rate of 60/month and the median survival time for patients randomized to the active control arm is expected to be 18 months.

12.2.1 Single-Look Design

We will use East to create an initial single-look design having 80% power to detect the alternative hypothesis H_1 : $\lambda_t/\lambda_c = 1$ with a one sided level 0.025 non-inferiority test.

To begin click Survival: Two Samples on the Design tab and then click Parallel Design: Log

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Rank Test Given Accrual Duration and Accrual Rates.



A new screen will appear. Enter the appropriate design parameters into the dialog box as shown below.

Design: S	urvival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Accrual Rate
	ber of Looks: 1 💌
Design Parameters Accrual/Dropout Info Test Type: 1-Sided Type I Error (α): 0.025 Power: 0.8 No. of Events: Computed	# of Hazard Pieces: 1 Input Method: Median Survival Times Image: Hazard Ratio (Optional) Null Alternative Image: Hazard Ratio (λ_t / λ_c) 1.045 1 Ratio of Medians (m, m,) 0.957 1
Allocation Ratio: 1 (n_t/n_c)	Period # At Med. Surv. Time (Control) Med. Surv. Time (Treatment: Null) Med. Surv. Time (Treatment: Null) 1 18.000 17.225 18.000
	Variance of Log Hazard Ratio O Null O Alternative

The box labeled **Variance of Log Hazard Ratio** specifies whether the calculation of the required number of events is to be based on the variance estimate of the log hazard ratio under the null hypothesis or the alternative hypothesis. The default choice in East is **Null**. Most textbooks recommend this choice as well (see, for example Collett, 1994, equation (2.21) specialized to no ties). It will usually not be necessary to change this default. For a technical discussion of this issue refer to Appendix **??**, Section **??**.

Next click on the **Accrual/Dropout Info** tab. Here we will specify the accrual information and dropout rates. Enter an accrual rate of 60. Suppose that there are 5% drop-outs per year in

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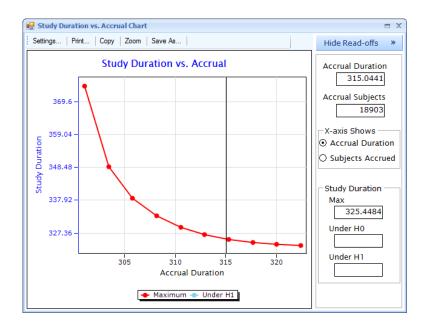
each arm. Enter these values as shown below.

Design Parameters Accrual/Dropout Info	
Subjects are followed: Until End of Study	Piecewise Constant Dropout Rates
# of Accrual Periods: 1	# of Pieces: 1 Input Method: Dropout Rates
Period # Starting At Accrual Rate 1 0.000 60.000	Period # At Cum. % Dropouts Cum. % Dropouts (Treatment)
	1 12.000 5.000 5.000
Accrual	
Min. Comtd. Sugg. Max.	
O Duration: 300.05 311.733 323.4	
⊙ Subjects: 18003 18704 19404	

On the bottom of this screen is where you can specify the accrual duration or number of subjects. East automatically computes a range that is necessary to achieve the desired power of the study and selects the midpoint of the range, as the committed accrual duration or subjects. If your study has a restriction on accrual duration or subject accrual, you may enter this value in the **Comtd.** column. In our example, East computes a minimum accrual duration of 300.05 months and a suggested maximum of 323.4 months. Also, if you click the *icon* a chart which shows the relationship between accrual duration (or subject accrual, depending

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on whether you choose to specify accrual duration or subject accrual) and study duration.

Looking at this chart, choosing an accrual duration longer that 315 months will not result in a substantial decrease in study duration. Thus, we commit to an accrual duration of 315 months. Close this chart, select the radio button next to **Duration** and enter 315 in the **Comtd.** column.

Click on **Compute** to complete the design. The design is shown as a row in the **Output Preview** located in the lower pane of this window. You can select this design by clicking anywhere along the row in the **Output Preview**. With Des1 selected, click the *Located* icon to display the details of this design in the upper pane, which are shown below. You may also wish to save this design. Select Des1 in the **Output Preview** window and click the to save



this design to Workbook1 in the Library.

	Wbk1:Des1
Mnemonic	SU-2S-LRAR
Test Parameters	50 25 210 11
Design Type	Noninferiority
No. of Looks	1
Test Type	1-Sided
Specified a	0.025
Power	0.8
Model Parameters	
Hazard Ratio (Null)	1.045
Hazard Ratio (Alt.)	1
Var (Log HR)	Null
Allocation Ratio (nt/nc)	1
Accrual & Dropout Parameters	
Accrual Rate	60
Subjects are Followed	Until End of Study
No. of Accrual Periods	1
No. of Dropout Pieces	1
Sample Size	
Maximum	18900
Expected Under H0	18900
Expected Under H1	18900
Events	
Maximum	16205
Expected Under H0	16205
Expected Under H1	16205
Accrual Duration	
Maximum	315
Expected Under H0	315
Expected Under H1	315
Study Duration	
Maximum	325.466
Expected Under H0	323.839
Expected Under H1	325.466

It is immediately evident that Des1 is untenable. It requires 16,205 events to be fully powered. The problem lies with trying to power the trial to detect a hazard ratio of 1 under the alternative hypothesis. Suppose instead that the investigators actually believe that the treatment is slightly superior to the active control, but the difference is too small to be

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detected in a superiority trial. In that case a non-inferiority design powered at a hazard ratio less than 1 (0.95, say) would be a better option because such a trial would require fewer events.

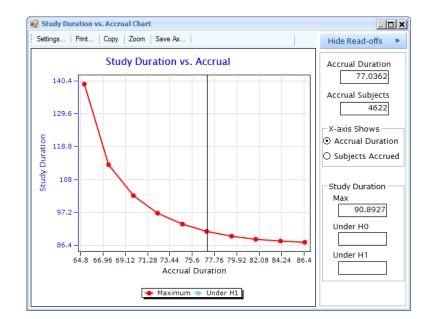
To see this create a new design by selecting Des1 in the **Library**, and clicking the *sicon* on the **Library** toolbar. Then edit this design by specifying a hazard ratio of 0.95 under the alternative hypothesis as shown below.

Design Parameters	Accrual/Dropout Info					
Test Type: [Type I Error (α): [Power: [1-Sided		ard Pieces: rd Ratio (Opt d Ratio		nput Method: Media Null	Alternative
No. of Events:	Computed	O Ratio	of Medians	$(m_t^{}/m_c^{})$	0.	957 1.053
Allocation Ratio: (n,/n,)	1	Period #	At	Med. Surv. Time (Control)	Med. Surv. Time (Treatment: Null)	Med. Surv. Time (Treatment: Alt.)
(··t/··c/		1		18.000	17.225	18.947
		Variano	e of Log Haz	ard Ratio		
		⊙ Null		○ Alternative		

Next, click on the **Accrual/Dropout Info** tab. Notice that the minimum and suggested maximum accrual have changed to 64.167 and 87.45 months, respectively. Click the *icon* to display the study duration versus accrual chart.

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Suppose that after examining this chart, you decide that an accrual duration longer than 77 months is not worth the small decrease in study duration one would gain from a longer accrual duration. Close this chart. Select the radio button next to **Duration** and enter 77 in the **Comtd.** column.

Design Parameters Accrual/Dropout Info												
Subjects are followed: Until End of Study												
Accrual Info	Piecewise Constant Dropout Rates											
# of Accrual Periods: 1	# of Pieces: 1 Input Method: Dropout Rates V											
Period # Starting At Accrual Rate 1 0.000 60.000	Period # At Cum. % Dropouts Cum. % Dropouts (Control) (Treatment)											
	1 12.000 5.000 5.000											
Accrual												
Min. Comtd. Sugg. Max.												
⑦ Duration: 64.167 77 87.45												
O Subjects: 3850 4620 5247												

Click the **Compute** button to generate output for Des2. With Des2 selected in the **Output**

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Preview, click the icon to save Des2 to the **Library**. In the **Library**, select the rows for Des1 and Des2, by holding the Ctrl key, and then click the icon. The upper pane will display the details of the two designs side-by-side:

	Wbk1:Des1	Wbk1:Des2
Mnemonic	SU-2S-LRAR	SU-2S-LRAR
Test Parameters		
Design Type	Noninferiority	Noninferiority
No. of Looks	1	1
Test Type	1–Sided	1-Sided
Specified α	0.025	0.025
Power	0.8	0.8
Model Parameters		
Hazard Ratio (Null)	1.045	1.045
Hazard Ratio (Alt.)	1	0.95
Var (Log HR)	Null	Null
Allocation Ratio (nt/nc)	1	1
Accrual & Dropout Parameters		
Accrual Rate	60	60
Subjects are Followed	Until End of Study	Until End of Study
No. of Accrual Periods	1	1
No. of Dropout Pieces	1	1
Sample Size		
Maximum	18900	4620
Expected Under H0	18900	4620
Expected Under H1	18900	4620
Events		
Maximum	16205	3457
Expected Under H0	16205	3457
Expected Under H1	16205	3457
Accrual Duration		
Maximum	315	77
Expected Under H0	315	77
Expected Under H1	315	77
Study Duration		
Maximum	325.466	90.946
Expected Under H0	323.839	88.962
Expected Under H1	325.466	90.946

Des2 is clearly easier to implement than Des1. It requires only 3,457 events and 4620 subjects to be fully powered. Also note the marked decrease in study duration under either the null or alternative hypothesis. Nevertheless, Des2 is also unsatisfactory. The maximum study duration for Des2 (accrual plus follow-up) is 90.9 months with 77 months of that amount of time being utilized to enroll 4620 patients. It is necessary to shorten the maximum study duration further.



One possible way to shorten the maximum study duration is to increase the rate of enrollment. Suppose that additional sites can be enlisted to enroll patients after the study is activated so that six months later the average rate of enrollment is increased to 110/month. To see the impact of the increased rate of enrollment select Des2 in the **Library**, and click on the **Solution** icon on the **Library** toolbar.

Next, click on the **Accrual/Dropout Info** tab. Change the accrual rates as shown below.

Design Parameters Accrual/Dropout Info	
Subjects are followed: Until End of Study	
Accrual Info	Piecewise Constant Dropout Rates
# of Accrual Periods: 1	# of Pieces: 1 Input Method: Dropout Rates V
Period # Starting At Accrual Rate 1 0.000 110.000	Period # At Cum. % Dropouts Cum. % Dropouts (Treatment)
	1 12.000 5.000 5.000
Accrual	
Min. Comtd. Sugg. Max.	
O Duration: 35 45.836 56.664	
Subjects: 3850 5042 6233	

Notice how East automatically updates the accrual duration and subject accrual. An accrual duration in the range of 35 to 56.664 months is sufficient to achieve the desired power. Suppose that after examining the study duration versus accrual chart, we decide on an accrual duration of 49 months. Enter 49 in the **Comtd.** column.

Click the **Compute** button to generate output for Des3. With Des3 selected in the **Output Preview**, click the icon to save Des3 to the **Library**. In the **Library**, select the rows for Des1, Des2, and Des3 by holding the Ctrl key, and then click the icon. The upper pane

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	Wbk1:Des1	Wbk1:Des2	Wbk1:Des3
Mnemonic	SU-2S-LRAR	SU-2S-LRAR	SU-2S-LRAR
Test Parameters			
Design Type	Noninferiority	Noninferiority	Noninferiority
No. of Looks	1	1	1
Test Type	1–Sided	1–Sided	1–Sided
Specified α	0.025	0.025	0.025
Power	0.8	0.8	0.8
Model Parameters			
Hazard Ratio (Null)	1.045	1.045	1.045
Hazard Ratio (Alt.)	1	0.95	0.95
Var (Log HR)	Null	Null	Null
Allocation Ratio (nt/nc)	1	1	1
Accrual & Dropout Parameters			
Accrual Rate	60	60	110
Subjects are Followed	Until End of Study	Until End of Study	Until End of Study
No. of Accrual Periods	1	1	1
No. of Dropout Pieces	1	1	1
Sample Size			
Maximum	18900	4620	5390
Expected Under H0	18900	4620	5390
Expected Under H1	18900	4620	5390
Events			
Maximum	16205	3457	3457
Expected Under H0	16205	3457	3457
Expected Under H1	16205	3457	3457
Accrual Duration			
Maximum	315	77	49
Expected Under H0	315	77	49
Expected Under H1	315	77	49
Study Duration			
Maximum	325.466	90.946	58.523
Expected Under H0	323.839	88.962	57.158
Expected Under H1	325.466	90.946	58.523

will display the details of the three designs side-by-side:

Des3 also requires 3457 events. However, because of the faster rate of enrollment the time that it takes to obtain these events is cut down to 58.5 months.

12.2.2 Early Stopping for Futility

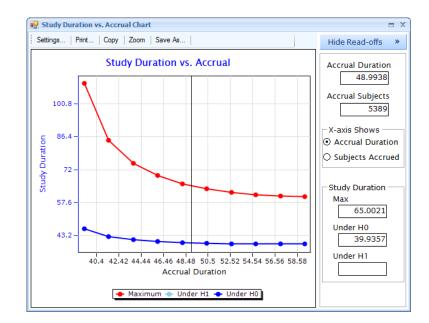
Under the null hypothesis Des3, with 3457 events, has an expected study duration of 57.2 months. This is a very long time commitment for a trial that is unlikely to be successful. Therefore it would be a good idea to introduce a futility boundary for possible early stopping. Since we wish to be fairly aggressive about early stopping for futility we will generate the futility boundary from the Gamma(-1) β -spending function. On the other hand, since there is no interest in early stopping for efficacy, we will not use an efficacy boundary.

Create a new design by selecting Des3 in the **Library**, and clicking the *icon* on the **Library** toolbar. Change the number of looks from 1 to 3. Next, click on the **Boundary Info** tab. Enter the parameters as shown below. Be sure to select the **Non-Binding** option. This choice gives us the flexibility to continue the trial even if a futility boundary has been crossed. Data monitoring committees usually want this flexibility; for example, to follow a secondary endpoint.

Desig	Design Type: Noninferiority 💽 Number of Looks: 3 💌											
Design	n Parameter:	Boundan	/ Info Accru	al/Dro	pout Info							
Efficacy Bounda	/ ————————————————————————————————————	None			Futility Boundary Family: Spending Function: Parameter (γ): Type II Error (β):	Spending Functions Gamma Family -1 0.2		 ⊙ Non-Binding ○ Binding 				
Spacing	g of Looks –	⊙ Equal	O Unequ	al	Futility Boundary:	Z Scale						
Look #	Info. Fraction	Cum. β Spent	Futility Boundary									
1	0.333	0.046	-0.007									
2	0.667	0.110	-1.056									
3	1.000	0.200	-1.960									

Next click on the **Accrual/Dropout Info** tab. Once again, East automatically computes the minimum and suggested maximum values for the accrual duration and subject accrual. Click the icon to display the study duration versus accrual chart. Notice that another line is added to the chart. Now, we can see the maximum study duration vs accrual under the null

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hypothesis.

Suppose that after examining this chart, you decide to set the accrual duration at 49 months. Any increase in accrual duration past 49 months will not result in a substantial decrease in study duration. Close this chart. Select the radio button for **Duration** and enter 49 in the **Comtd.** column.

Click the **Compute** button to generate output for Des4. With Des4 selected in the **Output Preview**, click the icon to save Des4 to the **Library**. In the **Library**, select the rows for Des3 and Des4 by holding the Ctrl key, and then click the icon. The upper pane will



display the details of the two designs side-by-side:

	Wbk1:Des3	Wbk1:Des4
Mnemonic	SU-2S-LRAR	SU-2S-LRAR
Test Parameters		
Design Type	Noninferiority	Noninferiority
No. of Looks	1	3
Test Type	1–Sided	1-Sided
Specified α	0.025	0.025
Attained α		0.022
Power	0.8	0.8
Model Parameters		
Hazard Ratio (Null)	1.045	1.045
Hazard Ratio (Alt.)	0.95	0.95
Var (Log HR)	Null	Null
Allocation Ratio (nt/nc)	1	1
Boundary Parameters		
Futility Boundary		Gm (-1) (NB)
Spacing of Looks		Equal
Accrual & Dropout Parameters		
Accrual Rate	110	110
Subjects are Followed	Until End of Study	Until End of Study
No. of Accrual Periods	1	1
No. of Dropout Pieces	1	1
Sample Size		
Maximum	5390	5390
Expected Under H0	5390	4140.262
Expected Under H1	5390	5271.053
Events		
Maximum	3457	3780
Expected Under H0	3457	2056.327
Expected Under H1	3457	3583.036
Accrual Duration		
Maximum	49	49
Expected Under H0	49	37.639
Expected Under H1	49	47.919
Study Duration		
Maximum	58.523	64.893
Expected Under H0	57.158	39.546
Expected Under H1	58.523	62.059

Observe that while the maximum study duration has been inflated by about 6 months compared to Des3, the expected study duration under H_0 has been cut down by almost 18 months.

It would be useful to simulate Des4 under a variety of scenarios for the hazard ratio. Select Des4 in the Library and click the sicon. You will be taken to the following simulation

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worksheet.

Simulation Parameters Response Gener		ation Info	Accrual/Dropout Info	Simulation Control Info					
Trial Type	Nor	inferiority 💌	·						
Test Type	1-Si	ded 💌	~	No	oninf. Margin (In(HRO)):	0.044	Test Statisti	c: Logrank	•
Max. # of	Events:	3780							
Fix at Eac	h Look: Tota	al No. of Events	•						
Look #	Info. Fraction	Futility Z							
1	0.333	-0.007							
2	0.667	-1.056							
3	1.000	-1.960							

We wish to simulate this trial under the null hypothesis that the hazard ratio is exp(0.044) = 1.045. To this end click on the **Response Generation Info** tab. In this tab change the control and treatment hazard rates as shown below.

Numl	per of Looks: 3	¥				
Simul	ation Parameters	Response Ge	Accrual/Dropo	ut Info	o Simulation Control Info	
- -	Hazard Rates Cum. % Survival					
# of Haz	zard Pieces 1	•				
Piece	Starting At	Hazaro	l Rates	Hazard Ratio		
FIECE	Starting Ac	Control Treatment		Tiazard Natio		
1	0.000	0.0385	0.0402	1.045		

Next, click the **Simulate** button to simulate 10000 trials. A new row labeled Sim1 will appear in the **Output Preview** window. Select Sim1 in the **Output Preview** and click the icon to save it to the **Library**. In the **Library**, double-click Sim1. A portion of the output is displayed



below. (The actual values may differ, depending on the starting seed used).

Simulation: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Accrual Rates

Simulation ID: Design Type: Number of Looks:	Sim1 Noninferiority	Look #	Events	Boundarie Futility	Early Stopping Fo	Unable To Reject H1		tal ations			
	3 1-Sided			Upper	Futility	Rejectini	Count	%			
Test Type: Fix at Each Look:	Total No. of Events	1	1260	-0.007	5008		5008	50.08	7		
Noninferiority Margin (In(HR0))		2	2520	-1.0555	3623		3623	36.23	1		
Test Statistic:	Logrank	3	3780	-1.96	1164	205	1369	13.69			
Average Events:	2061 486	Total			9795	205	10000				
Total Accrual Duration:	49	%			97.95	2.05					
Avg. Power at Termination:	0.0205	Average	Sample	Size, Dro	pouts and L	ook Times:					
Simulation Control Parame Starting Seed:	eters Clock	Look #	-	rage	Average			erage Dro	pouts	Average	Average
Number of Simulations:	10000	LOOK #	Sam	ple Size	Control	Treatment	Contr	ol T	reatment	Look Time	Follow u
number or omfulduons.	10000	1	321	3.0046	620.4686	639.5314	68.92	34	67.9725	29.2054	9.9645
		2		2.6635	1249.6314	1270.3686	137.19	93 1	36.4663	45.1094	12.8999
		3		5390	1883.5486	1896.4514	205.37		06.0351	63.168	17.8147
		Average	414	4.9649	1014.1761	1047.3099	112.59	43 1	11.2671	39.6178	12.1053
		Accrual/E Sample Si Subjects a Accrual In	Starting At 0 Dropout Ze: are Follow put Metho Starting A 0	0.039 Paramete 5390 red: Until En od: Accrual At Accrual 1	eatment Haza 0.04 ers d of Study Rates	rd Ratio 1.045					
		Dropout In Period # 1 Overall S Average S Starting Se	At C 12 Simulation tudy Dura eed:	ontrol Treat 5 on Result ation: 3	s 9.618 3985542						

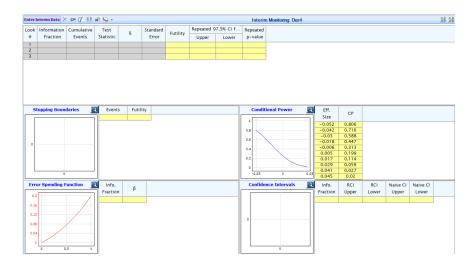
Note that 205 out of the 10000 simulations were unable to reject the alternative hypothesis, thus confirming (up to Monte Carlo accuracy) that this design achieves a type-1 error of 2.5%. Also, observe that 50.08% of these trials have crossed the futility boundary at the very first interim look after only 29.205 months of study duration.

12.3 Interim Monitoring

Suppose we have adopted Des4. Let us monitor the trial with the help of the Interim Monitoring Worksheet. Select Des4 in the **Library**, and click the **IM** icon from the Library toolbar. Alternatively, right-click on Des4 and select **IM Dashboard**. The interim monitoring dashboard contains various controls for monitoring the trial, and is divided into two sections. The top section contains several columns for displaying output values based on the interim

Chapter 12: Non-Inferiority Trials Given Accrual Duration and Accrual Rates

inputs. The bottom section contains four charts, each with a corresponding table to its right. These charts provide graphical and numerical descriptions of the progress of the clinical trial and are useful tools for decision making by a data monitoring committee.



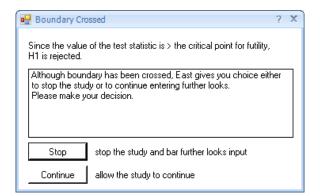
Suppose that the first interim look is taken after observing 1300 events. The observed hazard ratio is 1.15 and the standard error of the log hazard ratio is 0.06. Enter this information into the interim monitoring worksheet using Test Statistic calculator. Click on Enter Interim Data and



Enter I	inter Interim Data 🗙 🎯 🏹 🛄 🔊 💟 - 🛛 Interim Monitoring: Des4												
Look #	Information Fraction	Cumulative Events	Test Statistic	δ	Standar Error	Futility	Repeated 9 Upper	7.5% CI f Lower	Repeated p-value				
1					Te	est Statistic Cal	culator				×		
2					(-	Editing look #	1						
	□ Set Current Look as Last												
						Estimate o $\delta = \ln(\lambda_t)$	Survival end ι of δ: / λ _c)			1300 0.1398			
-						Output $\delta - \delta_0$ Test Statis	ecalc	ote of δ:	Can	0.06 0.0957 1.5958 cel			

enter the data in the test statistic calculator as shown below.

Next, click **OK**. East will indicate that the H_1 (futility) boundary has been crossed and hence, the alternative hypothesis of non-inferiority is rejected in favor of the null hypothesis of inferiority.



Click the Stop button to terminate the trial. You will see the IM sheet output including Final

Chapter 12: Non-Inferiority Trials Given Accrual Duration and Accrual Rates

Enter	Interim Data 🄀	(cp 📝 🛄	🕸 🔽 •						Interin	n Monitoring: Des4					
Look #	Information Fraction 0.344	Cumulative Events 1300	Test Statistic 1.596	δ 0.14	Standard Error 0.06	Futility -0.051	Repeated 9 Upper NA	7.5% CI f Lower NA	Repeated p-value NA						
								10							
2 1.8 1.6 1.4 1.2 1 0.8 0.6 0.4 0.2 0.4 0.2 0.2	· ·		Event: 1300						Naive 9 Naive 9 Upper Con Lower Con	Final Inferen iputs at Look ≠ Naive p-value ve Pt. Est. for δ 97.5% CI for δ fidence Bound ifidence Bound ost-Hoc Power		1 0.945 0.14 0.257 -Infinity			
Err 0.1 0.1 0.1 0.0 0.0	2		Info. Fraction 0.344	β 0.048					Confide 0.364 0.3276 0.2912 0.2548 0.2184 0.182 0.1455 0.1092 0.0728 0.0364 0 0 0	nce Intervals	Info. Fraction 0.344	RCI Upper NA	RCI Lower NA	Naive Cl Upper 0.257	Naive CI Lower -Infinity

Inference details as shown below.

Observe that the upper 97.5% confidence bound for δ , 0.257, is above the non-inferiority margin of 0.044 (on the log hazard ratio scale).

This chapter will illustrate through a worked example how to design and simulate a two-sample superiority trial with a time-to-event trial endpoint, where the accrual duration and study duration are constrained. Most trials in the pharmaceutical industry setting are designed in this manner, time being a more rigid constraint than the accrual rate of patients. The duration of a clinical trial impacts the duration of a drug development program, and thus time to market and potential revenues. Therefore it is of interest to fix the study duration as well as the accrual duration to finish the clinical trial according to schedule. The option to design a trial in this way is available in East.

13.1 Calculating a Sample Size

For this design, East obtains the maximum number of events D_{max} from the maximum information I_{max} , as described in Appendix sections **??** and **??**. To calculate the sample size, we first equate the expected number of events $d(S_a + S_f)$ (as calculated in Appendix **??** which depends on the accrual duration (S_a) and the duration of follow-up (S_f) to the maximum number of events D_{max} .

$$d(S_a + S_f) = D_{max} \tag{13.1}$$

In this type of design the accrual duration S_a and the study duration $S_a + S_f$ are given as input. East iterates between sample sizes, increasing onwards from a minimum value of D_{max} , enrolled over a duration of S_a until D_{max} events are found to occur within a study duration of $S_a + S_f$. The result is the unique sample size required to obtain the proper power for the study.

13.2 The RALES Clinical Trial: Initial Design

The RALES trial (Pitt et. al., 1999) was a double blind study of aldosterone-receptor blocker spironolactone at a daily dose of 25 mg in combination with standard doses of an ACE inhibitor (treatment arm) versus standard therapy of an ACE inhibitor (control arm) in patients who had severe heart failure as a result of systolic left ventricular dysfunction. The primary endpoint was death from any cause. Six equally-spaced looks at the data using the Lan-DeMets-O'Brien-Fleming spending function were planned. The trial was designed to detect a hazard ratio of 0.83 with 90% power at a two-sided 0.05 level of significance. The hazard rate of the control arm was estimated to be 0.38.

Randomization was scheduled to begin in March 1995 and complete in December 1996 for a total of 1.8 years of enrollment. Follow-up was planned through December 1999, so that the total study duration from first patient enrolled to last patient visit should be 4.8 years.

We begin by using East to design RALES under these basic assumptions. To begin click Survival: Two Samples on the Design tab and then click Parallel Design: Logrank Test Given Accrual Duration and Study Duration as shown below



A new screen will appear. Enter the appropriate design parameters into the dialog box as



shown below.

	Design: S	urvival Endpoint:	Two-Sample Test - P	arallel Design - Logrank Give	en Accrual Duration and Study Durat
Design Type: Superiority	• Num	ber of Looks: 6	•		
Design Parameters Boundary	nfo Accru	al/Dropout Info			
Test Type: 2-Sided	•	# of Hazard Pie	ces: 1 💌	Input Method: Hazard I	Rates
Type I Error (α): 0.05		Hazard Ratio	(Optional)		Alternative
Power: 0.9	0	⊙ Hazard Ratio	(λ_t/λ_c)		0.83
Sample Size (n): Computed		O Log Hazard F	atio $\ln(\lambda_t/\lambda_c)$		-0.1863
No. of Events: Computed	•	Period Start # A		Hazard Rate (Treatment: Alt.)	
Allocation Ratio: 1		1 0.00	00 0.38	0.3154	
(n _t /n _c)					
		Variance of Lo	Hazard Ratio		
		⊙ Null	O Alternative	2	

The box labeled **Variance of Log Hazard Ratio** specifies whether the calculation of the required number of events is to be based on the variance estimate of the log hazard ratio under the null hypothesis or the alternative hypothesis. The default choice in East is **Null**. Most textbooks recommend this choice as well (see, for example Collett, 1994, equation (2.21) specialized to no ties). It will usually not be necessary to change this default. For a technical discussion of this issue refer to Appendix **??**, Section **??**.

Next, click on the **Boundary Info** tab. We will take six equally spaced looks at the data using the Lan-DeMets O'Brien-Fleming spending function. These are the default setting in East.

Desigr	n Parameter	s Boundary	Info Accru	al/Dropou	ut Info					
Efficacy					Futility –					
Bounda	ary Family:	Spending	Functions	•	Boundan	/ Family:	None		•	
Spendir	ng Function	: Lan-DeM	ets 💌							
Parameter: OF 💌										
Type I I	Error (α):	0.05								
Spacing	g of Looks -	⊙ Equal	O Unequ	al	Efficacy	Boundary:	Z Scale	•		
Look #	Info.	Cum. α	Efficacy	Boundary						
LOOK #	Fraction	Spent	Upper	Lower						
1	0.1667	0.0000	5.3666	-5.366	6					
2	0.3333	0.0002	3.7103	-3.710	3					
3	0.5000	0.0031	2.9697	-2.969	7					
4	0.6667	0.0121	2.5387	-2.538	7					
5	0.8333	0.0282	2.2522	-2.252	2					-

Note that we do not select a futility boundary in this case. Next click on the Accrual/Dropout Info tab. Here we will specify the accrual information and dropout rates. The software allows a specification of piecewise constant hazards and variable accrual rates but we start by looking at an example that does not require any of these options. In the drop-down menu next to Subjects are followed: select Until End of Study. Set the Accrual Duration to 1.8 years and the Study Duration to 4.8 years. Notice that East has changed the settings so that at 1.8 years the study should be 100% accrued. Keep the number of accrual periods equal to the default of 1. To the right of the Accrual Info box is the Piecewise Constant Dropout Rates box. This box is used to enter that rate at which we expect patients to drop out of the study. For the present we will assume that there are no drop-outs.

Design Pa	rameters Bo	oundary Info A	ccrual/Dropout Info					
Subjects are f		l End of Study		Piecewise	e Constant Dro	opout Rates		
Accrual Dura	tion:	1.8 Study Du	uration: 4.8	# of Piece	s: 0 💌	Input Method:	Hazard Rates	•
# of Accrual	Periods: 1	•		Period #	Starting At	Hazard Rate (Control)	Hazard Rate (Treatment)	
Period #	At	Cum. % Accrued						-
1	1.8000	100.0000						

Click on **Compute** to complete the design. The design is shown as a row in the **Output Preview** located in the lower pane of this window. You can select this design by clicking anywhere along the row in the **Output Preview**. With Des1 selected, click the *lim* icon to display the details of this design in the upper pane, which are shown below. You may also wish to save this design. Select Des1 in the **Output Preview** window and click the *lim* to save



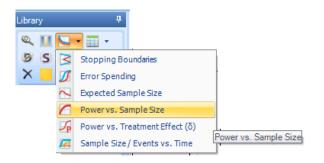
this design to Workbook1 in the Library.

	Wbk1:Des1
Mnemonic	SU-2S-LRSD
Test Parameters	
Design Type	Superiority
No. of Looks	6
Test Type	2–Sided
Specified α	0.05
Power	0.9
Model Parameters	
Hazard Ratio (Alt.)	0.83
Var (Log HR)	Null
Allocation Ratio (nt/nc)	1
Boundary Parameters	
Spacing of Looks	Equal
Efficacy Boundary	LD (OF)
Accrual & Dropout Parameters	
Subjects are Followed	Until End of Study
No. of Accrual Periods	1
No. of Dropout Pieces	0
Sample Size	
Maximum	1689
Expected Under H0	1688.978
Expected Under H1	1687.5564
Events	
Maximum	1243
Expected Under H0	1233.9843
Expected Under H1	903.5945
Accrual Duration	
Maximum	1.8
Expected Under H0	1.8
Expected Under H1	1.7985
Study Duration	
Maximum	4.8
Expected Under H0	4.4164
Expected Under H1	3.3044

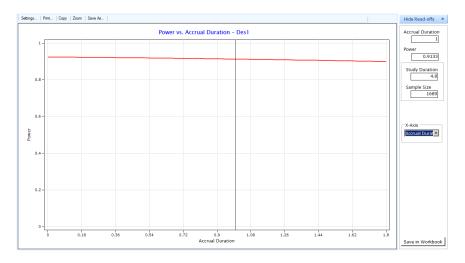
East notifies you that 1243 events and a sample size of 1689 are required to attain the desired 90% power in the allotted time.

East provides charts to examine the trade-offs between power and accrual duration, study

duration, sample size or number of events. Select Des1 in the **Library** click the **Select Power vs. Sample Size** as shown below.



To the right of the graph, swith the **X-Axis** to **Accrual Duration**.

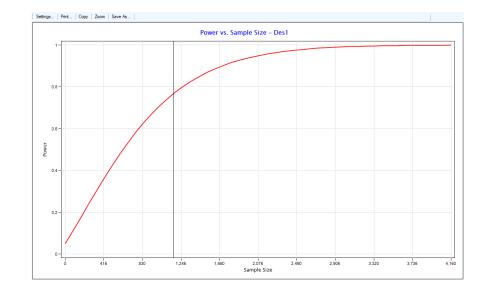


This graph shows for a fixed study duration of 4.8 years and a fixed sample size of 1689, the trade-off between power and accrual duration. For 1 year accrual, we see that the power will be 91.3%.

Now switch the X-Axis option from Accrual Duration to Sample Size. You will see the

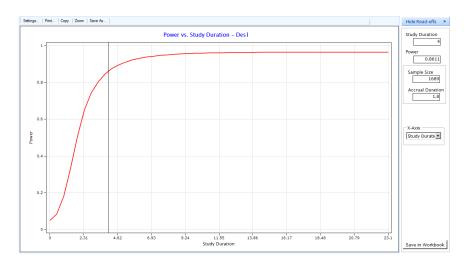
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following chart.

You can see that for a fixed Accrual Duration of 1.8 years and a fixed Study Duration of 4.8 years, 1170 subjects would provide you with 76.9% power. Switch the **X-Axis** option again,

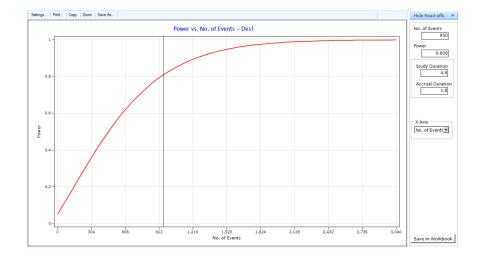


this time to **Study Duration**. The following chart will appear.

Here we see that closing the trial early after 4 years, given an accrual of 1689 patients over 1.8 years, we only have 86% power to detect the alternative hypothesis of interest. Finally, switch the **X-Axis** to **No**. **of Events**. The power of the study is really tied to the number of events that are observed. This chart shows the direct relationship between power and number

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of events.

Note that 950 events give us about 81% power. You may wish to save some or all of these charts to the **Library** by clicking on the **Save in Workbook** button.

13.3 Incorporating Drop-Outs

The investigators expect 5% of the patients in the spironolactone group and the control group to drop out each year. Create a new design by selecting Des1 in the **Library**, and clicking the **Solution** icon on the **Library** toolbar. Next, click on the **Accrual/Dropout Info** tab. In the **Piecewise Constant Dropout Rates** box, select 1 for the number of pieces and change the **Input Method** from Hazard Rates to Dropout Rates. Then enter 5% dropouts at 1 year for the treatment and control arm as shown below. Although East allows you to specify different dropout (hazard) rates for the two groups, it is recommended that you select equal

dropout (hazard) rates.

Design P	arameters Bo	undary Info A	accrual/Dropout Info					
-	e followed: Until	End of Study	•					
Accrual Inf	0			Piecewise	Constant D	ropout Rates		
Accrual Du	ration:	1.8 Study Du	uration: 4.8	# of Pieces	1 💌	Input Method:	Dropout Rates	•
# of Accrua	al Periods: 1	•		Period #	At	Cum. % Dropouts (Control)	Cum. % Dropouts (Treatment)	
Period #	At	Cum. % Accrued		1	1.0000	5.0000	5.0000	5
1	1.8000	100.0000						

Click the **Compute** button to generate output for Des2. With Des2 selected in the **Output Preview**, click the icon to save Des2 to the **Library**. In the **Library**, select the rows for Des1 and Des2, by holding the Ctrl key, and then click the icon. The upper pane will



display the details of the two designs side-by-side:

	Wbk1:Des1	Wbk1:Des2
Mnemonic	SU-2S-LRSD	SU-2S-LRSD
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	6	6
Test Type	2-Sided	2-Sided
Specified α	0.05	0.05
Power	0.9	0.9
Model Parameters		
Hazard Ratio (Alt.)	0.83	0.83
Var (Log HR)	Null	Null
Allocation Ratio (nt/nc)	1	1
Boundary Parameters		
Spacing of Looks	Equal	Equal
Efficacy Boundary	LD (OF)	LD (OF)
Accrual & Dropout Parameters		
Subjects are Followed	Until End of Study	Until End of Study
No. of Accrual Periods	1	1
No. of Dropout Pieces	0	1
Sample Size		
Maximum	1689	1824
Expected Under H0	1688.978	1823.9663
Expected Under H1	1687.5564	1820.7454
Events		
Maximum	1243	1243
Expected Under H0	1233.9843	1233.9843
Expected Under H1	903.5945	903.5945
Accrual Duration		
Maximum	1.8	1.8
Expected Under H0	1.8	1.8
Expected Under H1	1.7985	1.7968
Study Duration		
Maximum	4.8	4.8
Expected Under H0	4.4164	4.3608
Expected Under H1	3.3044	3.242

A comparison of the two plans reveals that, because of the drop-outs, we require 1,824 subjects to be enrolled under Des2 rather than 1689 under Des1. Also, the expected study duration will not change much under the alternative and null hypotheses between Des1 and Des2.

13.4 Incorporating Non-Constant Accrual Rates

In many clinical trials the enrollment rate is low in the beginning and reaches its maximum expected level a few months later when all the sites enrolling patients are onboard. Suppose that 20% of the total accrual is expected to occur during the first six months with the rest happening during the remaining 1.3 years. Create a new design by selecting Des2 in the **Library**, and clicking the site icon on the **Library** toolbar. Next, click on the **Accrual/Dropout Info** tab. Specify that there are two accrual periods and enter the cumulative accrual for each period in the dialog box as shown below.

Design Parameters Bo	undary Info A	ccrual/Dropout Info				
Subjects are followed: Unt	l End of Study	•	Piecewise	Constant D	ropout Rates	
Accrual Duration:	1.8 Study Du	uration: 4.8	# of Piece	: 1 💌	Input Method:	Dropout Rates 💌
# of Accrual Periods: 2	•		Period #	At	Cum. % Dropouts (Control)	Cum. % Dropouts (Treatment)
Period # At	Cum. % Accrued		1	1.0000	5.0000	5.0000
1 0.5	20.0000					
2 1.8	100.0000					

Click the **Compute** button to generate output for Des3. With Des3 selected in the **Output Preview**, click the icon to save Des3 to the **Library**. In the **Library**, select the rows for Des1, Des2, and Des3 by holding the Ctrl key, and then click the icon. The upper pane



	Wbk1:Des1	Wbk1:Des2	Wbk1:Des3
Mnemonic	SU-2S-LRSD	SU-2S-LRSD	SU-2S-LRSD
Test Parameters			
Design Type	Superiority	Superiority	Superiority
No. of Looks	6	6	6
Test Type	2-Sided	2-Sided	2-Sided
Specified α	0.05	0.05	0.05
Power	0.9	0.9	0.9
Model Parameters			
Hazard Ratio (Alt.)	0.83	0.83	0.83
Var (Log HR)	Null	Null	Null
Allocation Ratio (nt/nc)	1	1	1
Boundary Parameters			
Spacing of Looks	Equal	Equal	Equal
Efficacy Boundary	LD (OF)	LD (OF)	LD (OF)
Accrual & Dropout Parameters			
Subjects are Followed	Until End of Study	Until End of Study	Until End of Study
No. of Accrual Periods	1	1	2
No. of Dropout Pieces	0	1	1
Sample Size			
Maximum	1689	1824	1837
Expected Under H0	1688.978	1823.9663	1836.9775
Expected Under H1	1687.5564	1820.7454	1835.7774
Events			
Maximum	1243	1243	1243
Expected Under H0	1233.9843	1233.9843	1233.9843
Expected Under H1	903.5945	903.5945	903.5945
Accrual Duration			
Maximum	1.8	1.8	1.8
Expected Under H0	1.8	1.8	1.8
Expected Under H1	1.7985	1.7968	1.7989
Study Duration			
Maximum	4.8	4.8	4.8
Expected Under H0	4.4164	4.3608	4.3708
Expected Under H1	3.3044	3.242	3.2771

will display the details of the three designs side-by-side:

Notice that we now need 1837 subjects to be enrolled to compensate for the overall later enrollment of subjects.

13.5 Simulation

• 13.5.1 Simulating Under H_1 • 13.5.2 Simulating Under H_0

It would be useful to verify the operating characteristics of the various plans created in the previous section by simulation. Select Des3 in the **Library** and click the sicon. You will be

	er of Looks: 6	~				
Simula	tion Parameters	Response Gen	eration Info A	ccrual/Dropout Inf	o Simulation Control Info	2
rial Type	: Supe	riority	v.			
est Type	: 2-Sid	led	Y			Test Statistic: Logrank
 lav # of	Events:	1243	_			
iax. # 01		1243				
x at Eac	h Look: Total	No. of Events	•			
			ν Spent	Efficad	y Z	
x at Eac Look #	h Look: Total			Efficac	y Z Lower	
		Cum.	α Spent			
Look #	Info. Fraction	Cum. (Upper	α Spent Lower	Upper	Lower	
Look # 1	Info. Fraction	Cum. (Upper 0.0000	x Spent Lower 0.0000	Upper 5.3688	Lower -5.3688	
Look # 1 2	Info. Fraction -	Cum. (Upper 0.0000 0.0001	C Spent Lower 0.0000 0.0001	Upper 5.3688 3.7120	Lower -5.3688 -3.7120	

taken to the following simulation worksheet.

13.5.1 Simulating Under H_1

We will first simulate the trial under the alternative hypothesis H_1 . In the **Simulation Parameters** tab select **Total No.** of **Events** to fix at each look - the default option. Select **LogRank** from the drop-down menu next to **Test Statistic**. Other options for a test statistic include the Wilcoxon-Gehan and Harrington-Flemming. Next, click the **Simulate** button to simulate 10000 trials. A new row labeled Sim1 will appear in the **Output Preview** window. Select Sim1 in the **Output Preview** and click the **Simulate** icon to save it to the **Library**. In the **Library**, double-click Sim1. A portion of the output is displayed below. (The actual



values may differ, depending on the starting seed used).

Simulation ID:	Sim1			Bo	undaries	E	arly		Total		
Design Type:	Superiority	Look #	Events	E	fficacy		ing For	S	imulations		
Number of Looks: Fest Type:	6 2-Sided	LOOK #	Events	Upper	Lower	Upper Efficacy	Lower Efficacy	Cou	nt %		
Fix at Each Look:	Total No. of Events	1	207	5.3688	-5.3688	0	0		0 (5	
lest Statistic: Average Events:	Logrank 906.0727	2	414	3.712	-3.712	0	348	34	8 3.48	3	
verage Events: otal Accrual Duration:	1.8	3	622	2.9683	-2.9683	0	2192	219	2 21.92	2	
Avg. Power at Termination		4	829	2.5382	-2.5382	0	3058	305	i8 30.58	3	
5		5	1036	2.252	-2.252	0	2191	219	1 21.91	1	
Simulation Control Para	ameters	6	1243	2.0448	-2.0448	0	1210	221	1 22.11	1	
Starting Seed:	Clock	Total				0	8999	1000	10		
Number of Simulations:	10000	%				0	89.99				
			A	erage	opouts and Average			verage E	Dropouts	Average	Average
		Average	Sample	Size, Dro	opouts and	LOOK III	nes:				
			A	erage	Average	Events	A				
		Look #	AN Sam	erage ple Size	Average Control	Events Treatment	Av nt Cor	ntrol	Treatment	Look Time	Follow up
		Look #	Av Sam	erage ple Size	Average Control 111.9543	Events Treatmer 95.0451	Av nt Cor 3 15.1	ntrol 613	Treatment 15.4132	Look Time 1.2544	Follow up 0.4874
		Look #	Av Sam 1 122 2 179	erage ple Size 0.3248 6.2525	Average Control 111.9543 223.0408	Events Treatmen 95.0450 190.9592	Av nt Cor 3 15.1 2 30.1	1trol 613 314	Treatment 15.4132 30.9663	Look Time 1.2544 1.7683	Follow up 0.4874 0.663
		Look #	Av Sam 1 122 2 179 3	erage ple Size 0.3248 5.2525 1837	Average Control 111.9543 223.0408 332.9846	Events Treatmen 95.0450 190.9592 289.0154	Av nt Cor 3 15.1 2 30.1 4 45.0	ntrol 613 314 338	Treatment 15.4132 30.9663 46.7186	Look Time 1.2544 1.7683 2.2524	Follow up 0.4874 0.663 0.9745
		Look #	Av Sam 1 122 2 179 3	erage ple Size 0.3248 5.2525 1837 1837	Average Control 111.9543 223.0408 332.9846 438.4521	Events Treatmen 95.0450 190.9590 289.0154 390.5479	Av nt Cor 3 15.1 2 30.1 4 45.0 9 59.9	1trol 613 314 338 051	Treatment 15.4132 30.9663 46.7186 62.4934	Look Time 1.2544 1.7683 2.2524 2.8495	Follow up 0.4874 0.663 0.9745 1.2994
			Av Sam 1 122 2 179 3 4 5	erage ple Size 0.3248 5.2525 1837 1837 1837	Average Control 111.9543 223.0408 332.9846 438.4521 540.7971	Events Treatmer 95.0451 190.9592 289.0154 390.5479 495.2029	Av nt Cor 3 15.1 2 30.1 4 45.0 9 59.9 9 74.7	1trol 613 314 338 051 926	Treatment 15.4132 30.9663 46.7186 62.4934 78.366	Look Time 1.2544 1.7683 2.2524 2.8495 3.6357	Follow up 0.4874 0.663 0.9745 1.2994 1.6248
			Av Sam 1 122 2 179 3 4 5 5 5 5	erage ple Size 0.3248 5.2525 1837 1837 1837 1837	Average Control 111.9543 223.0408 332.9846 438.4521 540.7971 641.3609	Events Treatmen 95.0451 190.9592 289.0154 390.5475 495.2025 601.639	Av nt Cor 3 15.1 2 30.1 4 45.0 9 59.9 9 74.7 1 89.5	1trol 613 314 338 051 926 952	Treatment 15.4132 30.9663 46.7186 62.4934 78.366 94.1655	Look Time 1.2544 1.7683 2.2524 2.8495 3.6357 4.7846	Follow up 0.4874 0.663 0.9745 1.2994 1.6248 1.9496
			Av Sam 1 122 2 179 3 4 5 5 5 5	erage ple Size 0.3248 5.2525 1837 1837 1837	Average Control 111.9543 223.0408 332.9846 438.4521 540.7971	Events Treatmer 95.0451 190.9592 289.0154 390.5479 495.2029	Av nt Cor 3 15.1 2 30.1 4 45.0 9 59.9 9 74.7 1 89.5	1trol 613 314 338 051 926 952	Treatment 15.4132 30.9663 46.7186 62.4934 78.366	Look Time 1.2544 1.7683 2.2524 2.8495 3.6357	Follow up 0.4874 0.663 0.9745 1.2994 1.6248
		Look #	Ax Sam 1 122 2 179 3 4 5 5 5 183	erage ple Size 0.3248 5.2525 1837 1837 1837 1837 1837 5.6939	Average Control 111.9543 223.0408 332.9846 438.4521 540.7971 641.3609 482.2528	Events Treatmen 95.0451 190.9592 289.0154 390.5475 495.2025 601.639	Av nt Cor 3 15.1 2 30.1 4 45.0 9 59.9 9 74.7 1 89.5	1trol 613 314 338 051 926 952	Treatment 15.4132 30.9663 46.7186 62.4934 78.366 94.1655	Look Time 1.2544 1.7683 2.2524 2.8495 3.6357 4.7846	Follow up 0.4874 0.663 0.9745 1.2994 1.6248 1.9496
		Look #	Ax Sam 1 122 2 179 3 4 5 5 5 5 5 7 5 7 5 7 5 7 5 7 5 7 5 7 5 7	erage ple Size 0.3248 5.2525 1837 1837 1837 1837 1837 5.6939 ration Pa	Average Control 111.9543 223.0408 332.9846 438.4521 540.7971 641.3609	Events Treatmen 95.0451 190.9592 289.0154 390.5475 495.2025 601.639	Av nt Cor 3 15.1 2 30.1 4 45.0 9 59.9 9 74.7 1 89.5	1trol 613 314 338 051 926 952	Treatment 15.4132 30.9663 46.7186 62.4934 78.366 94.1655	Look Time 1.2544 1.7683 2.2524 2.8495 3.6357 4.7846	Follow up 0.4874 0.663 0.9745 1.2994 1.6248 1.9496
		Look #	Ax Sam 1 122 2 179 3 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	erage ple Size 0.3248 5.2525 1837 1837 1837 1837 1837 5.6939 ration Pa	Average Control 111.9543 223.0408 332.9846 438.4521 540.7971 641.3609 482.2528	Events Treatmen 95.0451 190.9592 289.0154 390.5475 495.2025 601.639	Av nt Cor 3 15.1 2 30.1 4 45.0 9 59.9 9 74.7 1 89.5	1trol 613 314 338 051 926 952	Treatment 15.4132 30.9663 46.7186 62.4934 78.366 94.1655	Look Time 1.2544 1.7683 2.2524 2.8495 3.6357 4.7846	Follow up 0.4874 0.663 0.9745 1.2994 1.6248 1.9496
		Look #	Ax Sam 1 122 2 179 3 4 5 5 6 183 se Gene card Piece nod:	erage ple Size 0.3248 5.2525 1837 1837 1837 1837 5.6939 ration Pa es: 1	Average Control 111.9543 223.0408 332.9846 438.4521 540.7971 641.3609 482.2528	Events Treatmen 95.0451 190.9592 289.0154 390.5475 495.2025 601.639	Av nt Cor 3 15.1 2 30.1 4 45.0 9 59.9 9 74.7 1 89.5	1trol 613 314 338 051 926 952	Treatment 15.4132 30.9663 46.7186 62.4934 78.366 94.1655	Look Time 1.2544 1.7683 2.2524 2.8495 3.6357 4.7846	Follow up 0.4874 0.663 0.9745 1.2994 1.6248 1.9496
		Look #	Ave Sam Sam 1 122 2 179 3	erage ple Size 3.3248 5.2525 1837 1837 1837 1837 5.6939 ration Pa is: 1 Hazard	Average Control 111.9543 223.0408 332.9846 438.4521 540.7971 641.3609 482.2528	Events Treatmen 95.0451 190.9592 289.015- 390.5473 495.2023 601.639 423.8193	Av nt Cor 3 15.1 2 30.1 4 45.0 9 59.9 9 74.7 1 89.5	1trol 613 314 338 051 926 952	Treatment 15.4132 30.9663 46.7186 62.4934 78.366 94.1655	Look Time 1.2544 1.7683 2.2524 2.8495 3.6357 4.7846	Follow up 0.4874 0.663 0.9745 1.2994 1.6248 1.9496

Simulation: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Study Duration

The column labeled **Average Look Time** displays the average calendar times at which each interim look was taken. Thus, the first interim look (taken after observing 207 events) occurred after an average elapse of 1.254 years; the second interim look (taken after observing 414 events) occurred after an average elapse of 1.768 years; etc. We see that 8999 of the 10000 simulations crossed the lower stopping boundary, thus confirming (up to Monte Carlo accuracy) that this design has 90% power.

We will now run another 10000 simulations, this time fixing the calendar time of each look instead of fixing the number of events. Select Des3 in the **Library** and click the sicon. In the **Simulation Parameters** tab select **Look Time** from the drop-down menu next to **Fix at Each Look**:

Simulation Param	neters Response Ge	neration Info	Accrual/Dropout Info	Simulation Con	trol Info		
Trial Type:	Superiority	Y					
Test Type:	2-Sided	Y			Test Statistic:	LogRank	•
Study Duration:	4.797						
Fix at Each Look:	Look Time	•					

When the Look Time option is selected the locations of the interim looks at which stopping

boundaries are computed are expressed in terms of the calendar time of each interim look instead of the number of events at each interim look.

Next, click the **Simulate** button to simulate 10000 trials. A new row labeled Sim2 will appear in the **Output Preview** window. Select Sim2 in the **Output Preview** and click the icon to save it to the **Library**. In the **Library**, double-click Sim2. A portion of the output is displayed below. (The actual values may differ, depending on the starting seed used).

\$		on Douna	arres arru	Boundary (Stossing	riobab	mues.	
Sim2			Bou	ndaries	E	arly	To	tal
	1.000	Look	Eff	icacy	Stopp	ing For	Simu	lations
2-Sided	LOOK #	Time	Upper	Lower	Upper Efficacy	Lower Efficacy	Count	%
	1	1.2556	5.3688	-5.3688	0	0	0	(
	2	1.7692	3.712	-3.712	0	355	355	3.58
	3	2.254	2.9683	-2.9683	0	2251	2251	22.5
Total Accrual Duration: 1.8 Avg. Power at Termination: 0.905		2.8522	2.5382	-2.5382	0	3046	3046	30.46
0.905	5	3.6404	2.252	-2.252	0	2195	2195	21.9
ameters	6	4.7968	2.0448	-2.0448	0	1203	2153	21.5
Clock	Total				0	9050	10000	
10000	%				0	90.5		
	_						rage Dropo	uts
	Sim2 Superiority 6 2-Sided Look Time Logrank 902.3466 1.8 n:0.905 rameters Clock	Sim2 Lock # 2-Sided Lock # Logrank 1 902-346 3 1.8 3 n0 905 5 Glock Total 10000 %	Sim2 Supportory 6 2.Sided Look Time Look # Look Time Look # Look # Look Time Look # 1.1255 Logrank 902 Side 2.17692 3.2 254 4.2 8522 5.3 5404 2.8404 Randerson 6.4 7956 5% 5%	Sim2 Superiority 6 Look # Look # Bou Time Bou 2.Sided Look Time 1 1.2556 5.3688 Upper 1.0 Jografik 902 3466 2 1.7692 3.712 2.9693 1.8 3 2.254 2.9693 3.254 2.9693 0.905 5 3.6404 2.252 2.5392 Clock 10000 7.104 2.052 0.448 Neorage Sample Size, Drop 54 Average Sample Size, Drop 0.044	Simperiority 6 2.Sided Look Time 109grafic Look # 10256 Boundaries 1000 1 12556 5.5888 -5.5688 1.00 1.7692 3.712 -3.712 902.3466 3 2.2542 2.5633 -2.5633 1.8 3 2.254 2.5633 -2.6323 3.6 3.2542 2.5632 -2.5322 -2.5323 2.00ck 1.0000 3.6 -2.0448 -2.0448 1.0000 5.6 - - -	Sim2 Superiotity 6 Look # Boundaries (Encacy Encacy Step Superiotity (Upper Look # Boundaries (Encacy Encacy Step Superiotity (Upper Look # Encacy Look # Encacy Encacy Look # Encacy Encacy <thencacy< th=""> Encacy Encacy<!--</td--><td>Sim2 Supportory 6 East Enclose East Enclose East Support Enclose East Support Enclose East Support Enclose East Support Enclose 2 Sided Look m 1 2566 5.3688 5.3688 0 0 10 2005 3 712 3.712 0 355 1 2565 5.3688 2.9693 2.9683 0 0 1 2565 3.640 2.2592 2.9592 0 3046 5 3.640 2.222 2.2532 0 2046 5 3.640 2.222 2.220 2.195 0 3046 5 3.640 2.222 2.242 0 195 10000 1000 1003 0 90.55</td><td>Sim2 Supportory 6 Look # Boundaries Stepring For Upper True Look T 2.Sided Look TH Time Dipper Lower Efficacy Stopping For True Upper 1.00 are 902 3460 1 1.2556 5.3684 5.3688 0 0 0 1.8 0.906 3 2.54 2.9683 -2.2651 2.251 2.511 3.0 996 3 2.54 2.9683 -2.9683 0 2.051 2.251 2.251 3.0 996 5 3.6404 2.252 -2.2582 0 3.046 3.046 1.0000 5 3.6404 2.448 -0.446 0 9.050 4 4.9688 2.0448 -0.4468 0 9.050 1.000 5 3.6404 2.822 2.2512 1.030 1.030 1.030 1.0000 5 3.0464 2.0448 0 9.050 1.000</td></thencacy<>	Sim2 Supportory 6 East Enclose East Enclose East Support Enclose East Support Enclose East Support Enclose East Support Enclose 2 Sided Look m 1 2566 5.3688 5.3688 0 0 10 2005 3 712 3.712 0 355 1 2565 5.3688 2.9693 2.9683 0 0 1 2565 3.640 2.2592 2.9592 0 3046 5 3.640 2.222 2.2532 0 2046 5 3.640 2.222 2.220 2.195 0 3046 5 3.640 2.222 2.242 0 195 10000 1000 1003 0 90.55	Sim2 Supportory 6 Look # Boundaries Stepring For Upper True Look T 2.Sided Look TH Time Dipper Lower Efficacy Stopping For True Upper 1.00 are 902 3460 1 1.2556 5.3684 5.3688 0 0 0 1.8 0.906 3 2.54 2.9683 -2.2651 2.251 2.511 3.0 996 3 2.54 2.9683 -2.9683 0 2.051 2.251 2.251 3.0 996 5 3.6404 2.252 -2.2582 0 3.046 3.046 1.0000 5 3.6404 2.448 -0.446 0 9.050 4 4.9688 2.0448 -0.4468 0 9.050 1.000 5 3.6404 2.822 2.2512 1.030 1.030 1.030 1.0000 5 3.0464 2.0448 0 9.050 1.000

Simulation: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Study Duration

We see that the first interim look is taken, on average, after 1.256 years during which time an average of 206.99 events are observed. In our simulations we have achieved 90.5% power, thus confirming (up to Monte Carlo accuracy) that the study has 90% power.

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13.5.2 Simulating Under H_0

To simulate under the null hypothesis we must go to the Response Generation Info tab in



the simulation worksheet. In this tab change the hazard rate for the treatment arm to 0.38.

Simula	ation Parameters	Response Ge	neration Info	Accrual/Dropout I	nfo	Simulation Control Info
		Survival Ir	nformation			
	Hazard Rates Cum. % Survival					
# of Haz	ard Pieces 1	•				
Piece	Starting At	Hazaro	l Rates	Hazard Ratio		
FIECE	Starting At	Control	Treatment			
1	0.0000	0.3800	0.38	1.0000		

This change implies that we will be simulating under the null hypothesis. Next, click on the **Simulation Parameters** tab and make sure that the **Total No. of Events** is fixed at each look. Next, click the **Simulate** button to simulate 10000 trials. A portion of the results are displayed below.

	-	Boundaries Efficacy			arly ing For	Total Simulations	
Look #	Events	Upper	Lower	Upper Efficacy	Lower Efficacy	Count	%
1	207	5.3688	-5.3688	0	0	0	0
2	414	3.712	-3.712	0	2	2	0.02
3	622	2.9683	-2.9683	11	17	28	0.28
4	829	2.5382	-2.5382	52	40	92	0.92
5	1036	2.252	-2.252	83	75	158	1.58
6	1243	2.0448	-2.0448	110	110	9720	97.2
Total				256	244	10000	
%				2.56	2.44		

Simulation Boundaries and Boundary Crossing Probabilities:

Average Sample Size, Dropouts and Look Times:

Leele #	Average	Average Events		Average Dropouts		Average	Average
LOOK #	Look # Sample Size		Treatment	Control	Treatment	Look Time	Follow up
1	1168.3164	103.604	103.396	13.9964	13.976	1.2082	0.4656
2	1726.9583	207.0993	206.9007	28.0179	27.9528	1.7026	0.6302
3	1837	311.1532	310.8468	42.0658	41.9334	2.1465	0.8907
4	1837	414.7712	414.2288	56.0412	55.8752	2.6867	1.1875
5	1837	518.3153	517.6847	69.9973	69.84	3.391	1.4839
6	1837	621.8174	621.1826	83.998	83.7572	4.4083	1.7803
Average	1836.9872	617.2857	616.7303	83.4076	83.1433	4.3693	1.7673

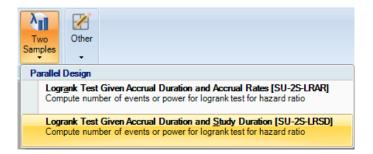
Out of 10000 simulated trials 244 crossed the lower stopping boundary and 256 crossed the upper stopping boundary thus confirming (up to Monte Carlo accuracy) that the type-1 error

is preserved for this design.

13.6 User Defined R Function

East allows you to customize simulations by inserting user-defined R functions for one or more of the following tasks: generate response, compute test statistic, randomize subjects, generate arrival times, and generate dropout information. The R functionality for arrivals and dropouts will be available only if you have entered such information at the design stage. Although the R functions are also available for all normal and binomial endpoints, we will illustrate this functionality for a time-to-event endpoint. Specifically, we will use an R function to generate Weibull survival responses.

Start East afresh. On the **Design** tab, click **Survival: Two Samples** and then **Logrank Test Given Accrual Duration and Study Duration**.



Choose the design parameters as shown below. In particular, select a one sided test with



type-1 error of $\alpha = 0.025$.

Desi	gn: Survival Endpoint: Two-Sam	ple Test - Parallel Design - Logrank Given Accr	ual Duration and Study Duration
Design Type: Superiority Numl Design Parameters Accrual/Dropout Info	per of Loo <u>k</u> s: 1 🔹		
Tegt Type: 1-Sided Type I Error (a): 0.025 Power: 0.9	# of <u>Hazard Pieces</u> : 1 • Hazard Ratio (Optional) Hazard Ratio (λ_t/λ_c) Log Hazard Ratio $\ln(\lambda_t/\lambda_c)$	Input Method: Hazard Rates	- live 0.5 .693
Sample Size (n): Computed No. of Events: Computed	Period Starting Hazard # At (Cont	Rate Hazard Rate	
Allocation <u>Ratio</u> : 1 (n_t/n_c)	1 0.000 0.03	35 0.017	
	Variance of Log Hazard Ratio • Null • Altern	nati <u>v</u> e	

Click **Compute** and save this design (Des1) to the **Library**. Right-click Des1 in the **Library** and click **Simulate**. In the **Simulation Control Info** tab, check the box for **Suppress All Intermediate Input**. Type 10000 for **Number of Simulations** and select **Clock** for **Random Number Seed**.

Simulation Parameters Response Generation Info	Accrual/Dropout Info Simulation Control Info
Number of Simulations: 10000 Refresh Frequency: 1000 Random Number Seed O Clock O Fixed 100	Output Options Output Type: Case Data Save summary statistics for every simulation run Save subject-level data for simulation runs Note: Max. 100,000 records will be saved.

In the top right-hand corner for the input window, click **Include Options**, and then click **User**

Defined R Function.

	Include Options
	Site Info
	Randomization Info
~	User Defined R Function
	Stratification Info

For now, leave the box **Initialize R simulation (optional)** unchecked. This optional task can be useful for loading required libraries, setting seeds for simulations, and initializing global variables.

Select the row for **Generate Response**, click **Browse...**, and navigate to the folder containing your R file. Select the file and click **Open**. The path should now be displayed under **File Name**.

Simulation Parame	ters Response Generation Info	Accrual/Dropout Info	User Defined R Function	Simulation
Tasks		File Name		Fun
Generate Response	C:\Program Files (x86)\Cytel\Cyte	el Architect\East 6.3\R Sa	mples\SurvivalWeibull.r	
Compute Test Sta				
Randomize Subje				0
Generate Arrival				
•	III			1
🗆 Initialize R Simu	llation (Optional)	Bro	wse View	Clear

Click **View** to open a notepad application to view your R file. In this example, I am generating survival responses for both control and treatment arms from a Weibull with shape parameter = 1 (i.e. exponential), with the same hazard rate in both arms.

Tasks	File Name	Function Name
	C:\Program Files (x86)\Cytel\Cytel A	
Compute Test Sta		
Randomize Subje		
Generate Arrival		

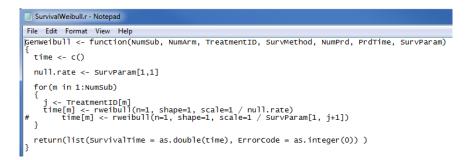
Copy the function name (in this case GenWeibull) and paste it into the cell for Function Name.



Save and close the R file, and click Simulate.

```
SurvivalWeibullr - Notepad
File Edit Format View Help
GenWeibull <- function(NumSub, NumArm, TreatmentID, SurvMethod, NumPrd, PrdTime, SurvParam)
{
    time <- c()
    null.rate <- SurvParam[1,1]
    for(m in 1:NumSub)
    {
        j <- TreatmentID[m]
        time[m] <- rweibull(n=1, shape=2, scale=1 / null.rate)
    }
    return(list(SurvivalTime = as.double(time), ErrorCode = as.integer(0)) )</pre>
```

Return to the tab for **User Defined R Function**, select the **Generate Response** row, and click **View**. In the R function, change the shape parameter = 2, to generate responses from a Weibull distribution with increasing hazards. Save and close the R file, and click **Simulate**.



Select both simulations (Sim1 and Sim2) from the Output Preview, and on the toolbar, click

	Sim1	Sim2
Mnemonic	SU-2S-LRSD	SU-2S-LRSD
Test Parameters		
Design Type	Superiority	Superiority
Test Type	1–Sided	1–Sided
Test Statistic	Logrank	Logrank
Power	0.026	0.027
No. of Looks	1	1
Model Parameters		
No. of Hazard Pieces	1	1
Accrual & Dropout Parameters		
Followup Duration	Until End of Study	Until End of Study
No. of Accrual Periods	1	1
Sample Size		
Maximum	182	182
Events		
Maximum	88	88
Simulation Results (Overall)		
Average Study Duration	34.637	30.681
Average Sample Size	182	182
Average Events	88	88

to display in the **Output Summary**.

Notice that the type-1 error appears to be controlled in both cases. When we simulated from the exponential (Sim1), the average study duration (30.7 months) was close to what was calculated at Des1 for the expected study duration under the null. However, when we simulated from the Weibull with decreasing hazards (Sim2), the average study duration increased to 34.6 months.

Appendix **??** contains detailed specifications for the required inputs and outputs of R functions for each task and endpoint. The ability to use custom R functions for many simulation tasks allows considerable flexibility in performing sensitivity analyses and assessment of key operating characteristics.

14 Non Inferiority Trials Given Accrual Duration and Study Duration

This chapter will illustrate through a worked example how to design and simulate a two-sample non inferiority trial with a time to event trial endpoint, when the accrual duration and study duration are fixed.

14.1 Calculating a Sample Size

For this design, East obtains the maximum number of events D_{max} from the maximum information I_{max} , as described in Appendix sections **??** and **??**. To calculate the sample size, we first equate the expected number of events $d(S_a + S_f)$ (as calculated in Appendix **??** which depends on the accrual duration (S_a) and the duration of follow-up (S_f) to the maximum number of events D_{max} .

$$d(S_a + S_f) = D_{max} \tag{14.1}$$

In this type of design the accrual duration S_a and the study duration $S_a + S_f$ are given as input. East iterates between sample sizes, increasing onwards from a minimum value of D_{max} , enrolled over a duration of S_a until D_{max} events are found to occur within a study duration of $S_a + S_f$. The result is the unique sample size required to obtain the proper power for the study.

14.2 The Non Inferiority Margin

The first step in designing a non-inferiority trial is to establish a suitable non inferiority margin. This is typically done by performing a meta-analysis on past clinical trials of the active control versus placebo. Regulatory agencies then require the sponsor of the clinical trial to

demonstrate that a fixed percentage of the active control effect (usually 50%) is retained by the new treatment. A further complication arises because the active control effect can only be estimated with error. We illustrate below with an example provided by reviewers at the FDA.

Rothman et al. (2003) have discussed a clinical trial to establish the non inferiority of the test drug Xeloda (treatment *t*) relative to the active control (treatment *c*) consisting of 5 fluorouracil with leucovarin (5FU+LV) for metastatic colorectal cancer. In order to establish a suitable non inferiority margin for this trial it is necessary to first establish the effect of 5FU+LV relative to the reference therapy of 5FU alone (treatment *p*, here regarded as placebo). To establish this effect the FDA conducted a ten study random effects meta analysis (FDA Medical Statistical review for Xeloda, NDA 20 896, April 2001) of randomized comparisons of 5-FU alone versus 5-FU+LV. Letting λ_t , λ_c and λ_p denote the constant hazard rates for the new treatment, the active control and the placebo, respectively, the FDA meta analysis established that

$$\ln\left(\widehat{\lambda_p}/\widehat{\lambda_c}\right) = 0.234$$

with standard error

$$\operatorname{se}[\ln{(\widehat{\lambda_p/\lambda_c})}] = 0.075$$
 .

Thus with 100γ % confidence the active control effect lies inside the interval

$$[0.234 - 0.075\Phi^{-1}(\frac{1+\gamma}{2}), 0.234 + 0.075\Phi^{1}(\frac{1+\gamma}{2})]$$
(14.2)

The new study is required to demonstrate that some fraction (usually 50%) of the active control effect is retained. Rothman et al. (2003) state that the claim of non inferiority for the new treatment relative to the active control can be demonstrated if the upper limit of a two sided $100(1 - \alpha)$ % confidence interval for $\ln(\lambda_t/\lambda_c)$ is less than a pre specified fraction of the lower limit of a two sided 100γ % confidence interval for the active control effect established by the meta-analysis. This is known as the "two confidence intervals procedure". Specifically in order to claim non inferiority in the current trial it is necessary to show that

$$\ln\left(\widehat{\lambda_t/\lambda_c}\right) + \Phi^{-1}(1 - \alpha/2)\mathsf{se}[\ln\left(\widehat{\lambda_t/\lambda_c}\right)] < (1 - f_0)\{\ln\left(\widehat{\lambda_p/\lambda_c}\right) - \Phi^{-1}(\frac{1 + \gamma}{2})\mathsf{se}[\ln\left(\widehat{\lambda_p/\lambda_c}\right)]\}.$$
(14.3)

We may re-write the non inferiority condition (14.3) in terms of a one-sided Wald test of the form

 $\frac{\ln\left(\widehat{\lambda_t/\lambda_c}\right) - \delta_0}{\mathsf{se}[\ln\left(\overline{\lambda_t/\lambda_c}\right)]} < \Phi^{-1}(1 - \alpha/2) , \qquad (14.4)$

where

$$\delta_0 = (1 - f_0) \{ \ln\left(\widehat{\lambda_p/\lambda_c}\right) - \Phi^{-1}\left(\frac{1 + \gamma}{2}\right) \operatorname{se}[\ln\left(\widehat{\lambda_p/\lambda_c}\right)] \}$$
(14.5)

is the non inferiority margin.

The choice $f_0 = 1$ implies that the entire active control effect must be retained in the new trial and amounts to running a superiority trial. At the other end of the spectrum, the choice $f_0 = 0$ implies that none of the active control effect need be retained; i.e., the new treatment is only required to demonstrate effectiveness relative to placebo. The usual choice is $f_0 = 0.5$, implying that the new treatment is required to retain at least 50% of the active control effect. The usual choice for α is $\alpha = 0.05$. A conservative choice for the coefficient γ is $\gamma = (1 - \alpha) = 0.95$. Rothman et al. (2003) refer to this method of establishing the non inferiority margin as the "two 95 percent two sided confidence interval procedure" or the "95-95 rule". In general this approach leads to rather tight margins unless the active control effect is substantial. Rothman et al. (2003) have also proposed more lenient margins that vary with the amount of power desired. Fleming (2007), however, argues for the stricter 95-95 rule on the grounds that it offers greater protection against an ineffective medical compound being approved in the event that the results of the previous trials used to establish the active control effect are of questionable relevance to the current setting. Accordingly we evaluate (14.5) with $\gamma = 0.95$, $f_0 = 0.5$, $\ln(\bar{\lambda}_p/\lambda_c) = 0.234$ and se $[\ln(\bar{\lambda}_p/\lambda_c)] = 0.075$ thereby obtaining the non inferiority margin to be $\delta_0 = 0.044$ for the log hazard ratio and $\exp(0.044) = 1.045$ for the hazard ratio.

14.3 Design of Metastatic Colorectal Cancer Trial

In this section we will use East to design a single-look non inferiority trial comparing the test drug Xeloda (treament *t*) to the active control 5FU+LV (treatment *c*) for the treatment of metastatic colorectal cancer. On the basis of a meta analysis of ten previous studies of the active control versus placebo (Rothman et. al. 2003), a non inferiority margin of 1.045 for

 λ_t/λ_c has been established. Thus we are interested in testing the null hypothesis of inferiority H_0 : $\lambda_t/\lambda_c \ge 1.045$ versus the one-sided alternative hypothesis that $\lambda_t/\lambda_c < 1.045$. Suppose the trial is planned to enroll for 30 months and finish within 70 months of the last patient enrolled.

14.3.1 Single-Look Design

We will use East to create an initial single-look design having 80% power to detect the alternative hypothesis H_1 : $\lambda_t/\lambda_c = 1$ with a one sided level-0.025 non-inferiority test.

To begin click **Survival: Two Samples** on the **Design** tab and then click **Parallel Design: Logrank Test Given Accrual Duration and Study Duration** as shown below.



A new screen will appear. Enter the appropriate design parameters into the dialog box as shown below.

D	Design: Survival Endpoint: Two-	Sample Test - Parallel	Design - Logrank Give	n Accrual Duration an	d Study Duration
Design Type: Noninferiority	Number of Looks: 1				
Design Parameters Accrual/Dropo	out Info				
Test Type: 1-Sided Type I Error (x): 0.025 Power: 0.8 Sample Size (n): 18527 No. of Events: 16205 Allocation Ratio: 1	O Ratio of Medians	ional) (λ_t / λ_c) (m_t / m_c) Med. Surv. Time		Alternative	
(n _t /n _c)	─ Variance of Log Haz	ard Ratio			

The box labeled Variance of Log Hazard Ratio specifies whether the calculation of the



required number of events is to be based on the variance estimate of the log hazard ratio under the null hypothesis or the alternative hypothesis. The default choice in East is **Null**. Most textbooks recommend this choice as well (see, for example Collett, 1994, equation (2.21) specialized to no ties). It will usually not be necessary to change this default. For a technical discussion of this issue refer to Appendix **??**, Section **??**.

Next click on the **Accrual/Dropout Info** tab. Here we will specify the accrual information and dropout rates. Set the accrual duration to 30 months and the study duration to 100 months in the **Accrual Info** box. Also, suppose that there are 5% drop-outs per year in each arm. Enter these values as shown below.

Design P	arameters Ac	crual/Dropout I	nfo						
-		End of Study	•						
Accrual Info Piecewise Constant Dropout Rates									
Accrual Du	ration:	30 Study Du	ration: 100		# of Pieces	: 1 💌	Input Method:	Dropout Rates	•
t of Accrua	l Periods: 1	•			Period #	At	Cum. % Dropouts (Control)	Cum. % Dropouts (Treatment)	
Period #	At	Cum. % Accrued			1	12.0000	5.0000	5.0000	_
1	30.0000	100.0000							
	ubjects are Accrual Inf Accrual Du	ubjects are followed: Until Accrual Info ccrual Duration: to f Accrual Periods: 1 Period # At	ubjects are followed: Until End of Study Accrual Info Accrual Duration: 30 Study Du t of Accrual Periods: 1 Period # At Cum. % Accrued	ubjects are followed: Until End of Study Accrual Info Accrual Duration: 30 Study Duration: 100 of Accrual Periods: 1 Period # At Cum. % Accrued	ubjects are followed: Until End of Study Accrual Info Accrual Duration: 30 Study Duration: 100 t of Accrual Periods: 1 Period # At Cum, % Accrued	ubjects are followed: Until End of Study Accrual Info Accrual Duration: 30 Study Duration: 100 # of Accrual Periods: 1 Period # At Cum. % Accrued	ubjects are followed: Until End of Study ▼ Accrual Info Accrual Duration: 30 Study Duration: 100 ≠ of Pieces: 1 ▼ Period ≠ At Curm. % Accrued Accrued 1 12.0000	ubjects are followed: Until End of Study Accrual Info Accrual Duration: 30 Study Duration: 100 t of Accrual Periods: 1 Period # At Cum. % Accrued At Cum. %	ubjects are followed: Until End of Study ▼ Accrual Info cccrual Periods: 1 ▼ Period # At Curn. % Accrual Accrued At Curn. % Accrual Periods: 1 ▼ Period # At Curn. % Accrued At Curn. % At Accrued At Curn. % Accrued At Curn. % Accrued At Curn. % Accrued At Curn. % At Accrued At Curn. % Accrued At Curn. % Accrued At Curn. % At Accrued At Curn. % Accrued At Curn. % Accrued At Curn. % At Accrued At Curn. % Accrued At Curn. % At Accrued At Accrue

Click on **Compute** to complete the design. The design is shown as a row in the **Output Preview** located in the lower pane of this window. You can select this design by clicking anywhere along the row in the **Output Preview**. With Des1 selected, click the *Located* icon to display the details of this design in the upper pane, which are shown below. You may also wish to save this design. Select Des1 in the **Output Preview** window and click the to save

this design to Workbook1 in the Library.

	Wbk1:Des1
Mnemonic	SU-2S-LRSD
Test Parameters	
Design Type	Noninferiority
No. of Looks	1
Test Type	1–Sided
Specified α	0.025
Power	0.8
Model Parameters	
Hazard Ratio (Null)	1.045
Hazard Ratio (Alt.)	1
Var (Log HR)	Null
Allocation Ratio (nt/nc)	1
Accrual & Dropout Parameters	
Subjects are Followed	Until End of Study
No. of Accrual Periods	1
No. of Dropout Pieces	1
Sample Size	
Maximum	18527
Expected Under H0	18527
Expected Under H1	18527
Events	
Maximum	16205
Expected Under H0	16205
Expected Under H1	16205
Accrual Duration	
Maximum	30
Expected Under H0	30
Expected Under H1	30
Study Duration	
Maximum	100
Expected Under H0	96.7434
Expected Under H1	99.9562

It is immediately evident that Des1 is untenable. It requires 16,205 events to be fully powered and 18,527 subjects to obtain those events within the course of the study. The problem lies with trying to power the trial to detect a hazard ratio of 1 under the alternative hypothesis. Suppose instead that the investigators actually believe that the treatment is slightly superior to the active control, but the difference is too small to be detected in a superiority trial. In that



case a non-inferiority design powered at a hazard ratio less than 1 (0.95, say) would be a better option because such a trial would require fewer events.

To see this create a new design by selecting Des1 in the **Library**, and clicking the *selecting* icon on the **Library** toolbar. Then edit this design by specifying a hazard ratio of 0.95 under the alternative hypothesis as shown below.

Design Parameter	rs Accrual/Dr	opout Info					
Test Type:	1-Sided	Y		ard Pieces:		nput Method: Media	an Survival Times 💌
Type I Error (α):	0.025		🗹 Haza	rd Ratio (Op	tional)	Null	Alternative
Power:	0.8	0	⊙ Hazar	d Ratio	(λ_t / λ_c)	1.	045 0.95
Sample Size (n):	Computed	7	O Ratio	of Medians	(m _t /m _c)	0.9	1.0526
No. of Events:	Computed	•	Period #	At	Med. Surv. Time (Control)	Med. Surv. Time (Treatment: Null)	Med. Surv. Time (Treatment: Alt.)
Allocation Ratio:	1		1		18.0000	17.2249	18.9474
(n _t /n _c)	1						
			Variano	e of Log Haz	ard Ratio		
			⊙ Null		O Alternative		

Click the **Compute** button to generate output for Des2. With Des2 selected in the **Output Preview**, click the icon to save Des2 to the **Library**. In the **Library**, select the rows for Des1 and Des2, by holding the Ctrl key, and then click the icon. The upper pane will

display the details of the two designs side-by-side:

	Wbk1:Des1	Wbk1:Des2
Mnemonic	SU-2S-LRSD	SU-2S-LRSD
Test Parameters		
Design Type	Noninferiority	Noninferiority
No. of Looks	1	1
Test Type	1–Sided	1–Sided
Specified α	0.025	0.025
Power	0.8	0.8001
Model Parameters		
Hazard Ratio (Null)	1.045	1.045
Hazard Ratio (Alt.)	1	0.95
Var (Log HR)	Null	Null
Allocation Ratio (nt/nc)	1	1
Accrual & Dropout Parameters		
Subjects are Followed	Until End of Study	Until End of Study
No. of Accrual Periods	1	1
No. of Dropout Pieces	1	1
Sample Size		
Maximum	18527	3973
Expected Under H0	18527	3973
Expected Under H1	18527	3973
Events		
Maximum	16205	3457
Expected Under H0	16205	3457
Expected Under H1	16205	3457
Accrual Duration		
Maximum	30	30
Expected Under H0	30	30
Expected Under H1	30	30
Study Duration		
Maximum	100	100
Expected Under H0	96.7434	93.2179
Expected Under H1	99.9562	99.8704

Des2 is clearly easier to implement than Des1. It requires only 3,457 events to be fully powered. This can be achieved with only 3,973 patients enrolled in the study.

14.3.2 Early Stopping for Futility

Under the null hypothesis, Des2, with 3,457 events, has an expected study duration of 93.2 months. This is a very long time commitment for a trial that is unlikely to be successful. Therefore it would be a good idea to introduce a futility boundary for possible early stopping. Since we wish to be fairly aggressive about early stopping for futility we will generate the futility boundary from the Gamma(-1) β spending function. On the other hand since there no interest in early stopping for efficacy we will not use an efficacy boundary.



Create a new design by selecting Des2 in the **Library**, and clicking the *selecting* icon on the **Library** toolbar. Change the number of looks from 1 to 3 as shown below.

Design Type: Noninferiority 💽 Numb	er of Looks: 3	
Design Parameters Boundary Info Accrual	I/Dropout Info	
Test Type: 1-Sided Type I Error (α): 0.025 Power: 0.8 Sample Size (n): Computed	# of Hazard Pieces: 1 Hazard Ratio (Optional) Hazard Ratio (λ_t/λ_c) Ratio of Medians (m_t/m_c)	Input Method: Median Survival Times Null Alternative 0.9569 1.0526
No. of Events: Computed Allocation Ratio: 1 (n_t/n_c)	Period At Med. Surv. Time # (Control) 1 18.0000	Med. Surv. Time (Treatment: Null) (Treatment: Alt.) 17.2249 18.9474
	Variance of Log Hazard Ratio	

Next, click on the **Boundary Info** tab. Enter the parameters as shown below. Be sure to select the **Non Binding** option. This choice gives us the flexibility to continue the trial even if a futility boundary has been crossed. Data monitoring committees usually want this flexibility; for example, to follow a secondary endpoint.

Desigr	n Parameter	s Boundary	Info Accru	al/Drop	oout Info			
Efficacy Bounda	ry Family:	None			Futility Boundary Spending Paramete Type II Er	Function: r (y):	Spending Function Gamma Family -1 0.2	 ⊘ Non-Binding ○ Binding
Spacing) of Looks –	⊙ Equal	O Unequ	al	Futility B	oundary:	Z Scale	
Look #	Info. Fraction	Cum. β Spent	Futility Boundary					
1	0.3333	0.0460	-0.0070					
2	0.6667	0.1103	-1.0555					
3	1.0000	0.2000	-1.9600					

Click the **Compute** button to generate output for Des3. With Des3 selected in the **Output Preview**, click the icon to save Des3 to the **Library**. In the **Library**, select the rows for Des1, Des2, and Des3 by holding the Ctrl key, and then click the icon. The upper pane

	Wbk1:Des1	Wbk1:Des2	Wbk1:Des3
Mnemonic	SU-2S-LRSD	SU-2S-LRSD	SU-2S-LRSD
Test Parameters			
Design Type	Noninferiority	Noninferiority	Noninferiority
No. of Looks	1	1	3
Test Type	1–Sided	1–Sided	1–Sided
Specified α	0.025	0.025	0.025
Attained α			0.0219
Power	0.8	0.8001	0.8
Model Parameters			
Hazard Ratio (Null)	1.045	1.045	1.045
Hazard Ratio (Alt.)	1	0.95	0.95
Var (Log HR)	Null	Null	Null
Allocation Ratio (nt/nc)	1	1	1
Boundary Parameters			
Futility Boundary			Gm (-1) (NB)
Spacing of Looks			Equal
Accrual & Dropout Parameters			
Subjects are Followed	Until End of Study	Until End of Study	Until End of Study
No. of Accrual Periods	1	1	1
No. of Dropout Pieces	1	1	1
Sample Size			
Maximum	18527	3973	4344
Expected Under H0	18527	3973	3965.0318
Expected Under H1	18527	3973	4312.7208
Events			
Maximum	16205	3457	3780
Expected Under H0	16205	3457	2056.3268
Expected Under H1	16205	3457	3583.036
Accrual Duration			
Maximum	30	30	30
Expected Under H0	30	30	27.3828
Expected Under H1	30	30	29.784
Study Duration			
Maximum	100	100	100
Expected Under H0	96.7434	93.2179	39.6138
Expected Under H1	99.9562	99.8704	92.7138

will display the details of the three designs side-by-side:

Observe that while the sample size has been inflated to 4,344 subjects compared to Des2, the expected study duration under H_0 has been cut down to 39.6 months and the expected sample size under H_0 is 3,965. It would also be useful to simulate Des3 under a variety of scenarios for the hazard ratio. Select Des3 in the **Library** and click the size icon. You will be



		Simulation: Surv	ival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Study Durat
Numbe	er of Looks: 3	¥.	
Simula	tion Parameters	Response Generation Info	Accrual/Dropout Info Simulation Control Info
Trial Type	e: Non	inferiority 🔻	
Test Type			Noninf. Margin (In(HR0)): 0.044 Test Statistic: Logrank
Max. # of	Events:	3780	
Fix at Eac	h Look: Tota	I No. of Events 💌	
Look #	Info. Fraction	Futility Z	
1	0.3333	-0.0070	
2	0.6667	-1.0555	
3	1.0000	-1.9600	

taken to the following simulation worksheet.

We wish to simulate this trial under the null hypothesis that the hazard ratio is exp(0.044) = 1.045. To do this go to the **Response Generation Info** tab in the simulation worksheet. In this tab change the control and treatment hazard rates as shown below.

Simula	ation Parameters	Response Ge	neration Info	Accrual/Dropo	ut Info	Simulation Control Info
		Survival Ir	formation			
-	<u>H</u> azard Rates Cum. % Su <u>r</u> vival					
# of Haz	ard <u>P</u> ieces 1	•				
Piece Starting At		Hazaro	Hazard Rates			
Piece	Starting At	Control	Treatment	Hazard Ratio		
1	0.0000	0.0385	0.04024	1.0450		

Next, click the **Simulate** button to simulate 10000 trials. A new row labeled Sim1 will appear in the **Output Preview** window. Select Sim1 in the **Output Preview** and click the icon to save it to the **Library**. In the **Library**, double-click Sim1. A portion of the output is displayed

below. (The actual values may differ, depending on the starting seed used).

Look #	Events	Boundaries Futility	Early Stopping For	Unable To Reject H1		
		Upper	Futility	Reject III	Count	%
1	1260	-0.007	5137		5137	51.37
2	2520	-1.0555	3542		3542	35.42
3	3780	-1.96	1095	226	1321	13.21
Total			9774	226	10000	
%			97.74	2.26		

Average Sample Size, Dropouts and Look Times:

Look #	Average Sample Size	Average Events		Average Dropouts		Average	Average
		Control	Treatment	Control	Treatment	Look Time	Follow up
1	3590.4581	619.7884	640.2116	68.9008	67.9243	24.7941	8.9151
2	4344	1250.1131	1269.8869	137.2229	136.4547	40.2259	14.742
3	4344	1887.2975	1892.7025	204.6775	205.084	93.2951	22.1092
Average	3956.4388	1003.1299	1036.0541	111.4037	110.0054	39.308	12.7206

Response Generation Parameters No. of Hazard Pieces: 1 Input Method: Hazard Rates Piece # Starting At Control Treatment Hazard Ratio 1 0 0.039 0.04 1.045

Note that 226 out of the 10000 simulations were unable to reject the alternative hypothesis, thus confirming (up to Monte Carlo accuracy) that this design achieves a type-1 error of 2.5%. Also, observe that 51.37% of these trials have crossed the futility boundary at the very first interim look after only 24.794 months of study duration.

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