

Architect - A Platform for Design and Analysis Software for Clinical Trials

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ABSTRACT

Design and Analysis of clinical trials involves evaluating several designs, simulating them to assess performance and proceeding with one chosen design, collecting and analyzing trial data, carrying out adaptations as permitted by the protocol, and reporting trial results. Each of these specialized operations is often supported by separate pieces of software that do not necessarily seamlessly share data and maintain a common workflow.

Cytel's **Architect** software platform addresses this need by providing common infrastructure to integrate the functional components. It provides common functionality such as data handling, comparing designs across different software components, reporting, workflow, and archiving of designs and results. Command line batch language supports scripting and workflow automation.

The platform standardizes data storage so as to smoothly interface with enterprise trial execution applications like Cytel's **ACESTM**, and also provides hooks for external code written in **SAS®** or **R**.

User can customize the GUI to suit their needs.

INTRODUCTION

During the definition and conduct of clinical trials, a statistician's participation is required at a number of stages.

Initially, the **statistical design** of the trial involves sample size computation based on the assumed effect size (the expected extent of effect of study intervention), the desired statistical power, the level of significance (or Type I error probability), and sometimes additional parameters.

At the planning stage the effect size can only be estimated, and therefore the statistician often wants to explore several different values of effect size. Each gives rise to one possible design scenario. The design statistician computes and compares multiple scenarios before deciding which scenario to actually implement in the trial.

Simulations, at the next stage, are useful to study operating characteristics of the trial. Simulations provide insight by letting the user play with parameter values to do *what-if* analyses. For instance, the user may try out different models for the arrival or dropout patterns of the trial subjects, or different dose-response relationships etc.

Finally, one design makes it to the protocol and into the execution. Several types of data are collected, such as arrival and dropout times of subjects; treatments or doses assigned to them (may be blinded); observed response to drug administered and any adverse events observed etc. These data are **analyzed** at the end of the trial, and also at interim points in a Group Sequential design, leading to a variety of reports targeted to varied functionaries.

Traditionally statisticians used a number of independent tools / software packages to accomplish these tasks. The tools may come from different vendors and may not inter-operate effectively, posing limitations on workflow and opportunities to automate. Also the users need to perform many small tasks manually or look for specialized tools to perform them, which adds to costs.

The **Architect** project is an effort to create a platform that integrates diverse tools for easy transition from one function to another, maintaining a consistent look and feel. Further, it supports extensible functionality with plug in modules and user's own code in R and SAS®. It also works in a distributed environment, over a network, so that users can share work with their colleagues. Along with the platform are available, the design and analysis tools targeted at different types and phases of clinical trial and implementing all popular statistical techniques. These products integrate into the **Architect** platform. User's own logic implemented in R can be connected with **Architect** to integrate with built-in features.

This paper illustrates this approach with a fixed sample phase III design using the product **SiZ**; then to make it group sequential using **East** and finally to perform interim analyses during the execution phase using **East**. Throughout this

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discussion, we also point out features of the **Architect** platform that enhance the user's convenience.

FEATURES OF THE ARCHITECT PLATFORM AND THE PRODUCTS

Architect and the integrated products facilitate the following:

- Designing a clinical trial:
 - Create several scenarios quickly from the scratch or by editing existing scenarios.
 - View and compare scenarios in a tabular format and graphically.
 - Sort, arrange and filter the scenarios using some criteria.
 - Design your own plots by choosing quantities to plot, in addition to standard plots like the power curve.
 - Extend a design created by one product using another product. For instance, convert a fixed sample design into group sequential, introduce adaptation at one or more looks etc.
 - Save a design template as favorite and use it to quickly create a new design in future.
 - Customize parts of the design by supplying custom R routines to compute them.
 - Import external data (standard formats like CSV and SAS dataset are supported).
 - Explore data graphically and using techniques like frequency distribution, ANOVA, regression etc.
- Analysis of a clinical trial:
 - Perform trial specific analysis of data using the appropriate product or using a custom R routine.
 - Perform conditional simulations during interim analysis to assess the chance of success at the end.
- Reporting:
 - Design custom outputs by drag-drop layout definition using the output library, inserting text and images.
 - Choose display precision for numeric output.
 - Create a custom report template using Report Writer and apply it to a design to produce reports.
- General:
 - Use a batch language to write scripts for creating designs and performing analysis.
 - Write custom help text and notes for specific fields in addition to system and context help.
 - Customize menus and define favorite commands added to Quick Access toolbar.
 - Save all the work in a workbook. Rearrange workbook items in a desired order.

FUNCTIONAL MODULES OF THE **ARCHITECT** PLATFORM

The following diagram shows the modules of the Architect platform.

Architect Platform and Products

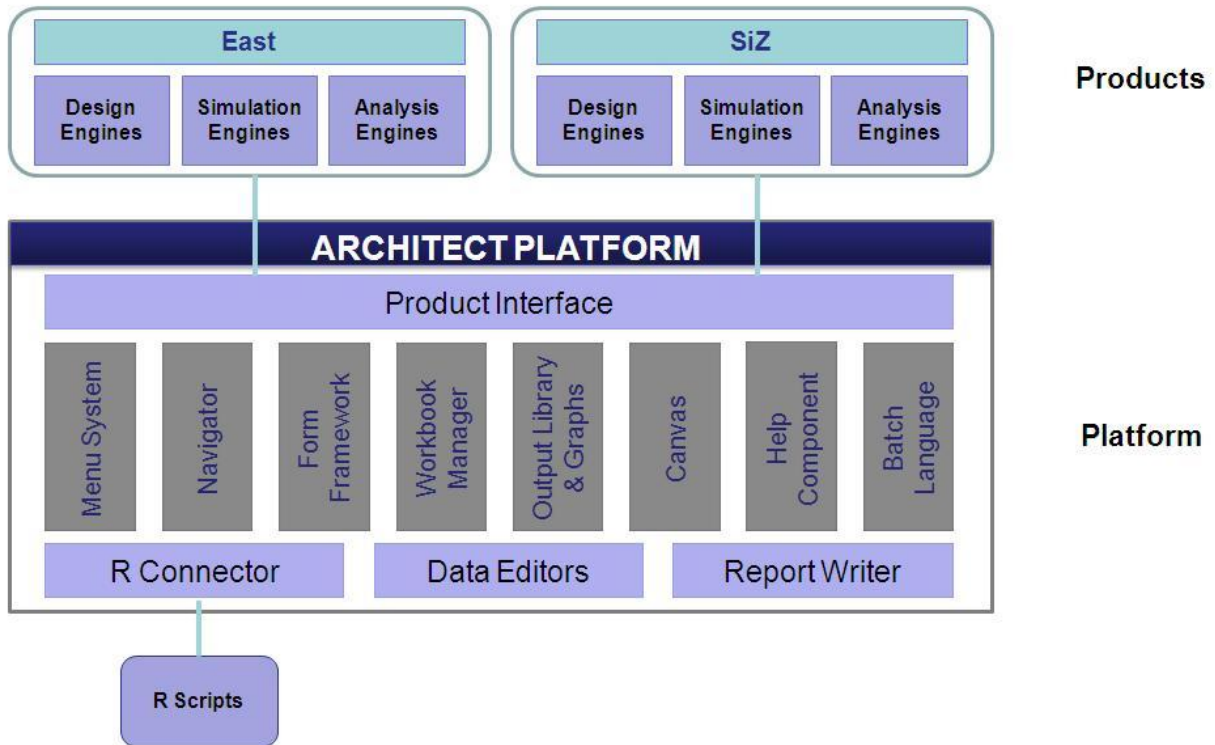


Figure 1: Architect Platform and Products

DESIGNING AND MONITORING A CLINICAL TRIAL USING ARCHITECT AND THE PRODUCTS

We will now illustrate the design and analysis features of the products **SiZ** and **East** with the **Architect** platform, using a hypothetical example: a phase III clinical trial for comparing two drugs— an active control and a new compound. The endpoint is a continuous variable. We will use difference in the mean response on the two arms as the comparison metric. Let δ denote the difference in means and σ denote the between-subjects standard deviation.

We will first design a fixed sample trial to test the null hypothesis that $\delta = 0$ versus the one-sided alternative hypothesis that $\delta > 0$. We choose the following parameters for this design:

Parameter	Value
α	0.025
δ	Several values between 58 and 62 60 is the clinically meaningful effect size.
σ	200
Power	0.9
Allocation ratio	1:1

We will now perform the following steps using **Architect**, **SiZ** and **East**:

1. Compute the sample size for the fixed sample test using **SiZ**.
2. Create multiple scenarios, one for each value of δ specified and compare them.
3. Use simulations to check how power is affected if sample size is reduced to 400.
4. Create a group sequential design using **East** with 2 interim analyses - first at one-third of the total recruitment, and second after the responses for an equal number of additional subjects are available.
5. Create a report describing the design output using the canvas tool.
6. During execution, perform interim analyses of the data using **East**.

The following workflow diagram summarizes these steps.

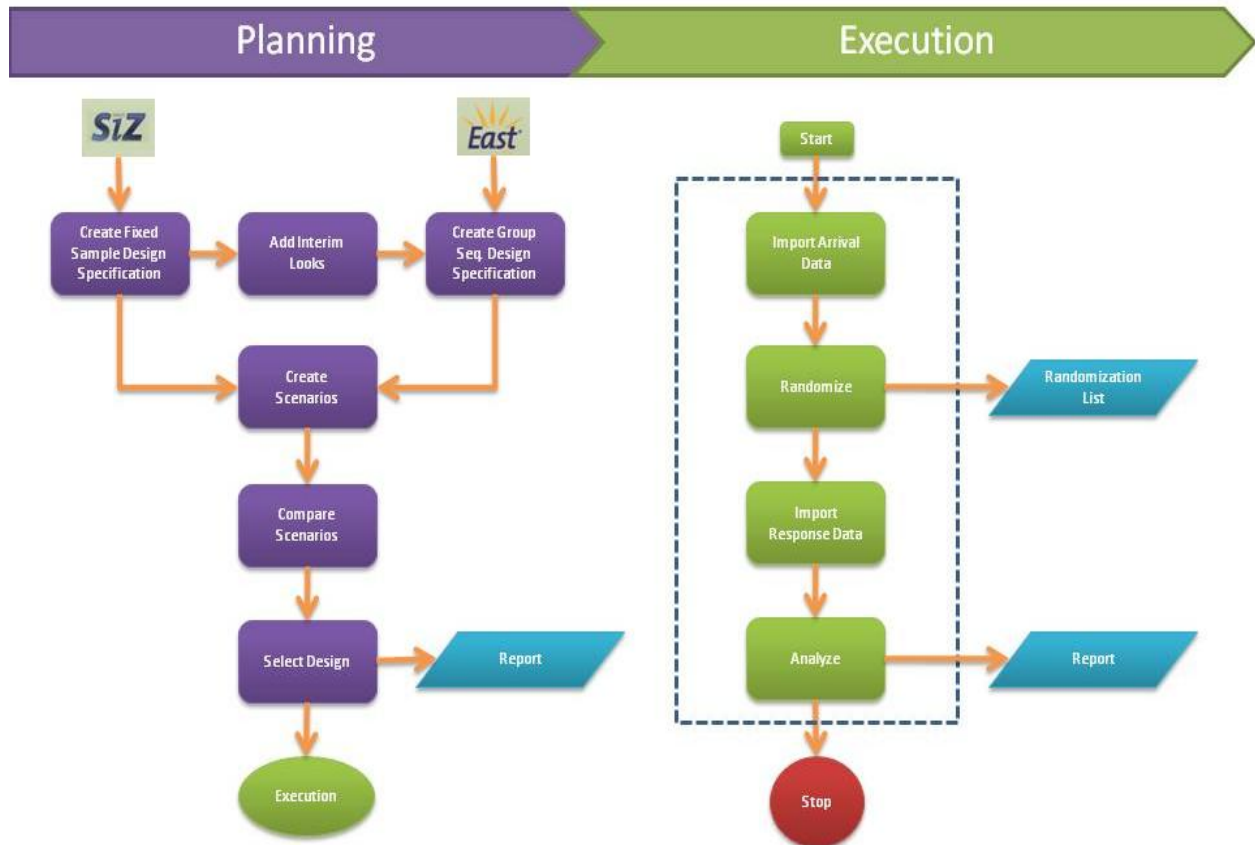


Figure 2: Tasks in Planning and Execution

We will now discuss how to design this trial using SiZ and then extend it to a group sequential trial using East.

CLINICAL TRIAL DESIGN

Suppose we are interested in creating designs with the δ values 58, 59, 60, 61, 62, all other parameters remaining the same. **Architect** facilitates this by allowing the user to enter multiple parameter values separated by commas, or in the form of a *from:to:step* range. One can also enter a formula that evaluates to a number in a field.

We thus create 5 designs in one go with different values of δ , **Architect** thus creating the 5 scenarios. If more than one parameter varies, **Architect** creates all combinations of these parameters, each as one scenario.

Performing step 1 and 2:

The following picture shows the design input screen from SiZ with multiple values specified for δ .

Continuous Response: Difference of Means for Independent Data

Design Parameters [Add to Favorites](#)

Design Name: Design	Trial Type: Superiority	Dist. of Test Stat.: Normal
Side Type: 1 Sided	Input Method: Diff. of Mean	
Type - 1 Error (α): 0.025	Diff. of Means (δ): 58,59,60,61,62	Std. Deviation: 200
Power (1- β): 0.9		
Sample Size (n):		
Allocation Ratio: (n / n ₀): 1		

* Value to be Computed: Sample Size

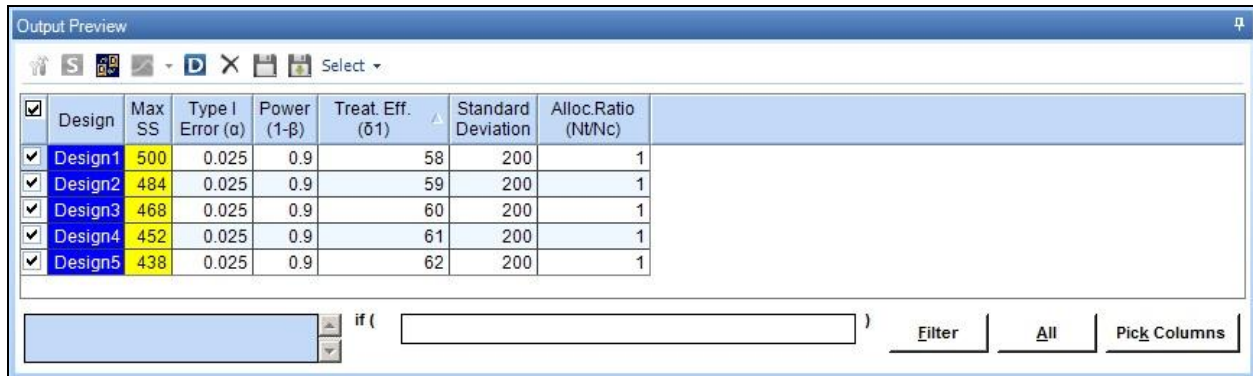
Compute Clear

Creating multiple scenarios

Figure 3: Design Input Dialog Box in SiZ

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Once all parameters have been specified, the possible designs or scenarios are created with a click of a button. When the “Compute” button is clicked, **Architect** creates the possible scenarios and invokes the product engines to perform the design computations. The computed scenarios are presented in a tabular format in a special window called the Output Preview Window (OPW) that facilitates easy comparison.



☒	Design	Max SS	Type I Error (α)	Power ($1-\beta$)	Treat. Eff. (δ_1)	Standard Deviation	Alloc. Ratio (N_t/N_c)
☒	Design1	500	0.025	0.9	58	200	1
☒	Design2	484	0.025	0.9	59	200	1
☒	Design3	468	0.025	0.9	60	200	1
☒	Design4	452	0.025	0.9	61	200	1
☒	Design5	438	0.025	0.9	62	200	1

Figure 4: Output Preview Window

The OPW allows the user to perform the following actions:

- Sort scenarios on some parameter.
- Filter scenarios based on some logic of parameters displayed. The OPW helps build this expression.
- Choose columns to display.
- Set display accuracy of one particular entry or an entire column in the table.
- View, save and edit scenarios.
- Delete uninteresting scenarios.

SiZ and **East** have a feature called Favorites. Just like the favorites in internet browsers, this is a collection of favorite design parameters that one would like to be saved. Just type in these values once and click the button “Add to Favorites”. The set of parameters is saved as a new favorite design template and is listed under the Favorites menu on the ribbon bar.

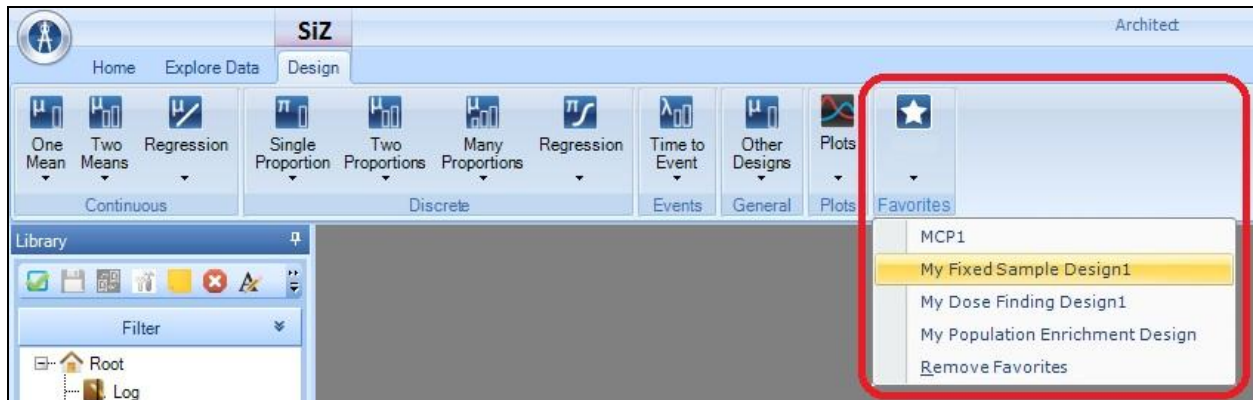


Figure 5: Favorites

Performing step 3:

We see that all designs require a sample size of 438 or more. Imagine that the sponsor would like to restrict sample size to 400. Simulations help us evaluate effect of reduced sample size on the power, possibly relaxing some design assumptions and restrictions. The following picture shows the OPW with the 5 scenarios and the resulting power for each scenario through simulations when the sample size is restricted to 400.

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Output Preview							
☒	Design	Max SS	Type I Error (α)	Power (1- β)	Treat. Eff. (δ_1)	Standard Deviation	Alloc. Ratio (N _t /N _c)
☒	Simulation1	400	0.025	0.828	58	200	1
☒	Simulation2	400	0.025	0.843	59	200	1
☒	Simulation3	400	0.025	0.85	60	200	1
☒	Simulation4	400	0.025	0.866	61	200	1
☒	Simulation5	400	0.025	0.871	62	200	1

if ()

Figure 6: Output Preview Window

We can see that the power has dropped from the desired 90% to as low as 83%.

In such a situation the sponsor can consider a group sequential design. Although this means a larger upfront commitment of total sample size, there is a chance that such a trial may stop midway if the drug is found to be working or has too many adverse side effects associated with it.

Performing step 4:

We will now use **East** to design a corresponding group sequential trial with 2 interim analyses as described before, resulting in several steps and numerous parameters displayed in the sequence of pictures below.

Design: Two Means - Difference of Means for Independent Data

Total Number of Looks: Number of Arms:

Type of Design
☒ Analytic Design
☐ Design By Simulation

Design Parameters | Look Settings | Efficacy Boundaries | Futility Boundaries

Error Rates

Trial: Input Method:

Side: Specify Alternative Hypothesis
 Difference in Means ($\mu_t - \mu_c$): Std. Deviation (σ):

Type I Error (α):

Power (1- β): ☐

Sample Size (N): ☒

Allocation Ratio (N_t/N_c):

Figure 7: Design Input Dialog Box in East

Design: Two Means - Difference of Means for Independent Data

Total Number of Looks: Number of Arms:

Type of Design
☒ Analytic Design
☐ Design By Simulation

Design Parameters | Look Settings | Efficacy Boundaries | Futility Boundaries

Interim Looks Settings

Look #	Select Interim Monitoring Time-Points		
	Info. Fraction	Stop for Efficacy	Stop for Futility
1	0.3333	☒	☒
2	0.6667	☒	☒
3	1.0000	☒	☒

Spacing of Looks
☒ Equal
☐ Unequal

☒ Stop Early for Efficacy
☒ Stop Early for Futility

Figure 8: Specifying Interim Looks in East

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Design: Two Means - Difference of Means for Independent Data

Total Number of Looks: Number of Arms:

Type of Design
☒ Analytic Design
☐ Design By Simulation

Design Parameters | Look Settings | Efficacy Boundaries | Futility Boundaries

One Sided Efficacy Boundary

Boundary Family:

Spending Function:

Parameter:

Type I Error (α):

Look #	Info. Fraction	Cumulative Alpha Spent
1	0.3333	0.000
2	0.6667	0.006
3	1.0000	0.025

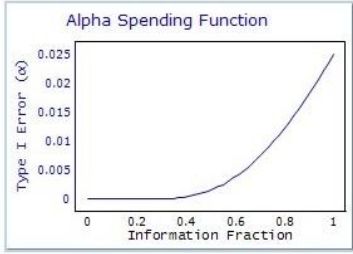


Figure 9: Specifying Stopping Boundaries in East

When these designs are computed, the OPW displays the scenarios and their output as shows in the picture below.

Output Preview

Design	Max SS	Type I Error (α)	Power (1- β)	Treat. Eff. (δ_1)	Standard Deviation	Alloc. Ratio (N1/N2)	Exp. SS (H1)
Design1	530	0.025	0.9	58	200	1	411
Design2	512	0.025	0.9	59	200	1	397
Design3	496	0.025	0.9	60	200	1	384
Design4	480	0.025	0.9	61	200	1	372
Design5	464	0.025	0.9	62	200	1	360

if () Filter All Pick Columns

Figure 10: Output Preview Window

As we can see, the total sample size now varies between 464 and 530. But if the drug works, the sample size expected to be actually used in the trial varies between 360 and 411.

The following plot from **East** displays the relationship between the average sample size of the trial and the effect size. Like this, **East** and **Siz** provide several plots to examine the operating characteristics of the trial.

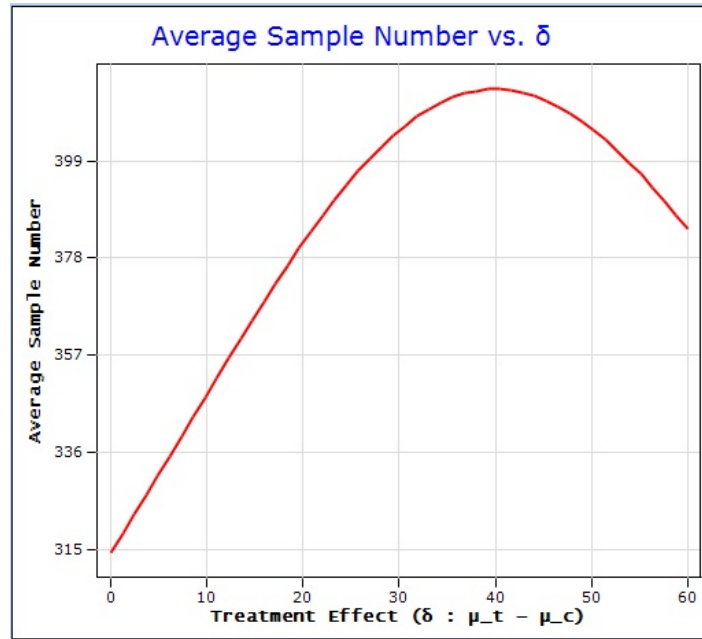


Figure 11: A Plot from East

Architect also provides a tool for comparing multiple scenarios. The comparison tool displays the scenarios in a tabular format and also compares them graphically. E.g. one can view the average sample size curves for all scenarios together in one plot or one can view them side by side and compare.

Following pictures show these features of the comparison tool.

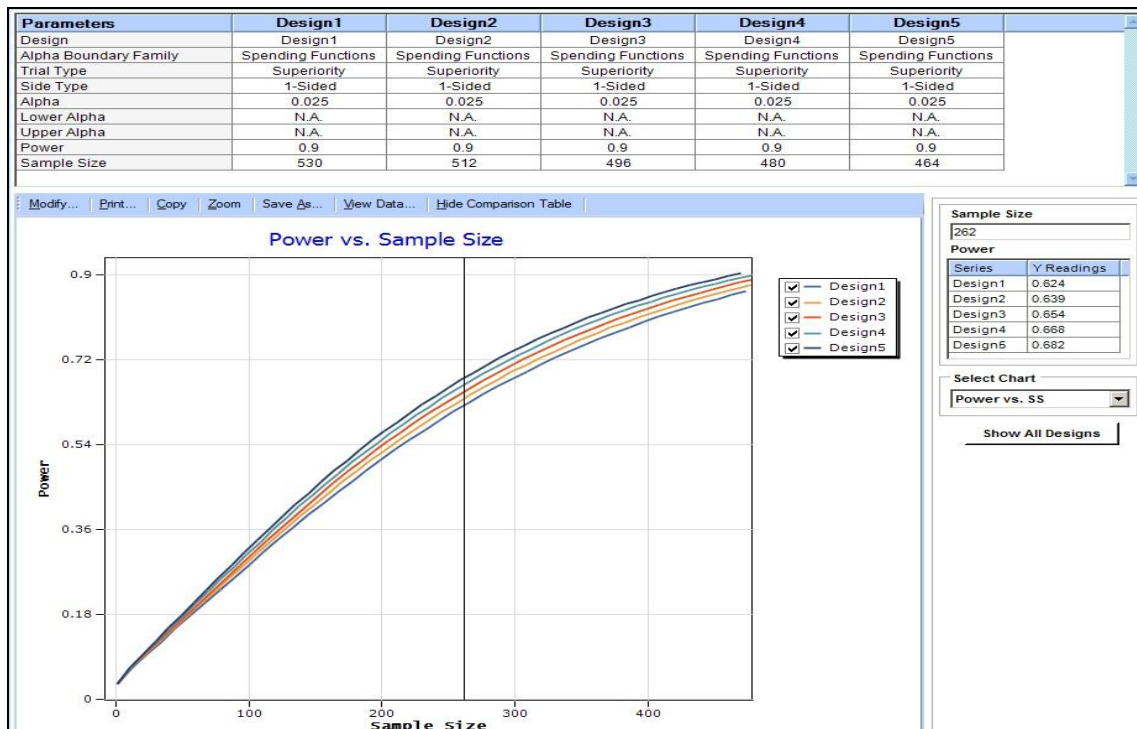


Figure 12: Comparing Scenarios

Using tools like these, one can create and compare several scenarios and choose the design that has the desired characteristics. In case of our trial, we assume that Design3 is the appropriate design.

Performing step 5:

While **East** produces a rich output screen for the design, sometimes the user needs additional custom text and

images. **Architect** supports this need with a tool called *Canvas*.

The canvas lets the user drag and drop output elements from the standard **East** output and also add custom text and images. The following screenshot shows an **East** output screen on the left and a canvas on the right. It shows the stopping boundaries plot dragged from the output screen and dropped onto the canvas.

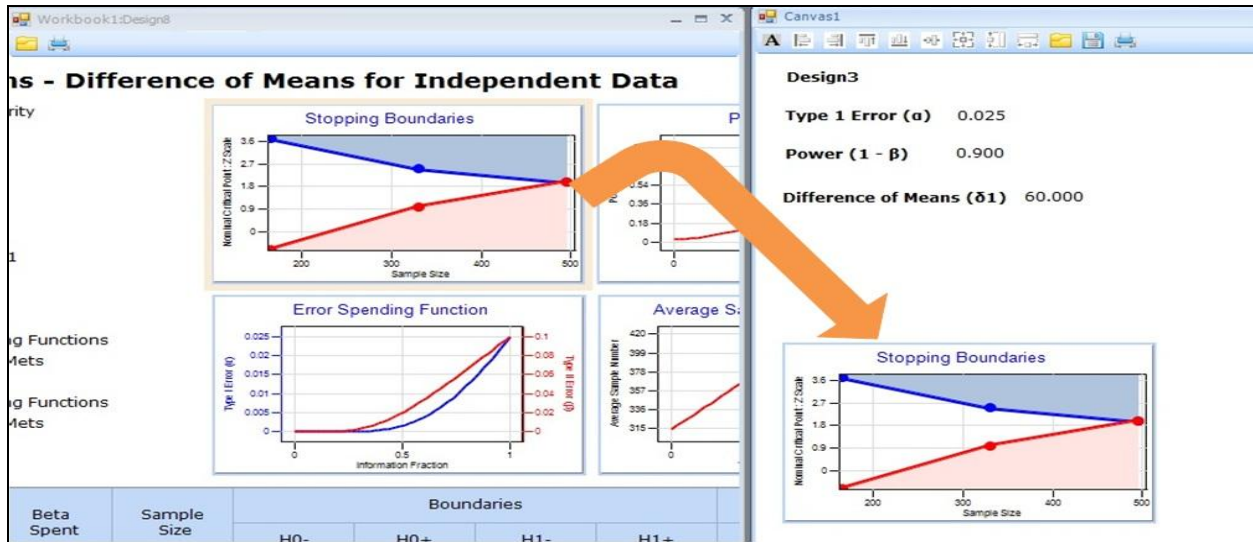


Figure 13: Composing Reports Using Canvas

The planning phase ends with selection of the design. In the following sections, we describe the tools offered by **Architect** and products like **East** that can be used effectively in the execution phase. For the purpose of this paper, we specifically describe the data analysis tools.

DATA ANALYSIS IN CLINICAL TRIALS

SiZ provides analysis tools for fixed sample trials whereas **East** provides these tools for group sequential and adaptive trials. The **Architect** platform, along with these products, provides several features that help the user perform the analysis tasks easily. These features are:

- Interim monitoring worksheet
- Case data editor – A graphical editor for clinical trial data
- Analysis and Interim Monitoring modules of **SiZ** and **East**
- Interface to external systems like R
- Reporting

We will now discuss these features continuing on the earlier example. Since it is a group sequential trial, we will discuss how the interim analyses are performed using **East**.

Performing step 6:

East provides an interim monitoring worksheet which records interim analyses and computes and displays useful output parameters such as the repeated and adjusted confidence intervals, conditional power etc.

To start the interim monitoring, we right click the design node in the navigator and choose the option “Perform Interim Analysis”. This brings up a blank interim analysis worksheet as shown in the screenshot below.

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Normal Superiority Trials: Two-Sample Test - Difference of Means (Plan2)													
Plan Details		Look #	Cumul. Accr.	Test Stat.	Info Fract.	Nominal Critical Point				Repeated 95.00% CI for δ		Interim Outputs	
1-Sided or 2-Sided Test	2-Sided					Reject H0		Reject H1		Lower	Upper	Lower	Upper
Significance Level (α)	0.05					Lower	Upper	Lower	Upper			Ideal Next Look Position	466
Power ($1 - \beta$)	0.9	1											
Assigned Fraction (Treatment)	0.5	2											
Planned Number of Looks	3	3											
Spacing of Looks	Equal	4											
Hypothesis to be Rejected	H0 or H1 (NB)	5											
Boundary Family	SpF (Pub)	6											
Boundary to Reject H0	LD (OF)	7											
Boundary to Reject H1	LD (OF)	8											
Difference of Means (δ_1)	60.0	9											
Standard Deviation (σ)	200.0	10											
Maximum Sample Size	485												
		Effect Size under H1: $\delta_1 = (\mu_t - \mu_c) = 60.0000$											

Figure 14: Interim Monitoring Worksheet

It is now time to perform the first analysis. For this we need to import the response data gathered so far. We use the case data editor tool from **Architect** to do this.

Importing data using Case Editor

Using the Import command on the ribbon bar, we can import data stored in formats like CSV, SAS dataset etc.

The clinical trial data is typically represented in the *case data* format where the rows correspond to the subject records or *cases* and the columns of the table correspond to the parameters or *variables*. When a case data is imported into **Architect**, it brings up the case editor. The case editor is a graphical editor for the case data. It has a spreadsheet like user interface with the cases displayed along the rows and the variables along the columns.

Subject_ID: 1 Value: 1							
	Subject ID	Arm	Response	var	var	var	var
1	1	Drug	63.8154085				
2	2	Control	127.485173				
3	3	Control	278.055148				
4	4	Control	281.874684				
5	5	Drug	275.874991				
6	6	Drug	4.23219118				
7	7	Control	110.769607				
8	8	Control	238.777914				
9	9	Control	-7.02108335				
10	10	Drug	2.82389951				
11	11	Drug	52.2143618				
12	12	Drug	224.377769				
13	13	Drug	473.322877				

Figure 15: Case Editor

Following are some of the key features of the case editor:

- Import data from standard formats like CSV, SAS dataset etc. or type it from the scratch.
- Add a new variable to the data and specify its properties like name, type, display format (fixed / scientific / percent etc.). Mark specific variable values as missing.
- Create a new variable with values based on some condition or formula involving other variables.
- Sort cases on one or more variables.
- Filter cases based on some condition.

Analysis and Interim Monitoring

After data are imported, one can analyze them using the analysis tools provided by **East**. This typically involves computing the test statistic value and performing the hypothesis test. **East** provides the Test Statistic Calculator as shown in the following screenshot.

Test Statistic Calculator

Editing look #1

Input for Normal end point

☒ Estimate from data Data: Responses1.cyd

Estimate of δ 90.771

$\delta = \mu_t - \mu_c$

Standard Error of Estimate of δ 35.205

☐ Use R Function for Estimation

Stopping Boundaries to Compute

☒ Efficacy ☒ Futility

Output

Test Statistic 2.578

Recalc OK Cancel

Figure 16: Test Statistic Calculator

In this calculator, one can either directly type in estimated value of δ and its standard error or one can use appropriate analysis method provided by **East**. Sometimes a custom computation of the estimate and standard error is required. **East** supports this by hooking to an external R function that contains the logic to compute the estimate of δ and its standard error. The calculator also supports checking for early stopping for efficacy and / or futility.

East then computes the test statistic and performs the hypothesis test. If a stopping boundary is crossed, **East** stops the trial. Otherwise, it keeps it open so that the user can take further looks at the accumulating data. The following screenshot shows the IM sheet for a completed trial.

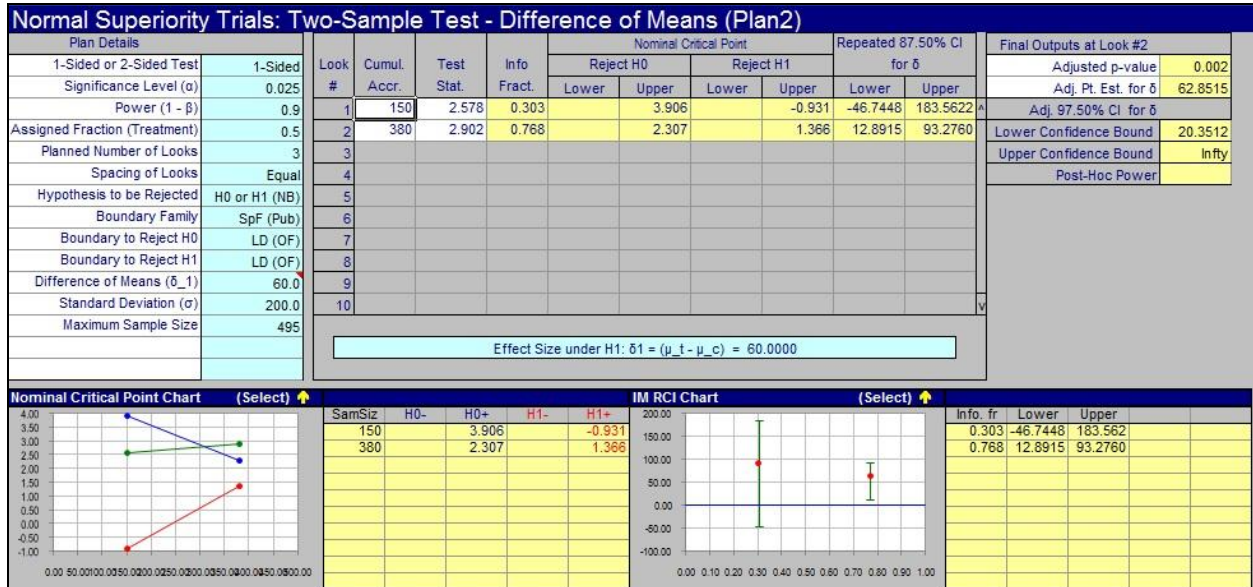


Figure 17: Interim Monitoring Worksheet for a Completed Trial

We summarize the features of IM worksheet below:

- Keep analysis by analysis record of the trial.
- At any look, use the analysis tools offered by the product or use a custom R script
- Compute repeated confidence interval and repeated p-value at each interim analysis.
- Compute the conditional power at every interim analysis.
- At the end of the trial, compute the stage wise adjusted confidence interval, the point estimate for the effect size and the adjusted p-value.

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Reporting

Just like the design output, one can use the canvas tool to create a custom output sheet by copying output elements from the IM worksheet into the canvas. One can also add notes and images to the custom output. Canvas allows the user to save the output in popular formats like PDF, HTML and RTF and also to print the output. In addition to the canvas, **Architect** also provides a tool called *Report Writer* that can be used to design report templates and apply them to the designs created by **SiZ** and **East**. Report Writer is a separate topic in itself. We will not cover it in this paper.

CONCLUDING REMARKS

The **Architect** platform has been designed to enhance the productivity of end-users. It helps the user arrive at the optimal design faster and more easily. With features like the *Canvas*, the user can easily create custom reports that incorporate elements of standard output produced by a product like **East** as well as other text and images. Even the computations can be extended with the help of the *R connector*.

East and **SiZ** are the first products to be integrated into the platform. These will be followed by modules like patient recruitment, randomization, adaptive dose finding and dose ranging designs, population enrichment, sample size re-estimation, seamless phase 2/3 designs etc. With these additions, the **Architect** platform and the product suite will offer end-to-end functionality for the clinical trial investigators.

CONTACT INFORMATION

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