

PROC EASTMONITOR – A SAS Add-on for Monitoring Adaptive Clinical Trials

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ABSTRACT

Typical clinical trial workflow involves creation of trial design by sponsor statisticians, statistical analysis by statisticians at the Independent Statistical Center (ISC) and decision making by the DMC. In a group sequential / adaptive trial, statisticians typically use custom SAS[®] macros to analyze patient data at interim analyses and produce required reports.

The product East[®] PROCs consists of PROC EASTMONITOR which can be used by ISC statisticians to perform interim analyses of subject data based on group sequential / adaptive methodology identified in the protocol in a statistically safe manner. It takes as input the design produced by the East[®] system and summarized subject data. It computes test statistic, performs a hypothesis test and produces a recommendation for early stopping or continuation of the trial. It also produces statistical inference about the treatment effect. Further the SAS[®] output generated by PROC EASTMONITOR can be imported back into East[®] and used by the DMC for advanced analysis and decision making using East[®].

SUMMARY

Clinical trials are experiments on human beings to demonstrate the efficacy and safety of new drugs or treatments. A clinical trial is conducted according to a plan called a *protocol*. A protocol details the objectives of the trial, the data collection process, and the analyses of the data.

In a fixed-sample trial, data about all individuals are first collected and then examined at the end of the study. Most major trials have data safety monitoring boards (DSMB) or data monitoring committees (DMC) that periodically monitor safety and efficacy data during the trial and recommend that a trial be stopped for safety concerns such as an unacceptable toxicity level. In contrast to a fixed-sample trial, a group sequential trial provides for interim analyses before the formal completion of the trial while maintaining the specified overall Type I and Type II error probability levels.

Statisticians working at the trial sponsor organization create the statistical design for the clinical trial. Software packages like East[™] are used for this purpose. East[®] is capable of designing group sequential and adaptive clinical trials for a wide variety of endpoints.

During the course of a group sequential / adaptive trial, data are periodically gathered and analyzed. These interim analysis points are generally planned at the design stage and specified in the protocol. However, the DMC may occasionally take one or more unplanned looks at the data. In any case, these datasets are made available to the independent statisticians working at the Independent Statistical Centers (ISC). They typically use SAS[®] for analyzing these data and related reporting. This job involves importing the design parameters into SAS[®] and using standard SAS[®] PROCs (like PROC FREQ, PROC MEANS etc.) and custom macros for performing the required analysis. Naturally, a lot of QC and validation is required in this process.

We have developed a new SAS[®]PROC called PROC EASTMONITOR[™] (hereafter referred to as 'the PROC') which aims to make this job easier. It takes as input the design specification and summarized subject response data and performs necessary group sequential / adaptive computations. Here is a list of features of the PROC.

- It takes as input the design specification as a SAS dataset (exported from East[®] as a CSV file and imported into SAS[®]) and the look by look parameter estimates and their standard errors. The latter are typically the output of standard PROCs like PROC FREQ, PROC MEANS etc.
- It can be used for monitoring group sequential trials as well as adaptive trials involving sample size re-estimation (SSR).

- The PROC uses well known group sequential / adaptive techniques with emphasis on controlling type I error and flexibility of taking unplanned looks as required by the DMC.
- It computes test statistic, performs hypothesis test and makes a recommendation of stopping the trial early for efficacy / futility or continuing to the next stage based on the available data.
- It also computes repeated confidence intervals and p-values based on the method of Jennison and Turnbull (2000) at every look. At the end of the trial, it computes stage wise adjusted confidence intervals and point estimate of the treatment effect and the adjusted p-value based on the method of Tsiatis, Rosner and Mehta (1984).
- The PROC uses thoroughly validated and well established computational engines from East® to perform these computations.
- It produces data tables for important operating characteristics like conditional power and post-hoc power and look by look repeated confidence intervals and stopping boundaries. These can be used to create plots using ODS.
- Output of the PROC can be exported as a CSV file which can be imported into East. DMC members can then use advanced forecasting techniques available in East® for deciding future course of the trial.

In this paper, we will discuss these features in detail using some relevant examples and also describe the PROC syntax.

WHAT IS EAST® PROCs

East® PROCs are a set of SAS® PROCs that provide tools to use East®, Cytel's product for designing and monitoring adaptive clinical trials, in the familiar SAS® environment. They work with version 6.3 of the East® platform. In **East® PROCs**, the procedure **PROC EASTMONITOR** can perform Interim Monitoring of a design created in East®. The trials can be Superiority or Noninferiority with either or both efficacy and futility boundaries. Apart from Interim Monitoring of the above mentioned group sequential designs, **PROC EASTMONITOR** can also be used with adaptive designs created in East®.

WHAT IS INTERIM MONITORING?

In clinical trials, there is a need of interim monitoring as the study runs over a number of years and data accumulate over the period. There could be ethical, economic reasons for terminating the study early. If the drug is promising enough or otherwise, early termination of trial with positive or negative result could save a lot of money. Group sequential designs lead to savings in sample size, time and cost as compared with fixed sample studies. If a group sequential design is to be monitored for interim analyses, accumulated data at every look is collected and analyzed to decide the further action in execution of clinical trial.

The quantities such as Post-hoc power, ideal next look position (INLP), conditional power at the INLP, predictive power, repeated confidence intervals etc are computed. When the trial concludes either by crossing a boundary or due to the fact that desired power is achieved, final inference including adjusted p value, adjusted confidence intervals are computed.

INTERIM MONITORING OF AN ADAPTIVE DESIGN

An adaptive trial is any clinical trial which uses accumulating data, possibly combined with external information, to modify aspects of the design without undermining the validity and integrity of the trial. They extend the group sequential methodology of East® in a natural way toward data-dependent changes in sample size, number of events (for event-driven trials), error spending function, and number and spacing of interim looks.

In recent years there has been a considerable amount of research on more flexible clinical trials where the sample size is re-estimated after the clinical trial is underway, on the basis of updated information about σ^2 and δ . The updated information may arise either from external sources, from interim results of the on-going trial, or from a combination of the two.

WHY PROC EASTMONITOR?

Clinical trial data are generally stored and analyzed using SAS®. The procedure **PROC EASTMONITOR** has been developed to enable the interim analysis of clinical trial data using SAS® where you store, explore and perform basic analysis. You can export the design from East®, analyze the subject response data in SAS®, and create a SAS® dataset from the summary of your analysis. This exported design and the interim analysis summary dataset are inputs to **PROC EASTMONITOR**.

PROC EASTMONITOR then performs the interim analysis calculations exactly the same way as East[®]. The resulting output is available in SAS[®] datasets as well as in the list files. The generated output datasets can be used in SAS[®] graphical and reporting tools for creating reports and plots as per requirement.

East[®] being the pioneering software in designing of phase 3 clinical trials encompasses numerous combinations of efficacy and futility boundaries and other features such as accrual, drop out etc. The boundaries that are available in **East[®]** run the gamut between extreme conservatism and extreme liberality for early stopping. It can also handle the designs with missing efficacy or futility boundaries at some looks. All these designs can be monitored using **Proc EastMonitor**. Besides the standard group sequential designs, **East[®]** can be used to create adaptive designs involving sample size re-estimation (SSR) following Cui, Hung and Wang (1999). This adaptive design allows modification of sample size at an interim look. In effect, the adaptive designs are also amenable to interim monitoring in SAS[®] through PROC EASTMONITOR. As a result, with **PROC EASTMONITOR** as an add-on to SAS, the interim monitoring capability of **East[®]** becomes available in SAS[®].

SYNTAX OF PROC EASTMONITOR

Note: Elements shown in **UPPERCASE BOLDFACE** are keywords. Elements shown in *italics* are names or numeric values supplied by the user. Elements enclosed in squared brackets [] are optional. Sets of elements enclosed in braces { } indicate choice of parameters. Each such element is separated by a vertical bar |.

The general structure of PROC EASTMONITOR is as follows:

```
PROC EASTMONITOR [<options>];
  [PLOTDATA] [<Options 1>];
  [CONDPower] [<Options 2>];
  [ERRSPEND] [<Options 3>];
  [PHP] [<Options 4>];
  [CI] [<Options 5>];
  [BOUNDARY] [<Options 6>];
  [OUTPUT] [<Options 7>];
```

SYNTAX SPECIFICATION

PROC EASTMONITOR [*<options >*];

The PROC EASTMONITOR statement is required to run EastPROC 1.0.

The *< options >* are described below.

The following options can be used with **Proc EastMonitor**

- **[METHOD]** = specifies the interim monitoring computation method used.
 - **[=CHW]** specifies that the underlying trial is an adaptive trial involving sample size re-estimation and use of a weighted statistic suggested by Cui, Hung and Wang (1999). If this option is not specified, the trial is assumed to be a standard group sequential (non-adaptive) one.
- **DESIGN** = *SASdataset* specifies a dataset in which all necessary design parameters including both input and output as a part of **East[®] Design** are stored.
- **[DATA]** = *SASdataset* specifies a dataset in which all input to the interim monitoring (IM) computations at the current look as well as previous looks are stored. In what follows is the consolidated list of variables across all tests.
 - Each row in the datafile corresponds to input for interim monitoring at that look.
 - **Look_num**: This variable contains the look number at which the interim monitoring is being performed.
 - **CumInfo**: Cumulative information accrued up to the current look
 - **CumN**: Cumulative sample size accrued up to the current look. This is the number of completers.
 - **CumEve**: Cumulative number of events accrued up to the current look in case of survival trials
 - **EstDelta**: Estimate of treatment effect based on cumulative data at current look
 - **StdErr**: Standard error of estimate of treatment effect at current look
 - **N_C**: Cumulative sample size on control arm at current look
 - **N_T**: Cumulative sample size on treatment arm at current look
 - **Mean_C**: Sample mean response on control arm based on cumulative data at current look
 - **Mean_T**: Sample mean response on treatment arm based on cumulative data at current look

- **Sigma_C**: Sample standard deviation of response on control arm based on cumulative data at current look
- **Sigma_T**: Sample standard deviation of response on treatment arm based on cumulative data at current look
- **Resp_C**: Cumulative number of responses observed on control arm at current look
- **Resp_T**: Cumulative number of responses observed on treatment arm at current look
- **N_00**: Cumulative number of subjects that did not respond on either arm
- **N_01**: Cumulative number of subjects that did not respond on control arm but responded on treatment arm
- **N_10**: Cumulative number of subjects that responded on control arm but did not respond on treatment arm
- **N_11**: Cumulative number of subjects that responded on both arms

- The dataset is cumulative. As explained earlier, it contains data for all looks starting from the first look up to and including the current look.

- Standard SAS® PROCs can be used for estimating the various quantities listed above.

- All sample sizes in the dataset are specified in terms of number of completers.

- The set of variables present in a data file needs to be as required by the specific test.

- **[MODEL]**= specifies the model to be used in the computation of cumulative information in case of information based designs only.
 - = **MN_2S_DI** specifies that the two sample design for difference of means of continuous endpoint is being monitored on the information scale.
 - = **PN_2S_DI** specifies that the two sample design for difference of proportions of binary endpoint is being monitored on the information scale.
 - = **PN_2S_RA** specifies that the two sample design for ratio of proportions of binary endpoint is being monitored on the information scale

- **[DI|DISP_ACC]** = *value* specifying the number of decimal digits to be printed in the output for every numeric quantity.

- **[LASTLOOK]** If present, current look is treated as the last look of the trial. This means all remaining type I error is spent at this look. If not specified, the **[PROC EASTMONITOR]** will spend appropriate amount of type I error at the current look as per the boundary family and the spending function in the design.

EXAMPLE-INTERIM MONITORING OF A STANDARD GROUP SEQUENTIAL DESIGN

Trial Design - Eighteen U.S. research centers participated in this trial, where obese adults were randomized to receive either Orlistat or placebo, combined with a dietary intervention for a period of two years (Davidson et al, 1999). Orlistat is an inhibitor of fat absorption, and the trial was intended to study its effectiveness in promoting weight loss and reduce cardiovascular risk factors. The study began in October 1992. More than one outcome measure was of interest, but we shall consider only body weight changes between baseline and the end of the first year intervention. We shall consider a group sequential design even though the original study was not intended as such. The published report does not give details concerning the treatment effect of interest or the desired significance level and power of the test. It does say, however, that 75% of subjects had been randomized to the Orlistat arm, probably to maximize the number of subjects receiving the active treatment.

Run the Proc EastMonitor with Design option only to view the design details. To do this, run the following SAS commands.

```
options nodate;
options nonumber;
libname input 'C:\Program Files (x86)\CytelProcForSAS9\procEM1v9\Examples';
libname out 'C:\Program Files (x86)\CytelProcForSAS9\procEM1v9\ExamplesOutput';
PROC EASTMONITOR DESIGN =input.Orlistat;
Run;
```

You will see the following output-

```

                                     The SAS System
Output from East (r) PROCs (v1.0) under _SAS9_1
```

PhUSE 2014

Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
INTERIM MONITORING: DIFFERENCE OF MEANS
Design Input Parameters

Design ID : Des15
Design DataSet : <INPUT.ORLISTAT>

Test Parameters
Design Type : Superiority
No. of Looks : 3
Test Type : 1-Sided
Specified Alpha : 0.0500
Power : 0.9001

Model Parameters
Input Method : Individual Means
Diff. in Mean : 3.0000
Mean Control : 6.0000
Mean Treatment : 9.0000
Std. Deviation : 8.0000
Test Statistic : Z
Allocation Ratio(nt/nc) : 3.0000

The SAS System
Output from East (r) PROCs (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.

Boundary Parameters
Efficacy Boundary : LD(OF)

The SAS System
Output from East (r) PROCs (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
Detailed Design: Two-Sample Test- Parallel Design - Difference of Means
Sample Size Information

	Control Arm	Treatment Arm	Total
Sample Size (n)			
Maximum:	83	248	331
Expected H1:	64.1428	192.4477	256.5906
Expected H0:	82.5210	246.5940	329.1150

Maximum Information for this design is 0.9697

The SAS System
Output from East (r) PROCs (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
Stopping Boundaries: Look by Look
Look Info Fract Sample Size Cumulative Boundaries Boundary Crossing Probability
No. (n/n_max) (n) Alpha Spent Efficacy (Incremental)
(Z) Under H0 Under H1
Efficacy Efficacy

1	0.3323	110	0.0007	3.2055	0.0007	0.0665
2	0.6677	220	0.0165	2.1387	0.0158	0.5429
3	1.0000	330	0.0500	1.6950	0.0335	0.2907

From the output, it is clear that the design is a 3 look unequally placed, one sided superiority design intended to determine the sample size required to have power of 90%. The values of **Mean Treatment (μ_c)** is 9 and **Mean Control (μ_t)** is 6 using a test with a one-sided type-1 error rate of 0.05. The value of **Std. Deviation (σ)** is 8. The **Efficacy Boundary Family** specified is of the **Spending Functions** type **Lan-DeMets** (Lan & DeMets, 1983), with **Parameter** as **OF** (O'Brien-Fleming). The cumulative alpha spent and the boundary values are also displayed. The design results in a maximum of 331 subjects in order to attain 90% power, with an expected sample size of 256 under the alternative hypothesis.

Interim Analysis using Proc EastMonitor

Although the study has been designed assuming three equally spaced analyses, departures from this strategy are permissible using the spending function methodology of Lan and DeMets (1983) and its extension to boundaries for early stopping in favor of H_0 proposed by Pampallona, Tsiatis and Kim (2001). At each interim analysis time point,

East[®] will determine the amount of type-1 error probability and type-2 error probability that it is permitted to spend based on the chosen spending functions specified in the design. **East**[®] will then re-compute the corresponding stopping boundaries. This strategy ensures that the overall type-1 error will not exceed the nominal significance level α . We shall also see how **East**[®] proceeds so as to control the type-2 error probability. **The First Interim Look** Assume that we take the first look after 110 patients (**Sample Size (Overall)**), with an **Estimate of δ** as 3, and **Standard Error of Estimate of δ** as 1.762. Data looks like:

	Look_Num	CumN	EstDelta	StdErr
1	1	110	3	1.761542024

Conduct interim analysis at the first look using the following syntax of the Proc EastMonitor.

```
/*Specify your library name and the path of Examples folder in the next
statement*/
libname input 'C:\Program Files\CytelProcForSAS9\procEMlv9\Examples';
PROC EASTMONITOR DESIGN=input.Orlistat DATA=input.OrlistatLk1 ;
CONDPOWER OUT=OrlistatCP1 ;
PHP OUT=OrlistatPHP1;
ERRSPEND OUT=OrlistatERR1 ;
CI OUT=OrlistatCI1;
BOUNDARY OUT=OrlistatBDRY1;
OUTPUT OUT=OrlistatIMOutput1;
run;
```

You will see the following output-

```

                                The SAS System
Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
INTERIM MONITORING: DIFFERENCE OF MEANS
Design Input Parameters
-----
Design ID : Des15
Design DataSet : <INPUT.ORLISTAT>
IM DataSet : <INPUT.ORLISTATLK1>
-----
Test Parameters
Design Type : Superiority
No. of Looks : 3
Test Type : 1-Sided
Specified Alpha : 0.0500
Power : 0.9001
-----
Model Parameters
Input Method : Individual Means
Diff. in Mean : 3.0000
Mean Control : 6.0000
Mean Treatment : 9.0000
Std. Deviation : 8.0000
Test Statistic : Z
Allocation Ratio(nt/nc) : 3.0000
-----
Boundary Parameters
Efficacy Boundary : LD(OF)
```

```

                                The SAS System
Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
Detailed Design: Two-Sample Test- Parallel Design - Difference of Means
Sample Size Information
```

	Control Arm	Treatment Arm	Total
Sample Size (n)			
Maximum:	83	248	331
Expected H1:	64.1428	192.4477	256.5906

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Expected H0: 82.5210 246.5940 329.1150

Maximum Information for this design is 0.9697

```

                                The SAS System
Output from East (r) PROCs (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
Stopping Boundaries: Look by Look
Look Info Fract Sample Size Cumulative Boundaries Boundary Crossing Probability
No.    (n/n_max)    (n)    Alpha Spent Efficacy    (Incremental)
              (Z)
              Under H0    Under H1
              Efficacy    Efficacy
1      0.3323      110      0.0007    3.2055    0.0007    0.0665
2      0.6677      220      0.0165    2.1387    0.0158    0.5429
3      1.0000      330      0.0500    1.6950    0.0335    0.2907

```

```

                                The SAS System
Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
Interim Monitoring Output
Look Information Cumulative Test Efficacy
No Fraction Sample Size Statistic
1 0.3323 110 1.7031 3.2055

Look Cumulative Effect Size Standard Repeated 95.00% CI Repeated
No. Sample Size Error Lower Upper p-value
1 110 3.0000 1.7615 -2.6466 Infinity 0.2462

Look Cumulative INLP CP Predictive
No. Sample Size Power
1 110 326 0.9438 0.8229

```

As the observed value 1.703 has not crossed the critical boundary value of 3.2055, the trial continues.

The Second Interim Look

Suppose the subjects are enrolled, and a second interim analysis with 300 subjects is conducted. Suppose that the **Estimate of δ** is 2, and **Standard Error of Estimate of δ** is 1.

Conduct interim analysis at the second look using the following syntax of the Proc EastMonitor.

```

/*Specify your library name and the path of Examples folder in the next
statement*/
libname input 'C:\Program Files\CytelProcForSAS9\procEMlv9\Examples';
PROC EASTMONITOR DESIGN=input.Orlistat DATA=input.OrlistatLk2 ;
CONDPOWER OUT=OrlistatCP2 ;
PHP OUT=OrlistatPHP2;
ERRSPEND OUT=OrlistatERR2 ;
CI OUT=OrlistatCI2;
BOUNDARY OUT=OrlistatBDRY2;
OUTPUT OUT=OrlistatIMOutput2;
run;

```

You will see the following output-

```

                                The SAS System
Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
INTERIM MONITORING: DIFFERENCE OF MEANS
Design Input Parameters
-----
Design ID : Des15
Design DataSet : <INPUT.ORLISTAT>
IM DataSet : <INPUT.ORLISTATLK1>

```

PhUSE 2014

Test Parameters

Design Type : Superiority
No. of Looks : 3
Test Type : 1-Sided
Specified Alpha : 0.0500
Power : 0.9001

Model Parameters

Input Method : Individual Means
Diff. in Mean : 3.0000
Mean Control : 6.0000
Mean Treatment : 9.0000
Std. Deviation : 8.0000
Test Statistic : Z
Allocation Ratio(nt/nc) : 3.0000

Boundary Parameters

Efficacy Boundary : LD(OF)

The SAS System

Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
Detailed Design: Two-Sample Test- Parallel Design - Difference of Means
Sample Size Information

	Control Arm	Treatment Arm	Total
Sample Size (n)			
Maximum:	83	248	331
Expected H1:	64.1428	192.4477	256.5906
Expected H0:	82.5210	246.5940	329.1150

Maximum Information for this design is 0.9697

The SAS System

Output from East (r) PROCs (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
Stopping Boundaries: Look by Look
Look Info Fract Sample Size Cumulative Boundaries Boundary Crossing Probability

No.	(n/n_max)	(n)	Alpha Spent	Efficacy (Z)	Under H0 Efficacy	Under H1 Efficacy
1	0.3323	110	0.0007	3.2055	0.0007	0.0665
2	0.6677	220	0.0165	2.1387	0.0158	0.5429
3	1.0000	330	0.0500	1.6950	0.0335	0.2907

The SAS System

Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
Interim Monitoring Output

Look Information	Cumulative	Test	Efficacy			
No	Fraction	Sample Size	Statistic			
1	0.3323	110	1.7031	3.2055		
2*	0.9063	300	2.0000	1.7590		
Look	Cumulative	Effect Size	Standard	Repeated	95.00% CI	Repeated
No.	Sample Size		Error	Lower	Upper	p-value
1	110	3.0000	1.7615	-2.6466	Infinity	0.2462
2*	300	2.0000	1.0000	0.2410	Infinity	0.0302

Look No.	Cumulative Sample Size	INLP	CP	Predictive Power
1	110	326	0.9438	0.8229
2*	300	NA	NA	NA

*: At Look 2 the value of Test Statistic is >= the critical point for efficacy, H0 is rejected.
Conditional Power Vs Treatment Effect

Output from Proc EastMonitor (r) PROC (v1.0) for East 6.3 under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.

Final Inference

```

Final Outputs at Look : 2
Adj. p-value : 0.0231
Adj. Pt. Est. for Effect Size : 1.9977
Adj. 90.00% CI for Effect Size
Upper confidence bound : 3.6434
Lower confidence bound : 0.3506
Post-Hoc Power : NA

```

The upper boundary has been crossed. The adjusted p-value of 0.0231 is consistent with the rejection of the null hypothesis. Note that the output consists of the following parts. The first part displays the design information in detail. Including maximum sample size and expected sample sizes under H_0 and H_1 . The second part consists of stopping boundaries table with look by look information such as boundaries, boundary crossing probabilities, cumulative alpha spent etc. This is followed by the Interim Monitoring Output consisting of Information fraction, cumulative sample size, test statistic, effect size, standard error, repeated confidence intervals, repeated p-value etc for the look(s) taken so far. Since in this case, the efficacy boundary has been crossed, the output also displays the **Final Inference**. This is comprised of adjusted p-value, adjusted point estimate of the effect size, adjusted confidence intervals for effect size etc.

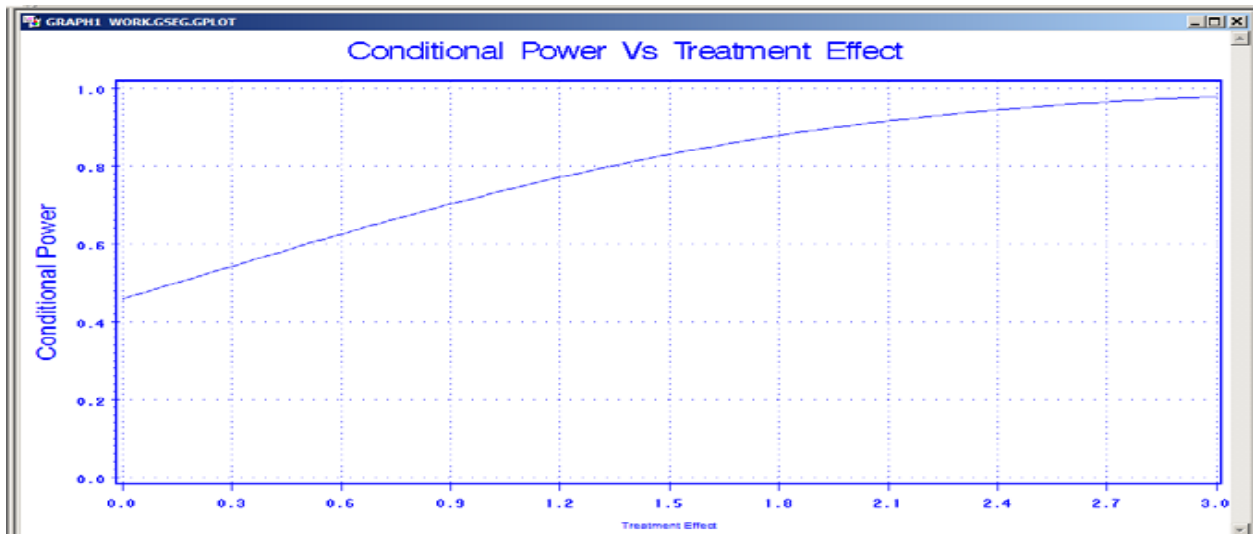
Charts

PROC EASTMONITOR produces plot datasets as output which can be used for further analysis in SAS.

Following are some illustrations of datasets generated by PROC EASTMONITOR and the corresponding plots drawn using SAS® graphics:

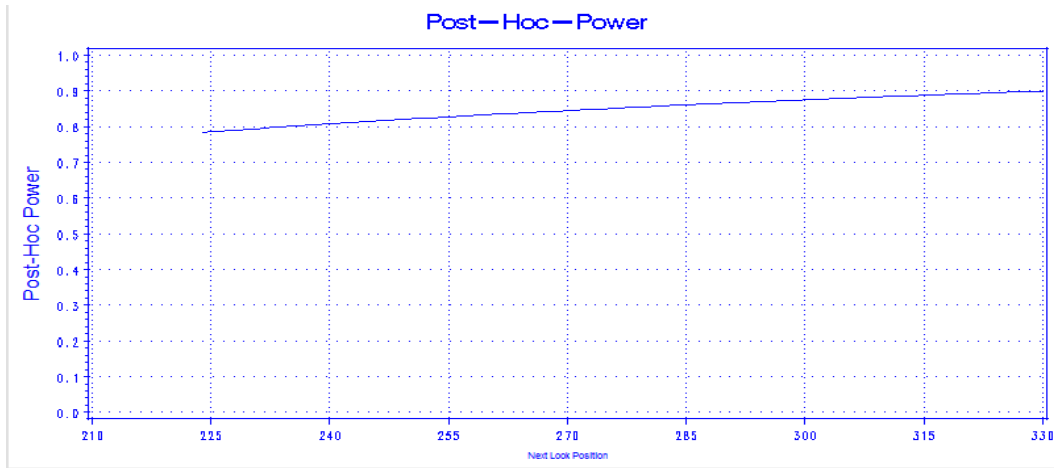
- Output dataset for Conditional Power chart

	DiffOfMeans	Conditional_Power
1	1E-7	0.4579910595
2	0.0612245878	0.4751611822
3	0.1224490755	0.4923775661
4	0.1836735633	0.5096081631
5	0.244898051	0.5268208456
6	0.3061225388	0.5439835862
7	0.3673470265	0.5610646362
8	0.4285715143	0.5780327018
9	0.489796002	0.594857116
10	0.5510204898	0.6115080046
11	0.6122449776	0.627956445
12	0.6734694653	0.6441746163
13	0.7346939531	0.6601359392
14	0.7959184408	0.6758152053
15	0.8571429286	0.6911886938



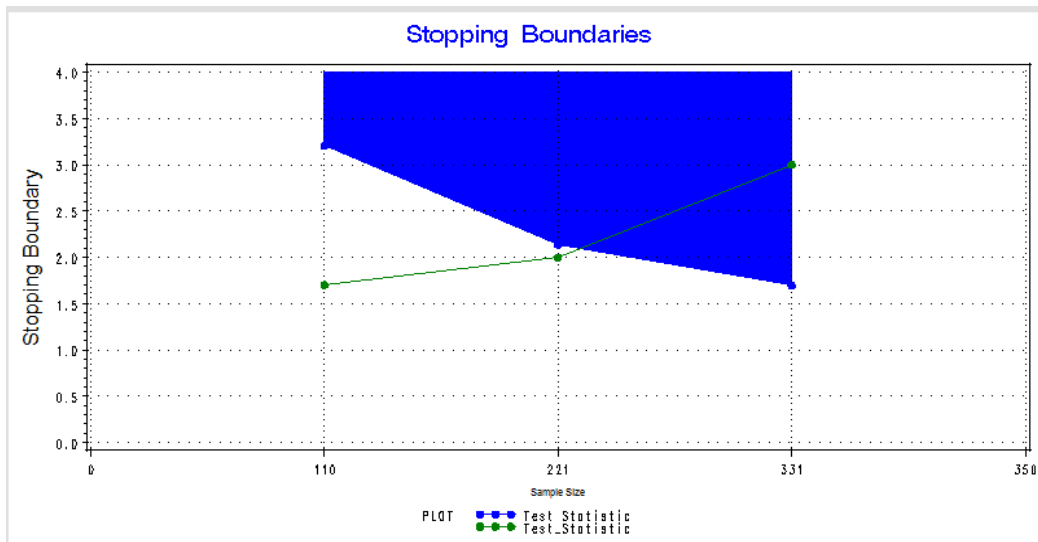
- Output dataset for Post-Hoc Power chart

	Next_Look_Position	Post_Hoc_Power
1	224	0.7837636321
2	226.24489796	0.7873015945
3	228.48979592	0.7907850084
4	230.73469388	0.7942100451
5	232.97959184	0.7975738882
6	235.2244898	0.8008754192
7	237.46938776	0.8041148333
8	239.71428571	0.807293116
9	241.95918367	0.8104118242
10	244.20408163	0.8134725606
11	246.44897959	0.8164771291
12	248.69387755	0.819427314
13	250.93877551	0.8223247137
14	253.18367347	0.8251711067
15	255.42857143	0.8279679976



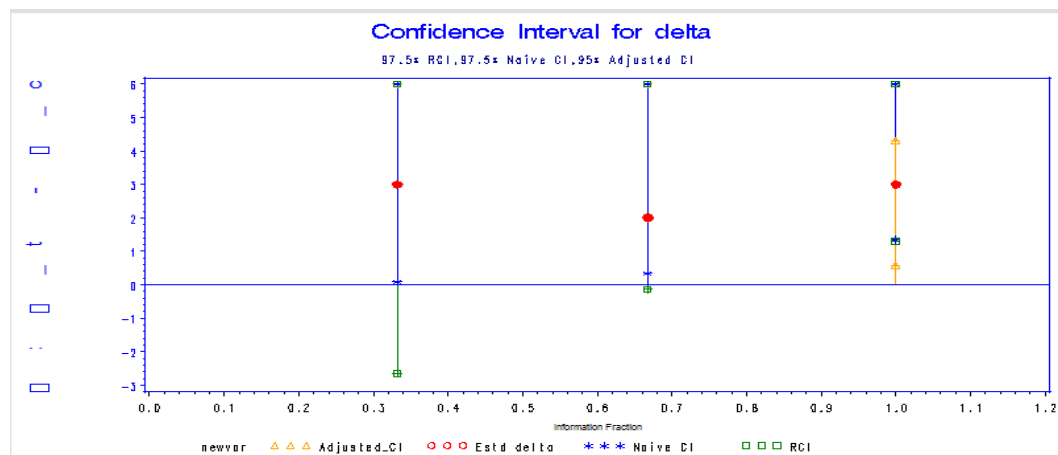
- Output dataset for Boundary chart

	Look_Number	Information_Fraction	Cumulative_Sample_Size	Efficacy	Test_Statistic	Look_Number_D	Cumulative_Sample_Size_Des	Efficacy_Des
1	1	0.332326284	110	3.20551172	1.7030533	1	110	3.20551172
2	2	0.667673716	221	2.138704542	2	2	221	2.1387045416
3	3	1	331	1.695042274	3	3	331	1.6950422745



- Output dataset for RCI chart

	Look_Number	Information_Fraction	EstD_DiffOfMeans	RCI_Lower	RCI_Upper	Naive_CI_Lower	Naive_CI_Upper	Adjusted_CI_Lower	Adjusted_CI_Upper	CI_For
1	1	0.332326284	3	-2.6466436	9999	0.102521212	9999			DiffOfMeans
2	2	0.667673716	2	-0.13870454	9999	0.355146372	9999			
3	3	1	3	1.304957726	9999	1.355146372	9999	0.582457075	4.314356217	



Note: Sample programs to draw these plots are provided with the application setup.

EXAMPLE-INTERIM MONITORING OF AN ADAPTIVE DESIGN

Trial Design-Consider a two-arm trial to determine if there is an efficacy gain for an experimental drug relative to the industry standard treatment for negative symptoms schizophrenia. The primary endpoint is the improvement from baseline to week 26 in the Negative Symptoms Assessment (NSA), a 16-item clinician-rated instrument for measuring the negative symptomatology of schizophrenia. Let μ_t denote the difference between the mean NSA at baseline and the mean NSA at week 26 for the treatment arm and let μ_c denote the corresponding difference of means for the control arm. It is expected, from limited data on related studies, that $\delta \geq 2$ and σ , the between-subject standard deviation, is believed to be about 7.5. To this end we use a 2-look design named, **NSA.csv** created in **East**[®] with 80% power to detect $\delta = 2$ with a one-sided level-0.025 test, and one interim analysis utilizing the γ (-24) spending function after data are available on 208 completers.

we will discuss the interim monitoring procedure taking the example of **NSA**. The input for adaptive interim monitoring differs from the usual interim monitoring. Patient accruals and corresponding test statistics are supposed to be entered incrementally for each look, rather than cumulatively for all looks taken thus far. The weighted statistic is obtained by combining these incremental test statistics using Pre-specified Weights.

Interim Analysis using Proc EastMonitor

Suppose the first look is taken as planned after enrolling 208 subjects. Suppose we observe estimated $\delta = 1.7$ and estimated $\sigma = 7.6$ thus leading to a standard error of $\text{sqrt}((4 * 7.6^2 / 208) = 1.0539$. The incremental statistic at the first look is thus $(1.7 / 1.0539) = 1.613$. Create the sas dataset with these quantities.

To do the interim analysis at the first look, first import the design **NSA.csv** in SAS[®] using following SAS commands.

```
/*Specify your library name and the path of Examples folder in the next
statement*/
libname input 'C:\Program Files\CytelProcForSAS9\procEM1v9\Examples';
PROC EASTMONITOR DESIGN = input.NSA ;
RUN;
```

Execute interim monitoring analysis using the following syntax of the Proc EastMonitor.

```
/*Specify your library name and the path of Examples folder in the next
statement*/
libname input 'C:\Program Files\CytelProcForSAS9\procEM1v9\Examples';
PROC EASTMONITOR DESIGN=input.NSA DATA=input.NSAlk1 method=CHW;
CONDPOWER OUT=NSACP1 ;
PHP OUT=NSAPH1;
ERRSPEND OUT=NSAERR1 ;
CI OUT=NSACI1;
BOUNDARY OUT=NSABDRY1;
```

PhUSE 2014

OUTPUT OUT=NSAIMOutput1;

You will see the following output containing incremental sample size, incremental statistics, cumulative sample size, pre-specified weights, repeated p-value etc. Notice that the efficacy boundary is not yet crossed.

The SAS System
Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
INTERIM MONITORING: DIFFERENCE OF MEANS
Design Input Parameters

Design ID : Des1
Design DataSet : <INPUT.NSA>
IM DataSet : <INPUT.NSALK1>

Test Parameters
Design Type : Superiority
No. of Looks : 2
Test Type : 1-Sided
Specified Alpha : 0.0250
Power : 0.8004

Model Parameters
Input Method : Difference of Means
Diff. in Mean : 2.0000
Std. Deviation : 7.5000
Test Statistic : Z
Allocation Ratio(nt/nc) : 1.0000

Boundary Parameters
Efficacy Boundary : Gm(-24.0000)

The SAS System
Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
Detailed Design: Two-Sample Test- Parallel Design - Difference of Means

	Control Arm	Treatment Arm	Total
Sample Size (n)			
Maximum:	221	221	442
Expected H1:	220.9488	220.9488	441.8975
Expected H0:	221.0000	221.0000	442.0000

Maximum Information for this design is 1.9644

The SAS System
Output from East (r) PROCs (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
Stopping Boundaries: Look by Look
Look Info Fract Sample Size Cumulative Boundaries Boundary Crossing Probability
No. (n/n_max) (n) Alpha Spent Efficacy (Incremental)
(Z) Under H0 Under H1
Efficacy Efficacy
1 0.4706 208 0.0000 5.2505 0.0000 0.0004
2 1 442 0.0250 1.9600 0.0250 0.8000

The SAS System
Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.

Interim Monitoring Output

Look No.	Incremental Sample Size	Incremental Statistic	Cumulative Sample Size	Prespecified Weights	Weighted Statistic	Effect Size	Standard Error
1	208	1.6131	208	0.4706	1.6131	1.7000	1.0539

Look Efficacy Repeated 97.50% CI Repeated

No.		Lower	Upper	p-value
1	5.2505	-3.8335	Infinity	1.0000

Since the nominal critical value for early stopping is 5.2505, the trial continues. We now need to decide on the sample size to use for the second and final look. Suppose we decide to enroll a total of 565 subjects. This implies that the incremental number to be entered at the second look is $565 - 208 = 357$ subjects. Suppose that, based only on these 357 incremental subjects, the estimate of delta is 1.5 and the estimate of sigma is 7.7. The standard error of estimate of δ is thus $\sqrt{4 * 7.7^2 / 357} = 0.8151$, leading to an incremental test statistic of 1.8404. These data constitute the Interim Monitoring data at the second look.

```
/*Specify your library name and the path of Examples folder in the next
statement*/
libname input 'C:\Program Files\CytelProcForSAS9\procEMlv9\Examples';
PROC EASTMONITOR DESIGN=input.NSA DATA=input.NSALK2 method=CHW;
CONDPOWER OUT=NSACP2 ;
PHP OUT=NSAPHP2;
ERRSPEND OUT=NSAERR2 ;
CI OUT=NSACI2;
BOUNDARY OUT=NSABDRY2;
OUTPUT OUT=NSAIMOutput2;
run;
```

You will see the following output-

```

                                The SAS System
Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
INTERIM MONITORING: DIFFERENCE OF MEANS
Design Input Parameters
-----
Design ID : Des1
Design DataSet : <INPUT.NSA>
IM DataSet : <INPUT.NSALK1>
-----
Test Parameters
Design Type : Superiority
No. of Looks : 2
Test Type : 1-Sided
Specified Alpha : 0.0250
Power : 0.8004
-----
Model Parameters
Input Method : Difference of Means
Diff. in Mean : 2.0000
Std. Deviation : 7.5000
Test Statistic : Z
Allocation Ratio(nt/nc) : 1.0000
-----
Boundary Parameters
Efficacy Boundary : Gm(-24.0000)
```

```

                                The SAS System
Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1
Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.
Detailed Design: Two-Sample Test- Parallel Design - Difference of Means
```

	Control Arm	Treatment Arm	Total
Sample Size (n)			
Maximum:	221	221	442
Expected H1:	220.9488	220.9488	441.8975
Expected H0:	221.0000	221.0000	442.0000

Maximum Information for this design is 1.9644

```

                                The SAS System
Output from East (r) PROCs (v1.0) under _SAS9_1
```

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Stopping Boundaries: Look by Look

Look No.	Fract (n/n_max)	Sample Size (n)	Cumulative Alpha Spent	Boundary Crossing Efficacy (Z)	Probability (Incremental) Under H0 Efficacy	Under H1 Efficacy
1	0.4706	208	0.0000	5.2505	0.0000	0.0004
2	1	442	0.025	1.96	0.025	0.8

The SAS System

Output from East (r) PROCs (v1.0) for Proc EastMonitor (v1.0) under _SAS9_1

Copyright (c) 1987-2014 Cytel Inc., Cambridge, MA, USA.

Interim Monitoring Output

Look No.	Incremental Sample Size	Incremental Statistic	Cumulative Sample Size	Prespecified Weights	Weighted Statistic	Effect Size	Standard Error
1	208	1.6131	208	0.4706	1.6131	1.7000	1.0539
2*	357	1.8403	565	0.5294	2.4455	1.5000	0.8151

Look No.	Efficacy	Repeated Lower	97.50% CI Upper	Repeated p-value
1	5.2505	-3.8335	Infinity	1.0000
2*	1.9600	0.3146	Infinity	0.0072

*: At Look 2 Since the value of weighted statistic is $\geq$ the critical point for efficacy, H0 is rejected.

Since the weighted statistic exceeds the nominal critical value, the null hypothesis is rejected. The confidence interval for delta is (0.3146, Infinity) and the p-value is 0.0072. These estimates are appropriately adjusted to preserve their validity in the face of adaptive sample size changes.

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