MWSUG 2016 - Paper PH06

Frequentist and Bayesian Interim Analysis in Clinical Trials: Group Sequential Testing and Posterior Predictive Probability Monitoring Using SAS

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ABSTRACT

In a fixed-sample clinical trial, data collected from all individuals are analyzed at the end of the trial. In contrast, an interim analysis conducts data analysis before the completion of data collection. An interim analysis in clinical trials provides advantages over a fixed-sample clinical trial. An interim analysis can effectively terminate a trial early for efficacy, futility or safety issues incurred. Not only does terminating a trial early cut cost, save valuable time and resources in drug development, prevent exposure of unsafe toxicity to the participants, but it also expedites the process of delivering an effective drug to the patients who need it most.

Two mainstream designs in interim analysis are group sequential designs and posterior predictive probability designs. This paper reviews basic concepts of group sequential testing and demonstrates its usage in PROC SEQDESIGN and PROC SEQTEST procedures. The paper also reviews basic concepts of posterior predictive probability and demonstrates its usage in one SAS Macro developed by the author. Another SAS Macro performs calibration of tuning parameters for achieving targeted operating characteristics (e.g. type I error below 5% and power above 80%) through simulations; it also compares the posterior predictive probability with the tuned parameter so that the trial can be stopped for efficacy or futility.

INTRODUCTION

Phase II/III trials focus on the evaluation of the compound's therapeutic effects and how well the compound performs at the recommended dose determined in Phase I trials. The goal of a typical Phase II oncological trial is to quickly screen compounds primarily based on their short-term efficacious effects. Interim monitoring is an important component of most Phase II/III clinical trials with the goal to stop a trial early for efficacy or for futility. Repeated hypothesis tests at a fixed level on accumulating data, however, inflate overall Type I error rate. To control Type I error, frequentist designs typically employ group sequential methods with alpha- or beta-spending functions, such as the Pocock and the O'Brien-Fleming (OBF) method, among others. The inflexible study designs, however, can be difficult to follow exactly because the interim data has to be evaluated at pre-specified fixed time point or fixed number of patients. In contrast, Bayesian methods, such as the Predictive Probability (PP) design, allow for continuous monitoring schedule flexibly with any number of stages and cohort sizes, which is more suitable in many clinical settings.

GROUP SEQUENTIAL DESIGNS

EXAMPLE 1: CONSTRUCTING A ONE-SIDED O'BRIEN-FLEMING DESIGN

Suppose that a clinical trial is conducted to test the short-term efficacy effects of a new anticancer drug that inhibits the PD-1 (programmed death) pathway, activating the immune system to attack tumors. The primary focus is anticancer activity characterized by patient status. Patient status may be classified as

complete response, partial response, progressive disease or stable disease. The trial is a single-arm or non-randomized trial, in which everyone enrolled in the trial receives the experiment drug. The primary endpoint is a response if patient status is classified as complete response or partial response; it is a non-response if patient status is classified as progressive disease or stable disease.

Suppose that each patient response follows a Bernoulli distribution with probability of a response p_t. Here we want to test if the probability of a patient response to the drug is greater than p_0=0.2. Then the null hypothesis of no effect for the new drug is H_0: θ=0, where θ=p_t-p_0. For this example, a data set named raw_counts consisting of Bernoulli trials under the alternative H_1: p_t = 0.3 are generated.

For a fixed-sample single-arm design with sample size n, the maximum likelihood estimator (MLE) is for θ is $\hat{\theta} = \hat{p}_t$-p_0, where $\hat{p}_t$ and p_0 are the estimated probability of response to the drug and the probability of response under the null hypothesis of no effect, respectively. Thus, under the null hypothesis H_0: θ=0, the standardized test statistics Z converges to a standard normal distribution N (0, 1)

$$Z = \frac{\hat{\theta}}{\sqrt{\frac{p_0(1-p_0)}{n}}} \rightarrow N(0, 1). \qquad \textbf{Equation 1}$$

The Z statistic can be used to test the null hypothesis H_0 and the Z statistic has an approximate standard normal distribution with large n.

For a one-sided test with Type I error level α = 0.05, the critical value for Z is 1.64, the 95%th quantile of a standard normal distribution. At the end of the study, the null hypothesis H_0: θ=0 is rejected for efficacy if Z $\geq$ 1.64. Otherwise, the null hypothesis is not rejected.

In an interim analysis, a critical value for Z is determined for each stage prior to the trial. The following statements invoke the SEQDEIGNS procedure and call for a four-stage O'Brien-Fleming design:

```
ods graphics on;
proc seqdesign altref=0.10
               boundaryscale=stdz
                     plots=boundary(hscale=samplesize)
               ;
   OneSidedOBrienFleming: design method=obf
                          nstages=4 stop=reject
                          alt=upper
                          alpha = 0.05 beta=0.20
                          ;
   samplesize model=onesamplefreq(nullprop=0.2);
ods output Boundary=Bnd_Prop;
run;
ods graphics off;
```

The ALTREF=0.10 option specifies that the magnitude of difference between alternative and null is 0.10. The BOUNDARYSCALE=STDZ specifies standardized Z scale for values in the boundary information table and the boundary plot. With the ODS GRAPHICS ON statement, the PLOT=BOUNDARY option displays boundary plot shown in **Figure 1**. With the HSCALE=SAMPLESIZE option, the horizontal axis of the boundary plot is displayed in scale of sample size.

The label "OneSidedBrienFleming" make explicit about the design in the output. The DESIGN METHOD=OBF option specifies that the O'Brien-Fleming method is used to compute the rejection boundary for the design. The NSTAGES=4 option specifies the total number of stages in the design. The

STOP=REJECT option specifies early stopping in the interim analysis only when rejecting the null hypothesis. In other words, at each interim stage, the trial is stopped to reject the null hypothesis or otherwise is continued to the next stage. The ALT=UPPER option specifies a one-sided alternative hypothesis. The upper α boundary consists of upper rejection critical values. The ALPHA=0.05 option specifies the overall Type I error probability for a trial. The BETA=0.20 options specifies the Type II error probability β = 0.20 which corresponds to a power of 0.80 at the alternative p_t = 0.3.

The MODEL=ONESAMPLEFREQ option computes required sample sizes for a one-sample test for proportion difference at each interim stage. The ODS OUTPUT statement with the BOUNDARY=BND_PROP option creates an output data set named BND_PROP which contains the resulting boundary information under the design settings. The BND_PROP data set is required for conducting interim statistical testing in the SEQTEST procedure.

By default, the SEQDESIGN procedure computes boundary values with equally spaced information (referring to Fisher's Information) levels for all stages. In other words, same information increment equally between two successive interim stages. The "Design Information", "Method Information" and "Boundary Information" tables are displayed by default.

Importantly, the "Boundary Information" table in **Figure 1**displays the upper boundary values for rejection at each stage. The table also displays the information level, including the proportion, actual level and corresponding required sample size at each stage.

Figure 1 Boundary Information

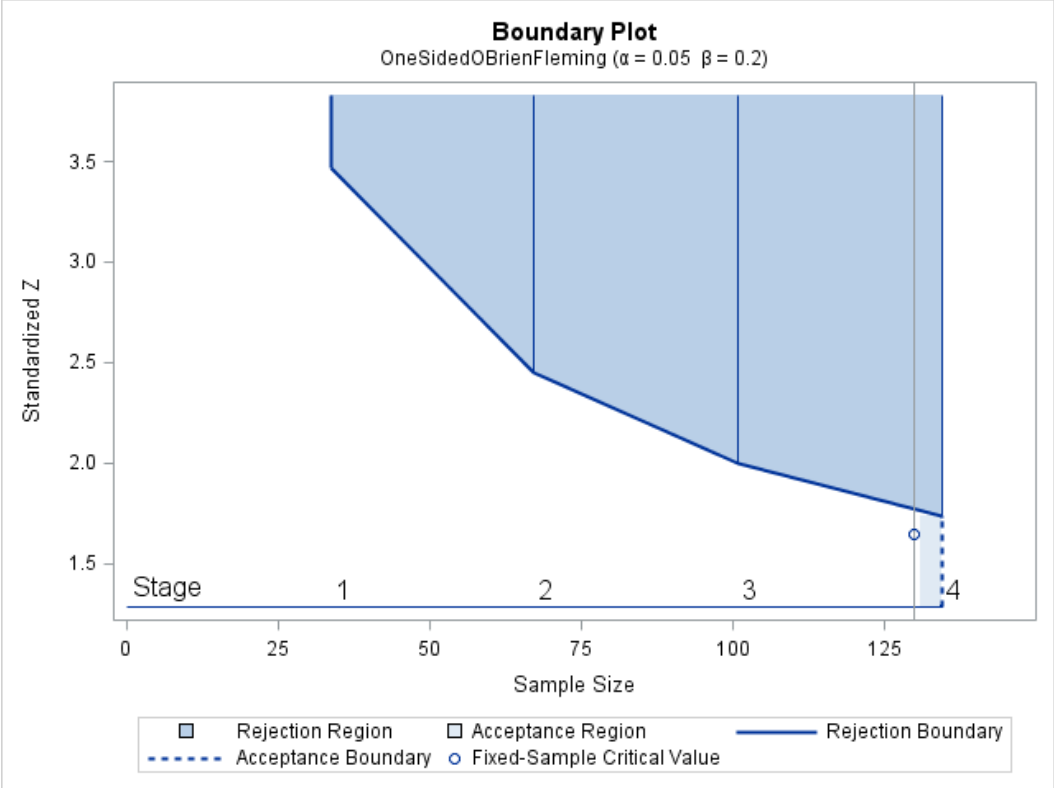
Boundary Information (Standardized Z Scale)
Null Reference = 0

Stage	Information Level			Alternative Reference	Boundary Values
	Proportion	Actual	N	Upper	Upper Alpha
1	0.2500	159.9232	33.58387	1.26461	3.46620
2	0.5000	319.8464	67.16774	1.78842	2.45097
3	0.7500	479.7695	100.7516	2.19036	2.00121
4	1.0000	639.6927	134.3355	2.52921	1.73310

With BOUNDARYSCALE=STDZ, the table also displays upper boundary values in standardized Z statistic scale. In this example, a standardized Z statistic is computed according to **Equation 1** and a positive Z statistic indicates an efficacious effect. Consequently, at each interim stage, if the standardized Z statistic is less than or equal to the corresponding upper α boundary value, the hypothesis H_0 is not rejected and the trial continues to the next stage. Conversely, if the Z statistic is greater than the corresponding upper α boundary value, the hypothesis H_0 is rejected for efficacy and the trial would be terminated for efficacy. At the final stage, if the Z statistic is greater than 1.73 the hypothesis H_0 is rejected for efficacy. Otherwise, the null hypothesis H_0 is not rejected for efficacy in the trial.

With ODS GRAPHICS ON statement and the PLOTS=BOUNDARY(HSCALE=SAMPLESIZE) option , a boundary plot is displayed in **Plot 2**. The plot is a visual summarization of the values in the "Boundary Information" table. The horizontal axis indicates the sample sizes required for the stages, and the stages are displayed by vertical bar lines with corresponding stage number.

Plot 2 Boundary Plot



In the plot, if a statistic falls into the rejection region (blue shaded area), the trial stops and the null hypothesis H_0 is rejected. Otherwise, the null hypothesis H_0 is not rejected. The circular symbol indicates the critical Z value of 1.64 for a one-sided fixed-sample design and the corresponding vertical line indicates the required sample size for the fixed-sample design. Noticeably, the boundary value 1.73 at final stage is numerically similar to the fixed-sample critical value 1.67.

Figure 1displays the required sample sizes at each stage. In practice, the actual required sample sizes are obtained by rounding up the theoretically required sample sized display in the table, which slightly increases the resulting information level.

EXAMPLE 2: FERFORMING GROUP SEQUENTIAL TESTS

This example is a continuation of Example 1. Here, a standardized Z statistic is computed at each stage according to **Equation 1**. In the SEQTEST procedure, interim analyses are conducted by comparing the observed Z statistics against corresponding boundary values obtained with the SEQDESIGN procedure. Note that in a typical trial, the actual observed information levels do not match the information levels obtained with the SEQDESIGN procedure due to rounding-up or process of data collection deviating from the design plan. If the observed information levels for the observed Z statistics do not match the

information levels obtained with SEQDESIGN procedure, the SEQTEST procedure modifies the original boundary values to adjust for the observed information levels.

Suppose that 34 required individuals are available at stage 1. **Figure 4** lists the first five observations in the data set raw_counts, a description of which can be found in previous session of this paper.

Figure 4 Partial Data at Stage 1

Obs	Resp
1	1
2	0
3	0
4	0
5	1

The variable Resp is an indicator variable with value 1 for individual positively responding to the drug and value 0 for individuals not responding to the drug.

The following statements use the MEANS procedure to compute the mean response ($\hat{p}_t$) at stage 1:

```
proc means data=raw_counts (obs = 34);
   var Resp;
   ods output Summary=Data_Prop1;
run;
```

The following statements create and display the data set for the standardized test statistic, $Z = \frac{\hat{\theta}}{\sqrt{\frac{p_0(1-p_0)}{n}}}$. The resulting table is shown in **Figure 5**.

```
data Data_Prop1;
   set Data_Prop1;
   _Scale_='stdz';
   _Stage_= 1;
   NObs= Resp_N;
   PDiff= (Resp_Mean - 0.2)/sqrt(0.16/135);
   keep _Scale_ _Stage_ NObs PDiff;
run;
proc print data=Data_Prop1;
   title 'Statistics Computed at Stage 1';
run;
```

Figure 5 Stage 1 Test Statistics

Obs	_Scale_	_Stage_	NObs	STDZ
1	stdz	1	34	0.51450

The following statements invoke the SEQTEST procedure to test for early stopping at stage 1:

```
ods graphics on;
proc seqtest Boundary=Bnd_Prop
             Data(Testvar=STDZ)=accum_props
             infoadj=prop
             boundaryscale=stdz
                   plots=test(hscale=samplesize)
             ;
ods output Test=Test_Prop1;
run;
ods graphics off;
```

The BOUNDARY= option specifies the input data set that provides the boundary information for the interim analysis at stage 1, which was generated by the SEQDESIGN procedure. The DATA=ACCUM_PROPS options specifies the input data set accum_props that contains the test statistic and its associated sample size at stage 1. The TESTVAR=STDZ option identifies the test variable STDZ in the data set accum_props. If the observed information level at stage 1 does not match the information level provided in the Bnd_Prop data set, the INFOADJ=PROP option proportionally adjusts the information levels at future interim stages from the levels provided in the Bnd_Prop data set. The BOUNDARYSCALE=stdz option specifies the output boundary in standardized Z scale.

The ODS OUTPUT statement with the TEST=TEST_PROP1 creates an output data set named TEST_PROP1 which contains the modified boundary information for group sequential at stage 1 and future stages.

The "Test Information" table in **Figure 6** displays boundary values by using the default standardized Z scale.

Figure 6 Test Information

Test Information (Standardized Z Scale)
Null Reference = 0

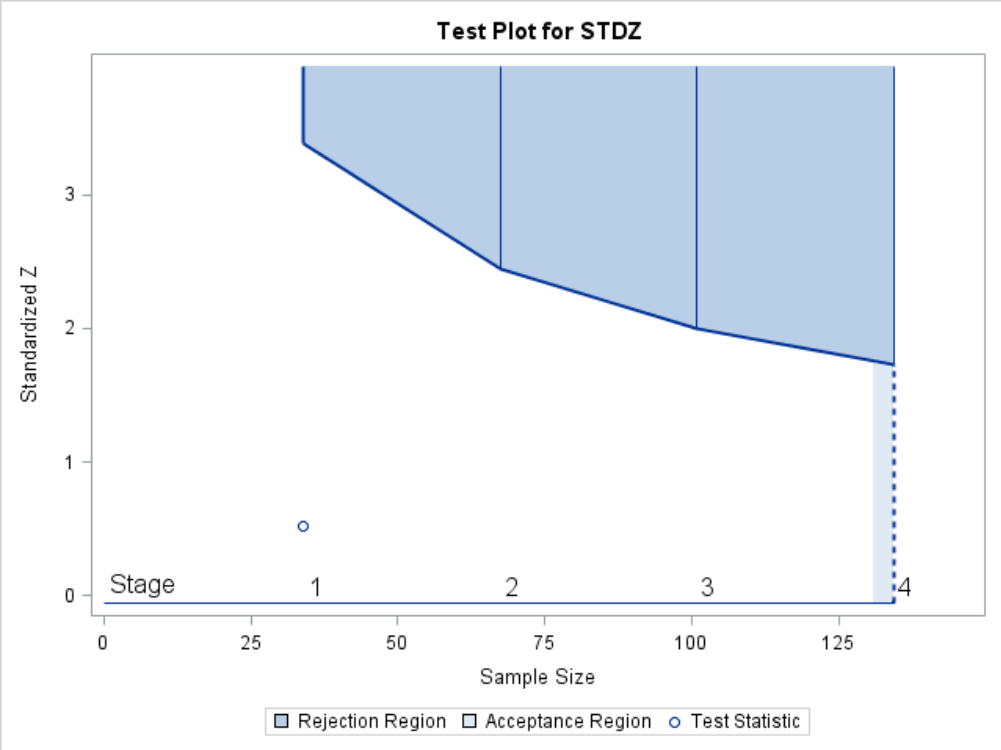
Stage	Information Level			Alternative Reference	Boundary Values	Test STDZ	
	Proportion	Actual	N	Upper	Upper Alpha	Estimate	Action
1	0.2531	161.9048	34	1.27242	3.38938	0.51450	Continue
2	0.5021	321.1674	67.44516	1.79211	2.44561	.	
3	0.7510	480.4301	100.8903	2.19187	2.00054	.	
4	1.0000	639.6927	134.3355	2.52921	1.73369	.	

At stage1, the standardized Z statistic 0.51 lies under the upper boundary value, and the procedure calls for continuing to stage 2. Since the observed actual information level at stage 1, I_1= 161.9, is only slightly greater the designed target information level 159.9, the trial can continue to the next stage without an

adjustment of the sample size according the study plan. Note that if an observed information levels substantially from the originally designed target level, then the required sample size should be adjusted for the later stages.

With ODS GRAPHICS ON statement invoked, a test plot with rejection region is displayed in **Figure 7**. This plot is a visual summarization of the boundary values in the "Test Information" table. The stages are indicates by vertical lines with corresponding stage numbers. The horizontal axis indicates the sample size for stages. The Z test statistic lies below the upper rejection region and the trial continue to the next stage.

Figure 7 Sequential Test Plot



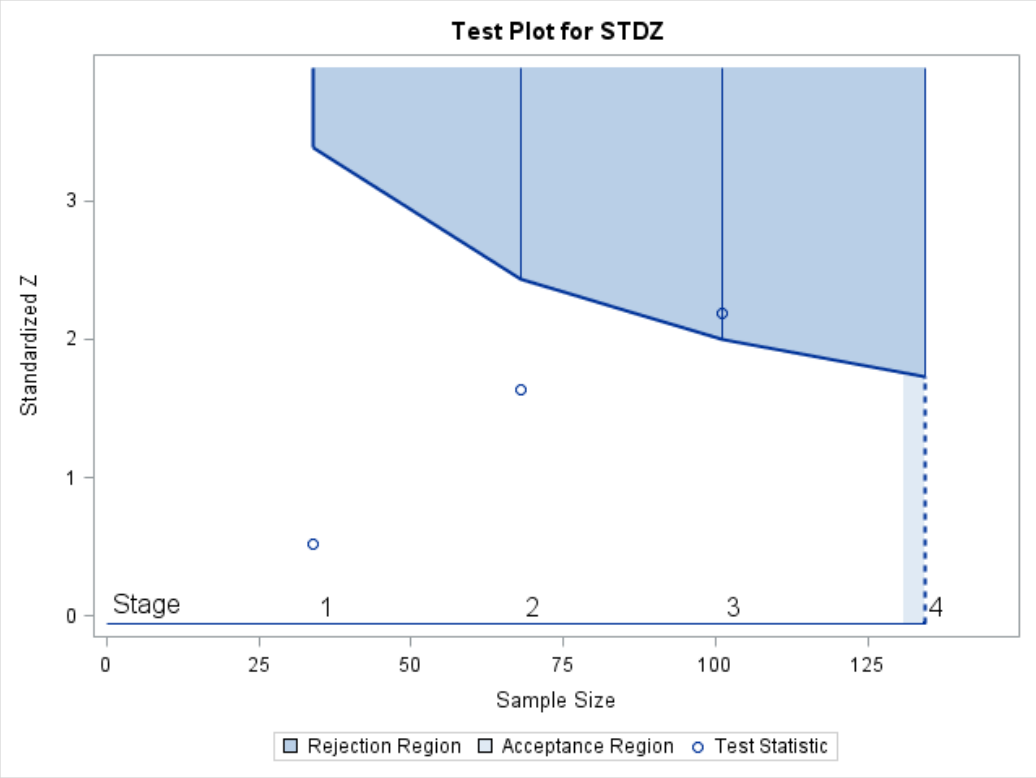
The interim analysis continues until the null hypothesis H_0 is rejected or the final stage is reached. **Figure 8** and **Figure 9** display the interim analysis results in stage 1, stage 2 and stage 3. At stage 2, the standardized Z statistic 1.64 lies under the upper boundary value and the procedure calls for continuing to stage 3. At stage 3, the standardized Z statistic 2.19 lies above the upper boundary value and the null hypothesis H_0 is rejected. Subsequently, the trial terminates early for efficacy at stage 3. The test demonstrates statistically significantly beneficial effect for the new drug.

Figure 8 Group Sequential Test Information

Test Information (Standardized Z Scale) **Null Reference = 0**

Stage				Alternative	Boundary Values	Test	
	Information Level			Reference	Upper	STDZ	
	Proportion	Actual	N	Upper	Alpha	Estimate	Action
1	0.2531	161.9048	34	1.27242	3.38938	0.51450	Continue
2	0.5062	323.8095	68	1.79947	2.43105	1.63712	Continue
3	0.7518	480.9524	101	2.19306	2.00109	2.18908	Reject Null
4	1.0000	639.6927	134.3355	2.52921	1.73427	.	

Figure 9 Sequential Test Plot



The “Parameter Estimates” table in **Figure 10** displays the stopping stage, parameter estimate, p-value under the null hypothesis H_0, unbiased median estimate, and confidence limits, The ORDER=STAGEWISE option specifies the stage-wise ordering of the sample space used to compute the p-value, unbiased median estimate, and confidence limits. As expected, the p-value 0.021 is significant at the one-sided α level 0.05, and the confidence interval does not contain the value zero.

Figure 10 Parameter Estimates

Parameter Estimates Stagewise Ordering					
Parameter	**Stopping Stage**	**MLE**	**p-Value for H0:Parm=0**	**Median Estimate**	**Lower 95% CL**
STDZ	3	0.099818	0.0179	0.097770	0.02141

BAYESIAN POSTERIOR PREDICTIVE PROBABILITY DESIGNS

EXAMPLE 3: PERFORMING POERSTERIOR PREDICTIVE INTERIM MONITORING

Consider again the single-arm Phase II trial in Example 1. Let p_E denote the probability of response for the experimental compound. Let *n* be the number of patients who have entered the trials thus far and *N* be pre-specified maximum sample size for the entire trial. Let *Y* denote the number of responses among the *n* treated patients, then Y ~ Binomial(n, p_E). Suppose we take a non-informative beta prior distribution for the unknown parameterp_E, then p_E~Beta(1, 1). At the interim analysis, if we observe Y = y responses among the n treated patients, the posterior distribution of p_E is

$$p_E|y \sim \text{Beta}(1+ y, 1 + n - y).$$

Thus the number of patients remained to be recruited in the future is N – n. Let X denote the number of patients who would respond and the probability of X = x given the current data y follows a beta-binomial distribution,

$$X|y \sim \text{Beta-Binomial}(N - n, 1+ y, 1 + n - y),$$

with the probability mass function of

$$P(x|y) = \int_0^1 \frac{(N-n)!}{(N-n-x)!x!} p^x (1-p)^{N-n-x} \frac{p^y(1-p)^{n-y}}{B(1+y,1+n-y)} dp$$

$$= \frac{(N-n)!}{(N-n-x)!x!} \frac{B(1+y+x,1+N-y-x)}{B(1+y,1+n-y)},$$

where B(.) is the standard beta function. By the end of the trial, suppose we observe X = x, then the posterior distribution of the response probability given both y and x would be

$$p_E|x,y \sim \text{Beta}(1+ y + x, 1 + n - y - x).$$

Given the current data y, if we observe the future data X = x at the end of the trial, we would claim the experiment is promising if,

$$\Pr(p_E > p_s + \delta \mid x, y) > \theta_T,$$

where p_s is the response probability from one standard treatment, δ is a threshold and θ_T is the pre-specified target probability, e.g., $\theta_T \in [0.85, 0.95]$. δ and θ_T are tuning parameters that needs to be

calibrated to achieve targeted operating characteristics. Given that X is not observed, predictive probability (PP) is defined by taking an average over all possible outcomes in the future,

$$\text{PP} = \sum_{x=0}^{N-n} P(x|y) I\{\Pr(p_E > p_s \mid \text{x}, \text{y}) > \theta_T\}.$$

Let θ_U and θ_L denote the cutoff probability for decision making, which need to be calibrated through simulations to achieve targeted operating characteristics. Under predictive probability monitoring proposed by Lee and Liu (2008), the experiment proceeds as follows:

- If PP > θ_U, stop the trial and claim experimental compound is promising.
- If PP < θ_L, stop the trial and claim experimental compound is not promising.
- Otherwise, continue the trial until all planned patients are exhausted.

The interim procedure stated above is fully implemented in Macro %***PredProb***. At each interim stage, %***PredProb*** uses observed data specified in the Macro arguments to compute predictive probability and determines if the trial should stop at current stage or continue to the next stage. Note that at the final stage the null hypothesis is either rejected or not reject. **Figure 11** displays the results by invoking the Macro %***PredProb***:

```
%PredProb(maxN=40, cohort_n=30, alpha=1, beta=1, obs_y=11, targ_prob=0.9).
```

Figure 11 %***PredProb*** outputs

Posterior Predictive Probability Monitoring in a Single-arm Phase II Trial

i	cond_prob	post_prob	indicator	pp
0	0.0178664	0.897842	0	0

i	cond_prob	post_prob	indicator	pp
1	0.0739299	0.9479057	1	0.0739299

i	cond_prob	post_prob	indicator	pp
2	0.1544607	0.9758258	1	0.2283907

i	cond_prob	post_prob	indicator	pp
3	0.2135754	0.9897858	1	0.441966

i	cond_prob	post_prob	indicator	pp
4	0.215629	0.9960679	1	0.657595

i	cond_prob	post_prob	indicator	pp
5	0.165603	0.9986199	1	0.823198

i	cond_prob	post_prob	indicator	pp
6	0.0977518	0.9995582	1	0.9209498

i	cond_prob	post_prob	indicator	pp
7	0.0437151	0.999871	1	0.9646649

i	cond_prob	post_prob	indicator	pp
8	0.0141577	0.9999656	1	0.9788226

i	cond_prob	post_prob	indicator	pp
9	0.0029963	0.9999916	1	0.981819

i	cond_prob	post_prob	indicator	pp
10	0.0003146	0.9999981	1	0.9821336

Stop for Efficacy

The maxN=40 option specifies total sample size. The cohort_n=30 option specifies number of observed individuals out of the total sample size. The alpha=1 and beta=1 option specifies that a non-informative beta prior distribution is used for p_E. The obs_y option specifies the number of positive responses in the observed individuals. The targ_prob=0.9 option specifies a tuning parameter that usually takes its value from 0.8 to 1. Given the data, %***PredProb*** computes and outputs the predictive probability 0.98. Since the predictive probability is greater than the specified threshold 0.9, %***PredProb*** indicates that the trial can be stopped for efficacy.

EXAMPLE 4: CALIBRATING TUNING PARAMETERS TO ACHIEVE TARGETED TYPE I ERROR RATE AND POWER

The design needs to calibrate four parameters $(\delta, \theta_T, \theta_L, \theta_U)$ to ensure the trial achieve desired frequentist properties. That is to ensure the type I error probability rate is below 5% and achieve a power above 80%. A two-stage procedure is developed to first calibrate the main design parameters (δ, θ_T) and then the early termination parameters (θ_L, θ_U). In stage 1, a gird of values of (δ, θ_T) are explored while fixing θ_L=0 and θ_U=1, such that the trial would not terminate early. In this example, we consider the null hypothesis, H_0: p_S = 0.2 and the alternative hypothesis H_a: p_E=0.3. Noninformative beta prior is specified for p_E. The total sample size is N=160, with the first 40 patients in stage 1 and an increment of 40 patients in each subsequent stage. For each configuration, 10000 simulated trials are recorded to compute the percentages of trials rejecting H_0. The procedure is implemented in Macro %***PP_tuning***. **Table 12-15** display result obtained by invoking %***PP_tuning***.

Table 12 displays the cases under the null hypothesis H_0. In **Table 13**, the color-shaded type I errors are 5% or less.

Table 12 Type I Error Rates in Stage 1 Parameter Calibration

$\delta \backslash \theta_T$	0.7	0.75	0.8	**0.85**	0.9
0.00	0.3095	0.2434	0.2462	0.182	0.1018
0.01	0.2404	0.1893	0.1413	0.1009	0.0676
0.02	0.1378	0.1038	0.0729	**0.0467**	0.0333
0.03	0.0681	0.0524	0.0511	0.0249	0.0153
0.04	0.0501	0.0297	0.0214	0.0136	0.004
0.05	0.022	0.0137	0.0103	0.0049	0.0025
0.06	0.0083	0.0051	0.0037	0.0016	0.0009
0.07	0.0051	0.0029	0.0018	0.001	0.0003
0.08	0.0017	0.0005	0.0004	0.0001	0.0001
0.09	0.0003	0.0001	0.0001	0	0.0001

Table 13 displays the cases under the alternative hypothesis H_a. The color-shaded powers are 80% or higher.

Table 13 Powers in Stage 1 Parameter Calibration

$\delta \backslash \theta_T$	0.7	0.75	0.8	**0.85**	0.9
0.00	0.9932	0.985	0.9861	0.9798	0.9534
0.01	0.986	0.9797	0.9638	0.953	0.9335
0.02	0.9679	0.9544	0.9322	**0.9063**	0.8693
0.03	0.9322	0.9029	0.9014	0.8266	0.7742
0.04	0.9024	0.8729	0.8276	0.7702	0.6629
0.05	0.8249	0.7805	0.7281	0.6593	0.603
0.06	0.7279	0.6578	0.5928	0.5259	0.4553
0.07	0.6634	0.5908	0.5306	0.4657	0.3342
0.08	0.532	0.4591	0.3935	0.3233	0.2656
0.09	0.387	0.331	0.2711	0.2161	0.1706

The red- and yellow-shaded areas meet both the type I error and power requirement, from which the red-shaded pair, δ=0.02 and θ_T=0.85, are chosen.

In stage 2 of parameter calibration, a similar approach is used to determine the early termination parameters (θ_L, θ_U) while fixing δ=0.02 and θ_T=0.85.

Table 14 displays the cases under the null hypothesis H_0. In **Table 15**, the color-shaded type I errors are 5% or less.

Table 14 Type I Error Rates in Stage 2 Parameter Calibration

$\theta_U \backslash \theta_L$	**0**	**0.05**	**0.1**	**0.15**	**0.2**
0.95	0.0643	0.0609	0.0573	0.0591	0.0562
0.96	0.0547	0.0548	0.0556	0.0512	0.046
0.97	0.0539	0.0552	0.053	0.0445	0.0447
0.98	0.0574	0.0535	0.0493	0.0467	0.047
0.99	0.0525	0.0489	0.0446	0.0426	0.042
1.00	0.0471	0.0467	0.043	0.0397	0.0401

Table 15 displays the cases under the alternative hypothesis H_a. The color-shaded powers are 80% or higher.

Table 15 Powers in Stage 1 Parameter Calibration

$\theta_U \backslash \theta_L$	**0**	**0.05**	**0.1**	**0.15**	**0.2**
0.95	0.9136	0.8948	0.883	0.8605	0.8428
0.96	0.9056	0.8877	0.8788	0.8603	0.8502
0.97	0.9018	0.8963	0.8771	0.8462	0.8492
0.98	0.9062	0.8918	0.8781	0.8565	0.8495
0.99	0.9042	0.8872	0.8773	0.855	0.8507
1.00	0.8988	0.8813	0.8795	0.8526	0.8526

The red- and yellow-shaded areas meet both the type I error and power requirement, from which the red-shaded pair, θ_L=0.1 and θ_U=0.98, are chosen.

CONCLUSIONS

This paper reviews basic concepts of group sequential analysis and introduces the SEQDESIGN and SEQTEST procedures. Real examples are provided to demonstrate their usage in an interim analysis. This paper also reviews basic concepts of posterior predictive interim monitoring. The procedure is implemented in two author-developed SAS Macros %***PredProb*** and %***PP_tuning***. Real examples are provided to demonstrate their usages in an interim analysis. Please feel free to ask the author for the most up-to-date version of Macros %***PredProb*** and %***PP_tuning***.

ACKNOWLEDGMENT

The author is grateful to Cindy Lee and MWSUG committee for their support.

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