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Posch-Bauer Seamless Test with SAS

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ABSTRACT
Use of adaptive designs is currently increasing exponentially in clinical development programs. An adaptive design incorporates the possibility of pre-specified modifications at an interim analysis while the clinical trial is ongoing. A seamless phase II/III design usually consists of two parts. In the first part, several dose/schedule levels of experimental and control arms are tested. Then, after selection of the best dose/schedule for the experimental arm following protocol guidelines, a second part tests the selected dose/schedule for the experimental arm versus the control arm. This design implies statistical methods required to control the pre-specified type I error. Herein we present a SAS© macro to calculate combined p-values according to the closed testing procedure proposed by Posch and Bauer (Statistics in Medicine, 2005).

KEYWORDS
Adaptive design; Seamless; Multiplicity; Type I error.

INTRODUCTION

In recent years, adaptive designs have become a common tool in clinical development programs mainly because they have some inherent advantages with respect to standard clinical designs. Some examples are the possibility of increasing the sample size if results are encouraging but without enough statistical power, or the option to choose between different dose/schedules to test then the selected one *versus* a control arm (i.e., “seamless designs”).

We focus here on seamless designs. A seamless design is usually referred as a phase II/III clinical trial that consists of two parts: a first part (phase II design) where several dose/schedule levels of experimental and control arm are investigated, and a second part (phase III design) where the experimental arm and the control arm are properly compared. The main advantage of these designs is that phase II information can be joined with phase III one to obtain a more robust and powerful conclusion from the comparison. Other remarkable advantage is the avoiding of a long time gap between phase II and III processes in the clinical development program.

A seamless design involves statistical methods to control the pre-specified type I error. Then, it is highly recommendable to clearly pre-specify all main decision rules in the statistical section of the study protocol. Furthermore, a very detailed summary process has to be present in the statistical analysis plan of the study.

Under these considerations, this paper has the aim of helping programmers/statisticians to calculate combined p-values according to the closed testing procedure proposed by Posch and Bauer (*Statistics in Medicine*, 2005).

SEAMLESS DESIGN

An adaptive design in a planned study involves the option of implementing design modifications based on the results of an interim analysis. This type of design may speed up the clinical development program of a drug while maintaining statistical and regulatory standards.

Different types of adaptive designs are available, but the most commonly used is the so-called “group-sequential design”. Alternative designs that offer the possibility of increasing sample size if results are encouraging but without enough statistical power can be also very appealing.

In this paper we focus on seamless design. As previously explained, a seamless design is a phase II/III clinical trial where the first part (phase II design) consists of several dose/schedule levels tested in

experimental and control arms. Further to the selection of the dose/schedule in the experimental arm, a second part (phase III design) is conducted in which the experimental and control arms are compared. In the development program timeline, the use of these designs avoids a long pause between conduction of phase II and III clinical trials; therefore, the drug development process can be speed up. However, in our opinion, the main advantage of this type of designs is that phase II information can be joined with phase III information then obtaining a more robust conclusion when doing comparison with the standard treatment (control arms).

For the sake of simplicity, our macro is based on a seamless design with two active experimental arms and one control arm, but this macro can be easily adapted to fulfill any other requirement.

TYPE I ERROR CONTROL

As an evident result, adaptive designs involve the use of statistical methods to control the pre-specified type I error.

Type I error is defined as the rejection of the null hypothesis when in reality is true. In adaptive designs, multiplicity concerns are present because data is looked more than once. In the case of seamless design, p-values from first and second stage are combined to get an overall p-value. Therefore, statistical tests need to to be implemented to avoid type I error inflation. Several methods to control type I error are available, but the Bonferroni's approach is probably the most common used tool.

In the current seamless design, we used the Posch-Bauer method, in which treatment effectiveness is derived according to a closed testing procedure (Simes test) and p-values of both stages are combined into an adjusted p-value. A closed testing procedure is a method for the simultaneous performing of more than one hypothesis test.

POSCH BAUER (MACRO)

In the following lines, the description of the Posch-Bauer macro implementation is provided.

As mentioned above, we considered two experimental arms (each one with a different promising schedule for the same drug) and a control arm. First, we have to fix the overall type I error for the design (e.g., alpha=0.05). Then, in the first stage of the seamless design we select the best schedule of the two experimental arms, and then, in the second stage, the chosen experimental arm is compared with respect to the control arm. The global conclusion about effectiveness is obtained adding the combined information from both stages.

Consequently, after recruitment of the number of patients selected for the first stage, we define p1_1st as the p-value for the first stage of one of the treatment schedule arm *versus* the control arm, and p2_1st as the p-value for the first stage of the other treatment schedule arm *versus* the control arm, and then by means of Simes test we obtain p12_1st. Simes proposed the use of the entire set of ordered p-values for testing a composite hypothesis. The test is rejected if the minimum (kp_j/j) is lower than the pre-specified alpha, where k is the number of groups and j is the corresponding p-value.

Subsequently to the selection of the experimental arm, the second stage p-value is combined with the first stage p-value to get the global adjusted combined p-value. The combined p-value is obtained by means of the inverse normal function.

$C(p,q)=1-\Phi\{\text{sqrt}(n_1/n_1+n_2)\ \Phi^{-1}(1-p)+\ \text{sqrt}(n_2/n_1+n_2)\ \Phi^{-1}(1-q)\}$; where n_1 and n_2 are sample sizes of each stage.

CONCLUSION

This paper describes a SAS® program for obtaining a global adjusted combined p-value according to the closed testing procedure proposed by Posch and Bauer.

RECOMMENDATION

Although is out of the scope for this macro, the selection of the experimental arm schedule rarely is going to be based on the p-values observed in the first stage only, as other features can play a relevant role in the decision making (e.g., safety or quality of life). Then, we strongly recommend to pre-specify the

process as detailed as possible in the protocol and Statistical Analysis Plan if the decision is not going to be based only on p-value. The implementation of an Independent Data Monitoring Committee to oversee the decision of the selected arm is also very recommendable.

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Disclaimer. We implemented a SAS code that fulfill correctly the process above explained, but we cannot fully guarantee that this code can be free of errors.

Appendix 1

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/*Macro to test a seamless design with two active groups vs. control (e.g. placebo)

Variables

-alpha=Type I error, to reject the elementary null hypothesis all the intersections should be
rejected too
-p1_1st=P-value for the 1st stage 1st comparison vs. control
-p2_1st=P-value for the 1st stage 2nd comparison vs. control

-n1=1st stage sample size (number of events in time to event variables) by group
-g_selected=treatment group selected value 1 or 2;
-p_2nd=P-value for the 2nd stage selected comparison vs. control
-n2=2nd stage sample size (number of events in time to event variables) by group

*/


%macro Posch_Bauer_test (alpha=,p1_1st=,p2_1st=,n1=,g_selected=,p_2nd=,n2=);

Data Posch_Bauer_dataset;
length label_txt $100.;
p1_1st=&p1_1st;
p2_1st=&p2_1st;
*Simes test;
p12_1st=min(2*ordinal(1,p1_1st,p2_1st),ordinal(2,p1_1st,p2_1st));

*;
p_2nd=&p_2nd;

n1=&n1;
n2=&n2;

c1=1-probnorm((sqrt(n1/(n1+n2))*probit(1-p1_1st))+(sqrt(n2/(n1+n2))*probit(1-p_2nd)));
c2=1-probnorm((sqrt(n1/(n1+n2))*probit(1-p2_1st))+(sqrt(n2/(n1+n2))*probit(1-p_2nd)));
c12=1-probnorm((sqrt(n1/(n1+n2))*probit(1-p12_1st))+(sqrt(n2/(n1+n2))*probit(1-p_2nd)));

m1=max(c1,c12);
m2=max(c2,c12);

alpha=&alpha;

If &g_selected=1 then do;
If m1<=alpha then label_txt='Reject null hypothesis:Treatment group 1 vs. Control arm';
else label_txt='Cannot Reject null hypothesis:Treatment group 1 vs.Control arm';
end;
If &g_selected=2 then do;
If m2<=alpha then label_txt='Reject null hypothesis:Treatment group 2 vs. Control arm';
else label_txt='Cannot Reject null hypothesis:Treatment group 2 vs.Control arm';
end;


run;

%If &g_selected=1 %then %do;
Proc print data=Posch_Bauer_dataset noobs l;
var alpha label_txt m1;
label alpha='Alpha' label_txt='00'x m1='Combined Posch-Bauer controlled type I-error';
run;
%end;
%If &g_selected=2 %then %do;
Proc print data=Posch_Bauer_dataset noobs l;
var alpha label_txt m2;
label alpha='Alpha' label_txt='00'x m2='Combined Posch-Bauer controlled type I-error';
run;
%end;


%mend Posch_Bauer_test;
```