

Power calculation in a multi-stage design following the main endpoint a binomial distribution

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ABSTRACT

Many phase II clinical trials are designed in multi-stage processes using a dichotomous variable (e.g. response to treatment) that follows a binomial distribution as the primary endpoint. The usual process to calculate sample size is to specify type I/II error, then a null and an alternative hypotheses and finally the sample size, usually obtained using a Gaussian approximation, is split in several stages where the study proceeds to the next stage if the results observed in the prior stages are compelling enough to continue the recruitment.

Being binomial distribution a well-known function, we present a SAS[®] macro to calculate the exact binomial power in a three stage design where study conduct is determined by the results observed in the first and the second stage.

INTRODUCTION

This paper presents a SAS macro to calculate exact power calculation when the primary endpoint follows a binomial distribution and the study conduct is split in different stages. As an example, we will show power calculation in a three stage design where study conduct is determined by the results observed in the first and the second stage.

SAMPLE SIZE CALCULATION

Parameters needed to calculate sample size are: type I error, type II error, null hypothesis, alternative hypothesis and spending functions to split the design in the different stages required.

ACTUAL POWER CALCULATION MACRO

As the sample size and study design are based on a dichotomous variable, but a Gaussian approximation is used where a binomial distribution underlies, the binomial mass probability and cumulative probability functions will be used to get the actual power, obtained after taking into account the restrictions set for the prior stages according to the study design.

MACRO PARAMETERS

As an example, we present a macro when a three stage design is selected and the go / no-go decisions are determined by the results observed in the first and the second stage.

```
pA=,/*Probability of alternative response*/  
n1=,/*Cumulative sample size for first stage*/  
n2=,/*Cumulative sample size for second stage*/  
n3=,/*Cumulative sample size for third stage*/  
s1=,/*Number of successes (greater or equal) observed after first stage*/  
s2=,/*Number of successes (greater or equal) observed after second stage*/  
s3=,/*Number of successes (greater or equal) observed after third stage*/  
f1=,/*Number of failures (lower) observed after first stage*/  
f2=,/*Number of failures (lower) observed after second stage*/
```

MACRO SENTENCES

The probability of stopping or continuing accrual in the different stages will be calculated by means of PDF and CDF SAS functions for the Binomial distribution. PDF function computes probability density (mass) functions and CDF function computes cumulative distribution.

SAS MACRO

```
/*  
Power calculations.  
*/
```

```
%macro
```

```
binomial_power_3stages(pA=,n1=,n2=,n3=,s1=,s2=,s3=,f1=,f2=);
```

```
*Initialize variables;
```

```
Data binom1;
```

```
pA=&pA;
```

```
n1=&n1;
```

```
n2=&n2;
```

```
n3=&n3;
```

```
s1=&s1;
```

```
s2=&s2;
```

```
s3=&s3;
```

```
f1=&f1;
```

```
f2=&f2;
```

```
f3=&f3;
```

```
add_n2_to_n1=n2-n1;
```

```
add_n3_to_n2_n1=n3-n2;
```

```
output;
```

```
run;
```

```
* Probability of success in the first stage -> having >=s1  
successes in the first n1 patients;
```

```
Data success_1st_stage;
```

```
set binom1;
```

```
stage1=1;
```

```
prob_s1=1-CDF('BINOMIAL',s1-1,pA,n1);
```

```
run;
```

```
* Probability of success in the second stage -> having >=s2  
successes in the first n2 patients;
```

```
Data success_2nd_stage_aux1;
```

```
set binom1;
```

```
do i=f1 to s1-1;
```

```
do j=0 to add_n2_to_n1;
```

```
stage2=1;
```

```
r1=i;
```

```
r2=j;
```

```
output;
```

```
end;
```

```
end;
```

```
run;
```

```

Data success_2nd_stage_aux2;
set success_2nd_stage_aux1;
sum=r1+r2;
If sum<&s2 then delete;
prob_s2=PDF( 'BINOMIAL' ,r1,pA,n1)*PDF( 'BINOMIAL' ,r2,pA,add_n2_to_
n1);
run;

```

```

PROC SQL;
CREATE TABLE success_2nd_stage AS
SELECT stage2,sum(prob_s2) as prob_s2
FROM success_2nd_stage_aux2
GROUP BY stage2
ORDER BY stage2;
quit;

```

* Probability of success in the third stage -> having $\geq s3$ successes in the $n3$ patients;

```

Data success_3rd_stage_aux1;
set success_2nd_stage_aux1;
sum=r1+r2;
If &f2<=sum<&s2;
run;

```

```

Data success_3rd_stage_aux2;
set success_3rd_stage_aux1;
do j=&f2 to add_n3_to_n2_n1;
r3=j;output;
end;
run;

```

```

Data success_3rd_stage_aux3;
set success_3rd_stage_aux2;
sum=r1+r2+r3;
If sum<&s3 then delete;
prob_s3=PDF( 'BINOMIAL' ,r1,pA,n1)*PDF( 'BINOMIAL' ,r2,pA,add_n2_to_
n1)*PDF( 'BINOMIAL' ,r3,pA,add_n3_to_n2_n1);
stage3=1;
run;

```

```

PROC SQL;
CREATE TABLE success_3rd_stage AS
SELECT stage3,sum(prob_s3) as prob_s3
FROM success_3rd_stage_aux3
GROUP BY stage3
ORDER BY stage3;
quit;

```

*Sum of success probabilities in each stage to get the overall estimate;

```
Data binom2;  
merge binom1 success_1st_stage success_2nd_stage  
success_3rd_stage;  
run;
```

```
Data binom3;  
set binom2;  
power=prob_s1+prob_s2+prob_s3;  
run;
```

%MEND;

EXAMPLE

50 patients. Two interim analyses (15 and 25). Alternative hypothesis is 25%.

BOUNDARIES:

	15 PATS	25 PATS	50 PATS
SUCCESS	>=5	>=7	>=10
CONTINUE	2-4	3-6	
FAIL	<2	<3	<10

```
%BINOMIAL_POWER_3STAGES(PA=0.25,N1=15,N2=25,N3=50,S1=5,S2=7,S3=10,F1=2,F2=3);
```

The result obtained for Power is 0.80546663.

CONCLUSION

In multi-stage clinical trials where primary endpoint is based on a dichotomous variable that follows a binomial distribution, the calculation of the actual power that we can achieve with the study design should be performed taken into account the restrictions fixed in the prior stages and the exact binomial function. Comparing the actual calculated power with the type II error probability specified in the initial design we can re-adjust the parameters and simulate new designs with a realistic probability of success.

This macro can easily be transformed to get power calculation if the number of stages in the trial is different than three.

Contact Information

Your comments and questions are valued and encouraged.

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