*Stat 622/422 (Dr. Baron) Advanced Biostatistics*

**Sequential clinical trials – two-stage designs**

**# Calculating optimal designs “by hand” is tedious but feasible, for small samples.**

**# First, create a function that calculates error probabilities α and β, probabilities of**

**# early termination PET, and the average sample number ASN.**

> TwoStageDesign = function(n1,n,r1,r,p0,p1){

+ k = (r1+1):n1;

+ n2=n-n1;

+ alpha = sum( dbinom(k,n1,p0)\*(1-pbinom(r-k,n2,p0)) );

+ beta = pbinom(r1,n1,p1) + sum( dbinom(k,n1,p1)\*pbinom(r-k,n2,p1) );

+ PET0 = pbinom(r1,n1,p0)

+ PET1 = pbinom(r1,n1,p1)

+ ASN0 = n1 + (1-PET0)\*n2

+ ASN1 = n1 + (1-PET1)\*n2

+ return(data.frame(alpha,beta,PET0,PET1,ASN0,ASN1))}

**# For example:**

> TwoStageDesign(5, 10, 3, 7, 0.5, 0.8)

alpha beta PET0 PET1 ASN0 ASN1

1 0.04492187 0.3893093 0.8125 0.26272 5.9375 8.6864

**# Then, we’ll search for the optimal design, minimizing ASN0 = E0(T) in nested loops.**

**# If a new design yields a smaller ASN0, we update the design parameters.**

> OptimalDesign=function(p0,p1,alpha,beta,Nmax){

+ BestComb = data.frame(n1=0,r1=0,r=0,ASN0=Nmax+1)

+ for (n1 in 1:Nmax){ for (r1 in 1:n1){ for (r in (r1+1):n){

+ Params = TwoStageDesign(n1,Nmax,r1,r,p0,p1)

+ if ( Params$alpha <= alpha & Params$beta <= beta & Params$ASN0 < BestComb$ASN0 ){

+ BestComb$n1 = n1; BestComb$r1=r1; BestComb$r=r; BestComb$ASN0=Params$ASN0; }}}}

+ if (BestComb$ASN0 <= Nmax){ return(BestComb) } else {return("The optimal design cannot be found. Increase Nmax.")}}

**# For any α and β, this function calculates the optimal design or state that it is impossible.**

**# For example:**

> OptimalDesign(0.5,0.8,0.1,0.33,10)

n1 r1 r ASN0

1 6 3 7 7.375

> OptimalDesign(0.5,0.8,0.05,0.1,10)

[1] "The optimal design cannot be found. Increase Nmax."

**# R package “clinfun” (**Clinical Trial Design and Data Analysis Functions**) contains designs for**

**# standard two-stage and group sequential clinical trials**

> install.packages("clinfun")

> library(clinfun)

**# Calculate parameters of a two-stage design for the Binomial one-sample testing of**

**# H0: p = 0.25 (unacceptable response rate) vs HA: p=0.40 (acceptable response rate)**

**# with the significance level 0.05 and power 0.90.**

> ph2simon(0.25, 0.40, 0.05, 0.10)

Simon 2-stage Phase II design

Unacceptable response rate: 0.25

Desirable response rate: 0.4

Error rates: alpha = 0.05 ; beta = 0.1

r1 n1 r n EN(p0) PET(p0)

Optimal 10 37 31 99 56.16 0.6909

Minimax 13 57 27 83 72.11 0.4190

Warning message:

In print.ph2simon(x) : Optimal sample size too close to nmax.

Try increasing nmax (current value = 100)

**# By default, Nmax = 100. We can set the maximum sample size, but notice that it may be**

**# insufficient to attain the required significance level and power.**

> ph2simon(0.25, 0.40, 0.05, 0.10, nmax=90)

Simon 2-stage Phase II design

Unacceptable response rate: 0.25

Desirable response rate: 0.4

Error rates: alpha = 0.05 ; beta = 0.1

r1 n1 r n EN(p0) PET(p0)

Optimal 9 37 28 87 59.48 0.5503

Minimax 13 57 27 83 72.11 0.4190

Warning message:

In print.ph2simon(x) : Optimal sample size too close to nmax.

Try increasing nmax (current value = 90)

**# So, for Nmax = 90, solution can still be found. But not for Nmax = 50…**

> ph2simon(0.25, 0.40, 0.05, 0.10, nmax=50)

Error in ph2simon(0.25, 0.4, 0.05, 0.1, nmax = 50) :

No feasible solution found.

Increase maximum sample size. Current nmax value = 50.