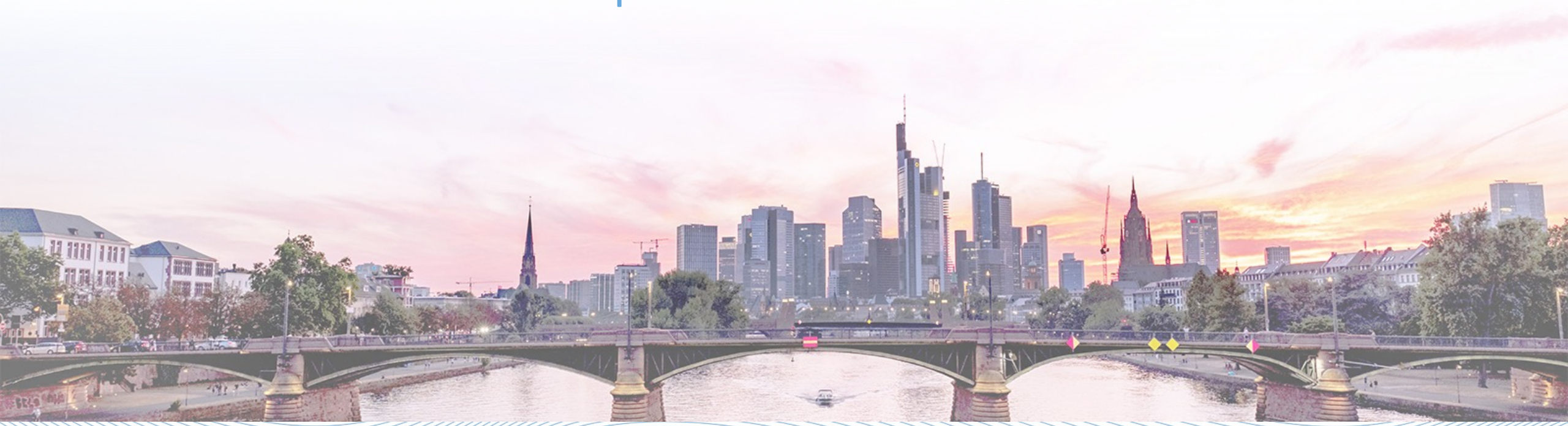
AS02

Size matters - sample size calculation with SAS and R



www.mainanalytics.de

Table of Content

Background

Comparison of Sample Size Computation

Conclusion

Background

SAS

- Programming tool of choice over many years
- PROC POWER is a useful function to determine sample sizes

R

- Open-source software becomes more popular
- Many flexible functions included in different packages (e.g. pwr, rpact and DoseFinding)

Table of Content

Background

Comparison of Sample Size Computation

Conclusion

Example 1

- Evaluate the efficacy of Treatment A versus Treatment B where main endpoint is a dichotomous variable (“Response” or “No response”)

- Assumptions:
  - Power: 80%, 2-sided significance level: 5%
  - Response rate Treatment A: 55%, response rate Treatment B: 45%

- Estimate the sample size needed to detect a difference in the response rate of 10%

Example 1

SAS

```
PROC POWER;
     TWOSAMPLEFREQ TEST = PCHI
     GROUPPROPORTIONS= (0.55 0.45)
     ALPHA = 0.05
     SIDES = 2
     POWER = 0.80
     NPERGROUP = .;
RUN;
```

R

```
library("pwr")
pwr.2p.test(h = ES.h(p1 = 0.55, p2 = 0.45),
            n=NULL, power = 0.80,
            alternative = "two.sided",
            sig.level = 0.05)
```

Example 1

SAS

The POWER Procedure
Pearson Chi-square Test for Proportion Difference

Fixed Scenario Elements	
Distribution	Asymptotic normal
Method	Normal approximation
Number of Sides	2
Alpha	0.05
Group 1 Proportion	0.55
Group 2 Proportion	0.45
Nominal Power	0.8
Null Proportion Difference	0

Computed N per Group	
Actual Power	N per Group
0.801	392

R

```
Difference of proportion power calculation for binomial
distribution (arcsine transformation)

              h = 0.2003348
              n = 391.1323
      sig.level = 0.05
          power = 0.8
    alternative = two.sided

NOTE: same sample sizes
```

Example 2

- Evaluate the difference in the average change from baseline in a continuous variable between Treatment A and Treatment B.

- Assumptions:
  - Power: 80%, 2-sided significance level: 5%
  - Average change from baseline Treatment A: 15% with standard deviation of 1.5%
  - Average change from baseline Treatment B: 12% with standard deviation of 1.9%

- Estimate the sample size needed to detect a difference of 3% in the average change from baseline

Example 2

Pooled standard deviation

$$\sigma = \sqrt{\frac{std(Treatment\ A)^2 + std(Treatment\ B)^2}{2}} \approx 1.711724$$

Effect size (only for R)

$$d = \frac{Difference\ in\ means}{Pooled\ standard\ deviation} \approx 1.752619$$

SAS

```
proc power;
     TWOSAMPLEMEANS
     MEANDIFF = 3
     STDDEV = 1.711724
     ALPHA = 0.05
     SIDES = 2
     POWER = 0.8
     NPERGROUP = .;
run;
```

R

```
library("pwr")
pwr.t.test(d = 1.752619, power = 0.80,
           sig.level = 0.05, alternative = "two.sided")
```

Example 2

SAS

The POWER Procedure
Two-Sample t Test for Mean Difference

Fixed Scenario Elements	
Distribution	Normal
Method	Exact
Number of Sides	2
Alpha	0.05
Mean Difference	3
Standard Deviation	1.711724
Nominal Power	0.8
Null Difference	0

Computed N per Group	
Actual Power	N per Group
0.853	7

R

```
     Two-sample t test power calculation

              n = 6.234288
              d = 1.752619
      sig.level = 0.05
          power = 0.8
    alternative = two.sided

NOTE: n is number in *each* group
```

Example 3

- Evaluate the difference in survival times between Treatment A and Treatment B

- Assumptions:
  - Power: 80%, 2-sided significance level: 5%
  - Treatment A: 41% survival at five years (-> hazard of 0.178)
  - Treatment B: 60% survival at five years (-> hazard of 0.102)
  - Accrual time of two years
  - Follow-up time of six years

Example 3

SAS

```
proc power;
    TWOSAMPLESURVIVAL TEST = logrank
    GROUPSURVEXPHAZARDS = 0.178 | 0.102
    FOLLOWUPTIME = 6
    ACCRUALTIME = 2
    POWER = 0.80
    ALPHA = 0.05
    SIDES = 2
    NPERGROUP = . ;
run;
```

R

```
library('rpact')
getSampleSizeSurvival(alpha = 0.05, sided = 2, beta = 0.2,
                      lambda1 =  0.102, lambda2 = 0.178,
                      accrualTime = 2, followUpTime=6)
```

Example 3

SAS

The POWER Procedure
Log-Rank Test for Two Survival Curves

Fixed Scenario Elements	
Method	Lakatos normal approximation
Form of Survival Curve 1	Exponential
Form of Survival Curve 2	Exponential
Number of Sides	2
Accrual Time	2
Follow-up Time	6
Alpha	0.05
Group 1 Survival Exponential Hazard	0.178
Group 2 Survival Exponential Hazard	0.102
Nominal Power	0.8
Number of Time Sub-Intervals	12
Group 1 Loss Exponential Hazard	0
Group 2 Loss Exponential Hazard	0

Computed N per Group	
Actual Power	N per Group
0.801	83

R

```
Design parameters:
  Critical values                                : 1.96
  Two-sided power                                : FALSE
  Significance level                             : 0.0500
  Type II error rate                             : 0.2000
  Test                                           : two-sided

User defined parameters:
  lambda(1)                                      : 0.102
  lambda(2)                                      : 0.178
  Accrual time                                   : 2.00

Default parameters:
  Theta H0                                       : 1
  Type of computation                            : Schoenfeld
  Planned allocation ratio                       : 1
  kappa                                          : 1
  Piecewise survival times                       : 0.00
  Follow up time                                 : 6.00
  Drop-out rate (1)                              : 0.000
  Drop-out rate (2)                              : 0.000
  Drop-out time                                  : 12.00

Sample size and output:
  Direction upper                                : FALSE
  median(1)                                      : 6.8
  median(2)                                      : 3.9
  Hazard ratio                                   : 0.573
  Number of events                               : 101.3
  Accrual intensity                              : 83.0
  Number of events fixed                         : 101.3
  Number of subjects fixed                       : 166
  Number of subjects fixed (1)                   : 83
  Number of subjects fixed (2)                   : 83
  Analysis times                                 : 8.00
  Study duration                                 : 8.00
  Lower critical values (treatment effect scale) : 0.677
  Upper critical values (treatment effect scale) : 1.476
  Local two-sided significance levels            : 0.0500

Legend:
  (i): values of treatment arm i
```

Example 4

- Show a significant non-flat dose-response curve across three different doses of Treatment A and placebo for a binary endpoint (“Response” vs “No response”)
- Analysis will be performed using multiple comparison and modelling techniques (MCPMod)
- Assumptions:
  - Power: 80%, 2-sided significance level: 5%
  - linear comparator model
  - Response rate of 20% with placebo
  - Maximum response rate of Treatment A of 40%
  - Same number of patients in each dose group

Example 4

SAS

<Manual implementation of formula used for sample size estimation>

R

```
library('DoseFinding')
models <- Mods(doses = c(0,1,2,3), placEff=0.2, maxEff=0.4,
               linear = NULL)
sampSizeMCT(upperN=80, contMat = optContr(models, w=1),
            sigma = 1, altModels=models, alRatio = rep(1, 4),
            power = 0.8, alpha = 0.05)
```

Example 4

SAS

R

```
Sample size calculation

alRatio: 1 1 1 1
Total sample size: 280
Sample size per arm: 70 70 70 70
targFunc: 0.8005
```

Example 5

- For more complex study designs, there might be no formula for sample size computation at all or it might be very difficult to adapt existing formula to fit the needs
- Use a “guess and check” approach based on simulation-based power calculations:
  - Assume power of 80%
  - Select a sample size and run simulations to estimate the power (i.e. repeatedly simulate entire study and determine the power as the proportion of studies in which the null hypothesis is rejected)
  - If the power is estimated to be higher than 80%, select a new and lower sample size and estimate the power again
  - Repeat until the estimated power approximately equals 80%

Table of Content

Background

Comparison of Sample Size Computation

Conclusion

Conclusion

SAS

- For simple and standard study designs, proc power is an efficient procedure for sample size calculation
- Limitations when it comes to more complex study designs

R

- For simple and standard study designs, efficient functions for sample size calculation are available from the pwr, rpact and DoseFinding package
- Flexible solutions for complex study designs

Thank you for your attention

Fenja Seither
fenja.seither@mainanalytics.de