Adaptive Methods in Clinical Research
Practical 1: Single-arm binary outcome designs

In this practical, we will obtain different types of single-arm binary outcome designs that are suitable for a planned study, and compare them.

Note: For this session we will use the `clinfun` package (on CRAN) and the `curtailment` package. The simplest way to install and load these is to first install the `librarian` package, then use its `shelf` command to install and load the required packages:

```
install.packages("librarian")
```

```
librarian::shelf(clinfun, martinlaw/curtailment)
```

You will then be able to install and load all other packages for the course in the same way (e.g., `librarian::shelf(package1, package2, package3)`). Note: this installs the latest version of `curtailment` from github, but an earlier version package is available on CRAN.

An investigator would like your advice regarding planning a trial of a new treatment for pulmonary arterial hypertension.

The investigator considers a response rate of 0.05 to be poor (p_0), and would like to control the type-I error-rate (α) to be at most 0.05 at this poor response rate. He thinks that the response rate for the new treatment will be 0.3 (p_1), and would like to power the trial for this magnitude of response rate. The power ($1-\beta$) must be at least 80%.

1. Use the `ph2single` command from the `clinfun` package to obtain a selection of single-stage designs for this study.

- What is the smallest sample size returned?
- What is the type-I error-rate and power of the design with the smallest sample size?

```
ph2single(pu = 0.05, pa = 0.3, ep1 = 0.05, ep2 = 1-0.8)
```

```
##    n r Type I error Type II error
## 1 14 2   0.03005364    0.16083576
## 2 15 2   0.03620024    0.12682771
## 3 16 2   0.04293785    0.09935968
## 4 18 3   0.01087322    0.16455048
## 5 19 3   0.01323601    0.13317100
```

```
# The design with the smallest sample size is in row 1, with N=14, type-I
# error-rate 0.03 and power 100*(1-0.16)=84%.
```

Now use the `ph2simon` command from the `clinfun` package to find the Simon two-stage designs that would minimise the maximum sample size ("Minimax") and minimise the expected sample size under the null hypothesis ("Optimal"), for this study. You will also obtain any sets of admissible design parameters.

2. Given the choice, which of these designs (both the choice of single-stage or two-stage and the choice of design parameters) would you select for this study, and why?

```
ph2simon(pu = 0.05, pa = 0.3, ep1 = 0.05, ep2 = 1-0.8)
```

```
##
```

```
##  Simon 2-stage Phase II design
##
## Unacceptable response rate:  0.05
## Desirable response rate:  0.3
## Error rates: alpha =  0.05 ; beta =  0.2
##
##            r1 n1 r  n EN(p0) PET(p0)   qLo   qHi
## Minimax     0  7 2 14  9.112  0.6983 0.421 1.000
## Admissible  0  6 2 15  8.384  0.7351 0.129 0.421
## Optimal     0  5 2 18  7.941  0.7738 0.000 0.129
```

```
# Personal opinion.
# Single-stage design is the most simple to run.
# Minimax has the same N_max as the single-stage, but lower ESS(H0).
# Optimal has lowest ESS(H0) (7.9, vs 9.1 for minimax), but greater N_max (18 vs 14).
# Admissible has a low ESS(H0) (8.4) with only a slight increase in N_max (15 vs 14).
```

You ask the investigator their opinion regarding the importance of minimising the maximum sample size versus minimising the expected sample size under the null hypothesis. They respond that they would like to give them equal weight when considering which set of design parameters to select.

3. With this in mind,

- What are the design parameters of the most appropriate design for this study?
- For this design, what is the probability that the trial will end early if the response rate is equal to 0.05?

```
# For each design, the values qLo and qHi denote the interval of weights for N_max
# for which the trial is optimal. Allocating equal weighting to N_max and ESS(H0)
# means giving both optimality criteria a weight of 0.5.

# As such, the most appropriate design is the design that contains 0.5 in the
# [qLo, qHi] interval. In this case, this is the Minimax design, which has a
# [qLo, qHi] interval of [0.421, 1.000]. The parameters of this design are

# r1=0, n1=7, r=2, n=14.

# The probability that the trial will end early if the response rate is equal
# to 0.05 is PET(p0)=0.6983.
```

The investigator confesses that his earlier thoughts on the response rate was a guess, but he assures you that his current Phase I trial will give him a better idea of the true response rate. The results of that trial are not yet available, but he's certain that the observed response rate will be at least 0.2, and will be no greater than 0.4. He adds that the recruitment rate will be slow, around two participants per month, and the treatment will be relatively expensive.

4. At each of these extremes for response rate,

- What Simon designs would be appropriate?
- How do they differ from the "best" Simon two-stage design you obtained above?

```
# For p1=0.2:
response.lo <- ph2simon(pu = 0.05, pa = 0.2, ep1 = 0.05, ep2 = 1-0.8)
response.lo
```

```
##
##  Simon 2-stage Phase II design
##
```

```
## Unacceptable response rate:  0.05
## Desirable response rate:  0.2
## Error rates: alpha =  0.05 ; beta =  0.2
##
##            r1 n1 r  n EN(p0) PET(p0)   qLo   qHi
## Minimax     0 13 3 27  19.81  0.5133 0.597 1.000
## Admissible  0 11 3 28  18.33  0.5688 0.414 0.597
## Optimal     0 10 3 29  17.62  0.5987 0.000 0.414
```

```
# For p1=0.2, the most appropriate design for the weight (0.5) is the Admissible design.
# This design has a greater N_max and ESS(H0) compared to the earlier Simon design.
```

```
# For p1=0.4:
response.hi <- ph2simon(pu = 0.05, pa = 0.4, ep1 = 0.05, ep2 = 1-0.8)
response.hi
```

```
##
##  Simon 2-stage Phase II design
##
## Unacceptable response rate:  0.05
## Desirable response rate:  0.4
## Error rates: alpha =  0.05 ; beta =  0.2
##
##         r1 n1 r n EN(p0) PET(p0)   qLo   qHi
## Minimax  0  5 1 7  5.452  0.7738 0.415 1.000
## Optimal  0  4 1 8  4.742  0.8145 0.000 0.415
```

```
# For p1=0.4, the most appropriate design for the weight (0.5) is the minimax design.
# This design has a lower N_max and ESS(H0) compared to the earlier Simon design.
```

The data from the Phase I trial are analysed, and the investigator is still satisfied with an anticipated response rate of 0.3. However, he has heard from a colleague that his trial could be made even more efficient by using a two-stage design that allows stopping for benefit.

5. Use the `find2stageDesigns` command from the `curtailment` package to find Mander and Thompson two-stage designs, which permit stopping for benefit. Compare the Mander & Thompson design with the lowest maximum sample size to the "best" Simon design from Question 2/3. Use the same values for the desirable and undesirable response rates and type-I error-rate and power as Question 2.

```
mander <- find2stageDesigns(nmin=,    # min value of n_max
                            nmax=,    # max value of n_max
                            p0=,
                            p1=,
                            alpha=,
                            power=,
                            benefit=)  # allow stopping for benefit (TRUE or FALSE)
```

```
mander <- find2stageDesigns(nmin=6,
                            nmax=25,
                            p0=0.05,
                            p1=0.3,
                            alpha=0.05,
                            power=0.8,
                            benefit = TRUE)
mander
```

```
## $input
```

```
##   nmin nmax   p0  p1 alpha power maxthetaF
## 1    6   25 0.05 0.3  0.05   0.8        NA
##
## $all.des
##   n1 n2  n r1 r      alpha     power    EssH0      Ess e1    thetaF
## 1  6  8 14  0 2 0.04606227 0.8051166 7.857074 8.420208  1 0.4482262
## 2  5 12 17  0 2 0.04669371 0.8013082 7.443519 9.321800  1 0.7471847
##
## attr(,"class")
## [1] "list"              "curtailment_simon"
```

```
# The Mander & Thompson design with the lowest maximum sample size is similar to
# the best design from Question 2/3: same max sample size (14), same ESS(H0)
# (7.9 to 1 d.p.) and same futility boundaries (0 at interim, 2 at end).
```

6. How do the two designs (Mander & Thompson from Question 5 and Simon design from Question 2/3) compare in terms of expected sample size under $p = p_1$? This is not provided in the output from the `clinfun` package, so use `find2stageDesigns` to obtain the Simon design.

```
simon <- find2stageDesigns(nmin=6,
                           nmax=25,
                           p0=0.05,
                           p1=0.3,
                           alpha=0.05,
                           power=0.8,
                           benefit = FALSE) # The difference
simon
```

```
## $input
##   nmin nmax   p0  p1 alpha power maxthetaF
## 1    6   25 0.05 0.3  0.05   0.8        NA
##
## $all.des
##   n1 n2  n r1 r      alpha     power    EssH0      Ess    thetaF
## 1  7  7 14  0 2 0.02742996 0.8100989 9.111639 13.42352 0.3529305
## 2  6  9 15  0 2 0.03005411 0.8099749 8.384173 13.94116 0.5371688
## 3  5 13 18  0 2 0.03916523 0.8060083 7.940848 15.81509 0.7975217
##
## attr(,"class")
## [1] "list"              "curtailment_simon"
```

```
# The Simon design with N=14 has ESS(H1)=13.4 compared to 8.4 for the Mander
# & Thompson design.
```