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, curtailment)
```

You will then be able to install all other packages for the course in the same way.

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 find the best single-stage design for this study.

- What is the sample size of this design?
- What is the type-I error-rate and power?

```
ph2single(pu = 0.05, pa = 0.3, ep1 = 0.05, ep2 = 1-0.8, nsoln = 5)
```

```
##    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
```

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 most appropriate design parameters 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 range 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] range. In this case, this is the minimax design, which is the most
# appropriate design for N_max weights in the range [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 available, but he's certain that the observed response rate will be at least 0.2, and could be as much as 0.4.

4. At each of these extremes,

- What designs would be appropriate?
- How do they differ from the earlier "best" design you obtained?

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 a Mander and Thompson two-stage design that permits stopping for benefit. Use the same values for the desirable and undesirable response rates and the type-I error-rate and power.

```
mander <- find2stageDesigns(nmin=,     # min value of n_max
                            nmax=,     # min 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 = T)
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
## 71912  5 12 17  0 2 0.04669371 0.8013082 7.443519 9.321800  1 0.7471847
## 77418  6  8 14  0 2 0.04606227 0.8051166 7.857074 8.420208  1 0.4482262
##
## attr(,"class")
## [1] "list"              "curtailment_simon"
```