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, a rare disease that has limited treatment options.

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 the response rate for the new treatment will be 0.30 (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?

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

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

You ask the investigator for 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?

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 is relatively expensive.

4. At *each* of these extremes for response rate,

- What Simon design would be most appropriate?
- How does each design differ from the "best" Simon two-stage design you chose above?

The investigator is still satisfied overall with using 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 your preferred Simon design from Questions 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(n.max=,
                            p0=,
                            p1=,
                            alpha=,
                            power=,
                            benefit=)  # allow stopping for benefit (TRUE or FALSE)
```

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 $p = p_1$? Which design would you choose? This is not provided in the output from the `clinfun` package, so use `find2stageDesigns` to obtain the Simon design.

7a. The data from the Phase I trial are analysed, and the estimated response rate is much smaller than anticipated: instead of 0.30, the response rate was 0.20. Use the `find2stageDesigns` command to obtain possible Simon designs and choose an appropriate design from these. (Note: the designs have a maximum sample size of less than 30).

7b. Find a stochastic curtailment design that satisfies the same requirements (in terms of type-I error-rate, power, p_0 and p_1), using the `singlearmDesign` command. Simon designs may not stop until data are available for n_1 participants. To find only stochastic curtailment designs that do not stop earlier than your chosen Simon design, use the `minstop` argument: this argument sets the earliest point at which a trial may stop. Compare the properties of both kinds of design.

7c. Examine the Simon designs and the stochastic curtailment designs visually, using the `plot` command. It requires two arguments: the output of a call to `find2stageDesigns` or `singlearmDesign`, and the row number of the design. For example:

```
simon.p20 <- find2stageDesigns(n.max=,
                               p0=,
                               p1=,
                               alpha=,
                               power=,
                               benefit=)
plot(simon.p20, 2)
```