1 Introduction

This software computes the stopping boundaries for single-arm clinical trials with either binary or right-censored time-to-event outcomes. It also can compute operating characteristics for specified scenarios.

The stopping rules implemented by the software are explained in [paper TBD] by Valen E. Johnson and John D. Cook.

For a given null hypothesis $\theta = \theta_0$, the prior for the alternative model is given by

$$\pi(\theta) \propto (\theta - \theta_0)^{-3} \exp\left(\left(\frac{\theta - \theta_0}{\sigma}\right)^2\right)$$

for $\theta > \theta_0$. The parameter σ is chosen so that the prior mode is at the alternative hypothesis.

Note that time-to-event trials are only supported for monitoring time to an undesirable event, such as monitoring time to disease progression or death.

2 Software parameters

The BFDesigner software has five required parameters. To specify a numerical argument n for a parameter, append $= n$ to the parameter name. Parameters may be specified in any order.

The `--null` parameter specifies the null hypothesis. For binary outcomes this is a response rate. For time-to-event outcomes, this is a median time-to-event in units of months.

The `--alt` parameter specifies the alternative hypothesis, either a response rate or ta median time-to-event in units of months.

The `--inf` parameter specifies the cutoff for stopping due to inferiority.

The trial will stop for inferiority if the posterior probability of the alternative hypothesis is less than this cutoff. This is typically a small value such as 0.1.

The `--sup` parameter specifies the corresponding cutoff for stopping due to superiority. The trial will stop for superiority if the posterior probability of the null hypothesis less than this cutoff. Also a moderately small value.

Note that one may design a trial to stop only for inferiority by setting the superiority cutoff value to zero. Likewise one may stop only for superiority by setting the inferiority cutoff to zero.

The `--maxpatients` parameter gives the maximum number of patients to be treated if the trial does not stop early.

If the trial has a time-to-event outcome, specify the `--tte` option. If this option is not specified, it is assumed that the trial monitors a binary outcome.

The optional `--scenario` parameter allows the user to enter a hypothetical true value (response rate for binary outcomes, median time-to-event for time-to-event outcomes) to be used in a simulating operating characteristics.

Parameter names may be truncated as long as enough characters are present to uniquely identify arguments. This means all parameters may be abbreviated to their initial letter except for the `--sup` and `--scenario` parameters, which may be abbreviated `-su` and `--sc`.

See examples provided below.

3 Stopping boundaries

3.1 Binary outcomes

Two lists of stopping boundaries are give as output. The first is a list of stopping boundaries for stopping due to inferiority. For example, an output 0/5, 1/7, 2/10, etc. would mean that a trial should stop due to inferiority if there are 0 successes out of the first 0 patients, or only 1 success out of the first 7 patients, or only 2 successes out of the first 10 patients, etc.

The second list gives the corresponding stopping boundaries for stopping for superiority. Each pair m/n says to stop for superiority if there are m or fewer failures out of the first n patients.

3.2 Time-to-event outcomes

There are also two lists of stopping boundaries for time-to-event outcomes, one for inferiority and one for superiority.

NB: The software requires times to be entered in units of **months** but outputs stopping boundaries in units of **days**. This is because physicians, at least in oncology, think of survival times in units of months. However, for trial conduct, outcome times are measured in units of days.

For the inferiority stopping rules, a pair m/n says that for m events, a trial should stop for inferiority if total time-on-test is less than n days.

For the superiority stopping rules, a pair m/n says that for m events, one may stop for superiority if total time-on-test exceeds n days.

4 Simulations

Simulations are carried out based on 10,000 trial replications. Operating characteristics include the probabilities of stopping for the null and alternative hypotheses, and the average number of patients treated.

In the case of time-to-event outcomes, survival times are simulated from an exponential distribution. Patient arrivals are simulated according to a Poisson process at the rate of 1 patient per month.

Note that the stopping boundaries have nothing to do with accrual rate. Thus the software can be used directly to calculate stopping boundaries independent of the accrual rate.

One can also use the software to simulate operating characteristics for different accrual rates: simply change the time scale so that the accrual rate is 1. In other words, specify the true time to event in multiples of the average time between patients. Note that in this case the stopping boundaries will no longer be in units of days.

5 Examples

5.1 Binary

Suppose a trial of 50 patients is designed to test the null hypothesis that an experimental treatment has a 20% response rate compared to an alternative hypothesis of a 30% response rate. The trial will stop for inferiority if the posterior probability of the alternative model is less than 0.12. The trial will stop for inferiority if the posterior probability for the alternative model is less than 0.12, and will stop for superiority if the posterior probability for the null

model is less than 0.08. The following command prints the stopping boundaries for this design.

```
BFDesigner.exe --m=50 --null=.2 --alt=.3 --inf=.12 --sup=.08
```

If we only wanted to stop for inferiority, we would set `--sup=0`.

Recall that parameter names may be abbreviated or spelled out in full and that parameter may be specified in any order.

5.2 Time-to-event

Suppose a trial is designed to test the null hypothesis that median survival on an experimental treatment is 6 months compared to an alternative hypothesis of 8 months. The trial has a maximum of 100 patients. The trial will stop for inferiority if the posterior probability of the alternative model is less than 0.13. The trial will stop for superiority if the posterior probability of the null model is less than 0.07. The following command will output the stopping boundaries as well as the operating characteristics if the true median survival time were 5.1 months.

```
BFDesigner.exe --n=6 --a=8 --m=100 --i=.13 --sup=.07 --sc=5.1 -tte
```