Designing group-sequential trials with two groups and a continuous endpoint with rpact

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This R markdown file provides examples for designing trials with continuous endpoints using rpact. These examples are not intended to replace the official rpact documentation and help pages but rather to supplement them. They also only cover a selection of all rpact features.

Load rpact package.

```
# Load rpact
library(rpact)
packageVersion("rpact") # version should be version 2.0.1 or later
```

```
## [1] '2.0.1'
```

Sample size calculation for a superiority trial without interim analyses

Sample size for a trial with continuous endpoints can be calculated using the function `getSampleSizeMeans`. This function is fully document in the relevant help page (`?getSampleSizeMeans`). Some examples are provided below.

`getSampleSizeMeans` requires that the mean difference between the two arms is larger under the alternative than under the null hypothesis. For superiority trials, this implies, that **rpact requires that the targeted mean difference is >0 under the alternative hypothesis**. If this is not the case, the function gives an error. To circumvent this and power for a negative mean difference, **one can simply switch the two arms** (leading to a positive mean difference) as the situation is perfectly symmetric.

By default, `getSampleSizeMeans` tests hypotheses about the mean difference. rpact also supports testing hypotheses about mean ratios if the argument `meanRatio` is set to `TRUE` but this will not be discussed further in this document.

By default, rpact uses sample size formulas for the t-test, i.e., it assumes that the standard deviation in the two groups is equal but unknown and estimated from the data. If sample size calculations for the Z-test are desired, one can set the argument `normalApproximation` to `TRUE` but this is usually not recommended.

```
# Example of a standard trial:
# - targeted mean difference is 10 (alternative=10)
# - standard deviation in both arms is assumed to be 24 (stDev=24)
# - two-sided test (sided=2), type I error 0.05 (alpha=0.05) and power 80% (beta=0.2)
sampleSizeResult <- getSampleSizeMeans(alternative=10, stDev=24, sided=2, alpha=0.05, beta=0.2)
sampleSizeResult
```

```
## Design plan parameters and output for means:
##
## Design parameters:
##   Significance level                        : 0.0500
##   Type II error rate                        : 0.2
```

```
##   Test                                          : two-sided
##
## User defined parameters:
##   Alternatives                                  : 10
##   Standard deviation                            : 24
##
## Default parameters:
##   Normal approximation                          : FALSE
##   Mean ratio                                    : FALSE
##   Theta H0                                      : 0
##   Treatment groups                              : 2
##   Planned allocation ratio                      : 1
##
## Sample size and output:
##   Number of subjects fixed                      : 182.8
##   Number of subjects fixed (1)                  : 91.4
##   Number of subjects fixed (2)                  : 91.4
##   Lower critical values (effect scale)          : -6.959
##   Upper critical values (effect scale)          : 6.959
##   Local two-sided significance levels           : 0.0500
##
## Legend:
##   (i): values of treatment arm i
```

As per the output above, the required **total sample size** for the trial is 183 and the critical value corresponds to a minimal detectable mean difference of approximately 6.96.

Unequal randomization between the treatment groups can be defind with `allocationRatioPlanned`, for example,

```
# Extension of standard trial:
# - 2(intervention):1(control) randomization (allocationRatioPlanned=2)
getSampleSizeMeans(alternative=10, stDev=24,
    allocationRatioPlanned=2, sided=2, alpha=0.05, beta=0.2)
```

```
## Design plan parameters and output for means:
##
## Design parameters:
##   Significance level                            : 0.0500
##   Type II error rate                            : 0.2
##   Test                                          : two-sided
##
## User defined parameters:
##   Alternatives                                  : 10
##   Standard deviation                            : 24
##   Planned allocation ratio                      : 2
##
## Default parameters:
##   Normal approximation                          : FALSE
##   Mean ratio                                    : FALSE
##   Theta H0                                      : 0
##   Treatment groups                              : 2
##
## Sample size and output:
##   Number of subjects fixed                      : 205.4
##   Number of subjects fixed (1)                  : 136.9
```

```
##   Number of subjects fixed (2)                : 68.5
##   Lower critical values (effect scale)        : -6.963
##   Upper critical values (effect scale)        : 6.963
##   Local two-sided significance levels         : 0.0500
##
## Legend:
##   (i): values of treatment arm i
```

Power for a given sample size can be calculated using the function `getPowerMeans` which has the same arguments as `getSampleSizeMeans` except that the maximum total sample is given (`maxNumberOfSubjects`) instead of the type II error (`beta`).

```
# Calculate power for the 2:1 rendomized trial with total sample size 206
# (as above) assuming a larger difference of 12
powerResult <- getPowerMeans(alternative=12, stDev=24, allocationRatioPlanned=2,
    maxNumberOfSubjects = 206, sided=2, alpha=0.05)
powerResult
```

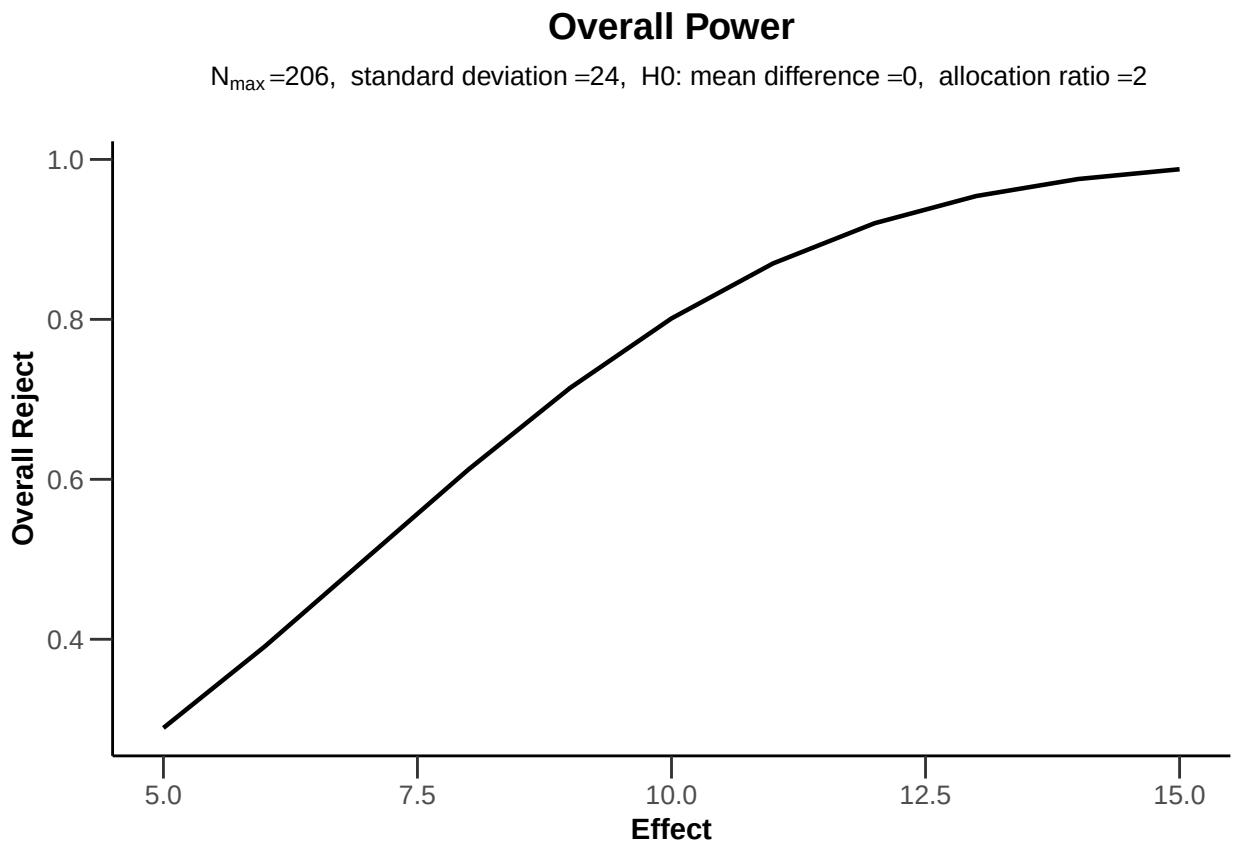
```
## Design plan parameters and output for means:
##
## Design parameters:
##   Significance level                          : 0.0500
##   Test                                        : two-sided
##
## User defined parameters:
##   Alternatives                                : 12
##   Standard deviation                          : 24
##   Planned allocation ratio                    : 2
##   Direction upper                             : NA
##   Maximum number of subjects                  : 206.0
##
## Default parameters:
##   Normal approximation                        : FALSE
##   Mean ratio                                  : FALSE
##   Theta H0                                    : 0
##   Treatment groups                            : 2
##
## Sample size and output:
##   Number of subjects fixed                    : 206.0
##   Number of subjects fixed (1)                : 137.3
##   Number of subjects fixed (2)                : 68.7
##   Effect                                      : 12
##   Overall reject                              : 0.92
##   Lower critical values (effect scale)        : -6.952
##   Upper critical values (effect scale)        : 6.952
##   Local two-sided significance levels         : 0.0500
##
## Legend:
##   (i): values of treatment arm i
```

The calculated **power** is provided in the output as **"Overall reject"** and is 0.92 for the example `alternative = 12`.

`getPowerMeans` (as well as `getSampleSizeMeans`) can also be called with a vector argument for the mean difference under the alternative H1 (`alternative`). This is illustrated below via a plot of power depending on these values. For examples of all available plots, see the R markdown file How to create admirable plots

with rpact.

```
# Example: Calculate power for design with sample size 206 as above
# alternative values ranging from 5 to 15
powerResult <- getPowerMeans(alternative=5:15, stDev=24, allocationRatioPlanned=2,
    maxNumberOfSubjects = 206, sided=2, alpha=0.05)
plot(powerResult,type=7) # one of several possible plots
```



Sample size calculation for a non-inferiority trial without interim analyses

Sample size calculation proceeds in the same fashion as for superiority trials except that the role of the null and the alternative hypothesis are reversed and the test is always one-sided. In this case, the non-inferiority margin Δ corresponds to the treatment effect under the null hypothesis (`thetaH0`) which one aims to reject.

```
# Example: Non-inferiority trial with margin delta=10, standard deviation=14
# - One-sided alpha=0.05, 1:1 randomization
# - Test H0: treatment difference <= -12 (i.e. = -12 for calculations, thetaH0=-1)
#    vs. alternative H1: treatment difference = 0 (alternative=0)
sampleSizeNoninf <- getSampleSizeMeans(thetaH0=-12,alternative=0,
    stDev=14,alpha=0.025,beta=0.2,sided=1)
sampleSizeNoninf
```

```
## Design plan parameters and output for means:
##
## Design parameters:
```

```
##   Significance level                          : 0.0250
##   Type II error rate                          : 0.2
##   Test                                        : one-sided
##
## User defined parameters:
##   Theta H0                                    : -12
##   Alternatives                                : 0
##   Standard deviation                          : 14
##
## Default parameters:
##   Normal approximation                        : FALSE
##   Mean ratio                                  : FALSE
##   Treatment groups                            : 2
##   Planned allocation ratio                    : 1
##
## Sample size and output:
##   Number of subjects fixed                    : 44.7
##   Number of subjects fixed (1)                : 22.4
##   Number of subjects fixed (2)                : 22.4
##   Critical values (effect scale)              : -3.795
##   Local one-sided significance levels         : 0.0250
##
## Legend:
##   (i): values of treatment arm i
```

Sample size calculation for group-sequential designs

Sample size calculation for a group-sequential trials is performed in **two steps**:

1. **Define the (abstract) group-sequential design** using the function `getDesignGroupSequential`. For details regarding this step, see the R markdown file "Defining group-sequential boundaries with rpact".
2. **Calculate sample size** for the continuous endpoint by feeding the abstract design into the function `getSampleSizeMeans`.

In general, rpact supports both one-sided and two-sided group-sequential designs. However, if futility boundaries are specified, only one-sided tests are permitted. **For simplicity, it is often preferred to use one-sided tests for group-sequntial designs** (typically with $\alpha = 0.025$).

R code for a simple example is provided below:

```
# Example: Group-sequential design with  O'Brien&Fleming type alpha-spending and
# one interim at 60% information
design <- getDesignGroupSequential(sided = 1, alpha = 0.025, beta = 0.2,
    informationRates = c(0.6,1), typeOfDesign="asOF")

# Trial assumes an effect size of 10 as above, a stDev=24, and an allocation ratio of 2
sampleSizeResultGs <- getSampleSizeMeans(design, alternative = 10, stDev=24,
                                         allocationRatioPlanned=2)
# Standard rpact output (sample size object only, not design object)
sampleSizeResultGs
```

```
## Design plan parameters and output for means:
##
## Design parameters:
##   Significance level                          : 0.0250
```

```
##   Type II error rate                            : 0.2
##   Test                                          : one-sided
##
## User defined parameters:
##   Alternatives                                  : 10
##   Standard deviation                            : 24
##   Planned allocation ratio                      : 2
##
## Default parameters:
##   Normal approximation                          : FALSE
##   Mean ratio                                    : FALSE
##   Theta H0                                      : 0
##   Treatment groups                              : 2
##
## Sample size and output:
##   Information rates [1]                         : 0.600
##   Information rates [2]                         : 1.000
##   Maximum number of subjects                    : 207.1
##   Maximum number of subjects (1)                : 138.1
##   Maximum number of subjects (2)                : 69.0
##   Number of subjects [1]                        : 124.3
##   Number of subjects [2]                        : 207.1
##   Number of subjects (1) [1]                    : 82.9
##   Number of subjects (1) [2]                    : 138.1
##   Number of subjects (2) [1]                    : 41.4
##   Number of subjects (2) [2]                    : 69.0
##   Expected number of subjects under H0          : 206.8
##   Expected number of subjects under H0/H1       : 202.4
##   Expected number of subjects under H1          : 181.3
##   Reject per stage [1]                          : 0.312
##   Reject per stage [2]                          : 0.488
##   Early stop                                    : 0.312
##   Critical values (effect scale) [1]            : 12.187
##   Critical values (effect scale) [2]            : 7.008
##   Local one-sided significance levels [1]       : 0.003808
##   Local one-sided significance levels [2]       : 0.023798
##
## Legend:
##   (i): values of treatment arm i
##   [k]: values at stage k
```

System: rpact 2.0.1, R version 3.5.2 (2018-12-20), platform: x86_64-w64-mingw32

To cite package 'rpact' in publications use:

Gernot Wassmer and Friedrich Pahlke (2019). rpact: Confirmatory Adaptive Clinical Trial Design and Analysis. R package version 2.0.1. https://CRAN.R-project.org/package=rpact

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