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

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Summary

This R Markdown document provides examples for designing trials with continuous endpoints using rpact.

1 Introduction

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.

General convention: In rpact, arguments containing the index “2” always refer to the control group, “1” refer to the intervention group, and treatment effects compare treatment versus control.

First, load the rpact package

```r
library(rpact)
packageVersion("rpact") # version should be version 2.0.5 or later
```

## [1] '2.0.6'

2 Sample size calculation for a superiority trial without interim analyses

The sample size for a trial with continuous endpoints can be calculated using the function `getSampleSizeMeans()`. This function is fully documented 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 produces an error message. 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.

```r
# 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
## Two-sided power : FALSE
## 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) : -7.006
## Upper critical values (effect scale) : 7.006
## Local two-sided significance levels : 0.0500

## Legend:
## (i): values of treatment arm i
```

The generic `summary()` function produces the output

```r
summary(sampleSizeResult)
```

```
## Sample size calculation for a continuous endpoint
##
## Fixed sample analysis.
## The sample size was calculated for a two-sample t-test (two-sided),
## alternative = 10, standard deviation = 24, allocation ratio = 1, and power 80%.

## Stage
## Fixed
```
## Efficacy boundary (z-value scale) 1.960
## Number of subjects 183
## Two-sided local significance level 0.0500
## Lower efficacy boundary (t) -7.006
## Upper efficacy boundary (t) 7.006
##
## Legend:
## (t): approximate treatment effect scale

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 7.01.

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

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

## Sample size calculation for a continuous endpoint

## Fixed sample analysis.
## The sample size was calculated for a two-sample t-test (two-sided),
## alternative = 10, standard deviation = 24, allocation ratio = 2, and power 80%.
##
## Stage          Fixed
## Efficacy boundary (z-value scale) 1.960
## Number of subjects 206
## Two-sided local significance level 0.0500
## Lower efficacy boundary (t) -7.004
## Upper efficacy boundary (t) 7.004
##
## Legend:
## (t): approximate treatment effect scale

**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`).

```r
# Calculate power for the 2:1 randomized 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)
```

## 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): -6.994
- Upper critical values (effect scale): 6.994
- 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.

The **summary**() function produces

```r
summary(powerResult)
```

### Power calculation for a continuous endpoint

### Fixed sample analysis.
- The results were calculated for a two-sample t-test (two-sided),
- **alternative** = 12, standard deviation = 24, allocation ratio = 2.

### Stage Fixed
- Efficacy boundary (z-value scale): 1.960
- Number of subjects: 206
- Power: 0.9203
- Two-sided local significance level: 0.0500
- Lower efficacy boundary (t): -6.994
- Upper efficacy boundary (t): 6.994

### Legend:
- \( (t) \): approximate treatment effect scale

**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 document 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
```
3 Sample size calculation for a non-inferiority trial without interim analyses

The 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 \( \Delta \) corresponds to the treatment effect under the null hypothesis \( \theta_{H0} \) 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, \(\theta_{H0}=-1\))
- vs. alternative H1: treatment difference = 0 (alternative=0)

```r
sampleSizeNoninf <- getSampleSizeMeans(thetaH0=-12,alternative=0, stDev=14, alpha=0.025, beta=0.2, sided=1)
```

---

```
## 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
```

---

![Overall Power](image.png)

Overall Power

\( N_{max} = 206 \), standard deviation = 24, \( H_0: \text{mean difference} = 0 \), allocation ratio = 2
## 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) : -3.556
## Local one-sided significance levels : 0.0250
##
## Legend:
## (i): values of treatment arm i

### 4 Sample size calculation for group-sequential designs

Sample size calculation for 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-sequential designs** (typically with $\alpha = 0.025$).

R code for a simple example is provided below:

```r
# 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

### 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
- Reject per stage [1]: 0.312
- Reject per stage [2]: 0.488
- Critical values (effect scale) [1]: 12.393
- Critical values (effect scale) [2]: 7.050
- 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

```r
table <- cbind(1, 2)
summary(supplyResultGs)
```

### Summary rpact output for sample size object

```r
summary(supplySizeResultGs)
```

### Sample size calculation for a continuous endpoint

### Sequential analysis with a maximum of 2 looks (group sequential design).

The sample size was calculated for a two-sample t-test (one-sided),
alternative = 10, standard deviation = 24, allocation ratio = 2, and power 80%.

```r
table <- cbind(1, 2)
summary(supplyResultGs)
```

### Exit probability for efficacy (under H0) 0.0038
### Exit probability for efficacy (under H1) 0.3123
## Legend:
## (t): approximate treatment effect scale

System: rpact 2.0.6, R version 3.6.1 (2019-07-05), platform: x86_64-w64-mingw32

To cite R in publications use:


To cite package ‘rpact’ in publications use:


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