Introduction to rpact

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CEN Short Course
Basel, September 3rd, 2023

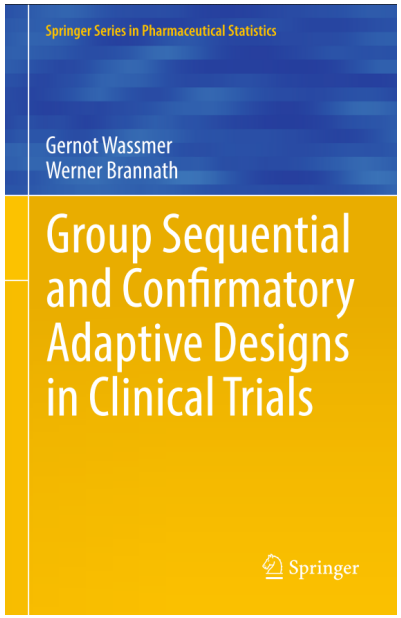
Part I: Basic Concept, Sample Size Calculation

What is `rpact`?

rpact / RPACT

- `rpact`
  - Comprehensive validated R package, freely available on CRAN
  - Design, simulation, and analysis of confirmatory adaptive group sequential designs
  - Monograph by Wassmer and Brannath, Springer, 2016

  → www.rpact.org



- RPACT is a company which offers
  - technical support for the `rpact` package
  - consultancy and user training for clinical researchers using R
  - enterprise R/Shiny software development services

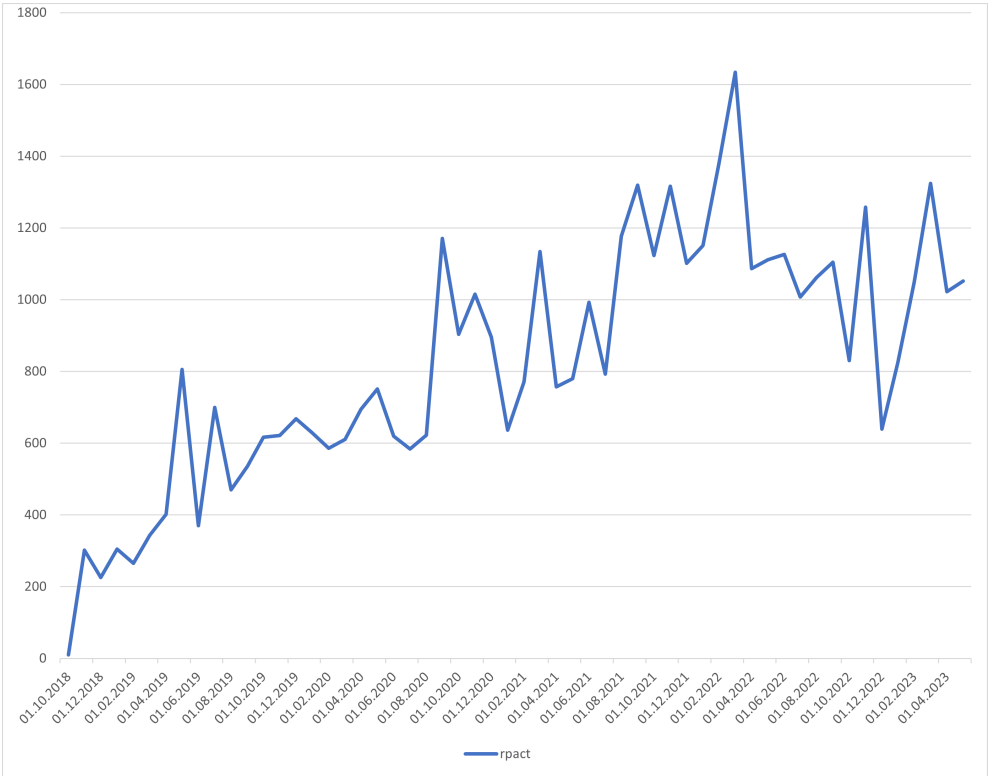
  → www.rpact.com

Company RPACT in Figures

- Founded in May 2017 by GW and FP
- Idea: open source development with help of "crowd funding"
- Currently supported by 22 companies
  $\rightarrow$ "Service Level Agreement" (SLA)
- 78 presentations and training courses since 2018

R package rpact in Figures

- 25 releases on CRAN since October 2018
- CRAN download stats:



- rpact on github: github.com/rpact-com/rpact
- Comes with 26 vignettes

The rpact Vignettes

rpact.org/vignettes

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Vignettes

Developed for practical use: below you find a collection of practical examples and use-cases, the so-called rpact vignettes.

In addition to these public open access vignettes, our RPACT SLA customers have access to exclusive vignettes on special topics such as the *analysis of multi-stage data with covariates from raw data*.

Jul 6, 2023
Daniel Lakens, Friedrich Pahlke, Gernot Wassmer

Step-by-Step rpact Tutorial

GETTING STARTED

The R package rpact has been developed to design sequential and adaptive experiments. Many of the functions of the R package are available in an online [Shiny...

Jul 6, 2023
Marcel Wolbers, Gernot Wassmer, and Friedrich Pahlke

Designing Group Sequential Trials with a Binary Endpoint with rpact

PLANNING RATES

This document provides examples for designing trials with binary endpoints using rpact.

Categories

All (26)
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Multi-arm (4)
Planning (13)
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Power simulation (8)
Rates (5)
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Survival (7)
Utilities (8)

rpact – Functional Range

- Design
  - Comprehensive set of group sequential designs, e.g., Wang & Tsiatis Δ-class, α-spending, β-spending, ...
  - Inverse normal design
  - Fisher's combination test
- Sample size and power calculation for
  - testing means (continuous endpoint)
  - testing rates (binary endpoint)
  - survival trials with, e.g.,
    - piecewise accrual time and intensity
    - flexible follow-up time specification
    - piecewise exponential survival time
  - fixed sample size design

rpact – Functional Range

- Analysis tool for
  - continuous, binary, and survival data
  - multi-arm adaptive trials
  - population enrichment designs
- Simulation tool for assessing adaptive strategies, e.g.,
  - sample size reassessment
  - treatment arm or population selection rules
  - different methodologies
- Graphical user interface:

  Shiny app cloud.rpact.com

The rpact Package Concept

Package Concept – Workflow

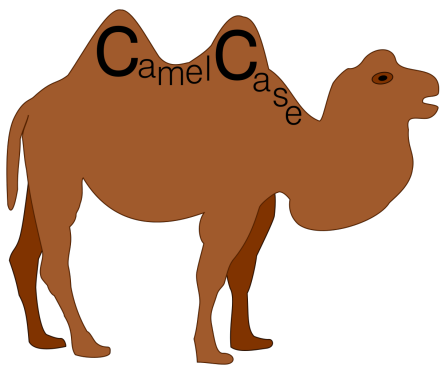
Usage inspired by the typical workflow in trial design and conduct:

- Everything is starting with a design, e.g.:
  `design <- getDesignGroupSequential()`
- Find the optimal design parameters with help of rpact comparison tools: `getDesignSet()`
- Calculate the required sample size and power, e.g.:
  `getSampleSizeMeans()` , `getPowerMeans()`
- Simulate specific characteristics of an adaptive design, e.g.:
  `getSimulationMeans()`
- Collect your data, import it into R and create an `rpact` dataset:
  `data <- getDataset()`
- Analyze your data:
  `getAnalysisResults(design, data)`

Package Concept – Focus on Usability

Almost all functions, arguments, and objects are self-explanatory due to their names:

- `getDesign[GroupSequential/InverseNormal/Fisher]()`
- `getDesignCharacteristics()`
- `getSampleSize[Means/Rates/Survival]()`
- `getPower[Means/Rates/Survival]()`
- `getSimulation[MultiArm/Enrichment][Means/Rates/Survival]()`
- `getDataset()`
- `getAnalysisResults()`



Package Concept – Utilities

Several utility functions are available, e.g.:

- Survival helper functions:
  - `getAccrualTime()`
  - `getPiecewiseSurvivalTime()`
  - `getNumberOfSubjects()`
  - `getEventProbabilities()`
  - `getPiecewiseExponentialDistribution()`
- `getObjectRCode()`
- `testPackage()`: installation qualification on a client computer or company server ($\rightarrow$ unit tests)

Package Concept – The rpact Manual

`help(package = "rpact")`: Inline help

Confirmatory Adaptive Clinical Trial Design and Analysis

Documentation for package 'rpact'

- DESCRIPTION file.
- User guides, package vignettes and other documentation.

Help Pages

rpact-package	rpact - Confirmatory Adaptive Clinical Trial Design and Analysis
getAccrualTime	Get Accrual Time
getAnalysisResults	Get Analysis Results
getAvailablePlotTypes	Get Available Plot Types
getClosedCombinationTestResults	Get Closed Combination Test Results
getClosedCombinationTestResultsEnrichment	Get Closed Combination Test Results
getClosedConditionalDunnettTestResults	Get Closed Conditional Dunnett Test Results
getConditionalPower	Get Conditional Power
getConditionalRejectionProbabilities	Get Conditional Rejection Probabilities
getData	Get Simulation Data
getDataset	Get Dataset
getDesignCharacteristics	Get Design Characteristics
getDesignConditionalDunnett	Get Design Conditional Dunnett Test
getDesignFisher	Get Design Fisher
getDesignGroupSequential	Get Design Group Sequential
getDesignInverseNormal	Get Design Inverse Normal
getDesignSet	Get Design Set
getEventProbabilities	Get Event Probabilities
getFinalConfidenceInterval	Get Final Confidence Interval
getFinalPValue	Get Final P Value

Package Concept – Most parameters have a default value

Example: `getDesignGroupSequential()` produces the output:

```
Design parameters and output of group sequential design:

User defined parameters: not available

Derived from user defined parameters: not available

Default parameters:
  Type of design             : O'Brien & Fleming
  Maximum number of stages   : 3
  Stages                     : 1, 2, 3
  Information rates          : 0.333, 0.667, 1.000
  Significance level         : 0.0250
  Type II error rate         : 0.2
  Two-sided power            : FALSE
  Test                       : one-sided
  Tolerance                  : 1e-08

Output:
  Cumulative alpha spending : 0.0002592, 0.0071601, 0.0250000
  Critical values           : 3.471, 2.454, 2.004
  Stage levels              : 0.0002592, 0.0070554, 0.0225331
```

Package Concept – Most parameters have a default value

Example: `getDesignGroupSequential(kMax = 2)` produces:

```
Design parameters and output of group sequential design:

User defined parameters:
  Maximum number of stages  : 2
  Stages                    : 1, 2

Derived from user defined parameters:
  Information rates         : 0.500, 1.000

Default parameters:
  Type of design            : O'Brien & Fleming
  Significance level        : 0.0250
  Type II error rate        : 0.2
  Two-sided power           : FALSE
  Test                      : one-sided
  Tolerance                 : 1e-08

Output:
  Cumulative alpha spending : 0.002583, 0.025000
  Critical values           : 2.797, 1.977
  Stage levels              : 0.002583, 0.023996
```

Sample Size and Power Calculation

Work-flow for sample size calculations in rpact

1. Define abstract group-sequential boundaries which are applicable to any type of endpoint (`getDesignGroupSequential()`).
2. Feed these boundaries into endpoint-specific sample size formulas (e.g., `getSampleSizeMeans()` , `getSampleSizeRates()` , `getSampleSizeSurvival()` , `getSimulationSurvival()`).

   For trials without interim analyses, Step 1. can be omitted.
3. `getDesignInverseNormal()` yields the same results as `getDesignGroupSequential()` , it has an effect only for simulation and analysis.
4. `getDesignFisher()` provides no planning calculation, use the simulation tools instead.

Abstract group-sequential boundaries

- Function `getDesignGroupSequential()` derives group-sequential boundaries in the mathematically simplest case:
  - Single arm trial with independent $X_i \sim N(\mu, 1)$
  - Test $H_0 : \mu = 0$ against $H_1 : \mu = 1$
- Correlation structure between Z-statistics at interim and final analyses is identical for more complex situations (e.g., binary, continuous and survival endpoints).

Group-sequential boundaries and properties of the design apply to all endpoints!

Example: O'Brien-Fleming type α-spending

```
# Efficacy interim analyses at 30%, 60% and 100% information
design <- getDesignGroupSequential(
    sided = 1, alpha = 0.025, beta = 0.2,
    informationRates = c(0.3, 0.6, 1),
    futilityBounds = c(0, 0),
    bindingFutility = FALSE,
    typeOfDesign = "asOF")
```

- `informationRates`: information fractions at which interim and final analysis are conducted.
- Information fraction t_k at analysis k:
  - Binary and normal outcomes: $t_k = n_k / N_{max}$
  - Survival outcomes: $t_k = d_k / D_{max}$ where d is # events.
- `futilityBounds`: Vector on z-value scale for interim analyses (excluding final analysis, only one-sided testing).
- `bindingFutility = FALSE` (default): no effect on efficacy boundaries.
- `typeOfDesign = "asOF"`: O'Brien & Fleming type α-spending.

Additional characteristics of the design

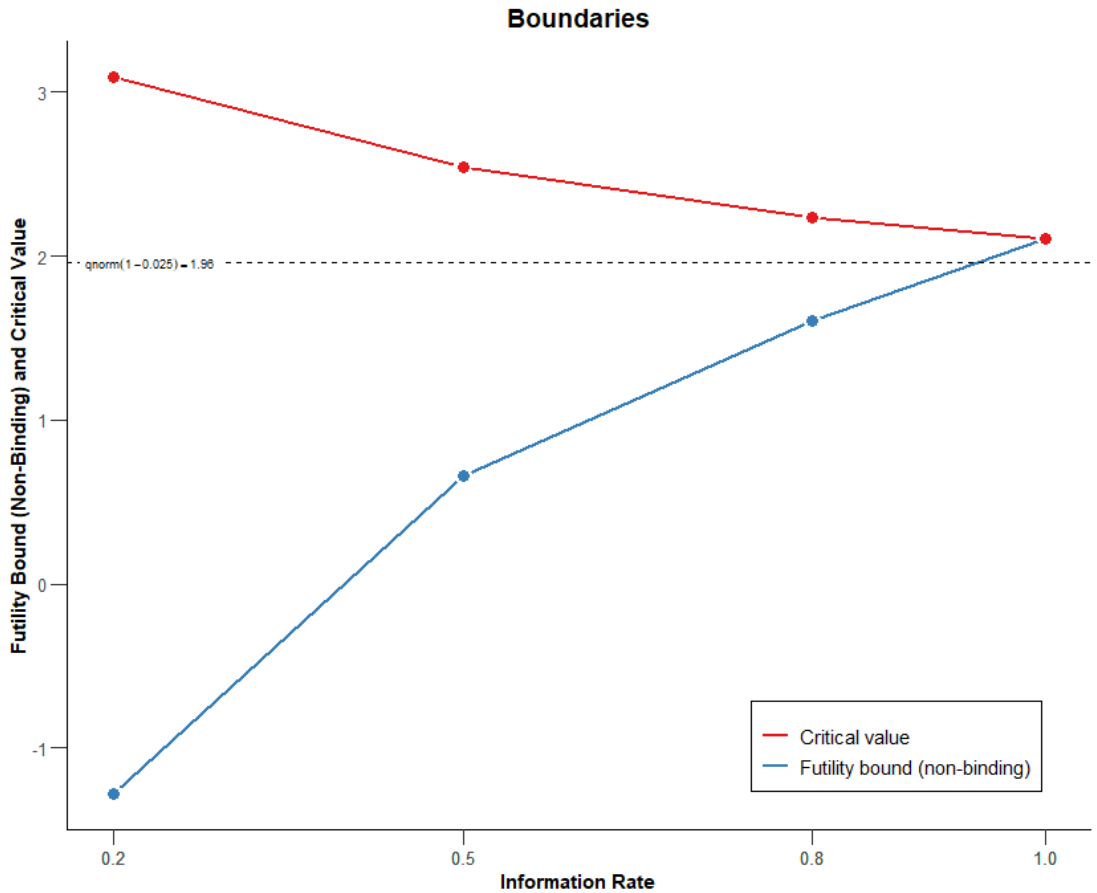
```
getDesignCharacteristics(design)
```

```
Group sequential design characteristics:
  Number of subjects fixed                          : 7.8489
  Shift                                             : 8.4183
  Inflation factor                                  : 1.0725
  Informations                                      : 2.525, 5.051, 8.418
  Power                                             : 0.009657, 0.336174, 0.800000
  Rejection probabilities under H1                  : 0.009657, 0.326517, 0.463826
  Futility probabilities under H1                   : 0.056010, 0.004585
  Ratio expected vs fixed sample size under H1 : 0.8812
  Ratio expected vs fixed sample size under a value between H0 and H1 : 0.8676
  Ratio expected vs fixed sample size under H0 : 0.6419
```

- `Number of subjects fixed` : for abstract design without interim analyses.
- `Shift` : Maximal sample size for abstract design with interim analyses.
- `Inflaction factor` : Maximum sample size increase of sequential design relative to design without interim analyses.
- `Ratio expected vs fixed sample size` : Reduction in expected sample size of sequential relative to fixed design.

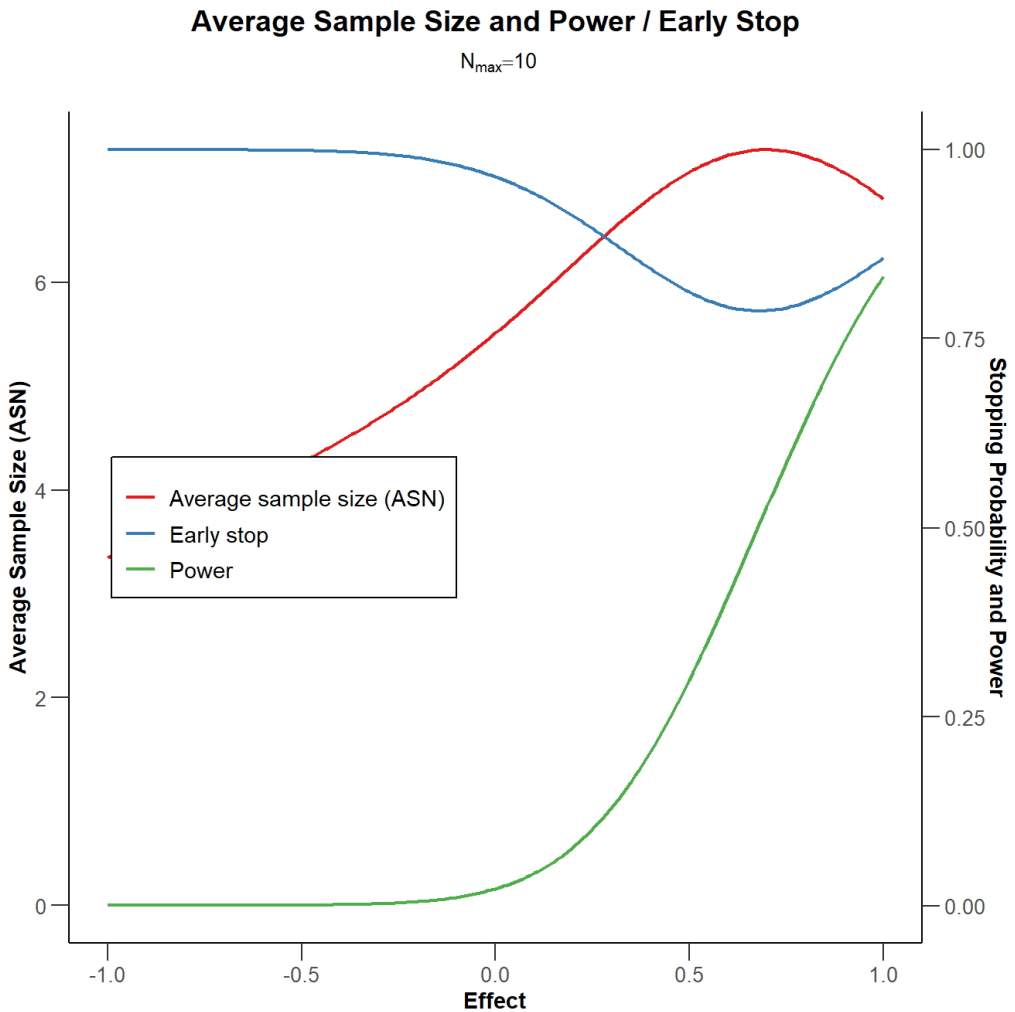
Example: Derivation of futility bounds

```
design <- getDesignInverseNormal(kMax = 4, alpha = 0.025,
    typeOfDesign = "asKD", gammaA = 2,
    informationRates = c(0.2, 0.5, 0.8, 1),
    typeBetaSpending = "bsOF")
plot(design, type = 1)
```



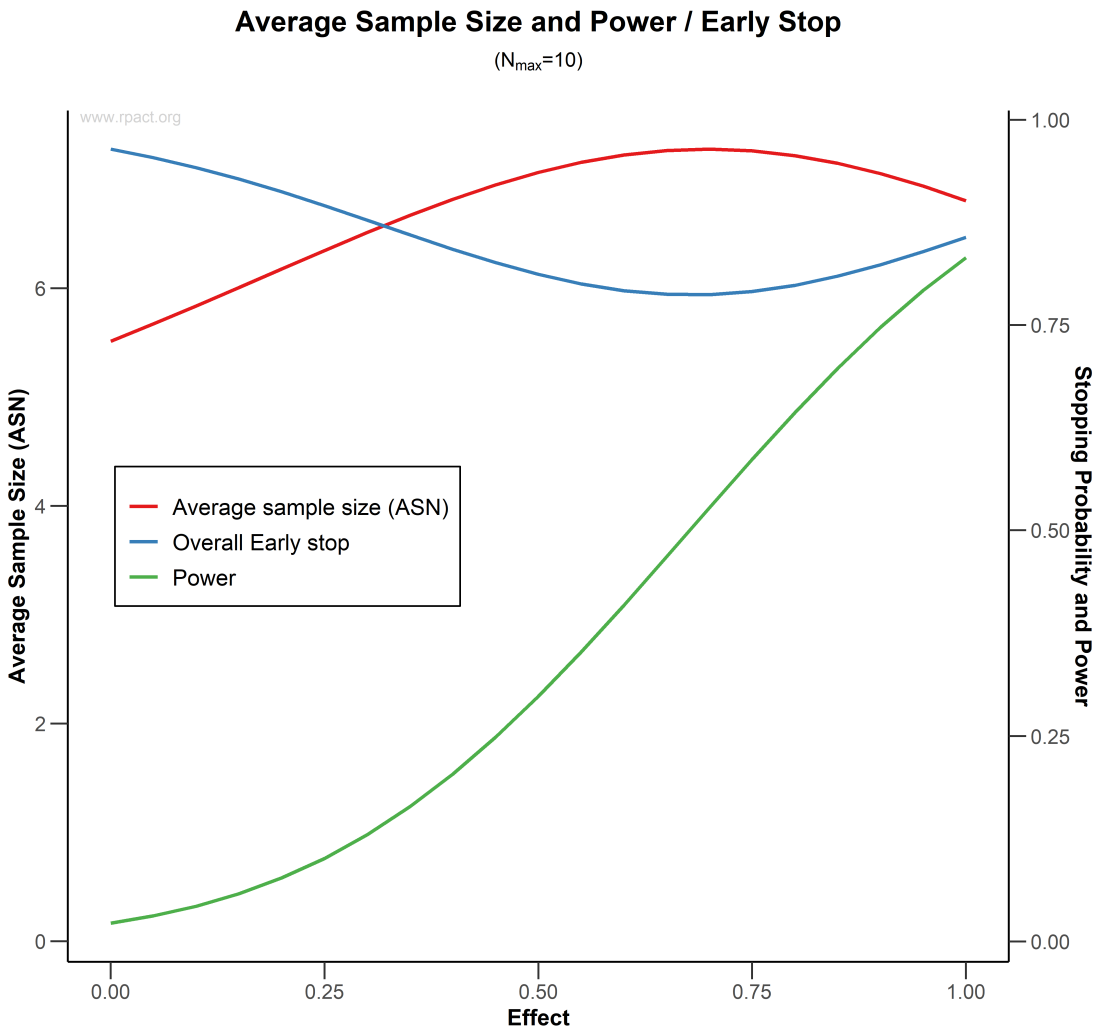
Example: Derivation of futility bounds

```
plot(design, type = 6, nMax = 10)
```



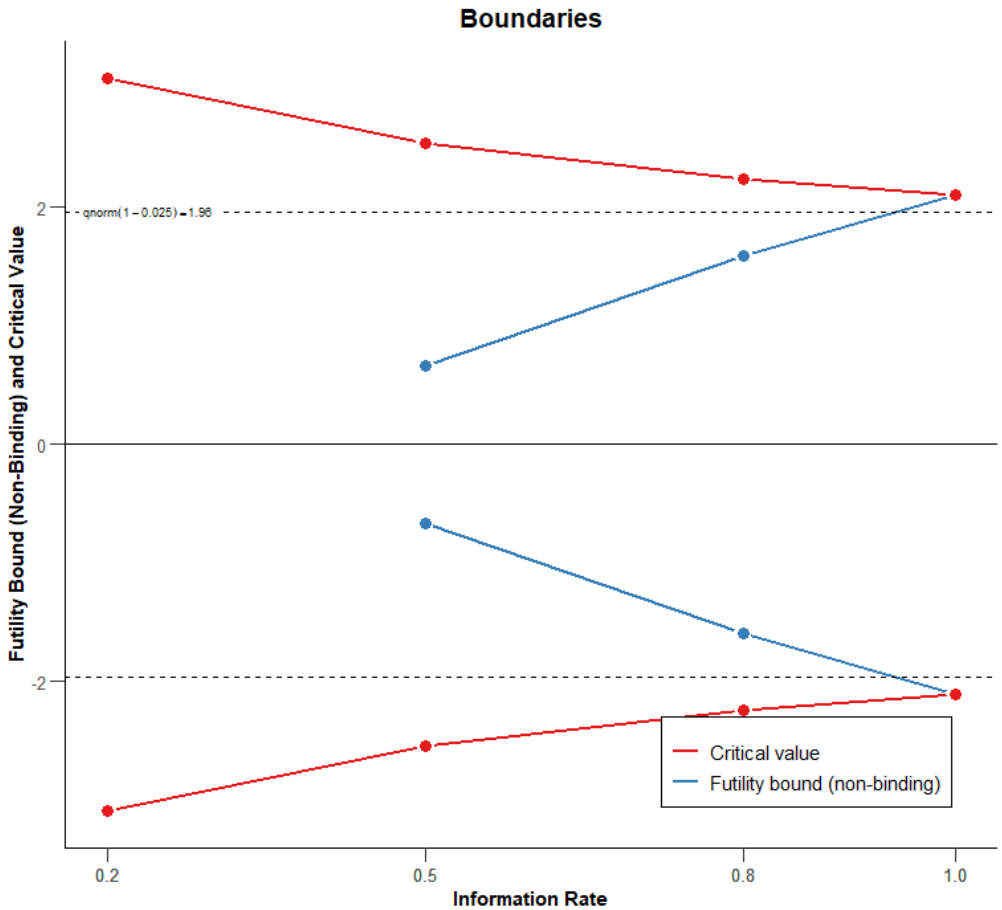
Example: Derivation of futility bounds

```
plot(design, type = 6, nMax = 10, theta = seq(0, 1, 0.05))
```



Example: Derivation futility bounds for two-sided testing

```
design <- getDesignInverseNormal(kMax = 4, alpha = 0.05,
    sided = 2, typeOfDesign = "asKD", gammaA = 2,
    informationRates = c(0.2, 0.5, 0.8, 1),
    typeBetaSpending = "bsOF")
plot(design, type = 1)
```



More on group-sequential boundaries

E.g., vignette "Defining group-sequential boundaries with rpact", written by Marcel Wolbers.

Also contains information on:

- Extracting information from `rpact` objects
- β-spending functions for futility
- Plotting `rpact` objects

Sample Size Calculation for Continuous Endpoint

Design without interim analyses

```
sampleSizeResult <- getSampleSizeMeans(
    alternative = 10, stDev = 24, sided = 2,
    alpha = 0.05, beta = 0.2,
    allocationRatioPlanned = 2)
```

- `alternative` is the alternative hypothesis value. This can be a vector of assumed alternatives (default is `seq(0.2, 1, 0.2)`)
- `stDev` is the standard deviation (default is 1). If `meanRatio = TRUE` is specified, `stDev` defines the coefficient of variation `sigma/mu2`
- `allocationRatioPlanned` The planned allocation ratio for a two treatment groups design (default is 1);
  e.g., `allocationRatioPlanned = 2` : 2(intervention) : 1(control)
  If `allocationRatioPlanned = 0` is entered, the optimal allocation ratio yielding the smallest overall sample size is determined

Design with interim analyses

```
# Design from above
design <- getDesignGroupSequential(
    sided = 1, alpha = 0.025, beta = 0.2,
    informationRates = c(0.3, 0.6, 1),
    typeOfDesign = "asOF",
    futilityBounds = c(0, -Inf),
    bindingFutility = FALSE)

# Sample size calculation
sampleSizeResult <- getSampleSizeMeans(
    design = design, alternative = 10, stDev = 24,
    allocationRatioPlanned = 2)
```

Design with interim analyses

```
summary(sampleSizeResult)
```

```
Sequential analysis with a maximum of 3 looks (group sequential design), overall
significance level 2.5% (one-sided).
The sample size was calculated for a two-sample t-test, H0: mu(1) - mu(2) = 0,
H1: effect = 10, standard deviation = 24, planned allocation ratio = 2, power 80%.

Stage                                        1       2       3
Information rate                           30%     60%    100%
Efficacy boundary (z-value scale)        3.929   2.670   1.981
Futility boundary (z-value scale)            0    -Inf
Overall power                           0.0096  0.3359  0.8000
Expected number of subjects              181.3
Number of subjects                        66.0   132.1   220.1
Cumulative alpha spent                <0.0001  0.0038  0.0250
One-sided local significance level    <0.0001  0.0038  0.0238
Efficacy boundary (t)                  26.286  12.016   6.836
Futility boundary (t)                       0
Overall exit probability (under H0)    0.5000  0.0038
Overall exit probability (under H1)    0.0657  0.3262
Exit probability for efficacy (under H0) <0.0001  0.0038
Exit probability for efficacy (under H1)  0.0096  0.3262
Exit probability for futility (under H0)  0.5000       0
Exit probability for futility (under H1)  0.0561       0

Legend:
  (t): treatment effect scale
```

Design with interim analyses

```
print(sampleSizeResult)
```

```
  ⋮

  Number of subjects (1) [1]                  : 44.0
  Number of subjects (1) [2]                  : 88.0
  Number of subjects (1) [3]                  : 146.7
  Number of subjects (2) [1]                  : 22.0
  Number of subjects (2) [2]                  : 44.0
  Number of subjects (2) [3]                  : 73.4
  Expected number of subjects under H0        : 142.7
  Expected number of subjects under H0/H1     : 181.8
  Expected number of subjects under H1        : 181.3
  Critical values (treatment effect scale) [1] : 26.286
  Critical values (treatment effect scale) [2] : 12.016
  Critical values (treatment effect scale) [3] : 6.836
  Futility bounds (treatment effect scale) [1] : 0.000
  Futility bounds (treatment effect scale) [2] : NA

Legend:
  (i): values of treatment arm i
  [k]: values at stage k
```

`Critical values (treatment effect scale)`: Minimal detectable difference (MDD), i.e., smallest difference in observed means that would lead to a rejection at this stage (assuming observed standard deviation as specified.)

Sample Size Calculation for Binary Endpoint

Exercise 3

Planning of Survival Designs

Exercise 1 and bonus exercises 6 / 7

Part II: Analysis Functions

Exercises 2 and 5

Current methods

Analysing a Trial with Interim Stages

- Group sequential test
- Inverse normal combination test
- Fisher's combination test
- Repeated confidence intervals, p-Values
- Conditional power assessment
- Final analysis adjusted confidence intervals, p-Values
- Conditional Rejection Probability (Müller & Schäfer)
- All this for continuous, binary, and survival endpoint

Group sequential analysis

`getAnalysisResults(design, dataInput, ...)`

Given a design and a data set, at given stage the function calculates the test results (effect sizes, stage-wise test statistics and p-values, overall p-values and test statistics, conditional rejection probability (CRP), conditional power, Repeated Confidence Intervals (RCIs), repeated overall p-values, and final stage p-values, median unbiased effect estimates, and confidence intervals.)

The conditional power is calculated only if (at least) the sample size for the subsequent stage(s) is specified.

- `design` The trial design.
- `dataInput` The summary data used for calculating the test results. This is either an element of DataSetMeans, of DataSetRates, or of DataSetSurvival.

Group sequential analysis

`dataInput`

- An element of DataSetMeans for one sample is created by `getDataset(means = , stDevs =, sampleSizes =)` where `means, stDevs, sampleSizes` are vectors with stagewise means, standard deviations, and sample sizes of length given by the number of available stages.
- An element of DataSetMeans for two samples is created by `getDataset(means1 = , means2 = , stDevs1 =, stDevs2 =, sampleSizes1 =, sampleSizes2 =)` where `means1, means2, stDevs1, stDevs2, sampleSizes1, sampleSizes2` are vectors with stagewise means, standard deviations, and sample sizes for the two treatment groups of length given by the number of available stages.
- An element of DataSetRates for one sample is created by `getDataset(events =, sampleSizes =)` where `events, sampleSizes` are vectors with stagewise events and sample sizes of length given by the number of available stages.

Group sequential analysis

`dataInput`

- An element of DataSetRates for two samples is created by `getDataset(events1 =, events2 =, sampleSizes1 =, sampleSizes2 =)` where `events1, events2, sampleSizes1, sampleSizes2` are vectors with stagewise events and sample sizes for the two treatment groups of length given by the number of available stages.
- An element of DataSetSurvival is created by `getDataset(events =, logRanks =, allocationRatios =)` where `events, logRanks, and allocation ratios` are the stagewise events, logrank statistics, and allocation ratios.

The data sets can also be created by importing raw data (e.g., from a SAS file), calculating estimated adjusted (marginal) means for a linear model (e.g., ANCOVA), and using the `emmeans` package to define the components in `getDataset()`.

Example

Specify design:

```
design <- getDesignInverseNormal(
    kMax = 4, typeOfDesign = "WT", deltaWT = 0.45)
```

Data summary for binary data:

```
dataExample <- getDataset(
        n1      = c( 8, 10,  9),
        n2      = c(11, 13, 12),
        events1 = c( 3,  4,  5),
        events2 = c( 8, 10, 12))
```

Create results object:

```
results <- getAnalysisResults(design = design,
    dataInput = dataExample, directionUpper = FALSE)
```

print(results)

```
Design parameters:
  Fixed weights                          : 0.500, 0.500, 0.500, 0.500
  Critical values                        : 2.456, 2.372, 2.325, 2.291
  Futility bounds (non-binding)          : -Inf, -Inf, -Inf
  Cumulative alpha spending              : 0.007026, 0.013828, 0.019778, 0.025000
  Local one-sided significance levels    : 0.007026, 0.008839, 0.010045, 0.010968
  Significance level                     : 0.0250
  Test                                   : one-sided
User defined parameters:
  Direction upper                        : FALSE
Default parameters:
  Normal approximation                   : TRUE
  Theta H0                               : 0
Stage results:
  Cumulative effect sizes                : -0.3523, -0.3611, -0.3889, NA
  Cumulative treatment rate              : 0.375, 0.389, 0.444, NA
  Cumulative control rate                : 0.727, 0.75, 0.833, NA
  Stage-wise test statistics             : -1.536, -1.799, -2.567, NA
  Stage-wise p-values                    : 0.062328, 0.036037, 0.005133, NA
  Combination test statistics            : 1.536, 2.358, 3.407, NA
Analysis results:
  Actions                                : continue, continue, reject and stop, NA
  Conditional rejection probability      : 0.07769, 0.30931, 0.90625, NA
  Conditional power                      : NA, NA, NA, NA
  Repeated confidence intervals (lower)  : -0.7386, -0.6456, -0.6185, NA
  Repeated confidence intervals (upper)  : 0.197323, 0.002224, -0.140459, NA
  Repeated p-values                      : 0.156147, 0.025923, 0.000906, NA
  Final stage                            : 3
  Final p-value                          : NA, NA, 0.01387, NA
  Final CIs (lower)                      : NA, NA, -0.5687, NA
  Final CIs (upper)                      : NA, NA, -0.03726, NA
  Median unbiased estimate               : NA, NA, -0.3168, NA
```

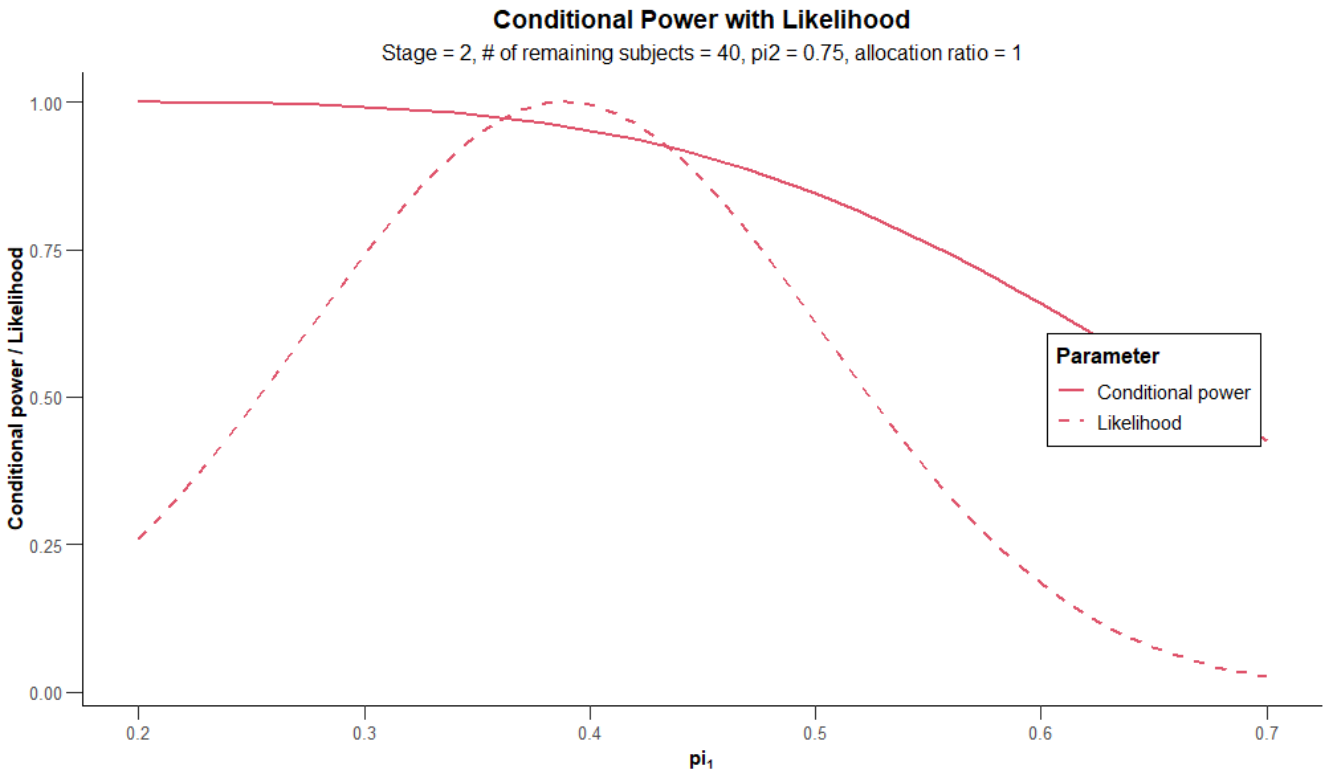
summary(results)

```
Analysis results for a binary endpoint

Sequential analysis with 4 looks (inverse normal combination test design).
The results were calculated using a two-sample test for rates (one-sided),
normal approximation test.
H0: pi(1) - pi(2) = 0 against H1: pi(1) - pi(2) < 0.
```

Stage	1	2	3	4
Fixed weight	0.5	0.5	0.5	0.5
Efficacy boundary (z-value scale)	2.456	2.372	2.325	2.291
Cumulative alpha spent	0.0070	0.0138	0.0198	0.0250
Stage level	0.0070	0.0088	0.0100	0.0110
Cumulative effect size	-0.352	-0.361	-0.389	
Cumulative treatment rate	0.375	0.389	0.444	
Cumulative control rate	0.727	0.750	0.833	
Stage-wise test statistic	-1.536	-1.799	-2.567	
Stage-wise p-value	0.0623	0.0360	0.0051	
Inverse normal combination	1.536	2.358	3.407	
Test action	continue	continue	reject and stop	
Conditional rejection probability	0.0777	0.3093	0.9062	
95% repeated confidence interval	[-0.739; 0.197]	[-0.646; 0.002]	[-0.618; -0.140]	
Repeated p-value	0.1561	0.0259	0.0009	
Final p-value			0.0139	
Final confidence interval			[-0.569; -0.037]	
Median unbiased estimate			-0.317	

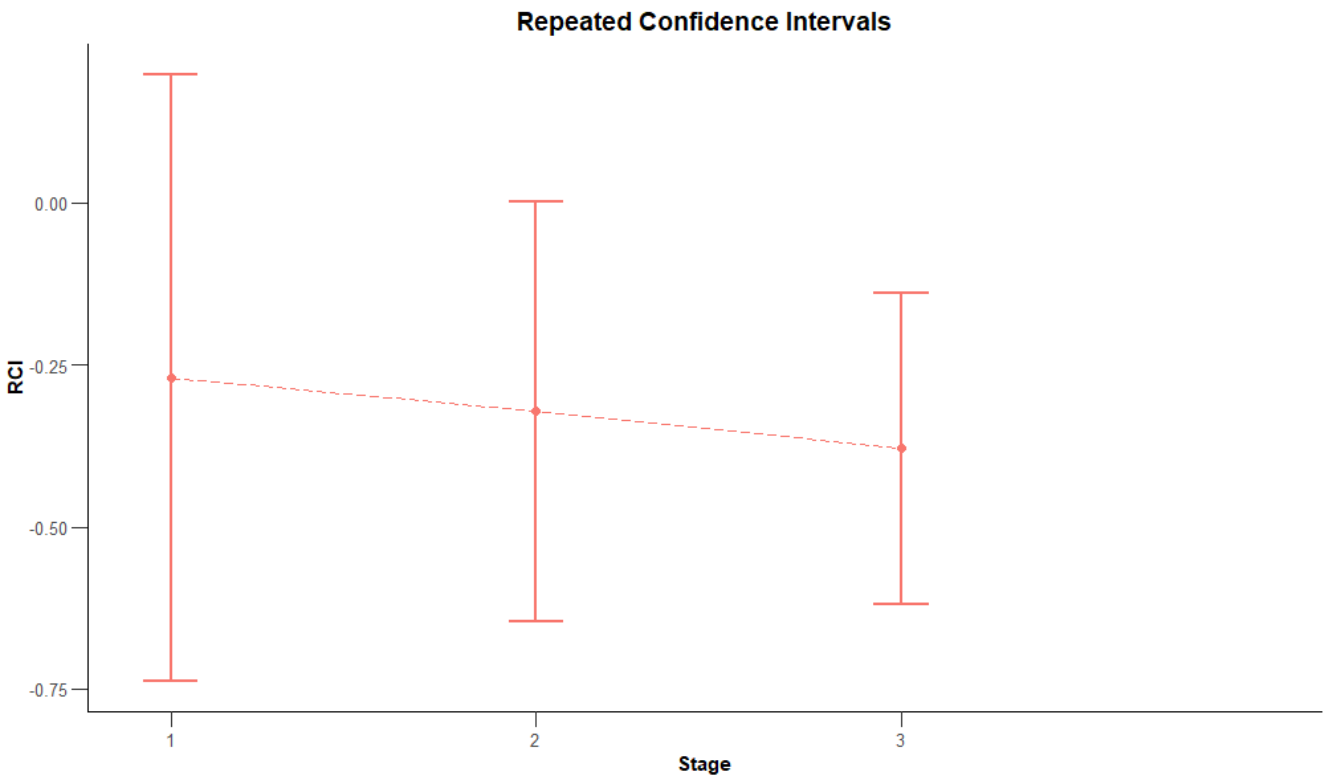
Example

```
resultsStage2 <- getAnalysisResults(design, dataInput = dataExample,
    stage = 2, pi1 = 0.45, pi2 = 0.75, nPlanned = c(20, 20),
    directionUpper = FALSE)

plot(resultsStage2, piTreatmentRange = c(0.2, 0.7))
```



Example

```
plot(results, type = 2)
```



Multi-Arm Analysis: Example 5

`dataInput`

- An element of DataSetMeans for [G + 1] samples is created by
  `getDataset(means1 =, ..., means[G+1] =, stDevs1 =, ..., stDevs[G+1] =, sampleSizes1 =, ..., sampleSizes[G+1] =)`,
  where `means1, ..., means[G+1], stDevs1, ..., stDevs[G+1], sampleSizes1, ..., sampleSizes[G+1]` are vectors with stagewise means, standard deviations, and sample sizes for [G+1] treatment groups of length given by the number of available stages.
- Last treatment arm [G + 1] always refers to the control group that cannot be deselected.
- Only for the first stage all treatment arms needs to be specified, so treatment arm selection with an arbitrary number of treatment arms for subsequent stage can be considered.
- Analogue definition of DataSetRates and DataSetSurvival.

Part III: Simulation Functions

Simulation functions

- Similar to power calculation, simulation tool available
- Fixed sample size or sample size recalculation can be assessed
- Very similar options as compared to power calculation functions for testing means, rates, and survival
- Survival simulation implemented in C++, so very fast
- `getSimulationMeans()`, `getSimulationRates()`, and `getSimulationSurvival()`
- Also: `getSimulationMultiArmxxx()` and `getSimulationEnrichmentxxx()`.

Example

Example

```
getSimulationMeans(plannedSubjects = 100)
```

```
User defined parameters:
  Seed                                  : -774025874
  Planned cumulative subjects           : 100

Default parameters:
  Planned allocation ratio              : 1
  Maximum number of iterations          : 1000
  Standard deviation                    : 1
  Alternatives                          : 0, 0.2, 0.4, 0.6, 0.8, 1
  Treatment groups                      : 2
  Direction upper                       : TRUE
  Theta H0                              : 0
  Mean ratio                            : FALSE
  Normal approximation                  : TRUE

Results:
  Iterations                            : 1000, 1000, 1000, 1000, 1000, 1000
  Overall reject                        : 0.0350, 0.1630, 0.5270, 0.8400, 0.9800, 0.9990
  Reject per stage                      : 0.0350, 0.1630, 0.5270, 0.8400, 0.9800, 0.9990
  Futility stop                         : 0, 0, 0, 0, 0, 0
  Early stop                            : 0.0000, 0.0000, 0.0000, 0.0000, 0.0000, 0.0000
  Expected number of subjects           : 100.0, 100.0, 100.0, 100.0, 100.0, 100.0
  Sample sizes                          : 100.0, 100.0, 100.0, 100.0, 100.0, 100.0
```

Example

```
getSimulationMeans(plannedSubjects = 100, showStatistics = TRUE)
```

```
Simulated data:
  Number of subjects [1], alternative = 0      : median [range]: 100 [100 - 100]; mean +/-sd: 100 +/-0
  Number of subjects [1], alternative = 0.2    : median [range]: 100 [100 - 100]; mean +/-sd: 100 +/-0
  Number of subjects [1], alternative = 0.4    : median [range]: 100 [100 - 100]; mean +/-sd: 100 +/-0
  Number of subjects [1], alternative = 0.6    : median [range]: 100 [100 - 100]; mean +/-sd: 100 +/-0
  Number of subjects [1], alternative = 0.8    : median [range]: 100 [100 - 100]; mean +/-sd: 100 +/-0
  Number of subjects [1], alternative = 1      : median [range]: 100 [100 - 100]; mean +/-sd: 100 +/-0
  Test statistic [1], alternative = 0          : median [range]: 0.081 [-3.236 - 3.414]; mean +/-sd: 0.076
  Test statistic [1], alternative = 0.2        : median [range]: 0.944 [-2.727 - 4.012]; mean +/-sd: 0.96
  Test statistic [1], alternative = 0.4        : median [range]: 2.033 [-1.377 - 5.147]; mean +/-sd: 2.018
  Test statistic [1], alternative = 0.6        : median [range]: 3.026 [-0.2 - 6.95]; mean +/-sd: 3.029 +/
  Test statistic [1], alternative = 0.8        : median [range]: 3.966 [0.883 - 7.331]; mean +/-sd: 3.982
  Test statistic [1], alternative = 1          : median [range]: 5.017 [1.676 - 8.095]; mean +/-sd: 4.991
```

Receive the data (i.e., test statistics etc., not raw data!) used for the simulation:

```
getData(getSimulationMeans(plannedSubjects = 100))
```

Example: Group sequential design

```
design <- getDesignGroupSequential()
```

```
getSimulationMeans(design, plannedSubjects = c(20, 40, 60))
```

```
Simulation of means (group sequential design):

.
.
.

Results:
  Alternatives                                : 0.0, 0.2, 0.4, 0.6, 0.8, 1.0
  Iterations [1]                              : 1000, 1000, 1000, 1000, 1000, 1000
  Iterations [2]                              : 1000, 996, 996, 986, 954, 903
  Iterations [3]                              : 994, 965, 881, 702, 466, 250
  Overall reject                              : 0.0240, 0.1110, 0.3450, 0.6540, 0.8670, 0.9670
  Reject per stage [1]                        : 0.0000, 0.0040, 0.0040, 0.0140, 0.0460, 0.0970
  Reject per stage [2]                        : 0.0060, 0.0310, 0.1150, 0.2840, 0.4880, 0.6530
  Reject per stage [3]                        : 0.0180, 0.0760, 0.2260, 0.3560, 0.3330, 0.2170
  Futility stop per stage [1]                 : 0.0000, 0.0000, 0.0000, 0.0000, 0.0000, 0.0000
  Futility stop per stage [2]                 : 0.0000, 0.0000, 0.0000, 0.0000, 0.0000, 0.0000
  Futility stop                               : 0, 0, 0, 0, 0, 0
  Early stop                                  : 0.0060, 0.0350, 0.1190, 0.2980, 0.5340, 0.7500
  Expected number of subjects                 : 59.9, 59.2, 57.5, 53.8, 48.4, 43.1
  Sample sizes [1]                            : 20.0, 20.0, 20.0, 20.0, 20.0, 20.0
  Sample sizes [2]                            : 20.0, 20.0, 20.0, 20.0, 20.0, 20.0
  Sample sizes [3]                            : 20.0, 20.0, 20.0, 20.0, 20.0, 20.0
  Conditional power (achieved) [1]            : NA, NA, NA, NA, NA, NA
  Conditional power (achieved) [2]            : 0.0595, 0.1174, 0.2138, 0.3723, 0.5127, 0.6254
  Conditional power (achieved) [3]            : 0.0644, 0.1322, 0.2677, 0.4448, 0.5555, 0.6582
```

Simulation of testing means

`getSimulationMeans(design, plannedSubjects, ...)`

Returns the sample size for testing means in one and two samples.

- `design` The trial design.
- `groups` The number of treatment groups (1 or 2) (default is 2).
- `meanRatio` If `meanRatio = TRUE` is specified the sample size for one-sided testing of H0: mu1/mu2 = thetaH0 is calculated (default is FALSE).
- `thetaH0` The null hypothesis value. For one-sided testing, a value != 0 (or a value != 1 for testing the mean ratio) can be specified (default is 0).
- `alternative` The alternative hypothesis value. This can ba a vector of assumed alternatives (default is seq(0.2, 1, 0.2)).
- `stDev` The standard deviation (default is 1). If `meanRatio = TRUE` is specified, `stDev` defines the coefficient of variation sigma/mu2.

Simulation of testing means

```
getSimulationMeans(design, plannedSubjects, ...)
```

- `plannedSubjects` `plannedSubjects` is a vector of length kMax (the number of stages of the design) that determines the number of cumulated (overall) subjects when the interim stages are planned.
- `directionUpper` Specifies the direction of the alternative, only applicable for one-sided testing, default is TRUE.
- `allocationRatioPlanned` The planned allocation ratio for a two treatment groups design (default is 1).
- `maxNumberOfIterations` The number of simulation iterations.
- `seed` The seed to reproduce the simulation, default is a random seed.

Simulation of testing means

```
getSimulationMeans(design, plannedSubjects, ...)
```

- `conditionalPower` The conditional power under which the sample size recalculation is performed.
- `minNumberOfSubjectsPerStage` When performing a data driven sample size recalculation, the vector with length kMax `minNumberOfSubjectsPerStage` determines the minimum number of subjects per stage (i.e., not cumulated), the first element is not taken into account.
- `maxNumberOfSubjectsPerStage` Analogously
- `thetaH1` If specified, the value of the alternative under which the conditional power calculation is performed.
- `calcSubjectsFunction` Optionally, a function can be entered that defines the way of performing the sample size recalculation.
  By default, the sample size recalculation is performed with specified conditional power and `minNumberOfSubjectsPerStage` and `maxNumberOfSubjectsPerStage`.

Simulation of testing means

Example

Assess power and average sample size if a sample size increase is foreseen at conditional power 80% for each subsequent stage based on observed overall effect and specified `minNumberOfSubjectsPerStage` and `maxNumberOfSubjectsPerStage`.

```
designIN <- getDesignInverseNormal()
getSimulationMeans(designIN, alternative = 0:4, stDev = 5,
    plannedSubjects = c(20, 40, 60),
    minNumberOfSubjectsPerStage = c(NA, 20, 20),
    maxNumberOfSubjectsPerStage = c(NA, 80, 80),
    conditionalPower = 0.8, maxNumberOfIterations = 1000)
```

Simulation of testing means

Example

Do the same under the assumption that a sample size increase only takes place at the first interim. The sample size for the third stage is set equal to the second stage sample size.

```
mySampleSizeCalculationFunction <- function(..., stage,
        minNumberOfSubjectsPerStage,
        maxNumberOfSubjectsPerStage, sampleSizesPerStage,
        conditionalPower, conditionalCriticalValue,
        thetaH1, stDevH1) {
    if (stage == 2) {
        stageSubjects <- 4 * (max(0,
            conditionalCriticalValue +
            qnorm(conditionalPower)))^2 /
            (max(1e-12, thetaH1 / stDevH1))^2
        stageSubjects <- min(max(
            minNumberOfSubjectsPerStage[stage], stageSubjects
        ), maxNumberOfSubjectsPerStage[stage])
    } else {
        stageSubjects <- sampleSizesPerStage[stage - 1]
    }
    return(stageSubjects)
}
```

Simulation of testing means

Example

```
getSimulationMeans(designIN, alternative = 2:4, stDev = 5,
    plannedSubjects = c(20, 40, 60),
    minNumberOfSubjectsPerStage = c(NA, 20, 20),
    maxNumberOfSubjectsPerStage = c(NA, 160, 160),
    conditionalPower = 0.8,
    calcSubjectsFunction = mySampleSizeCalculationFunction,
    maxNumberOfIterations = 1000)
```

- For testing rates, examples and sample size calculation formula can be found in `?getSimulationRates`
- Simulating rates: exercise 4
- Simulating survival: Bonus exercise 7