# Introduction to rpact

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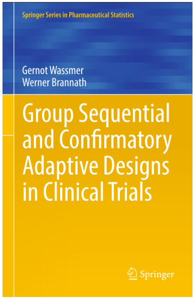
## **What is** `rpact`**?**

## 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

$\rightarrow$ www.rpact.org


Springer Series in Pharmaceutical Statistics
Gernot Wassmer
Werner Brannath
Group Sequential and Confirmatory Adaptive Designs in Clinical Trials
Springer

- 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

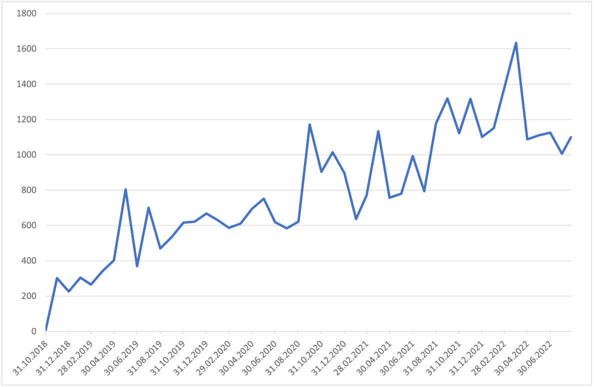
$\rightarrow$ www.rpact.com

## Company RPACT in Figures

- Founded in May 2017
- Idea: open source development with help of “crowd funding”
- Currently supported by 21 companies
  $\rightarrow$ “Service Level Agreement” (SLA)
- 53 presentations and training courses since 2018

## R package rpact in Figures

- 20 releases on CRAN since October 2018
- Comes with 25 vignettes
- CRAN download stats:



## `rpact` – Functional Range

- Design
  - Comprehensive set of group sequential designs, e.g., Wang & Tsiatis $\Delta$-class, $\alpha$-spending, $\beta$-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 shiny.rpact.com

# The rpact Package Concept

## Package Concept – Workflow

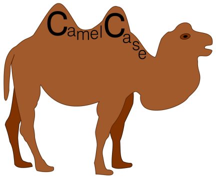
Usage inspired by the typical workflow in trial design and conduct:

- 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()`



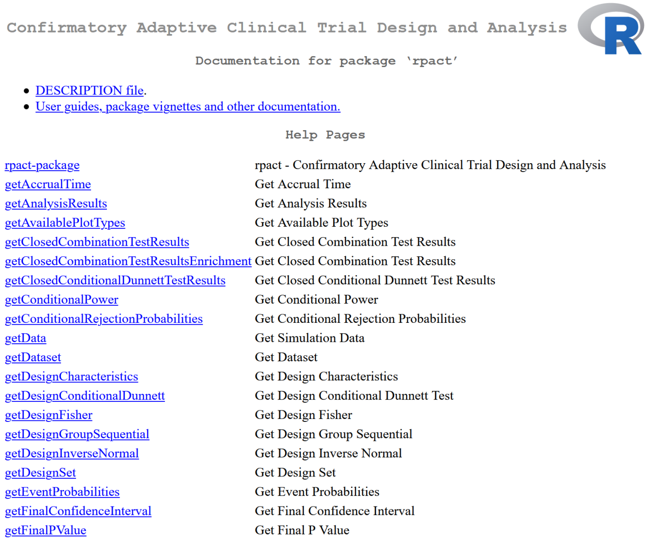
## Package Concept – Utilities

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**: `getDesignInverseNormal()` produces the output:

```
Design parameters and output of inverse normal combination test design:

User defined parameters: not available

Derived from user defined parameters: not available

Default parameters:
  Type of design              : OF
  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**: `getDesignInverseNormal(kMax = 2)` produces:

```
Design parameters and output of inverse normal combination test 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            : OF
  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 $\alpha$-spending

```
# Efficacy interim analyses at 30%, 60% and 100% information
design <- getDesignGroupSequential(
    sided = 2, alpha = 0.05, beta = 0.2,
    informationRates = c(0.3, 0.6, 1),
    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.
- `typeOfDesign = "asOF"` : O'Brien & Fleming type $\alpha$-spending.

## Supported efficacy boundaries

**Argument** `typeOfDesign`**:**

- Exact O'Brien & Fleming ("OF"), Pocock ("P"), Wang & Tsiatis ("WT"), Haybittle & Peto ("HP")
- Pampallona & Tsiatis ("PT") one-sided and two-sided designs
- O'Brien & Fleming and Pocock type $\alpha$-spending ("asOF" and "asP")
- Kim & DeMets ("asKD") and Hwang, Shi & DeCani $\alpha$-spending ("asHSD") and beta-spending ("bsKD" and ("bsHSD"))
- User-defined $\alpha$-spending ("asUser") and $\beta$-spending ("bsUser")
- No early efficacy stops ("noEarlyEfficacy")

## Example: Futility boundaries

```
# Example: non-binding futility boundary at first interim in
# case estimated treatment effect is null or in "the wrong
# direction", no futility at second interim
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)
```

- `futilityBounds`: Vector on $z$-value scale for interim analyses (excluding final analysis).
  - $z = 0$: Futility if “null effect or effect in wrong direction”
  - $z = -Inf$: No futility at this interim analysis
- `bindingFutility = FALSE` (default): no effect on efficacy boundaries.
- `futilityBounds` only supported for one-sided testing.

## Output

```r
print(design)
```

```
User defined parameters:
  Type of design                              : O'Brien & Fleming type alpha spending
  Information rates                           : 0.400, 0.800, 1.000
  Futility bounds (non-binding)               : 0, -Inf
Derived from user defined parameters:
  Maximum number of stages                    : 3
Default parameters:
  Stages                                      : 1, 2, 3
  Significance level                          : 0.0250
  Type II error rate                          : 0.2000
  Two-sided power                             : FALSE
  Binding futility                            : FALSE
  Test                                        : one-sided
  Tolerance                                   : 1e-08
  Type of beta spending                       : none
Output:
  Cumulative alpha spending                   : 0.0003942, 0.0122118, 0.0250000
  Critical values                             : 3.357, 2.255, 2.026
  Stage levels (one-sided)                    : 0.0003942, 0.0120779, 0.0213919
```

- `Critical values` : efficacy boundary values on *z*-value scale.
- `Stage levels` : local significance bounds.

## Additional characteristics of the design

```
getDesignCharacteristics(design)
```

```
Group sequential design characteristics:
  Number of subjects fixed                     : 7.8
  Shift                                        : 8.1984
  Inflation factor                             : 1.0445
  Informations                                 : 3.279, 6.559, 8.198
  Power                                        : 0.06106, 0.61940, 0.80000
  Rejection probabilities under H1             : 0.06106, 0.55835, 0.18060
  Futility probabilities under H1              : 0.03508, 0
  Ratio expected vs fixed sample size under H1 : 0.8676
  Ratio expected vs fixed sample size under a value between H0 and H1 : 0.8927
  Ratio expected vs fixed sample size under H0 : 0.7285
```

- `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.

## Stopping probabilities under $H_0$ and $H_1$

```
nMax <- getDesignCharacteristics(design)$shift
```

```
getPowerAndAverageSampleNumber(design,
    theta = 0, nMax = nMax)
```

```
Output:
  Average sample sizes (ASN)    : 5.455
  Power                         : 0.02344
  Early stop                    : 0.5038
  Early stop [1]                : 0.500043
  Early stop [2]                : 0.003758
  Early stop [3]                : NA
  Overall reject                : 0.02344
  Reject per stage [1]          : 4.273e-05
  Reject per stage [2]          : 0.003758
  Reject per stage [3]          : 0.01964
  Overall futility              : 0.5000
  Futility stop per stage [1]   : 0.5000
  Futility stop per stage [2]   : 0.0000

Legend:
  [k]: values at stage k
```

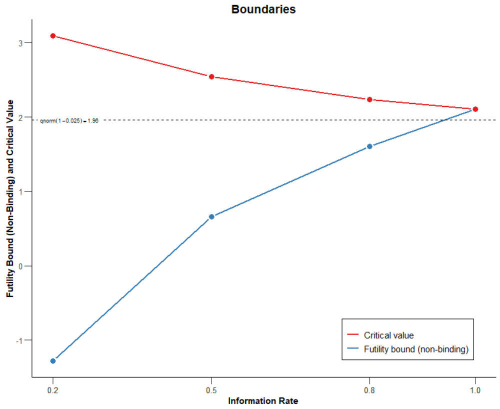
```
getPowerAndAverageSampleNumber(design,
    theta = 1, nMax = nMax)
```

```
Output:
  Average sample sizes (ASN)    : 6.928
  Power                         : 0.8000
  Early stop                    : 0.3920
  Early stop [1]                : 0.06572
  Early stop [2]                : 0.32624
  Early stop [3]                : NA
  Overall reject                : 0.8000
  Reject per stage [1]          : 0.009643
  Reject per stage [2]          : 0.326241
  Reject per stage [3]          : 0.464116
  Overall futility              : 0.05607
  Futility stop per stage [1]   : 0.05607
  Futility stop per stage [2]   : 0.00000

Legend:
  [k]: values at stage k
```

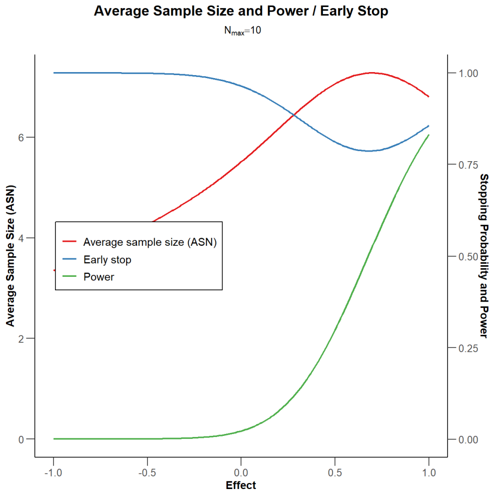
## Example: Derivation of futility bounds

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



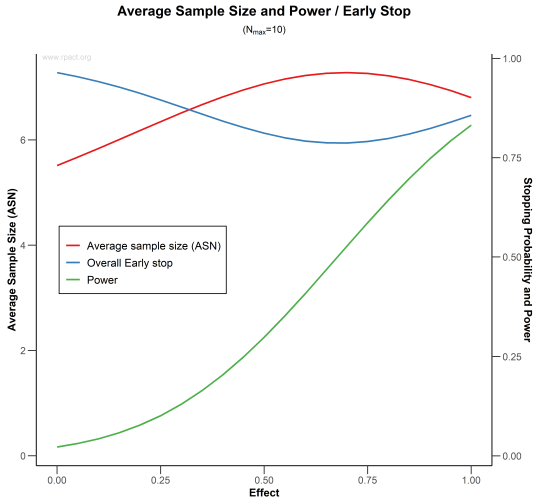
## Example: Derivation of futility bounds

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



## Example: Derivation of futility bounds

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



## 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
- $\beta$-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

```r
# 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

```r
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

```r
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

Exercises 4 and 5

## Planning of Survival Designs

Exercises 2 and 3

## 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
- Functions `getSimulationMeans()`, `getSimulationRates()`, and `getSimulationSurvival()`

## Example

### Example

```r
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: 0.07
  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: 2.01
  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

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

```r
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`

## Analysis with rpact

## 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:**

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

**Data summary for binary data:**

```r
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:**

```r
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)

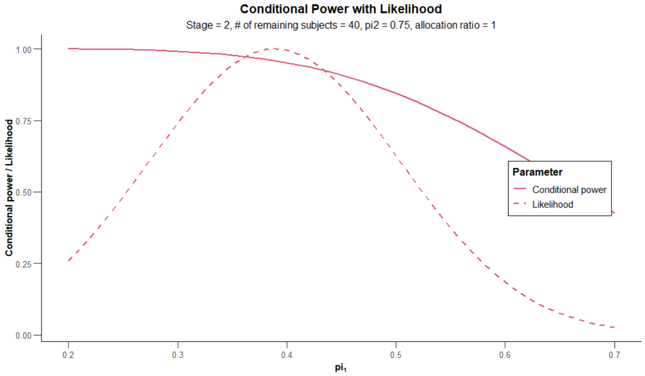
```
Analysis results for a binary endpoint

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
```

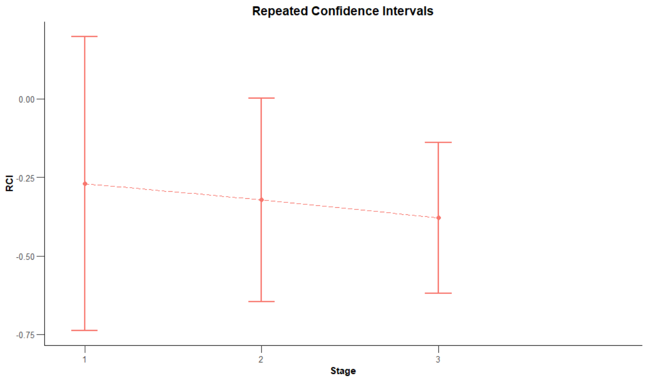
## Example

```
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

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


Repeated Confidence Intervals
RCI
Stage