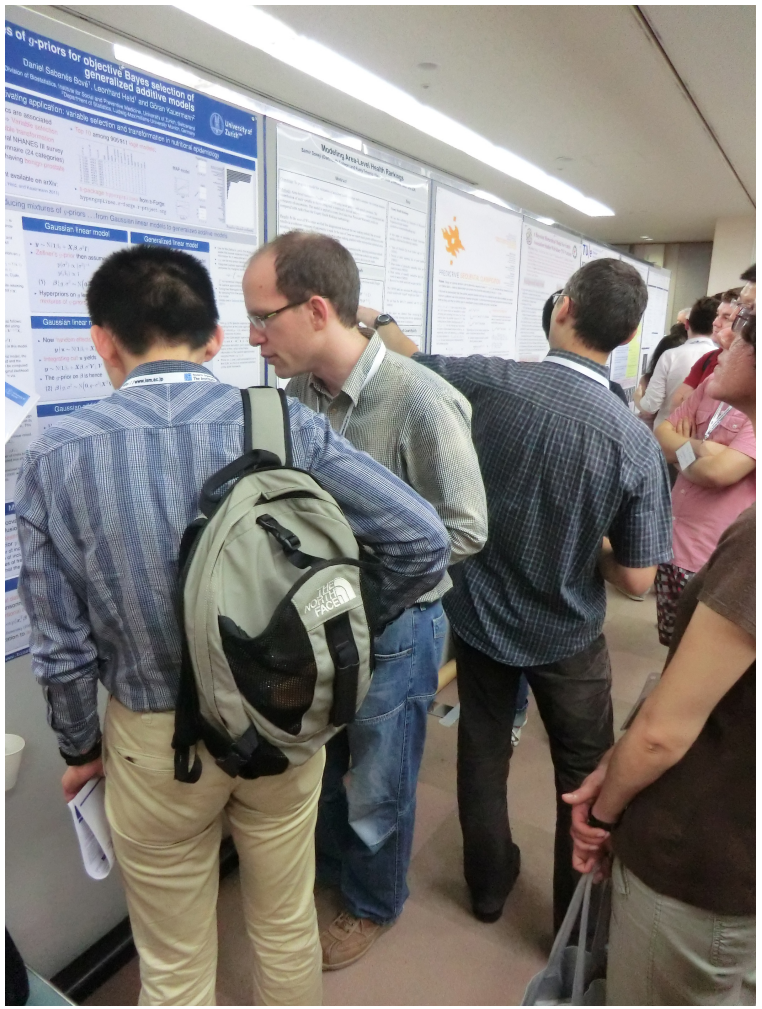
Designing Clinical Trials in R with rpact and crmPack

PharmaSUG SDE, Tokyo

Daniel Sabanés Bové, Friedrich Pahlke, Gernot Wassmer
RCONIS

April 7, 2025

日本に戻って来れてうれしい



ISBA 2012 Conference
Kyoto Japan

THURSDAY, JUNE 28TH — POSTERS

Mixtures of g-priors for objective Bayes selection of generalized additive models

Daniel SABANÉS BOVÉ (University of Zurich, Switzerland)

Recently, there has been increasing interest in mixtures of g-priors for objective Bayesian variable selection in linear models. These priors can be extended naturally to additive models, where smooth transformations of continuous covariates can be incorporated. We achieve this by using fixed-dimensional penalised splines in mixed model representation, and considering the implied marginal linear model with general covariance structure. The prior variances on the spline coefficients, defining the smoothness of the spline transformations, are taken from covariate-tailored finite sets of values and are part of the model index. Since the marginal likelihood has either a closed form or can be numerically approximated, efficient MCMC exploration of the discrete posterior model distribution is possible. We extend the approach to generalized additive models by deriving a generalized g-prior for non-normal mixed models. This directly extends the hyper-g priors for generalized linear models (Sabanes Bove and Held, 2011), from which the integrated Laplace approximation of the marginal likelihood is adopted (an efficient implementation is available in the R-package "hypergsplines"). Finally, we show how the methodology can be used for objective Bayes selection of proportional hazards models. We illustrate our approach with applications from nutritional epidemiology, where a large number of potentially influential dietary characteristics is available, and contrast it with competing methods from the literature.

Coauthors: Leonhard Held and Göran Kauermann

Me presenting my poster in Kyoto in 2012

Designing clinical trials in R

Task 📋

- Statistician needs to help with designing a clinical trial
- Evaluate different trial design options (fixed sample, group sequential, adaptive)
- Often starts with the clinician's question "How many patients do we need?"
- Need to calculate operating characteristics for the different trial designs (power, type I error, expected sample size, etc.)
- Need to assess adaptive designing strategies, e.g., sample size reassessment, treatment arm or population selection

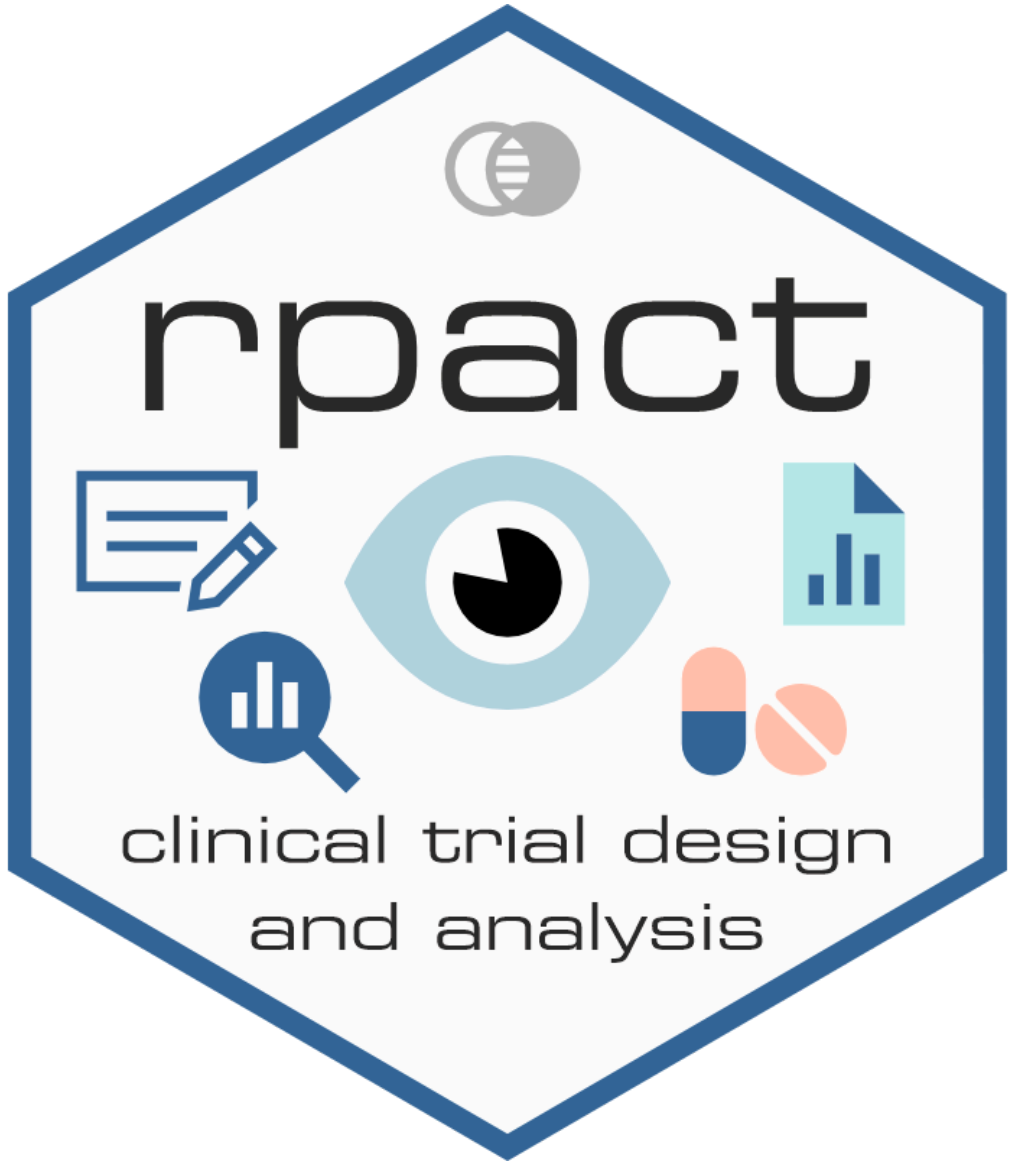
Ecosystem in R 

- From: First R package for clinical trial design was likely `S+SeqTrial`
  - Developed for S-PLUS by Emerson (2000)
  - Available for free at rct-design.com
- To: Clinical Trials CRAN task view
  - Includes `rpact` and `crmPack`
  - Also includes important other packages `pwr`, `DoseFinding`, `gsDesign`, `bcrm`, `Mediana`
  - Expect soon new task view version by openstatsware
  - Graphical view via TaskView Hexwall

Objectives of my talk 🎯

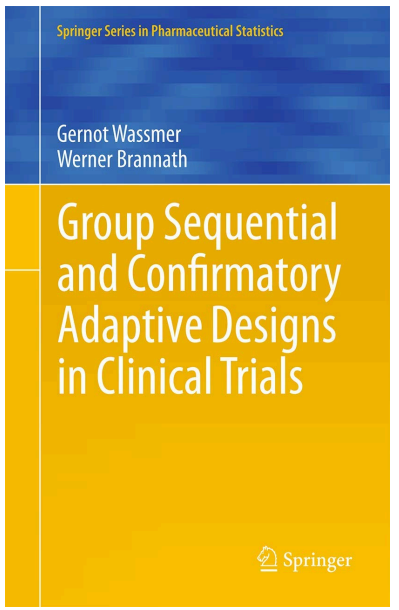
- Raise awareness of the open source R package
  `rpact` for confirmatory clinical trial designs
  - Show ***RPACT Cloud*** as alternative to traditional proprietary software for clinical trial design
- Raise awareness of the open source R package
  `crmPack` for dose escalation trial designs
- Inform about the options for ***professional support***
- Get ***RCONIS*** known as point of contact in Asia

rpact



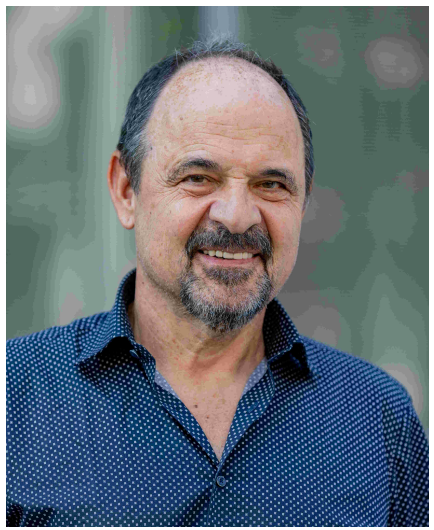
Overview

- Comprehensive ***validated R package*** implementing methodology described in Wassmer and Brannath (2016) (2nd edition coming in 2025 with R examples!)
- Enables the design of ***traditional and confirmatory adaptive group sequential designs***
- Provides interim data analysis including early ***efficacy stopping and futility analyses***
- Enables ***sample-size reassessment*** with different strategies
- Enables treatment arm selection in ***multi-stage multi-arm (MAMS)*** designs
- Enables subset selection in ***population enrichment designs***
- Provides a comprehensive and reliable ***sample size calculator***



Developed by RPACT 🏢

- RPACT company founded in 2017 by Gernot Wassmer and Friedrich Pahlke
- Idea: open source development with help of “crowd funding”
- Currently supported by 21 companies
- $>$ 80 presentations and training courses since 2018, e.g., FDA in March 2022
- ***29 vignettes*** based on Quarto and published on rpact.org/vignettes
- 28 releases on CRAN since 2018
- August 2024: New joint venture RCONIS (Daniel Sabanés Bové, Carrie Li)



RCONIS Team

RCONIS Idea 💡

- Grow RPACT company to offer a wider range of services
- Strengthen maintainer team for the `rpact` package
- Team growth combined with scope growth
- Statistical consulting and engineering services:
  Research ***Con***sulting and ***I***nnovative ***S***olutions
- Legal entity still in the making, currently a collaboration between RPACT GbR (rpact.com) and inferential.biostatistics GmbH (inferential.bio)
- Website: rconis.com

But now back to `rpact`!

Trial Designs 🔬

- ***Fixed sample*** designs:
  - continuous, binary, count, survival outcomes
- ***Group sequential*** designs:
  - efficacy interim analyses, futility stopping, alpha-spending functions
- ***Adaptive*** designs:
  - Inverse normal and Fisher's combination test, conditional error rate principle
  - Provides adjusted confidence intervals and bias corrected estimates
  - Multi-arm multi-stage (MAMS) and enrichment designs, sample size reassessment

Easy to understand R commands:

```
getDesignGroupSequential()
getDesignInverseNormal()
getDesignFisher()
getDesignConditionalDunnett()
```

Sample Size and Power Calculation 💻

Sample size and power can be calulcated for testing:

- ***means*** (continuous endpoint)
- ***proportions*** (binary endpoint)
- ***hazards*** (survival endpoint)
  - Note: flexible recruitment and survival time options
- ***rates*** (count endpoint)

Easy to understand R commands:

```
getSampleSize[Means / Rates / Survival / Counts]()
getPower[Means / Rates / Survival / Counts]()
```

Example: Sample Size Calculation

```
library(rpact)

# Define the design.
getDesignGroupSequential(
    typeOfDesign = "asOF",
    futilityBounds = c(0, 0)
) |>
    # Perform sample size calculation.
    getSampleSizeMeans(
        alternative = 2,
        stDev = 5
    ) |>
    # Obtain summary.
    summary()
```

Sample size calculation for a continuous endpoint

Sequential analysis with a maximum of 3 looks (group sequential design), one-sided overall significance level 2.5%, power 80%. The results were calculated for a two-sample t-test, H0: mu(1) - mu(2) = 0, H1: effect = 2, standard deviation = 5.

Stage	1	2	3
Planned information rate	33.3%	66.7%	100%
Cumulative alpha spent	0.0001	0.0060	0.0250

Stage	1	2	3
Stage levels (one-sided)	0.0001	0.0060	0.0231
Efficacy boundary (z-value scale)	3.710	2.511	1.993
Futility boundary (z-value scale)	0	0	
Efficacy boundary (t)	4.690	2.152	1.384
Futility boundary (t)	0	0	
Cumulative power	0.0204	0.4371	0.8000
Number of subjects	69.9	139.9	209.8
Expected number of subjects under H1			170.9
Overall exit probability (under H0)	0.5001	0.1309	
Overall exit probability (under H1)	0.0684	0.4202	
Exit probability for efficacy (under H0)	0.0001	0.0059	
Exit probability for efficacy (under H1)	0.0204	0.4167	
Exit probability for futility (under H0)	0.5000	0.1250	

Stage	1	2	3
Exit probability for futility (under H1)	0.0480	0.0035	

Legend:

- ***(t)***: treatment effect scale

Adaptive Analysis 

- Calculate ***adjusted*** point estimates and confidence intervals
- Some highlights:
  - Automatic ***boundary recalculations*** during the trial for analysis with alpha spending approach, including under- and over-running
  - Adaptive analysis tools for ***multi-arm trials***
  - Adaptive analysis tools for ***enrichment designs***

Easy to understand R commands:

```
getStageResults()
getRepeatedConfidenceIntervals()
getAnalysisResults()
```

Simulation Tool 🧪

Obtain ***operating characteristics*** of different designs:

- Assessment of ***adaptive sample size recalculation*** strategies
- Assessment of ***treatment selection strategies*** in multi-arm trials
- Assessment of ***population selection strategies*** in enrichment designs

Easy to understand R commands:

```
getSimulation[MultiArm / Enrichment][Means / Rates / Survival / Counts]()
```

Example:

```
getSimulationMeans()
getSimulationMultiArmMeans()
getSimulationEnrichmentMeans()
```

Package Validation Concept ✔

Why is rpact a reliable R package?

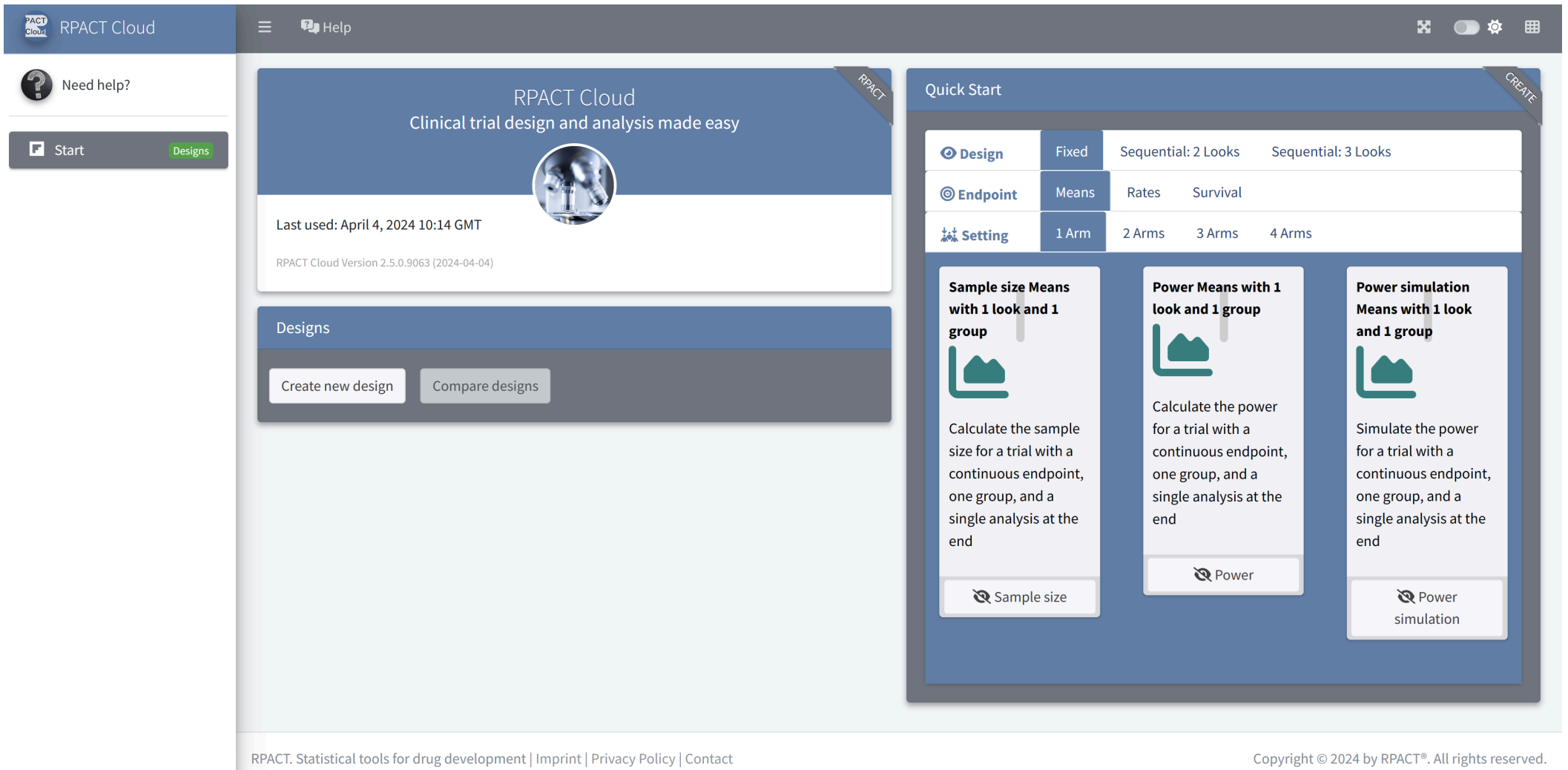
- Formal validation inspired by “GAMP 5” principles
- As few dependencies as possible:
  - Imports: Rcpp
  - Suggests: testthat, ggplot2, R6
- High ***test coverage***:
  - rpact 4.1.0 (Wassmer and Pahlke 2024): ***36,943*** unit tests (81% test coverage)
  - Usage of covr and codecov.io
- `testPackage()`: installation qualification on a client computer or company server (with professional support, more later)

RPACT Cloud

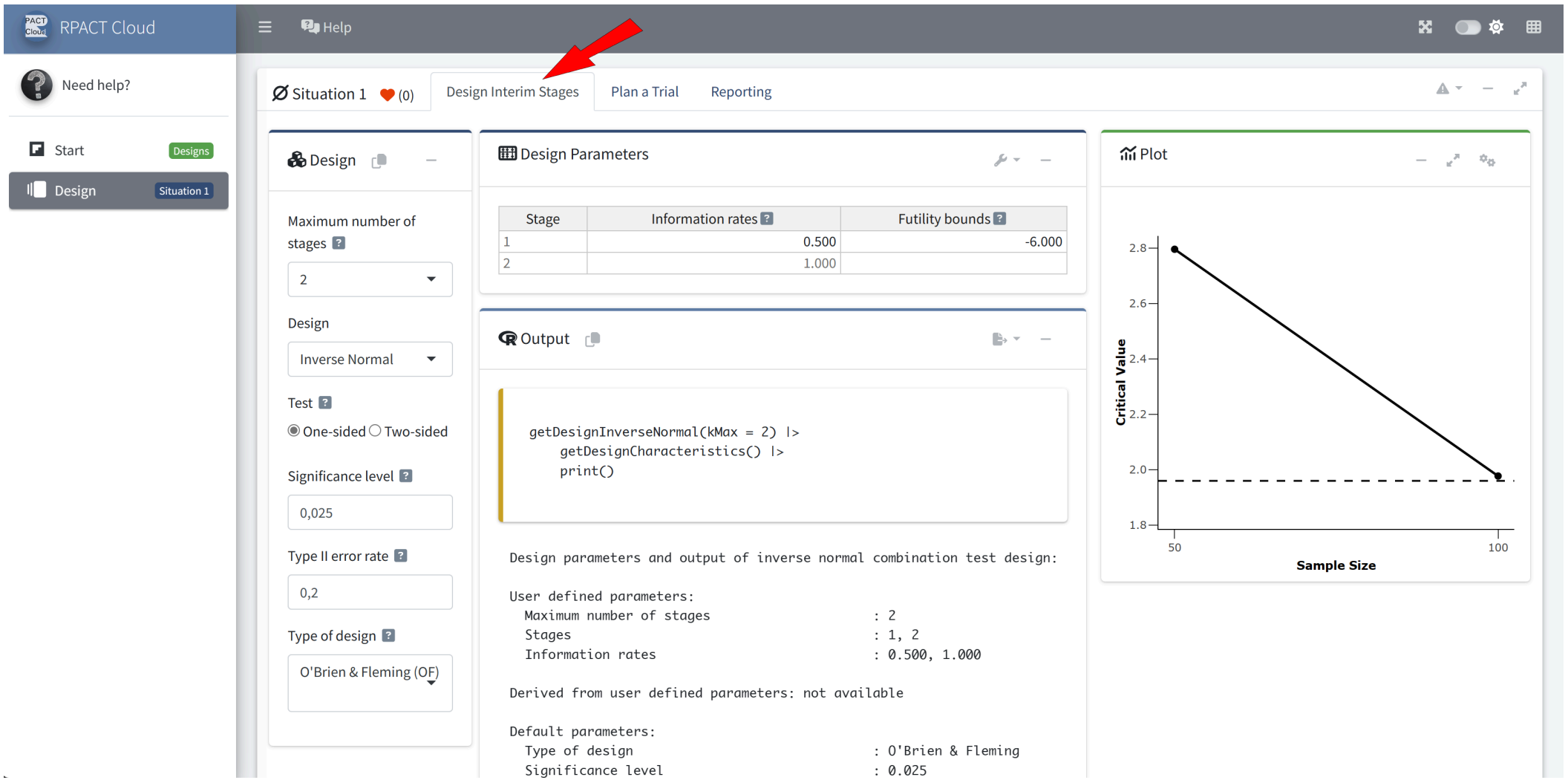
RPACT Cloud

- Graphical user interface
- Web based usage without local installation on nearly any device
- Provides an easy entry to `rpact`
- Starting point for your R Markdown or Quarto reports
- Helpful to learn/demonstrate the usage of `rpact` in a user friendly and intuitive way
- Online available at cloud.rpact.com

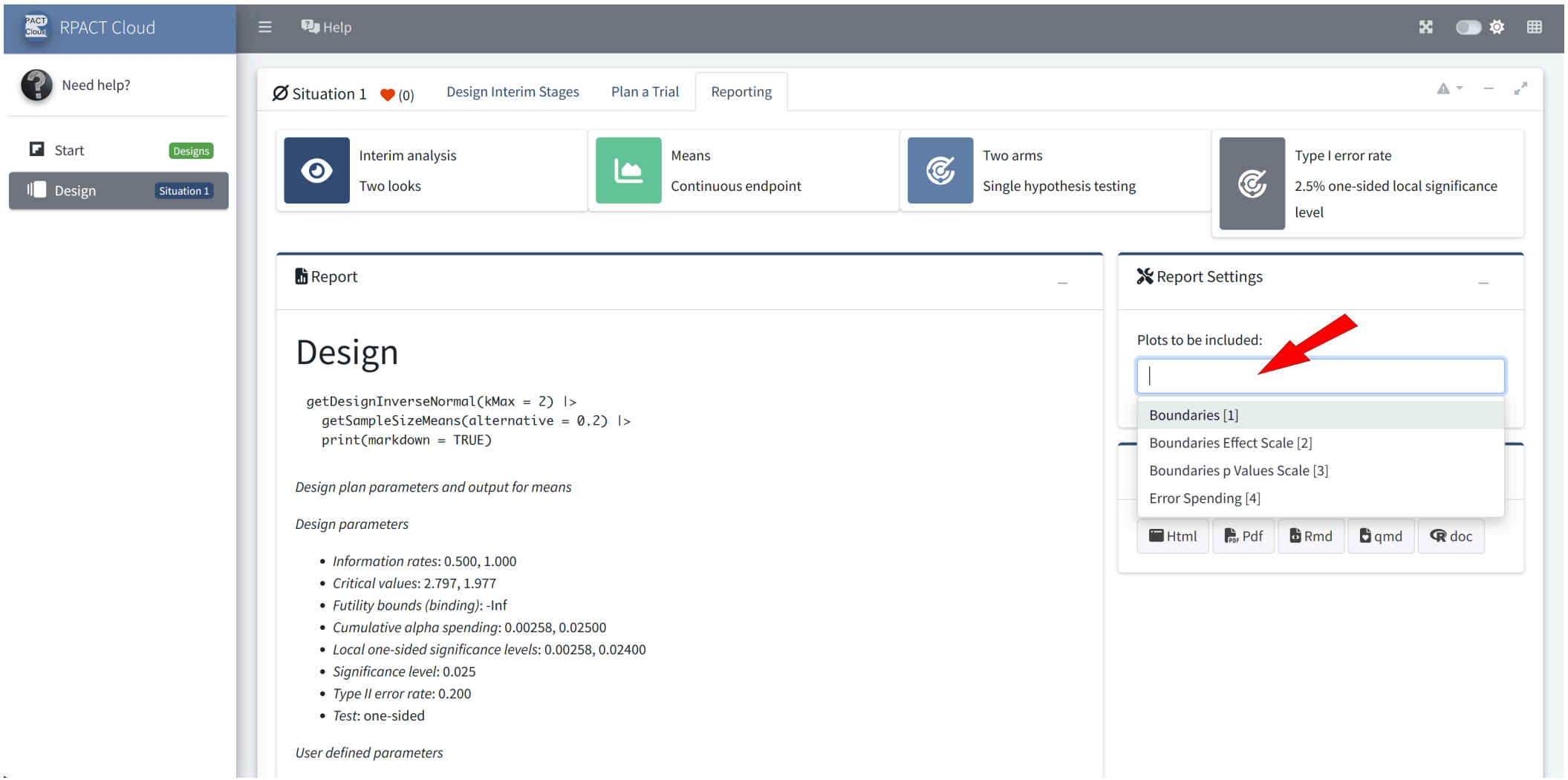
Start Page


RPACT Cloud
Help
Need help?
Start
Designs
RPACT Cloud
Clinical trial design and analysis made easy
RPACT
Last used: April 4, 2024 10:14 GMT
RPACT Cloud Version 2.5.0.9063 (2024-04-04)
Designs
Create new design
Compare designs
Quick Start
CREATE
Design
Fixed
Sequential: 2 Looks
Sequential: 3 Looks
Endpoint
Means
Rates
Survival
Setting
1 Arm
2 Arms
3 Arms
4 Arms
Sample size Means with 1 look and 1 group
Calculate the sample size for a trial with a continuous endpoint, one group, and a single analysis at the end
Sample size
Power Means with 1 look and 1 group
Calculate the power for a trial with a continuous endpoint, one group, and a single analysis at the end
Power
Power simulation Means with 1 look and 1 group
Simulate the power for a trial with a continuous endpoint, one group, and a single analysis at the end
Power simulation
RPACT. Statistical tools for drug development | Imprint | Privacy Policy | Contact
Copyright © 2024 by RPACT®. All rights reserved.

Design


RPACT Cloud
Help
Need help?
Start
Designs
Design
Situation 1
Situation 1
(0)
Design Interim Stages
Plan a Trial
Reporting
Design
Maximum number of stages
2
Design
Inverse Normal
Test
One-sided
Two-sided
Significance level
0,025
Type II error rate
0,2
Type of design
O'Brien & Fleming (OF)
Design Parameters
Stage
Information rates
Futility bounds
1
0.500
-6.000
2
1.000
Output
getDesignInverseNormal(kMax = 2) |>
getDesignCharacteristics() |>
print()
Design parameters and output of inverse normal combination test design:
User defined parameters:
Maximum number of stages : 2
Stages : 1, 2
Information rates : 0.500, 1.000
Derived from user defined parameters: not available
Default parameters:
Type of design : O'Brien & Fleming
Significance level : 0.025
Plot
Critical Value
2.8
2.6
2.4
2.2
2.0
1.8
50
100
Sample Size

Reporting


RPACT Cloud
Help
Need help?
Start
Designs
Design
Situation 1
Situation 1
(0)
Design Interim Stages
Plan a Trial
Reporting
Interim analysis
Two looks
Means
Continuous endpoint
Two arms
Single hypothesis testing
Type I error rate
2.5% one-sided local significance level
Report
Design
getDesignInverseNormal(kMax = 2) |>
getSampleSizeMeans(alternative = 0.2) |>
print(markdown = TRUE)
Design plan parameters and output for means
Design parameters
Information rates: 0.500, 1.000
Critical values: 2.797, 1.977
Futility bounds (binding): -Inf
Cumulative alpha spending: 0.00258, 0.02500
Local one-sided significance levels: 0.00258, 0.02400
Significance level: 0.025
Type II error rate: 0.200
Test: one-sided
User defined parameters
Report Settings
Plots to be included:
Boundaries [1]
Boundaries Effect Scale [2]
Boundaries p Values Scale [3]
Error Spending [4]
Html
Pdf
Rmd
qmd
doc

Export

Design Comparison

Professional Support Option 🤝

- ***Service Level Agreement*** (SLA) with RPACT
- Be part of the “RPACT User Group” → yearly ***customer meetings***
- Get ***technical software support*** for written support requests
- Get company specific ***training***
- Get company specific ***software validation documentation*** for each `rpact` release on CRAN
- Get access to the ***members area*** at www.rpact.com
- Make an `rpact` ***installation qualification*** on each company computer with your personal `testPackage()` token and secret
- Determine the direction of `rpact` ***future development activities***
- Optional support for health authority interactions
- Optional consultation to support specific clinical trials

crmPack

Overview

- Specialized R package for ***dose escalation trials***
- Initial CRAN release in 2016, publication by Sabanés Bové et al. (2019)
- Higher ***flexibility*** compared to other software, thanks to its modular design
- Easy ***extensibility*** and adoption of new designs
- Produces visual and numeric outputs for ***easy interpretation***
- Facilitates ***simulations*** to assess the performance under various scenarios

Journal of Statistical Software
May 2019, Volume 89, Issue 10. *doi: 10.18637/jss.v089.i10*

Model-Based Dose Escalation Designs in R with crmPack

Daniel Sabanés Bové
Wai Yin Yeung
Hoffmann-La Roche Ltd
Giuseppe Palermo
Hoffmann-La Roche Ltd
Thomas Jaki
Lancaster University

Abstract

Model-based dose escalation designs have gained increasing interest due to the need for more efficient and informative Phase I trials. The wide-spread implementation of such designs has been hindered by the need for either licensing specialized commercial software or programming the design and simulations from scratch for each project. The R package **crmPack** provides a simple and unified object-oriented framework for model-based dose escalation designs. This enables the standard use of such designs, while being able to flexibly adapt and extend them. The framework comprises classes and methods for the data structure including the dose grid, statistical models including prior specification, rules for maximum increments, next best dose, and adaptive stopping and cohort sizes. In addition to multiple modified classic continual reassessment method and escalation with overdose control designs with possibly advanced prior specifications (e.g., minimal informative and mixture priors), **crmPack** currently features dual-endpoint (safety and biomarker) designs and two-part designs. Optional assignment of a small number of patients in each cohort to placebo instead of treatment enables the use in trials outside oncology.

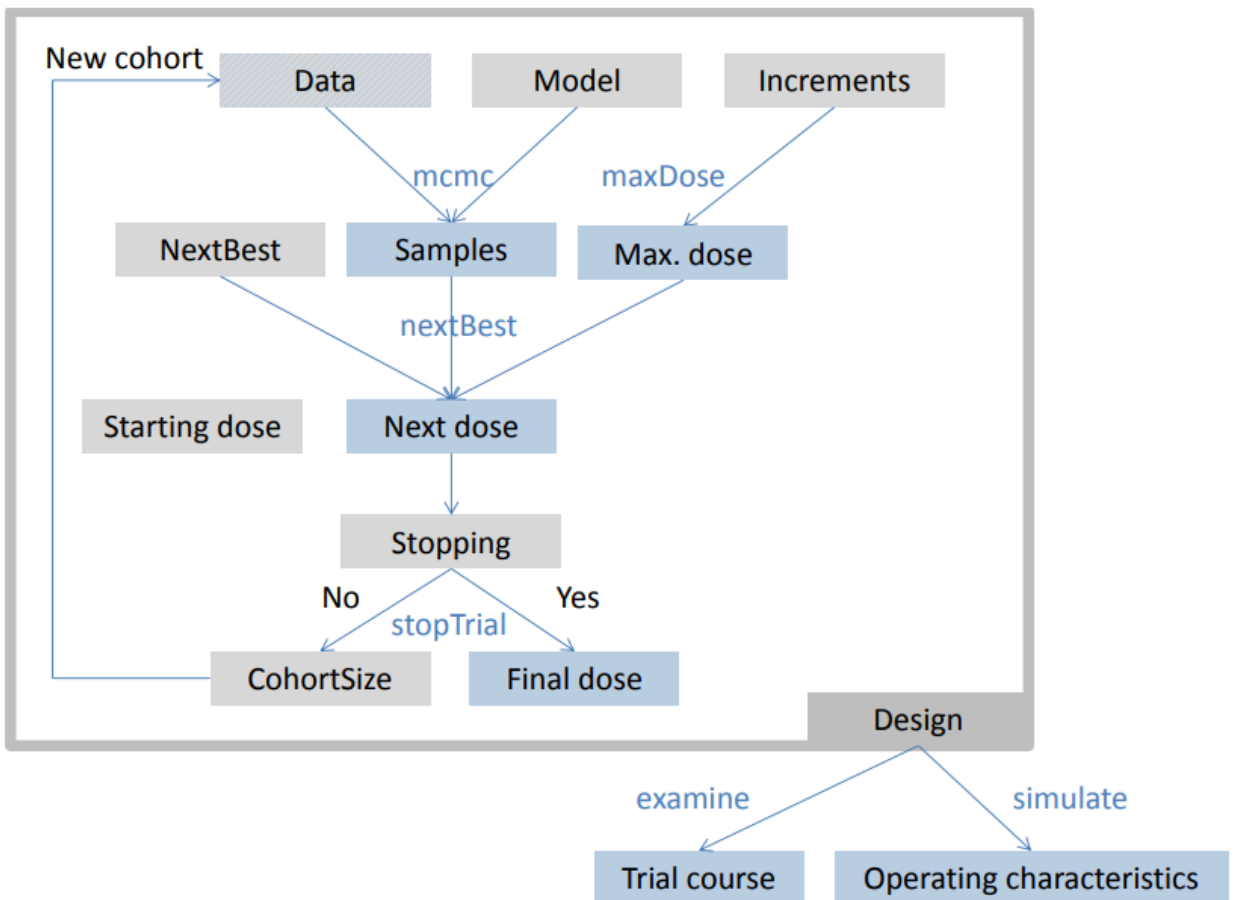
Keywords: continual reassessment method, model-based dose escalation, dual-endpoint design, R, object-oriented.

Large group of contributors 🏢

- Clara Beck (Bayer)
- Oliver Boix (Bayer)
- Prerana Chandratre (Bayer)
- Robert Adams (Bayer)
- Dimitris Kontos (ClinBAY/Bayer)
- Jiawen Zhu (Genentech)
- Ziwei Liao (Genentech)
- Daniel Sabanés Bové (Roche/RCONIS)
- John Kirkpatrick (Roche/Astellas)
- Giuseppe Palermo (Roche)
- Guanya Peng (Roche)
- Doug Kelkhoff (Roche)
- Wojciech Wojciak (Roche)
- Marlene Schulte-Goebel (Merck)
- Burak Kuersad Guenhan (Merck)
- Wai Yin Yeung (University of Lancaster/Roche)
- Thomas Jaki (University of Lancaster/Cambridge/Regensburg)

Framework

`crmPack` provides a highly flexible framework for the design and analysis of dose escalation trials. This schematic illustrates the framework's key components and their interactions:



Example: Dose Escalation Design

```
# remotes::install_github("openpharma/crmPack")
library(crmPack)

empty_data <- Data(doseGrid = c(1, 3, 5, 10, 15, 20, 25, 40, 50, 80, 100))

# Initialize the CRM model.
my_model <- LogisticLogNormal(
    mean = c(-0.85, 1),
    cov = matrix(c(1, -0.5, -0.5, 1), nrow = 2),
    ref_dose = 56
)

# Choose the rule for selecting the next dose.
my_next_best <- NextBestNCRM(
    target = c(0.2, 0.35),
    overdose = c(0.35, 1),
    max_overdose_prob = 0.25
)

# Choose the rule for the cohort-size.
my_size1 <- CohortSizeRange(
    intervals = c(0, 30),
    cohort_size = c(1, 3)
)
```

Current Status

The current development version of `crmPack` (Sabanés Bové et al. 2024) has the following features:

- Model-based designs (CRM), rule-based designs (3+3)
- Binary, time-to-event, dual efficacy/safety, ordinal outcomes
- 15 different models
- 14 different recommendation options
- 19 different stopping rules
- 9 cohort size rules
- 9 increment rules
- Reporting functionality (using `knitr`)
- 9 vignettes (documentation)

Professional Support Option 🤝

- ***Service Level Agreement*** (SLA) with RPACT
- Get ***technical software support*** for written support requests
- Get company specific ***training***
- Get company specific ***software validation documentation*** for each `crmPack` release on CRAN
- Make a `crmPack` ***installation qualification*** on each company computer
- Determine the direction of `crmPack` ***future development activities***
- Optional support for health authority interactions
- Optional consultation to support specific clinical trials

何かご質問はございますか ？

Slides and contact 📬

These slides are at
rpact-com.github.io/slides-shanghai-2025

Contact us:

- linkedin.com/in/danielsabanesbove
- info@rconis.com

References

Emerson, Scott. 2000. ***S+SeqTrial Technical Overview***. Insightful Corporation. https://www.msi.co.jp/splus/addon/pdf/seqtech.pdf.

Sabanés Bové, Daniel, Wai Yin Yeung, Giuseppe Palermo, and Thomas Jaki. 2019. "Model-Based Dose Escalation Designs in R with crmPack." ***Journal of Statistical Software*** 89 (10): 1–22. https://doi.org/10.18637/jss.v089.i10.

Sabanés Bové, Daniel, Wai Yin Yeung, Burak Kuersad Guenhan, Giuseppe Palermo, Thomas Jaki, Jiawen Zhu, Ziwei Liao, et al. 2024. ***crmPack: Object-Oriented Implementation of CRM Designs***. https://github.com/openpharma/crmPack.

Wassmer, Gernot, and Werner Brannath. 2016. ***Group Sequential and Confirmatory Adaptive Designs in Clinical Trials***. Springer. https://link.springer.com/book/10.1007/978-3-319-32562-0.

Wassmer, Gernot, and Friedrich Pahlke. 2024. ***rpact: Confirmatory Adaptive Clinical Trial Design and Analysis***. https://CRAN.R-project.org/package=rpact.