



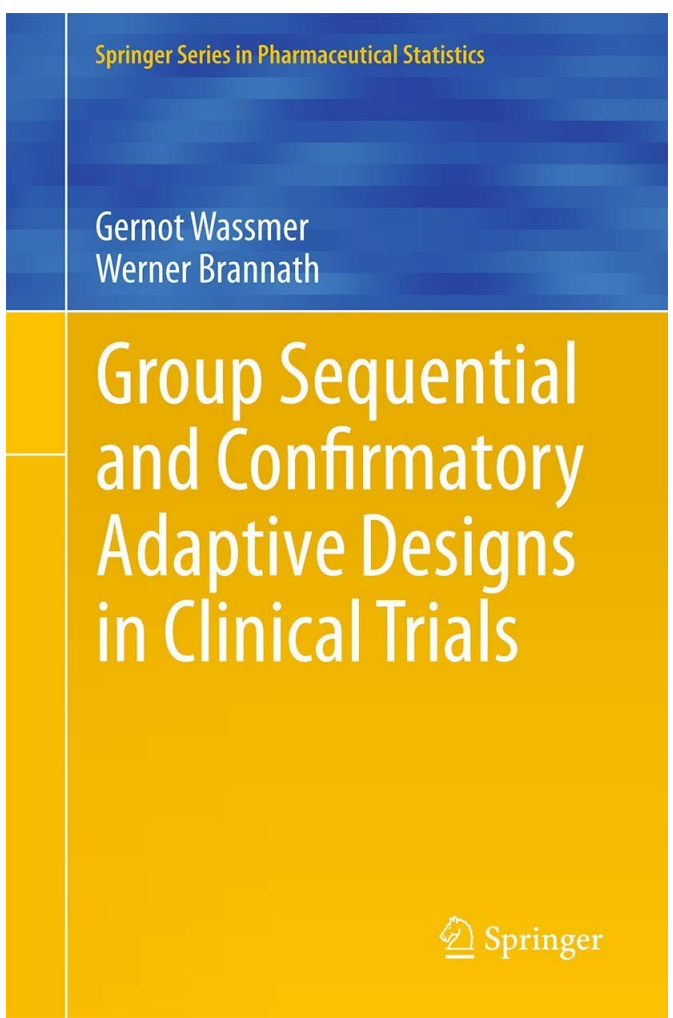
Designing Clinical Trials in R with rpact and crmPack

Daniel Sabanés Bové, Friedrich Pahlke, Gernot Wassmer



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**



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

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



Model-Based Dose Escalation Designs in R with crmPack

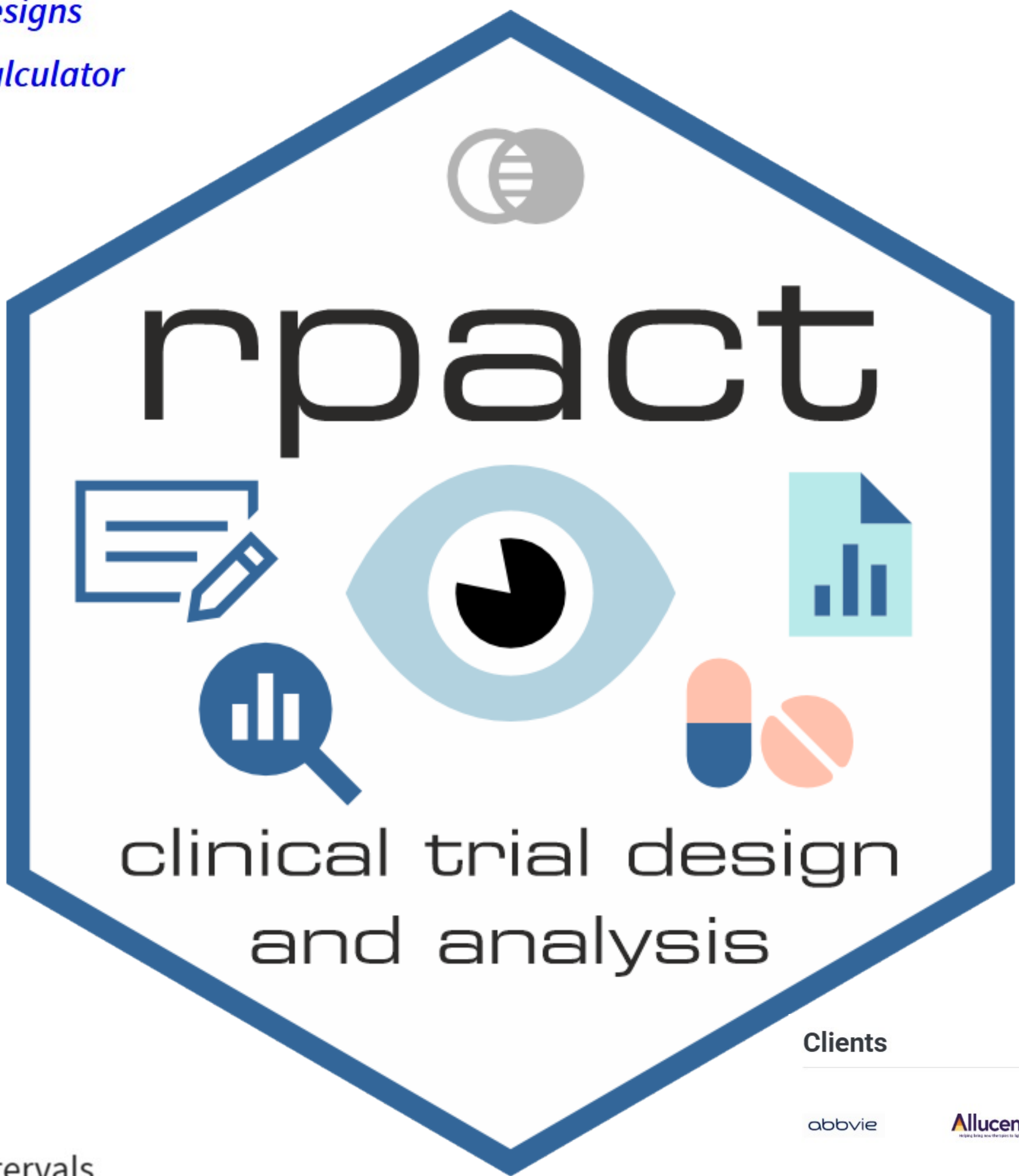
Daniel Sabanés Bové
Giusseppe Palermo
Wai Yin Yeung
Thomas Jaki
Hoffmann-La Roche Ltd
Lancaster University

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 simulation 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 integrates design 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 closed-cohort treatment method and escalation with overrule 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



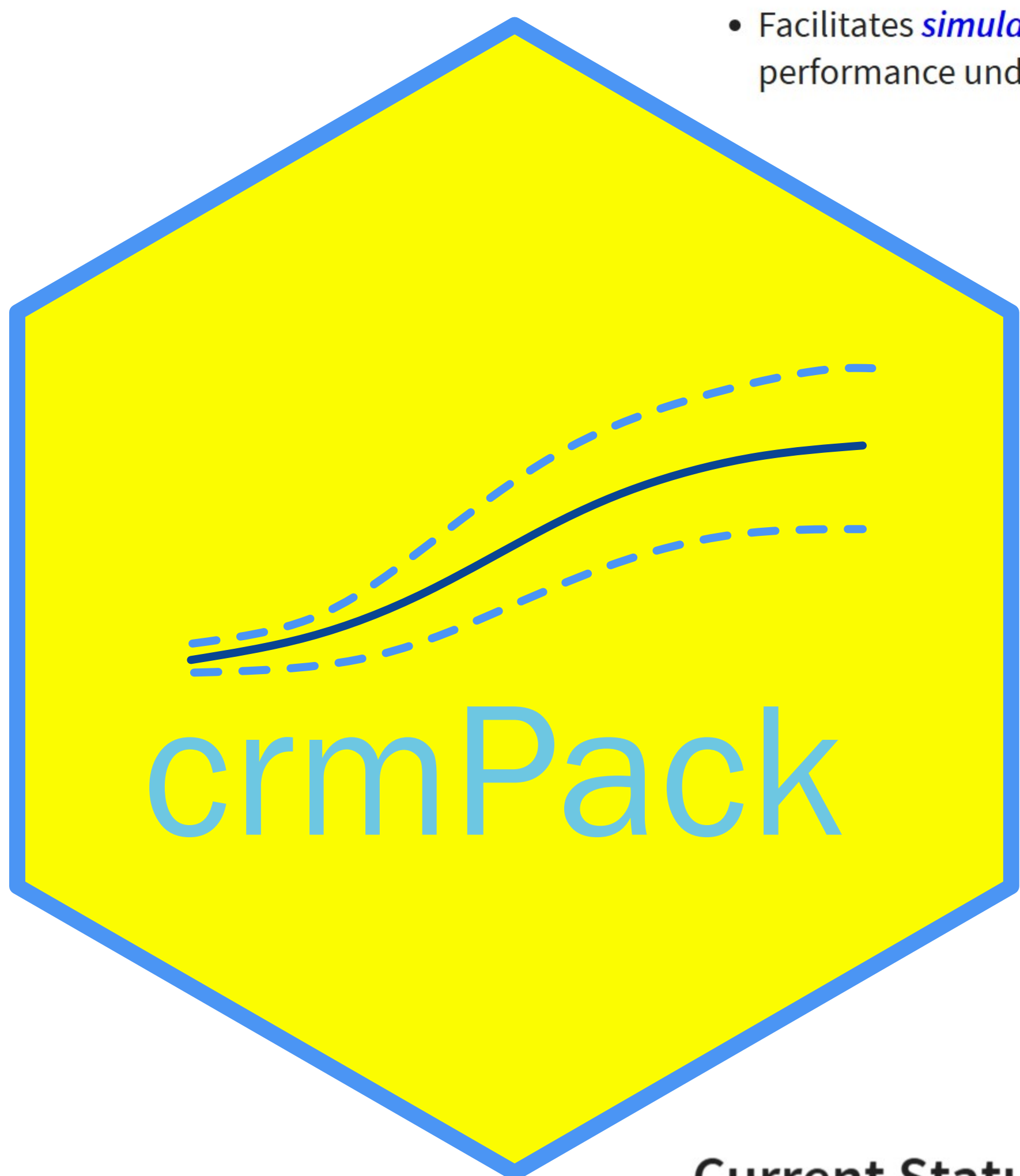
Developed by RPACT

- 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 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 Consulting and Innovative Solutions
- Legal entity still in the making, currently a collaboration between RPACT GbR (rpact.com) and inferential.biostatistics GmbH (inferential.bio)
- Website: rconis.com

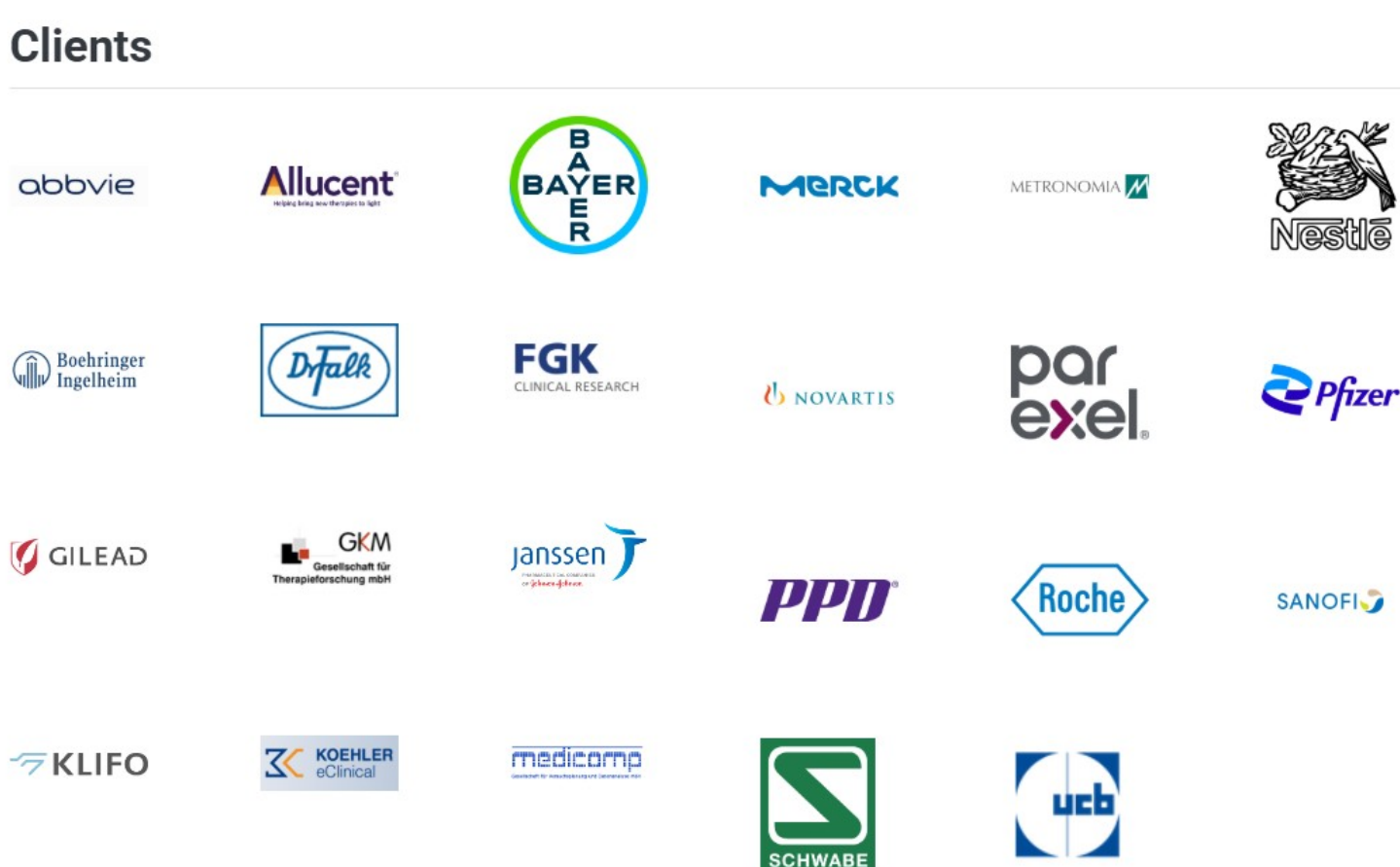


Large group of contributors

- Clara Beck (Bayer)
- Oliver Boix (Bayer)
- Prerana Chandratte (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)

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



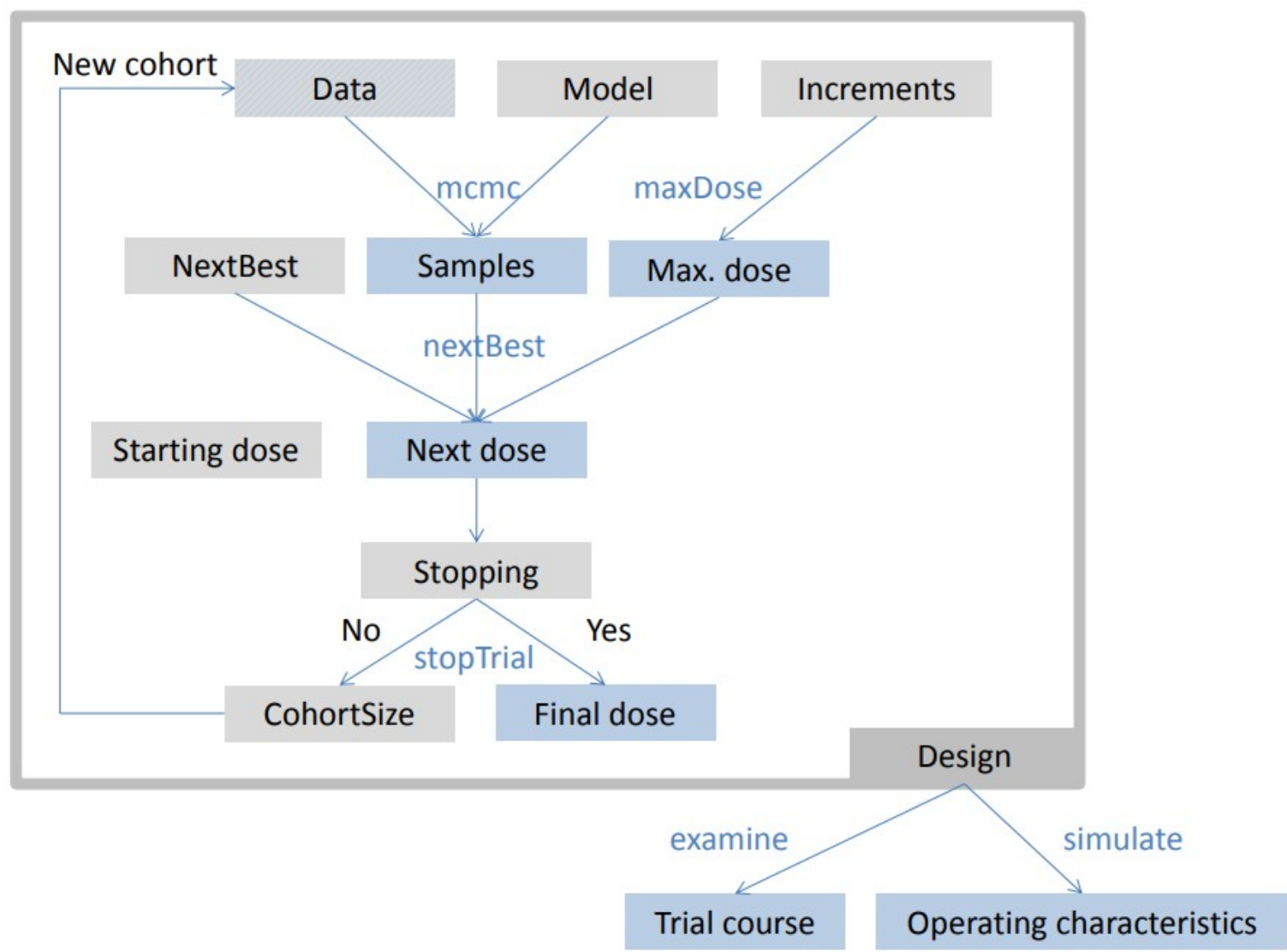
RPACT Cloud

- 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



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:



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)



www.rpact.com
www.rconis.com