# RPACT - R Package for Adaptive Clinical Trials

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# Disclaimer

I was a member of the consortium that organized funding to develop the rpact R package.

Roche has collaborated with RPACT (=the company) in amending the initial version of the package, and paid for this service.

I have **no ties to the company RPACT beyond that**.

# Key adaptations

Key adaptations:

- Set sample size to 0 after interim analysis $\Rightarrow$ **group-sequential** designs.
- Sample size **re-estimation**.
- Subgroup **enrichment**.
- **Multiarm** trial $\Rightarrow$ drop arm(s) after interim.

Features:

- Potentially on **surrogate** endpoint for time-to-event endpoint.
- Sample size planning, simulation, and analysis.
- Binary, continuous, time-to-event.

# Focus

rpact: R package for

- **Design**, **simulation**, and **analysis** of **confirmatory adaptive clinical trials** with continuous, binary, and survival endpoints,
- based on monograph Wassmer and Brannath (2016),
- `https://cran.r-project.org/package=rpact`.

Focus of rpact:

- **Usability**: very few basic functions.
- **"Clean code"** – intuitively understandable.
- Unit testing, summarized in comprehensive **validation document** (for prime members only).

# Available in rpact

| Adaptation | Sample size planning | | | Analysis | | |
|---|---|---|---|---|---|---|
| | Bin | Cont | T2E | Bin | Cont | T2E |
| Group-sequential | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Sample size re-estimation | – | – | – | **A** | **A** | **A** |
| Subgroup enrichment | **B**, planned Q3 2019 | | | | | |
| Multiarm trial | **B**, planned Q3 2019 | | | | | |

A Fisher combination test, inverse Normal combination test.

B Comprehensive engine to optimize operating characteristics, incl. using surrogate endpoint for time-to-event endpoint.

# Design and analyze trial with interim stages

For continuous, binary, and time-to-event endpoints:

- Simulation of trials with continuous, binary, and survival endpoints (incl. non-PH scenarios),
- group-sequential tests,
- repeated confidence intervals, $p$-values,
- confidence intervals and $p$-values for **final stage**,
- inverse normal combination test,
- Fisher's combination test,
- conditional power,
- conditional rejection probability Müller and Schäfer (2001),

Comprehensive overview of functionality of rpact:
`https://www.rpact.com/r-package`.

# Implementation aspects

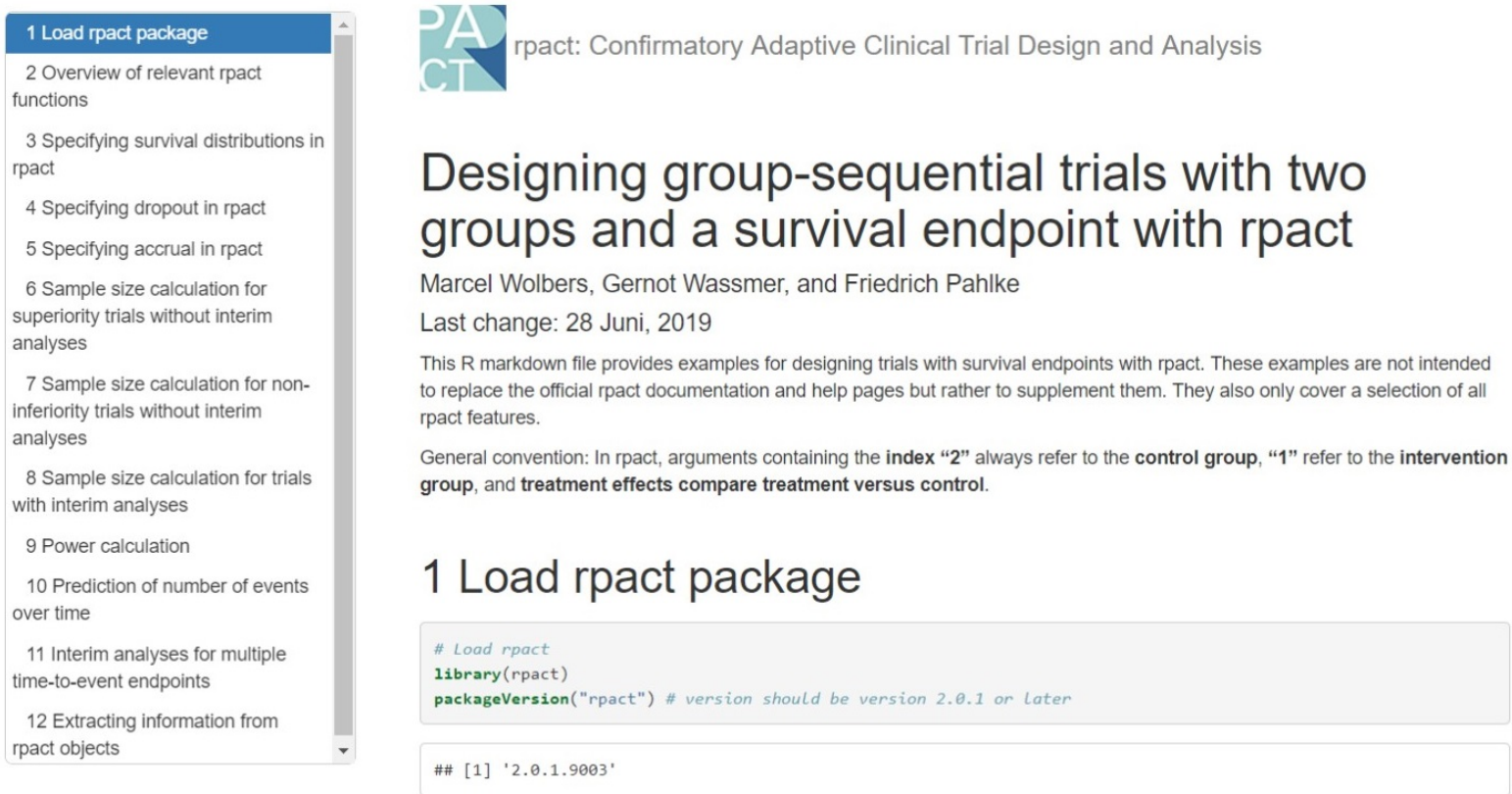
**Validation**:

- Results checked against other softwares and/or literature.
- Comprehensive validation documentation available (prime members).
  - user requirements specification,
  - functional specification,
  - technical design specification,
  - test plan,
  - installation guides,
  - user guides, and
  - release notes.
- Compliant to **FDA/GxP guidelines** and validation process of Base R, `https://www.r-project.org/doc/R-FDA.pdf`.
- **Independent** of any other R package.

**Shiny** app:

- Available soon.
- Will run on RPACT server, no need to install anything.

# Example




https://vignettes.rpact.org/html/rpact_survival_examples.html

# Further materials and packages

Extensive **vignettes** documenting planning, simulation, and analysis of group-sequential trials: `https://www.rpact.org/vignettes`.

Other relevant packages:

- **gsDesign** Anderson (2016),
- **asd** Parsons (2016),
- `http://www.rctdesign.org`,
- `http://www.medianainc.com`,
- **adaptTest**, **ADCT**, **AGSDest**, **ASSISTant**, **GroupSeq**, **gsbDesign**, **GSED**, **interAdapt**, **ldbounds**, **OneArmPhaseTwoStudy**, **PwrGsd**, **seqmon**, **spass**, **DoseFinding**. Search of packages courtesy of RPACT.
- Further packages for early-phase dose-finding.

# Conclusions

Conclusions:

- **High-quality open-source validated** software for many adaptive designs is available - and the amount is growing!
- rpact consortium: potential as funding model for open-source software.
- rpact being open source facilitates pick-up of methods also outside pharma industry, e.g. in academic or collaborative groups.

**Thank you for your attention.**

# Backup

# rpact

1. rpact `www.rpact.org`: Comprehensive validated R package that enables
   - design, simulation, and analysis of confirmatory adaptive group sequential designs,
   - implements methods in Wassmer and Brannath (2016).
2. Company RPACT `www.rpact.com` provides
   - consultancy and training for adaptive designs,
   - offers software solutions for adaptive designs,
   - performs simulation reports for assessing sample size and design characteristics of adaptive designs,

   all using R.

`https://cran.r-project.org/package=rpact`

# rpact concept

Members of consortium pay yearly fee for development and maintenance of rpact:

- General member: 5000 Euro / year 1st year, then 50% of that.
- Prime member: 10000 Euro / year 1st year, then 50% of that. Added benefits (among others): Training at site, validation documentation.

rpact package freely available on CRAN in any case.

3rd July 2019: 15 members of consortium listed on `www.rpact.org`.

# Membership options

| RPACT Services | | Level of membership | |
|---|---|---|---|
| | | General | Prime |
| Maintenance | Guaranteed maintenance, e.g. adaption to new R versions | ✓ | ✓ |
| | Free-of-charge technical software support via priority handling of written support requests to software owners hotline | ✓ | ✓ |
| Learning and training materials | Annual one-day RPACT package training meeting organized by the consortium leadership (free-of-charge for 2 participants) | ✓ | ✓ |
| | RPACT package training at a company site (free-of-charge for unlimited number of participants) | ✗ | ✓ |
| | Access to extended manuals, best practice descriptions and additional examples | ✗ | ✓ |
| RPACT package functionalities and usability | Actively plan capabilities and extensions of the software functionality | ✗ | ✓ |
| | Review user requirements specifications | ✗ | ✓ |
| | Review training material | ✗ | ✓ |
| | Test beta versions | ✗ | ✓ |
| | Access to written know-how and documents dealing with the formal validation of a R package | ✗ | ✓ |
| | Provide feedback on usability in the drug development practice | ✗ | ✓ |
| Options* | Customized design: company internal graphical user interfaces (GUI) with forms for the most frequently used functions | ✗ | ✓ |
| | Customer adaptions: "private" extensions, e.g. R programs for customer-specific needs which use the RPACT package | ✗ | ✓ |
| | Implementation of customer-specific sample programs | ✗ | ✓ |
| | Automation: implementation of frequent workflows / processes | ✗ | ✓ |
| | Setup of a validated user environment, e.g. with ValidR | ✗ | ✓ |

* Available at an extra charge only for prime members

# Group-sequential tests

- O'Brien & Fleming, Pocock,
- Wang & Tsiatis $\Delta$-class,
- Haybittle & Peto,
- $\alpha$-spending approaches,
- $\beta$-spending approaches,
- optimum designs within $\Delta$-class,
- Non-binding and binding futility bounds.

# Fisher's combination test

- Arbitrary information rates,
- Methods of Bauer and Köhne (1994) and Bauer and Röhmel (1995),
- $\alpha$-spending type approach,
- non-binding and binding futility bounds.

# References I


- Anderson, K. (2016). *gsDesign: Group Sequential Design*. R package version 3.0-1. `https://CRAN.R-project.org/package=gsDesign`
- Bauer, P. and Köhne, K. (1994). Evaluation of experiments with adaptive interim analyses. *Biometrics*, **50**(4), 1029–1041.
- Bauer, P. and Röhmel, J. (1995). An adaptive method for establishing a dose-response relationship. *Stat Med*, **14**(14), 1595–1607.
- Müller, H. H. and Schäfer, H. (2001). Adaptive group sequential designs for clinical trials: combining the advantages of adaptive and of classical group sequential approaches. *Biometrics*, **57**(3), 886–891.
- Parsons, N. (2016). *asd: Simulations for Adaptive Seamless Designs*. R package version 2.2. `https://CRAN.R-project.org/package=asd`
- Wassmer, G. and Brannath, W. (2016). *Group Sequential and Confirmatory Adaptive Designs in Clinical Trials*. Springer.

*Doing now what patients need next*

**R version and packages used to generate these slides:**

R version: R version 3.6.0 (2019-04-26)

Base packages: stats / graphics / grDevices / utils / datasets / methods / base

Other packages: rpact

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