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:

- Set sample size to 0 after interim analysis ⇒ group-sequential designs.
- Sample size re-estimation.
- Subgroup enrichment.
- Multiarm trial ⇒ 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

<table>
<thead>
<tr>
<th>Adaptation</th>
<th>Sample size planning</th>
<th>Analysis</th>
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<tbody>
<tr>
<td></td>
<td>Bin</td>
<td>Cont</td>
</tr>
<tr>
<td>Group-sequential</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Sample size re-estimation</td>
<td>−</td>
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<tr>
<td>Subgroup enrichment</td>
<td></td>
<td>B, planned Q3 2019</td>
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<tr>
<td>Multiarm trial</td>
<td></td>
<td>B, planned Q3 2019</td>
</tr>
</tbody>
</table>

**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:
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.
- **Independent** of any other R package.

**Shiny** app:

- Available soon.
- Will run on RPACT server, no need to install anything.
Designing group-sequential trials with two groups and a survival endpoint with rpact

Marcel Wolbers, Gernot Wassmer, and Friedrich Pahlke
Last change: 28 Juni, 2019

This R markdown file provides examples for designing trials with survival endpoints with rpact. These examples are not intended to replace the official rpact documentation and help pages but rather to supplement them. They also only cover a selection of all rpact features.

General convention: In rpact, arguments containing the \textit{index} “2” always refer to the \textit{control group}, “1” refer to the \textit{intervention group}, and \textit{treatment effects compare treatment versus control}.

1 Load rpact package

```r
# Load rpact
library(rpact)
packageVersion("rpact") # version should be version 2.0.1 or later
```

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, Idbounds, OneArmPhaseTwoStudy, PwrGsd, seqmon, spass, DoseFinding. Search of packages courtesy of RPACT.
- Further packages for early-phase dose-finding.
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

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).

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
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.

### Membership options

<table>
<thead>
<tr>
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<th>Level of membership</th>
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<td><strong>Maintenance</strong></td>
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<td>Guaranteed maintenance, e.g. adaption to new R</td>
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<td>(free-of-charge for unlimited number of participants)</td>
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<td><strong>Options</strong></td>
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<td>ValidR</td>
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</tbody>
</table>

* 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


Doing now what patients need next