

Validation Report for **adoptr** package

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Chapter 1

Introduction

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1.1 Preliminaries

R package validation for regulatory environments can be a tedious endeavour. The authors firmly believe that under the current regulation, there is no such thing as a ‘validated R package’: validation is by definition a process conducted by the *user*. This validation report merely aims at facilitating validation of **adoptr** as much as possible. No warranty whatsoever as to the correctness of **adoptr** nor the completeness of the validation report are given by the authors.

We assume that the reader is familiar with the notation and theoretical background of **adoptr**. Otherwise, the following resources might be of help:

- **adoptr** online documentation at <https://kkmann.github.io/adoptr/>
- paper on the theoretical background of the core **adoptr** functionality (Pilz et al., 2019)
- a general overview on adaptive designs is given in (Bauer et al., 2015)
- a more extensive treatment of the subject in (Wassmer and Brannath, 2016).

1.2 Scope

adoptr itself already makes extensive use of `unittesting` to ensure correctness of all implemented functions. Yet, due to constraints on the build-time for an R package, the range of scenarios covered in the `unittests` of **adoptr** is rather limited. Furthermore, the current R `unittesting` framework does not permit

an easy generation of a human-readable report of the test cases to ascertain coverage and test quality.

Therefore, **adoptr** splits testing in two parts: technical correctness is ensured via an extensive unittesting suit in **adoptr** itself (aiming to maintain a 100% code coverage). The validation report, however, runs through a wide range of possible application scenarios and ensures plausibility of results as well as consistency with existing methods wherever possible. The report itself is implemented as a collection of Rmarkdown documents allowing to show both the underlying code as well as the corresponding output in a human-readable format.

The online version of the report is dynamically re-generated on a weekly basis based on the respective most current version of **adoptr** on CRAN. The latest result of these builds is available at <https://kkmann.github.io/adoptr-validation-report/>. To ensure early warning in case of any test-case failures, formal tests are implemented using the **testthat** package (Wickham et al., 2018). I.e., the combination of using a unittesting framework, a continuous integration, and continuous deployment service leads to an always up-to-date validation report (build on the current R release on Linux). Any failure of the integrated formal tests will cause the build status of the validation report to switch from ‘passing’ to ‘failed’ and the respective maintainer will be notified immediately.

1.2.1 Validating a local installation of **adoptr**

Note that, strictly speaking, the online version of the validation report only provides evidence of the correctness on the respective Travis-CI cloud virtual machine infrastructure using the respective most recent release of R and the most recent versions of the dependencies available on CRAN. In some instances it might therefore be desirable to conduct a local validation of **adoptr**.

To do so, one should install **adoptr** with the `INSTALL_opts` option to include tests and invoke the test suit locally via

```
install.packages("adoptr", INSTALL_opts = c("--install-tests"))
tools::testInstalledPackage("adoptr", types = c("examples", "tests"))
```

Upon passing the test suit successfully, the validation report can be build locally. To do so, first clone the entire source directory and switch to the newly created folder

```
git clone https://github.com/kkmann/adoptr-validation-report.git
cd adoptr-validation-report
```

Make sure that all packages required for building the report are available, i.e., install all dependencies listed in the top-level `DESCRIPTION` file, e.g.,

```
install.packages(c(
  "adoptr",
  "tidyverse",
  "bookdown",
  "rpact",
  "testthat",
  "pwr" ) )
```

The book can then be build using the terminal command

```
Rscript -e 'bookdown::render_book("index.Rmd", output_format = "all")'
```

or directly from R via

```
bookdown::render_book("index.Rmd", output_format = "all")
```

This produces a new folder `_book` with the html and pdf versions of the report.

1.3 Validation Scenarios

1.3.1 Scenario I: Large effect, point prior

This is the default scenario.

- **Data distribution:** Two-armed trial with normally distributed test statistic
- **Prior:** $\delta \sim \mathbf{1}_{\delta=0.4}$
- **Null hypothesis:** $\mathcal{H}_0 : \delta \leq 0$

1.3.1.1 Variant I.1: Minimizing Expected Sample Size under the Alternative

- **Objective:** $ESS := E[n(X_1) | \delta = 0.4]$
- **Constraints:**
 1. $Power := Pr[c_2(X_1) < X_2 | \delta = 0.4] \geq 0.8$
 2. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$
 3. Three variants: two-stage, group-sequential, one-stage.
- **Formal tests:**
 1. Number of iterations are checked against default maximum to ensure proper convergence.

2. All three **adoptr** variants (two-stage, group-sequential, one-stage) comply with constraints. Internally validated by testing vs. simulated values of the power curve at respective points.
3. Is $n()$ of the optimal two-stage design monotonously decreasing on continuation area?
4. ESS of optimal two-stage design is lower than ESS of optimal group-sequential one and that is in turn lower than the one of the optimal one-stage design.
5. ESS of optimal group-sequential design is lower than ESS of externally computed group-sequential design using the `rpact` package.
6. Are the ESS values obtained from simulation the same as the ones obtained by using numerical integration via `adoptr::evaluate`?

1.3.1.2 Variant I.2: Minimizing Expected Sample Size under the Null Hypothesis

- **Objective:** $ESS := E[n(X_1) | \delta = 0.0]$
- **Constraints:**
 1. $Power := Pr[c_2(X_1) < X_2 | \delta = 0.4] \geq 0.8$
 2. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$
- **Formal tests:**
 1. Number of iterations are checked against default maximum to ensure proper convergence.
 2. Validate constraint compliance by testing vs. simulated values of the power curve at respective points.
 3. $n()$ of optimal design is monotonously increasing on continuation area.
 4. ESS of optimal two-stage design is lower than ESS of externally computed group-sequential design using the `rpact` package.
 5. Are the ESS values obtained from simulation the same as the ones obtained by using numerical integration via `adoptr::evaluate`?

1.3.1.3 Variant I.3: Conditional Power Constraint

- **Objective:** $ESS := E[n(X_1) | \delta = 0.4]$
- **Constraints:**
 1. $Power := Pr[c_2(X_1) < X_2 | \delta = 0.4] \geq 0.8$
 2. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$
 3. $CP := Pr[c_2(X_1) < X_2 | \delta = 0.4, X_1 = x_1] \geq 0.7$ for all $x_1 \in (c_1^f, c_1^e)$
- **Formal tests:**
 1. Number of iterations are checked against default maximum to ensure proper convergence.

2. Check *Power* and *TOER* constraints with simulation. Check *CP* constraint on 25 different values of x_1 in $[c_1^f, c_1^e]$
3. Are the *CP* values at the 25 test-pivots obtained from simulation the same as the ones obtained by using numerical integration via `adoptr::evaluate`?
4. Is *ESS* of optimal two-stage design with *CP* constraint higher than *ESS* of optimal two-stage design without this constraint?

1.3.2 Scenario II: Large effect, Gaussian prior

Similar scope to Scenario I, but with a continuous Gaussian prior on δ .

- **Data distribution:** Two-armed trial with normally distributed test statistic
- **Prior:** $\delta \sim \mathcal{N}(0.4, .3)$
- **Null hypothesis:** $\mathcal{H}_0 : \delta \leq 0$

1.3.2.1 Variant II.1: Minimizing Expected Sample Size

- **Objective:** $ESS := E[n(X_1)]$
- **Constraints:**
 1. $Power := Pr[c_2(X_1) < X_2 \mid \delta > 0.0] \geq 0.8$
 2. $TOER := Pr[c_2(X_1) < X_2 \mid \delta = 0.0] \leq 0.025$
 3. Three variants: two-stage, group-sequential, one-stage.
- **Formal tests:**
 1. Number of iterations are checked against default maximum to ensure proper convergence.
 2. All designs comply with type one error rate constraints (tested via simulation).
 3. *ESS* of optimal two-stage design is lower than *ESS* of optimal group-sequential one and that is in turn lower than the one of the optimal one-stage design.

1.3.2.2 Variant II.2: Minimizing Expected Sample Size under the Null hypothesis

- **Objective:** $ESS := E[n(X_1) \mid \delta \leq 0]$
- **Constraints:**
 1. $Power := Pr[c_2(X_1) < X_2 \mid \delta > 0.0] \geq 0.8$
 2. $TOER := Pr[c_2(X_1) < X_2 \mid \delta = 0.0] \leq 0.025$
- **Formal tests:**

1. Number of iterations are checked against default maximum to ensure proper convergence.
2. Does the design comply with *TOER* constraint (via simulation)?
3. Is *ESS* lower than expected sample size under the null hypothesis for the optimal two stage design from Variant II-1?

1.3.2.3 Variant II.3: Conditional Power Constraint

- **Objective:** $ESS := E[n(X_1)]$
- **Constraints:**
 1. $Power := Pr[c_2(X_1) < X_2 | \delta > 0.0] \geq 0.8$
 2. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$
 3. $CP := Pr[c_2(X_1) < X_2 | \delta > 0.0, X_1 = x_1] \geq 0.7$ for all $x_1 \in (c_1^f, c_1^e)$
- **Formal tests:**
 1. Number of iterations are checked against default maximum to ensure proper convergence.
 2. Check *TOER* constraint with simulation.
 3. Check *CP* constraint on three different values of x_1 in (c_1^f, c_1^e)
 4. Is *ESS* of optimal two-stage design with *CP* constraint higher than *ESS* of optimal two-stage design without the constraint?

1.3.3 Scenario III: Large effect, uniform prior

- **Data distribution:** Two-armed trial with normally distributed test statistic
- **Prior:** sequence of uniform distributions $\delta \sim \text{Unif}(0.4 - \Delta_i, 0.4 + \Delta_i)$ around 0.4 with $\Delta_i = (3 - i)/10$ for $i = 0 \dots 3$. I.e., for $\Delta_3 = 0$ reduces to a point prior on $\delta = 0.4$.
- **Null hypothesis:** $\mathcal{H}_0 : \delta \leq 0$

1.3.3.1 Variant III.1: Convergence under Prior Concentration

- **Objective:** $ESS := E[n(X_1)]$
- **Constraints:**
 1. $Power := Pr[c_2(X_1) < X_2 | \delta > 0.0] \geq 0.8$
 2. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$
- **Formal tests:**
 1. Number of iterations are checked against default maximum to ensure proper convergence.
 2. Simulated type one error rate is compared to *TOER* constraint for each design.

- 3. *ESS* decreases with prior variance.

Additionally, the designs are compared graphically. Inspect the plot to see convergence pattern.

1.3.4 Scenario IV: Smaller effect size, larger trials

1.3.4.1 Variant IV.1: Minimizing Expected Sample Size under the Alternative

- **Objective:** $ESS := E[n(X_1) | \delta = 0.2]$
- **Constraints:**
 1. $Power := Pr[c_2(X_1) < X_2 | \delta = 0.2] \geq 0.8$
 2. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$
 3. Three variants: two-stage, group-sequential, one-stage.
- **Formal tests:**
 1. Number of iterations are checked against default maximum to ensure proper convergence.
 2. All three adoptr variants (two-stage, group-sequential, one-stage) comply with constraints. Internally validated by testing vs. simulated values of the power curve at respective points.
 3. *ESS* of optimal two-stage design is lower than *ESS* of optimal group-sequential one and that is in turn lower than the one of the optimal one-stage design.
 4. *ESS* of optimal group-sequential design is lower than *ESS* of externally computed group-sequential design using the rpact package.
 5. Are the *ESS* values obtained from simulation the same as the ones obtained by using numerical integration via `adoptr::evaluate`?
 6. Is $n()$ of the optimal two-stage design monotonously decreasing on continuation area?

1.3.4.2 Variant IV.2: Increasing Power

- **Objective:** $ESS := E[n(X_1) | \delta = 0.2]$
- **Constraints:**
 1. $Power := Pr[c_2(X_1) < X_2 | \delta = 0.2] \geq 0.9$
 2. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$
 3. Three variants: two-stage, group-sequential, one-stage.
- **Formal tests:**
 1. Number of iterations are checked against default maximum to ensure proper convergence.

2. Does the design respect all constraints (via simulation)?
3. *ESS* of optimal two-stage design is lower than *ESS* of optimal group-sequential one and that is in turn lower than the one of the optimal one-stage design.
4. *ESS* of optimal group-sequential design is lower than *ESS* of externally computed group-sequential design using the `rpact` package.
5. Are the *ESS* values obtained from simulation the same as the ones obtained by using numerical integration via `adoptr::evaluate`?
6. Is $n()$ of the optimal two-stage design monotonously decreasing on continuation area?

1.3.4.3 Variant IV.3: Increasing Maximal Type One Error Rate

- **Objective:** $ESS := E[n(X_1) | \delta = 0.2]$
- **Constraints:**
 1. $Power := Pr[c_2(X_1) < X_2 | \delta = 0.2] \geq 0.8$
 2. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.05$
 3. Three variants: two-stage, group-sequential, one-stage.
- **Formal tests:**
 1. Number of iterations are checked against default maximum to ensure proper convergence.
 2. Does the design respect all constraints (via simulation)?
 3. *ESS* of optimal two-stage design is lower than *ESS* of optimal group-sequential one and that is in turn lower than the one of the optimal one-stage design.
 4. *ESS* of optimal group-sequential design is lower than *ESS* of externally computed group-sequential design using the `rpact` package.
 5. Are the *ESS* values obtained from simulation the same as the ones obtained by using numerical integration via `adoptr::evaluate`?
 6. Is $n()$ of the optimal two-stage design monotonously decreasing on continuation area?

1.3.5 Scenario V: Single-arm design, medium effect size

- **Data distribution:** One-armed trial with normally distributed test statistic
- **Prior:** $\delta \sim \delta_{0.3}$
- **Null hypothesis:** $\mathcal{H}_0 : \delta \leq 0$

1.3.5.1 Variant V.1: Sensitivity to Integration Order

- **Objective:** $ESS := E[n(X_1) | \delta = 0.3]$

- **Constraints:**

1. $Power := Pr[c_2(X_1) < X_2 | \delta = 0.3] \geq 0.8$
2. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$
3. Three variants: integration order 5, 8, 11 two-stage designs.

- **Formal tests:**

1. Do all designs converge within the respective iteration limit?
2. Do all designs respect all constraints (via simulation)?

1.3.5.2 Variant V.2: Utility Maximization

- **Objective:** $\lambda Power - ESS := \lambda Pr[c_2(X_1) < X_2 | \delta = 0.3] - E[n(X_1) | \delta = 0.3]$. for $\lambda = 100$ and 200

- **Constraints:**

1. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$

- **Formal tests:**

1. Number of iterations are checked against default maximum to ensure proper convergence.
2. Do both designs respect the type one error rate constraint (via simulation)?
3. Is the power of the design with larger λ larger?

1.3.5.3 Variant V.3: n_1 penalty

- **Objective:** $ESS := E[n(X_1) | \delta = 0.3] + \lambda n_1$ for $\lambda = 0.05$ and 0.2 .

- **Constraints:**

1. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$
2. $Power := Pr[c_2(X_1) < X_2 | \delta = 0.3] \geq 0.8$

- **Formal tests:**

1. Number of iterations are checked against default maximum to ensure proper convergence.
2. Do both designs respect the type one error rate and power constraints (via simulation)?
3. Is n_1 for the optimal design smaller than the order-5 design in V.1?

1.3.5.4 Variant V.4: n_2 penalty

- **Objective:** $ESS := E[n(X_1) | \delta = 0.3] + \lambda \text{AverageN2}$ for $\lambda = 0.01$ and 0.1 .

- **Constraints:**

1. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$
2. $Power := Pr[c_2(X_1) < X_2 | \delta = 0.3] \geq 0.8$

- **Formal tests:**

1. Number of iterations are checked against default maximum to ensure proper convergence.
2. Do both designs respect the type one error rate and power constraints (via simulation)?
3. Is the **AverageN2** for the optimal design smaller than for the order-5 design in V.1?

1.3.6 Scenario VI: Binomial distribution

This scenario investigates the implementation of the binomial distribution.

- **Data distribution:** Two-armed trial with binomial distributed outcomes. Thus $\delta := p_E - p_C$ refers to the rate difference here. The control rate is assumed to equal $p_C = 0.3$.
- **Prior:** $\delta \sim \mathbf{1}_{\delta=0.2}$
- **Null hypothesis:** $\mathcal{H}_0 : \delta \leq 0$

1.3.6.1 Variant VI.1: Minimizing Expected Sample Size under the Alternative

- **Objective:** $ESS := E[n(X_1) | \delta = 0.2]$
- **Constraints:**
 1. $Power := Pr[c_2(X_1) < X_2 | \delta = 0.2] \geq 0.9$
 2. $TOER := Pr[c_2(X_1) < X_2 | \delta = 0.0] \leq 0.025$
 3. Three variants: two-stage, group-sequential, one-stage.
- **Formal tests:**
 1. Number of iterations are checked against default maximum to ensure proper convergence.
 2. All three **adoptr** variants (two-stage, group-sequential, one-stage) comply with constraints. Internally validated by testing vs. simulated values of the power curve at respective points.
 3. ESS of optimal two-stage design is lower than ESS of optimal group-sequential one and that is in turn lower than the one of the optimal one-stage design.
 4. ESS of optimal group-sequential design is lower than ESS of externally computed group-sequential design using the `rpact` package.
 5. Are the ESS values obtained from simulation the same as the ones obtained by using numerical integration via `adoptr::evaluate`?

1.4 Technical Setup

All scenarios are run in a single, shared R session. Required packages are loaded here, the random seed is defined and set centrally, and the default number of iteration is increased to make sure that all scenarios converge properly. Additionally R scripts with convenience functions are sourced here as well. There are three additional functions for this report. `rpact_design` creates a two-stage design via the package `rpact` (Wassmer and Pahlke, 2018) in the notation of `adoptr`. `sim_pr_reject` and `sim_n` allow to simulate rejection probabilities and expected sample sizes respectively by the `adoptr` routine `simulate`. Furthermore, global tolerances for the validation are set. For error rates, a relative deviation of 1% from the target value is accepted. (Expected) Sample sizes deviations are more liberally accepted up to an absolute deviation of 0.5.

```
library(adoptr)
library(tidyverse)
```

```
## -- Attaching packages ----- tidyverse 1.3.1 --
```

```
## v ggplot2 3.3.5      v purrr  0.3.4
## v tibble  3.1.6      v dplyr  1.0.7
## v tidyr   1.1.4      v stringr 1.4.0
## v readr   2.1.1      v forcats 0.5.1
```

```
## -- Conflicts ----- tidyverse_conflicts() --
```

```
## x dplyr::filter() masks stats::filter()
## x dplyr::lag()     masks stats::lag()
## x dplyr::n()       masks adoptr::n()
```

```
library(rpact)
library(pwr)
library(testthat)
```

```
##
## Attaching package: 'testthat'
```

```
## The following object is masked from 'package:dplyr':
##
##      matches
```

```
## The following object is masked from 'package:purrr':
##
##      is_null
```

```
## The following objects are masked from 'package:readr':  
##  
##      edition_get, local_edition  
  
## The following object is masked from 'package:tidyr':  
##  
##      matches  
  
## The following object is masked from 'package:adoptr':  
##  
##      expectation
```

```
library(tinytex)  
  
# load custom functions in folder subfolder '/R'  
for (nm in list.files("R", pattern = "\\.[RrSsQq]$"))  
  source(file.path("R", nm))  
  
# define seed value  
seed <- 42  
  
# define absolute tolerance for error rates  
tol <- 0.01  
  
# define absolute tolerance for sample sizes  
tol_n <- 0.5  
  
# define custom tolerance and iteration limit for nloptr  
opts = list(  
  algorithm = "NLOPT_LN_COBYLA",  
  xtol_rel  = 1e-5,  
  maxeval   = 100000  
)
```


Chapter 2

Scenario I: large effect, point prior

2.1 Details

In this scenario, a classical two-arm trial with normal test statistic and known variance (w.l.o.g. variance of the test statistic is 1). This situation corresponds to a classical z -test for a difference in population means. The null hypothesis is no population mean difference, i.e. $\mathcal{H}_0 : \delta \leq 0$. An alternative effect size of $\delta = 0.4$ with point prior distribution is assumed. Across all variants in this scenario, the one-sided maximal type one error rate is restricted to $\alpha = 0.025$ and the power at the point alternative of $\delta = 0.4$ must be at least 0.8.

```
# data distribution and hypotheses
datadist  <- Normal(two_armed = TRUE)
H_0       <- PointMassPrior(.0, 1)
prior     <- PointMassPrior(.4, 1)

# define constraints
alpha     <- 0.025
min_power <- 0.8
toer_cnstr <- Power(datadist, H_0)  <= alpha
pow_cnstr  <- Power(datadist, prior) >= min_power
```

2.2 Variant I-1: Minimizing Expected Sample Size under Point Prior

2.2.1 Objective

Firstly, expected sample size under the alternative (point prior) is minimized, i.e., $E[n(\mathcal{D})]$.

```
ess <- ExpectedSampleSize(datadist, prior)
```

2.2.2 Constraints

No additional constraints besides type one error rate and power are considered in this variant.

2.2.3 Initial Designs

For this example, the optimal one-stage, group-sequential, and generic two-stage designs are computed. The initial design for the one-stage case is determined heuristically (cf. Scenario III where another initial design is applied on the same situation for stability of initial values). Both the group sequential and the generic two-stage designs are optimized starting from the corresponding group-sequential design as computed by the `rpact` package.

```
order <- 7L
# data frame of initial designs
tbl_designs <- tibble(
  type = c("one-stage", "group-sequential", "two-stage"),
  initial = list(
    OneStageDesign(200, 2.0),
    rpact_design(datadist, 0.4, 0.025, 0.8, TRUE, order),
    TwoStageDesign(rpact_design(datadist, 0.4, 0.025, 0.8, TRUE, order))) )
```

The order of integration is set to 7.

2.2.4 Optimization

```
tbl_designs <- tbl_designs %>%
  mutate(
    optimal = purrr::map(initial, ~minimize(
```

```

    ess,
    subject_to(
      toer_cnstr,
      pow_cnstr
    ),

    initial_design = .,
    opts           = opts)) )

```

2.2.5 Test Cases

To avoid improper solutions, it is first verified that the maximum number of iterations was not exceeded in any of the three cases.

```

tbl_designs %>%
  transmute(
    type,
    iterations = purrr::map_int(tbl_designs$optimal,
                                ~.$nloptr_return$iterations) ) %>%
  {print(.); .} %>%
  {testthat::expect_true(all(.$iterations < opts$maxeval))}

```

```

## # A tibble: 3 x 2
##   type      iterations
##   <chr>         <int>
## 1 one-stage         24
## 2 group-sequential 1447
## 3 two-stage        4268

```

Next, the type one error rate and power constraints are verified for all three designs by simulation:

```

tbl_designs %>%
  transmute(
    type,
    toer = purrr::map(tbl_designs$optimal,
                      ~sim_pr_reject(.[[1]], .0, datadist)$prob),
    power = purrr::map(tbl_designs$optimal,
                      ~sim_pr_reject(.[[1]], .4, datadist)$prob) ) %>%
  unnest(., cols = c(toer, power)) %>%
  {print(.); .} %>% {
    testthat::expect_true(all(.$toer <= alpha * (1 + tol)))
    testthat::expect_true(all(.$power >= min_power * (1 - tol))) }

```

```
## # A tibble: 3 x 3
##   type          toer power
##   <chr>          <dbl> <dbl>
## 1 one-stage      0.0251 0.799
## 2 group-sequential 0.0250 0.800
## 3 two-stage      0.0250 0.799
```

The n_2 function of the optimal two-stage design is expected to be monotonously decreasing:

```
expect_true(
  all(diff(
    # get optimal two-stage design n2 pivots
    tbl_designs %>% filter(type == "two-stage") %>%
    {.[["optimal"]][[1]]$design@n2_pivots}
  ) < 0) )
```

Since the degrees of freedom of the three design classes are ordered as ‘two-stage’ > ‘group-sequential’ > ‘one-stage’, the expected sample sizes (under the alternative) should be ordered in reverse (‘two-stage’ smallest). Additionally, expected sample sizes under both null and alternative are computed both via `evaluate()` and simulation-based.

```
ess0 <- ExpectedSampleSize(datadist, H_0)

tbl_designs %>%
  mutate(
    ess      = map_dbl(optimal,
                      ~evaluate(ess, .$design) ),
    ess_sim  = map_dbl(optimal,
                      ~sim_n(.$design, .4, datadist)$n ),
    ess0     = map_dbl(optimal,
                      ~evaluate(ess0, .$design) ),
    ess0_sim = map_dbl(optimal,
                      ~sim_n(.$design, .0, datadist)$n ) ) %>%
  {print(.); .} %>% {
    # sim/evaluate same under alternative?
    testthat::expect_equal(.$ess, .$ess_sim,
                          tolerance = tol_n,
                          scale = 1)
    # sim/evaluate same under null?
    testthat::expect_equal(.$ess0, .$ess0_sim,
                          tolerance = tol_n,
                          scale = 1)
    # monotonicity with respect to degrees of freedom
    testthat::expect_true(all(diff(.$ess) < 0)) }
```

2.3. VARIANT I-2: MINIMIZING EXPECTED SAMPLE SIZE UNDER NULL HYPOTHESIS 21

```
## # A tibble: 3 x 7
##   type          initial      optimal      ess ess_sim  ess0 ess0_sim
##   <chr>          <list>      <list>      <dbl>  <dbl> <dbl>  <dbl>
## 1 one-stage    <OnStgDsg> <adptrOpR [3]>  98      98    98      98
## 2 group-sequential <GrpSqntD> <adptrOpR [3]> 80.9    80.9  68.5    68.5
## 3 two-stage    <TwStgDsg> <adptrOpR [3]> 79.7    79.7  68.9    68.9
```

The expected sample size under the alternative must be lower or equal than the expected sample size of the initial `rpact` group-sequential design that is based on the inverse normal combination test.

```
testthat::expect_lte(
  evaluate(ess,
    tbl_designs %>%
      filter(type == "group-sequential") %>%
      pull(optimal) %>%
      .[[1]] %>%
      .$design ),
  evaluate(ess,
    tbl_designs %>%
      filter(type == "group-sequential") %>%
      pull(initial) %>%
      .[[1]] ) )
```

2.3 Variant I-2: Minimizing Expected Sample Size under Null Hypothesis

2.3.1 Objective

Expected sample size under the null hypothesis prior is minimized, i.e., `ess0`.

2.3.2 Constraints

The constraints remain unchanged from the base case.

2.3.3 Initial Design

Since optimization under the null favours an entirely different (monotonically increasing) sample size function, and thus also a different shape of the c_2 function, the `rpact` initial design is a suboptimal starting point. Instead, we start with a constant c_2 function by heuristically setting it to 2 on the continuation

area. Also, optimizing under the null favours extremely conservative boundaries for early efficacy stopping and we thus impose as fairly liberal upper bound of 3 for early efficacy stopping.

```
init_design_h0 <- tbl_designs %>%
  filter(type == "two-stage") %>%
  pull(initial) %>%
  .[[1]]
init_design_h0@c2_pivots <- rep(2, order)

ub_design <- TwoStageDesign(
  3 * init_design_h0@n1,
  2,
  3,
  rep(300, order),
  rep(3.0, order)
)
```

2.3.4 Optimization

The optimal two-stage design is computed.

```
opt_h0 <- minimize(
  ess0,
  subject_to(
    toer_cnstr,
    pow_cnstr
  ),
  initial_design = init_design_h0,
  upper_boundary_design = ub_design,
  opts = opts )
```

2.3.5 Test Cases

Make sure that the optimization algorithm converged within the set maximum number of iterations:

```
opt_h0$nlptr_return$iterations %>%
  {print(.); .} %>%
  {testthat::expect_true(. < opts$maxeval)}
```

2.3. VARIANT I-2: MINIMIZING EXPECTED SAMPLE SIZE UNDER NULL HYPOTHESIS23

```
## [1] 17412
```

The n_2 function of the optimal two-stage design is expected to be monotonously increasing.

```
expect_true(  
  all(diff(opt_h0$design@n2_pivots) > 0) )
```

Next, the type one error rate and power constraints are tested.

```
tbl_performance <- tibble(  
  delta = c(.0, .4) ) %>%  
  mutate(  
    power      = map(  
      delta,  
      ~evaluate(  
        Power(datadist, PointMassPrior(., 1)),  
        opt_h0$design) ),  
    power_sim = map(  
      delta,  
      ~sim_pr_reject(opt_h0$design, ., datadist)$prob),  
    ess        = map(  
      delta,  
      ~evaluate(ExpectedSampleSize(  
        datadist,  
        PointMassPrior(., 1) ),  
        opt_h0$design) ),  
    ess_sim    = map(  
      delta,  
      ~sim_n(opt_h0$design, ., datadist)$n ) ) %>%  
  unnest(., cols = c(power, power_sim, ess, ess_sim))  
  
print(tbl_performance)
```

```
## # A tibble: 2 x 5  
##   delta power power_sim  ess ess_sim  
##   <dbl> <dbl>   <dbl> <dbl>   <dbl>  
## 1    0  0.0250   0.0250  57.2    57.3  
## 2   0.4  0.802    0.802  118.    118.
```

```
testthat::expect_lte(  
  tbl_performance %>% filter(delta == 0) %>% pull(power_sim),  
  alpha * (1 + tol) )
```

```
testthat::expect_gte(
  tbl_performance %>% filter(delta == 0.4) %>% pull(power_sim),
  min_power * (1 - tol) )

# make sure that evaluate() leads to same results
testthat::expect_equal(
  tbl_performance$power, tbl_performance$power_sim,
  tol = tol,
  scale = 1 )

testthat::expect_equal(
  tbl_performance$ess, tbl_performance$ess_sim,
  tol = tol_n,
  scale = 1 )
```

The expected sample size under the null must be lower or equal than the expected sample size of the initial `rpact` group-sequential design.

```
testthat::expect_gte(
  evaluate(ess0,
    tbl_designs %>%
      filter(type == "two-stage") %>%
      pull(initial) %>%
      .[[1]] ),
  evaluate(ess0, opt_h0$design) )
```

2.4 Variant I-3: Conditional Power Constraint

2.4.1 Objective

Same as in I-1, i.e., expected sample size under the alternative point prior is minimized.

2.4.2 Constraints

Besides the previous global type one error rate and power constraints, an additional constraint on *conditional* power is imposed.

```
cp      <- ConditionalPower(datadist, prior)
cp_cnstr <- cp >= .7
```


2.4.3 Initial Design

The same initial (generic two-stage) design as in I-1 is used.

2.4.4 Optimization

```
opt_cp <- minimize(
  ess,
  subject_to(
    toer_cnstr,
    pow_cnstr,
    cp_cnstr # new constraint
  ),
  initial_design = tbl_designs %>%
    filter(type == "two-stage") %>%
    pull(initial) %>%
    .[[1]],
  opts = opts )
```

2.4.5 Test Cases

Check if the optimization algorithm converged.

```
opt_cp$nlptr_return$iterations %>%
  {print(.); .} %>%
  {testthat::expect_true(. < opts$maxeval)}
```

```
## [1] 4224
```

Check constraints.

```
tbl_performance <- tibble(
  delta = c(.0, .4) ) %>%
  mutate(
    power = map(
      delta,
      ~evaluate(
        Power(datadist, PointMassPrior(., 1)),
        opt_cp$design) ),
```

```

power_sim = map(
  delta,
  ~sim_pr_reject(opt_cp$design, ., datadist)$prob),
ess       = map(
  delta,
  ~evaluate(ExpectedSampleSize(
    datadist,
    PointMassPrior(., 1) ),
    opt_cp$design) ),
ess_sim   = map(
  delta,
  ~sim_n(opt_cp$design, ., datadist)$n ) ) %>%
unnest(., cols = c(power, power_sim, ess, ess_sim))

print(tbl_performance)

```

```

## # A tibble: 2 x 5
##   delta power power_sim   ess ess_sim
##   <dbl> <dbl>     <dbl> <dbl>   <dbl>
## 1  0    0.0250     0.0250  68.9    69.0
## 2  0.4  0.799      0.799   79.8    79.8

```

```

testthat::expect_lte(
  tbl_performance %>% filter(delta == 0) %>% pull(power_sim),
  alpha * (1 + tol) )

testthat::expect_gte(
  tbl_performance %>% filter(delta == 0.4) %>% pull(power_sim),
  min_power * (1 - tol) )

# make sure that evaluate() leads to same results
testthat::expect_equal(
  tbl_performance$power, tbl_performance$power_sim,
  tol = tol,
  scale = 1 )

testthat::expect_equal(
  tbl_performance$ess, tbl_performance$ess_sim,
  tol = tol_n,
  scale = 1 )

```

The conditional power constraint is evaluated and tested on a grid over the continuation region (both simulated and via numerical integration).

```
tibble(
  x1      = seq(opt_cp$design@c1f, opt_cp$design@c1e, length.out = 25),
  cp      = map_dbl(x1, ~evaluate(cp, opt_cp$design, .)),
  cp_sim  = map_dbl(x1, function(x1) {
    x2 <- simulate(datadist, 10^6, n2(opt_cp$design, x1), .4, 42)
    rej <- ifelse(x2 > c2(opt_cp$design, x1), 1, 0)
    return(mean(rej))
  }) ) %>%
{print(.); .} %>% {
  testthat::expect_true(all(.$cp      >= 0.7 * (1 - tol)))
  testthat::expect_true(all(.$cp_sim >= 0.7 * (1 - tol)))
  testthat::expect_true(all(abs(.$cp - .$cp_sim) <= tol)) }
```

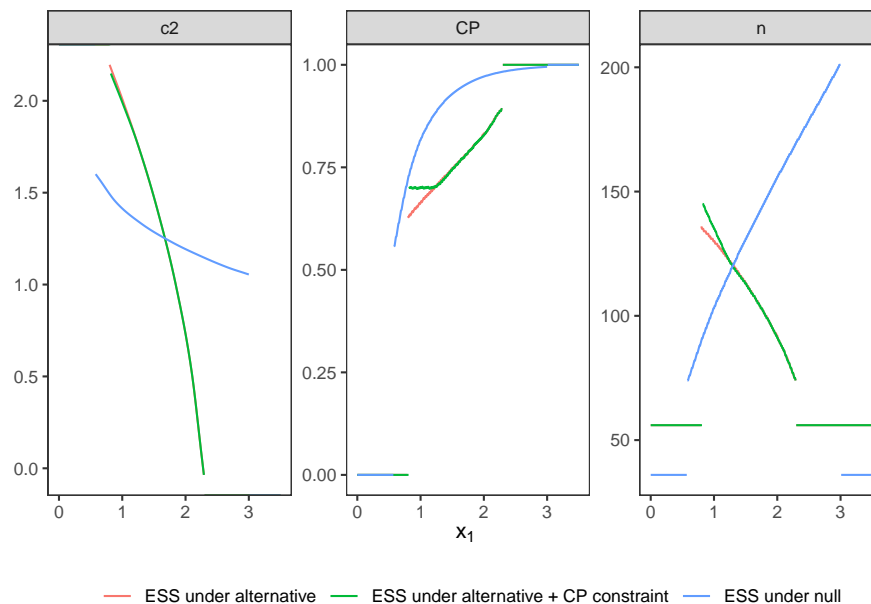
```
## # A tibble: 25 x 3
##       x1      cp cp_sim
##   <dbl> <dbl> <dbl>
## 1 0.810 0.701 0.701
## 2 0.872 0.698 0.699
## 3 0.934 0.701 0.701
## 4 0.995 0.698 0.698
## 5 1.06  0.700 0.700
## 6 1.12  0.702 0.703
## 7 1.18  0.699 0.699
## 8 1.24  0.703 0.703
## 9 1.30  0.713 0.713
## 10 1.37  0.718 0.718
## # ... with 15 more rows
```

Finally, the expected sample size under the alternative prior should be larger than in the case without the constraint I-1.

```
testthat::expect_gte(
  evaluate(ess, opt_cp$design),
  evaluate(
    ess,
    tbl_designs %>%
      filter(type == "two-stage") %>%
      pull(optimal) %>%
      .[[1]] %>%
      .$design ) )
```

2.5 Plot Two-Stage Designs

The following figure shows the three optimal two-stage designs side by side. The effect of the conditional power constraint (CP not below 0.7) is clearly visible and the very different characteristics between optimizing under the null or the alternative are clearly visible.



Chapter 3

Scenario II: large effect, Gaussian prior

3.1 Details

In this scenario, we revisit the case from Scenario I, but are not assuming a point prior any more. Instead, a Gaussian prior with mean $\vartheta = 0.4$ and variance $\tau^2 = 0.2^2$ on the effect size is assumed, i.e. $\delta \sim \mathcal{N}(0.4, 0.2^2)$.

In order to fulfill regulatory considerations, the type one error rate is still protected under the point prior $\delta = 0$ at the level of significance $\alpha = 0.025$.

The power constraint, however, needs to be modified. It is not sensible to compute the power as rejection probability under the full prior, because effect sizes less than a minimal clinically relevant effect do not show (sufficient) evidence against the null hypothesis. Therefore, we assume a minimal clinically relevant effect size $\delta = 0.0$ and condition the prior on values $\delta > 0$ to compute expected power. In the following, the expected power should be at least 0.8.

```
# data distribution and priors
datadist  <- Normal(two_armed = TRUE)
H_0       <- PointMassPrior(.0, 1)
prior     <- ContinuousPrior(function(delta) dnorm(delta, mean = .4, sd = .2),
                             support = c(-5, 5),
                             tighten_support = TRUE)

# define constraints on type one error rate and expected power
alpha     <- 0.025
min_epower <- 0.8
```

```
toer_cnstr <- Power(datadist, H_0) <= alpha
epow_cnstr <- Power(datadist, condition(prior, c(0.0, prior@support[2]))) >= min_epower
```

3.2 Variant II-1: Minimizing Expected Sample Size under Point Prior

3.2.1 Objective

Expected sample size under the full prior is minimized, i.e., $E[n(\mathcal{D})]$.

```
ess <- ExpectedSampleSize(datadist, prior)
```

3.2.2 Constraints

No additional constraints are considered in this variant.

3.2.3 Initial Design

For this example, the optimal one-stage, group-sequential, and generic two-stage designs are computed. While the initial design for the one-stage case is determined heuristically, both the group sequential and the generic two-stage designs are optimized starting from the a group-sequential design that is computed by the `rpact` package to fulfill the type one error rate constraint and that fulfills the power constraint at an effect size of $\delta = 0.3$.

```
order <- 5L
# data frame of initial designs
tbl_designs <- tibble(
  type      = c("one-stage", "group-sequential", "two-stage"),
  initial = list(
    OneStageDesign(250, 2.0),
    rpact_design(datadist, 0.3, 0.025, 0.8, TRUE, order),
    TwoStageDesign(rpact_design(datadist, 0.3, 0.025, 0.8, TRUE, order))) )
```

The order of integration is set to 5.

3.2.4 Optimization

For all these three initial designs, the resulting optimal designs are computed.

3.2. VARIANT II-1: MINIMIZING EXPECTED SAMPLE SIZE UNDER POINT PRIOR³¹

```
tbl_designs <- tbl_designs %>%  
  mutate(  
    optimal = purrr::map(initial, ~minimize(  
  
      ess,  
      subject_to(  
        toer_cnstr,  
        epow_cnstr  
      ),  
  
      initial_design = .,  
      opts           = opts)) )
```

3.2.5 Test Cases

Firstly, it is checked that the maximum number of iterations was not reached in all these cases.

```
tbl_designs %>%  
  transmute(  
    type,  
    iterations = purrr::map_int(tbl_designs$optimal,  
                                ~.$nloptr_return$iterations) ) %>%  
  {print(.); .} %>%  
  {testthat::expect_true(all(.$iterations < opts$maxeval))}
```

```
## # A tibble: 3 x 2  
##   type      iterations  
##   <chr>         <int>  
## 1 one-stage         26  
## 2 group-sequential  720  
## 3 two-stage       1965
```

Since type one error rate is defined under the point effect size $\delta = 0$, the type one error rate constraint can be tested for all three optimal designs.

```
tbl_designs %>%  
  transmute(  
    type,  
    toer = purrr::map(tbl_designs$optimal,  
                      ~sim_pr_reject(.[[1]], .0, datadist)$prob) ) %>%  
  unnest(., cols = c(toer)) %>%  
  {print(.); .} %>% {  
    testthat::expect_true(all(.$toer <= alpha * (1 + tol))) }
```

```
## # A tibble: 3 x 2
##   type      toer
##   <chr>      <dbl>
## 1 one-stage  0.0251
## 2 group-sequential 0.0250
## 3 two-stage  0.0249
```

Since the optimal two-stage design is more flexible than the optimal group-sequential design (constant n_2 function) and this is more flexible than the optimal one-stage design (no second stage), the expected sample sizes under the prior should be ordered in the opposite way. Additionally, expected sample sizes under the null hypothesis are computed both via `evaluate()` and simulation-based.

```
essh0 <- ExpectedSampleSize(datadist, H_0)

tbl_designs %>%
  mutate(
    ess      = map_dbl(optimal,
                      ~evaluate(ess, .$design) ),
    essh0     = map_dbl(optimal,
                      ~evaluate(essh0, .$design) ),
    essh0_sim = map_dbl(optimal,
                      ~sim_n(.$design, .0, datadist)$n ) ) %>%
  {print(.); .} %>% {
    # sim/evaluate same under null?
    testthat::expect_equal(.$essh0, .$essh0_sim,
                          tolerance = tol_n,
                          scale = 1)
    # monotonicity with respect to degrees of freedom
    testthat::expect_true(all(diff(.$ess) < 0)) }

```

```
## # A tibble: 3 x 6
##   type      initial      optimal      ess essh0 essh0_sim
##   <chr>      <list>      <list>      <dbl> <dbl>      <dbl>
## 1 one-stage  <OnStgDsg> <adptrOpR [3]> 165   165        165
## 2 group-sequential <GrpSqntD> <adptrOpR [3]> 117.  115.        115.
## 3 two-stage  <TwStgDsg> <adptrOpR [3]> 115.  119.        119.
```


3.3 Variant II-2: Minimizing Expected Sample Size under Null Hypothesis

3.3.1 Objective

Expected sample size conditioned on negative effect sizes is minimized, i.e.,

```
ess_0 <- ExpectedSampleSize(datadist, condition(prior, c(bounds(prior)[1], 0)))
```

3.3.2 Constraints

No additional constraints besides type one error rate and expected power are considered in this variant.

3.3.3 Initial Design

As in Variant I.2 another initial design is more appropriate for optimization under the null hypothesis. In this situation, one may expect a different (increasing) sample size function, and thus also a different shape of the c_2 function. Therefore, the `rpact` initial design is a suboptimal starting point. Instead, we start with a constant c_2 function by heuristically setting it to 2 on the continuation area. Since optimization under the null hypothesis favours extremely conservative boundaries for early efficacy stopping we impose as quite liberal upper bound of 3 for early efficacy stopping.

```
init_design_h0 <- tbl_designs %>%
  filter(type == "two-stage") %>%
  pull(initial) %>%
  .[[1]]
init_design_h0@c2_pivots <- rep(2, order)

ub_design <- TwoStageDesign(
  3 * init_design_h0@n1,
  2,
  3,
  rep(600, order),
  rep(3.0, order)
)
```

3.3.4 Optimization

```
opt_neg <- minimize(
  ess_0,
  subject_to(
    toer_cnstr,
    epow_cnstr
  ),
  initial_design = init_design_h0,
  upper_boundary_design = ub_design,
  opts = opts
)
```

3.3.5 Test Cases

First of all, check if the optimization algorithm converged. To avoid improper solutions, it is first verified that the maximum number of iterations was not exceeded in any of the three cases.

```
testthat::expect_true(opt_neg$nlptr_return$iterations < opts$maxeval)
print(opt_neg$nlptr_return$iterations)
```

```
## [1] 7197
```

Again, the type one error rate under the point null hypothesis $\delta = 0$ can be tested by simulation.

```
tbl_toer <- tibble(
  toer = evaluate(Power(datadist, H_0), opt_neg$design),
  toer_sim = sim_pr_reject(opt_neg$design, .0, datadist)$prob
)

print(tbl_toer)
```

```
## # A tibble: 1 x 2
##   toer toer_sim
##   <dbl> <dbl>
## 1 0.0249 0.0250
```

```
testthat::expect_true(tbl_toer$toer <= alpha * (1 + tol))
testthat::expect_true(tbl_toer$toer_sim <= alpha * (1 + tol))
```

Furthermore, the expected sample size under the prior conditioned on negative effect sizes ($\delta \leq 0$) should be lower for the optimal design derived in this variant than for the optimal design from Variant II.1 where expected sample size under the full prior was minimized.

```
testthat::expect_lte(
  evaluate(ess_0, opt_neg$design),
  evaluate(
    ess_0,
    tbl_designs %>%
      filter(type == "two-stage") %>%
      pull(optimal) %>%
      .[[1]] %>%
      .$design )
)
```

3.4 Variant II-3: Conditional Power Constraint

3.4.1 Objective

As in Variant II-1, expected sample size under the full prior is minimized.

3.4.2 Constraints

In addition to the constraints on type one error rate and expected power, a constraint on conditional power to be larger than 0.7 is included.

```
cp      <- ConditionalPower(datadist, condition(prior, c(0, prior@support[2])))
cp_cnstr <- cp >= 0.7
```

3.4.3 Initial Design

The previous initial design can still be applied.

3.4.4 Optimization

```

opt_cp <- minimize(
  ess,
  subject_to(
    toer_cnstr,
    epow_cnstr,
    cp_cnstr
  ),
  initial_design = tbl_designs$initial[[3]],
  opts = opts
)

```

3.4.5 Test Cases

We start checking whether the maximum number of iterations was not reached.

```
print(opt_cp$nlptr_return$iterations)
```

```
## [1] 2012
```

```
testthat::expect_true(opt_cp$nlptr_return$iterations < opts$maxeval)
```

The type one error rate is tested via simulation and compared to the value obtained by `evaluate()`.

```

tbl_toer <- tibble(
  toer      = evaluate(Power(datadist, H_0), opt_cp$design),
  toer_sim  = sim_pr_reject(opt_cp$design, .0, datadist)$prob
)

print(tbl_toer)

```

```

## # A tibble: 1 x 2
##   toer toer_sim
##   <dbl>   <dbl>
## 1 0.0250   0.0250

```

```

testthat::expect_true(tbl_toer$toer <= alpha * (1 + tol))
testthat::expect_true(tbl_toer$toer_sim <= alpha * (1 + tol))

```

The conditional power is evaluated via numerical integration on several points inside the continuation region and it is tested whether the constraint is fulfilled on all these points.

```
tibble(
  x1 = seq(opt_cp$design@c1f, opt_cp$design@c1e, length.out = 25),
  cp = map_dbl(x1, ~evaluate(cp, opt_cp$design, .)) ) %>%
{print(.); .} %>% {
  testthat::expect_true(all(.$cp >= 0.7 * (1 - tol))) }
```

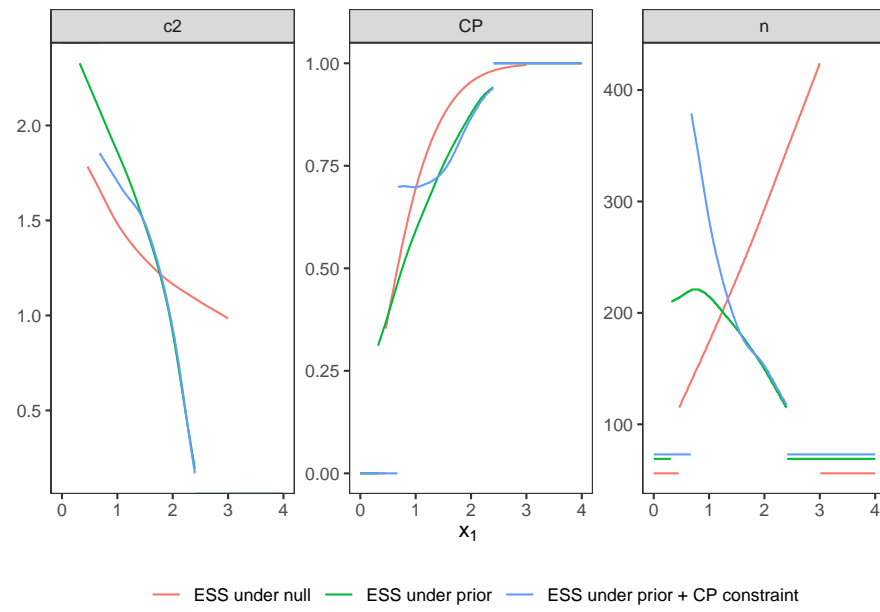
```
## # A tibble: 25 x 2
##       x1      cp
##   <dbl> <dbl>
## 1 0.675 0.698
## 2 0.747 0.700
## 3 0.819 0.700
## 4 0.891 0.699
## 5 0.963 0.698
## 6 1.03  0.698
## 7 1.11  0.701
## 8 1.18  0.705
## 9 1.25  0.709
## 10 1.32  0.715
## # ... with 15 more rows
```

Due to the additional constraint in comparison to Variant II.1, Variant II.3 should show a larger expected sample size under the prior than Variant II.1

```
testthat::expect_gte(
  evaluate(ess, opt_cp$design),
  evaluate(
    ess,
    tbl_designs %>%
      filter(type == "two-stage") %>%
      pull(optimal) %>%
      .[[1]] %>%
      .$design )
)
```

3.5 Plot Two-Stage Designs

The optimal two-stage designs stemming from the different variants are plotted together.



Chapter 4

Scenario III: large effect, uniform prior

4.1 Details

This scenario covers a similar setting as Scenario I. The purpose is to assess whether placing uniform priors with decreasing width of support centered at $\delta = 0.4$ leads to a sequence of optimal designs which converges towards the solution in variant I-1.

The trial is still considered to be two-armed with normally distributed outcomes and the type one error rate under the null hypothesis $\mathcal{H}_0 : \delta \leq 0$ is to be protected at $\alpha = 0.025$.

```
datadist <- Normal(two_armed = TRUE)
H_0 <- PointMassPrior(.0, 1)
alpha <- 0.025
toer_cnstr <- Power(datadist, H_0) <= alpha
```

In this scenario we consider a sequence of uniform distributions $\delta \sim \text{Unif}(0.4 - \Delta_i, 0.4 + \Delta_i)$ around 0.4 with $\Delta_i = (3 - i)/10$ for $i = 0 \dots 3$. I.e., for $\Delta_3 = 0$ reduces to `PointMassPrior` on $\delta = 0.4$.

```
prior <- function(delta) {
  if (delta == 0)
    return(PointMassPrior(.4, 1.0))
  a <- .4 - delta; b <- .4 + delta
  ContinuousPrior(function(x) dunif(x, a, b), support = c(a, b))
}
```

Across all variants in this scenario, the expected power under the respective prior conditioned on $\delta > 0$ must be at least 0.8. I.e., throughout this scenario, we always use the following constraint on expected power.

```
ep_cnstr <- function(delta) {
  prior      <- prior(delta)
  cnd_prior <- condition(prior, c(0, bounds(prior)[2]))
  return( Power(datadist, cnd_prior) >= 0.8 )
}
```

4.2 Variant III.1: Convergence under prior concentration

The goal of this variant is to make sure that the optimal solution converges as the prior is more and more concentrated at a point mass.

4.2.1 Objective

Expected sample size under the respective prior is minimized, i.e., $E[n(\mathcal{D})]$.

```
objective <- function(delta) {
  ExpectedSampleSize(datadist, prior(delta))
}
```

4.2.2 Constraints

The constraints have already been described under details.

4.2.3 Optimization problem

The optimization problem depending on Δ_i is defined below. The default optimization parameters, 5 pivot points, and a fixed initial design are used. The initial design is chosen such that the error constraints are fulfilled. Early stopping for futility is applied if the effect shows in the opponent direction to the alternative, i.e. $c_1^f = 0$. c_2 is chosen close to and c_1^e a little larger than the $1 - \alpha$ -quantile of the standard normal distribution. The sample sizes are selected to fulfill the error constraints.

4.2. VARIANT III.1: CONVERGENCE UNDER PRIOR CONCENTRATION41

```
init <- TwoStageDesign(
  n1    = 150,
  c1f   = 0,
  c1e   = 2.3,
  n2    = 125.0,
  c2    = 2.0,
  order = 5
)

optimal_design <- function(delta) {
  minimize(
    objective(delta),
    subject_to(
      toer_cnstr,
      ep_cnstr(delta)
    ),
    initial_design = init
  )
}

# compute the sequence of optimal designs
deltas <- 3:0/10
results <- lapply(deltas, optimal_design)
```

4.2.4 Test cases

Check that iteration limit was not exceeded in any case.

```
iters <- sapply(results, function(x) x$nlptr_return$iterations)
print(iters)
```

```
## [1] 2368 1891 2685 2789
```

```
testthat::expect_true(all(iters <= opts$maxeval))
```

Check type one error rate control by simulation and by calling `evaluate()`.

```
df_toer <- tibble(
  delta    = deltas,
  toer     = sapply(results, function(x) evaluate(Power(datadist, H_0), x$design)),
  toer_sim = sapply(results, function(x) sim_pr_reject(x$design, .0, datadist)$prob)
)
```

```
testthat::expect_true(all(df_toer$toer <= alpha * (1 + tol)))
testthat::expect_true(all(df_toer$toer_sim <= alpha * (1 + tol)))

print(df_toer)
```

```
## # A tibble: 4 x 3
##   delta   toer toer_sim
##   <dbl> <dbl>   <dbl>
## 1  0.3 0.0250  0.0250
## 2  0.2 0.0250  0.0250
## 3  0.1 0.0250  0.0250
## 4  0   0.0250  0.0250
```

Check that expected sample size decreases with decreasing prior variance.

```
testthat::expect_gte(
  evaluate(objective(deltas[1]), results[[1]]$design),
  evaluate(objective(deltas[2]), results[[2]]$design)
)

testthat::expect_gte(
  evaluate(objective(deltas[2]), results[[2]]$design),
  evaluate(objective(deltas[3]), results[[3]]$design)
)

testthat::expect_gte(
  evaluate(objective(deltas[3]), results[[3]]$design),
  evaluate(objective(deltas[4]), results[[4]]$design)
)
```

4.2.5 Plot designs

Finally, we plot the designs and assess for convergence.

4.2. VARIANT III.1: CONVERGENCE UNDER PRIOR CONCENTRATION43



Chapter 5

Scenario IV: smaller effect, point prior

5.1 Details

In this scenario, we return to point priors as investigated in Scenario I. The main goal is to validate `adoptr`'s sensitivity with regard to the assumed effect size and the constraints on power and type one error rate.

Therefore, we still assume a two-armed trial with normally distributed outcomes. The assumed effect size under the alternative is $\delta = 0.2$ in this setting. Type one error rate is protected at 2.5% and the power should be at least 80%. We will vary these values in the variants IV.2 and IV.3

```
# data distribution and hypotheses
datadist  <- Normal(two_armed = TRUE)
H_0       <- PointMassPrior(.0, 1)
prior     <- PointMassPrior(.2, 1)

# constraints
alpha     <- 0.025
min_power <- 0.8
toer_cnstr <- Power(datadist, H_0)  <= alpha
pow_cnstr  <- Power(datadist, prior) >= min_power
```

5.2 Variant IV-1: Minimizing Expected Sample Size under Point Prior

5.2.1 Objective

Expected sample size under the alternative point prior $\delta = 0.2$ is minimized.

```
ess <- ExpectedSampleSize(datadist, prior)
```

5.2.2 Constraints

No additional constraints are considered in this variant.

5.2.3 Initial Design

For this example, the optimal one-stage, group-sequential, and generic two-stage designs are computed. The initial design that is used as starting value of optimization is defined as a group-sequential design by the package `rpact` that fulfills type one error rate and power constraints in the case of group-sequential and two-stage design. The initial one-stage design is chosen heuristically. The order of integration is set to 5.

```
order <- 5L

tbl_designs <- tibble(
  type = c("one-stage", "group-sequential", "two-stage"),
  initial = list(
    OneStageDesign(500, 2.0),
    rpact_design(datadist, 0.2, 0.025, 0.8, TRUE, order),
    TwoStageDesign(rpact_design(datadist, 0.2, 0.025, 0.8, TRUE, order))) )
```

5.2.4 Optimization

```
tbl_designs <- tbl_designs %>%
  mutate(
    optimal = purrr::map(initial, ~minimize(
      ess,
      subject_to(
        toer_cnstr,
```

5.2. VARIANT IV-1: MINIMIZING EXPECTED SAMPLE SIZE UNDER POINT PRIOR⁴⁷

```
      pow_cnstr
    ),

    initial_design = .,
    opts           = opts)) )
```

5.2.5 Test Cases

Firstly, it is checked whether the maximum number of iterations was not exceeded in all three cases.

```
tbl_designs %>%
  transmute(
    type,
    iterations = purrr::map_int(tbl_designs$optimal,
                                ~.$nloptr_return$iterations) ) %>%
  {print(.); .} %>%
  {testthat::expect_true(all(.$iterations < opts$maxeval))}
```

```
## # A tibble: 3 x 2
##   type      iterations
##   <chr>         <int>
## 1 one-stage         20
## 2 group-sequential 959
## 3 two-stage       2096
```

Now, the constraints on type one error rate and power are tested via simulation.

```
tbl_designs %>%
  transmute(
    type,
    toer = purrr::map(tbl_designs$optimal,
                      ~sim_pr_reject(.[[1]], .0, datadist)$prob),
    power = purrr::map(tbl_designs$optimal,
                      ~sim_pr_reject(.[[1]], .2, datadist)$prob) ) %>%
  unnest(., cols = c(toer, power)) %>%
  {print(.); .} %>% {
    testthat::expect_true(all(.$toer <= alpha * (1 + tol)))
    testthat::expect_true(all(.$power >= min_power * (1 - tol))) }

## # A tibble: 3 x 3
##   type      toer power
##   <chr>         <dbl> <dbl>
```

```
## 1 one-stage          0.0251 0.799
## 2 group-sequential  0.0250 0.800
## 3 two-stage         0.0250 0.800
```

Due to increasing degrees of freedom, the expected sample sizes under the alternative should be ordered as ‘one-stage > group-sequential > two-stage’. They are evaluated by simulation as well as by `evaluate()`.

```
tbl_designs %>%
  mutate(
    ess      = map_dbl(optimal,
                      ~evaluate(ess, .$design) ),
    ess_sim  = map_dbl(optimal,
                      ~sim_n(.$design, .2, datadist)$n ) ) %>%
  {print(.); .} %>% {
    # sim/evaluate same under alternative?
    testthat::expect_equal(.$ess, .$ess_sim,
                          tolerance = tol_n,
                          scale = 1)
    # monotonicity with respect to degrees of freedom
    testthat::expect_true(all(diff(.$ess) < 0)) }

```

```
## # A tibble: 3 x 5
##   type          initial    optimal      ess ess_sim
##   <chr>         <list>    <list>    <dbl> <dbl>
## 1 one-stage    <OnStgDsg> <adptrOpR [3]> 392   392
## 2 group-sequential <GrpSqntD> <adptrOpR [3]> 324.  323.
## 3 two-stage    <TwStgDsg> <adptrOpR [3]> 320.  319.
```

Furthermore, the expected sample size under the alternative of the optimal group-sequential design should be lower than for the group-sequential design by `rpact` that is based on the inverse normal combination test.

```
tbl_designs %>%
  filter(type == "group-sequential") %>%
  { expect_lte(
    evaluate(ess, {.$[["optimal"]][[1]]$design}),
    evaluate(ess, {.$[["initial"]][[1]]})
  ) }

```

Finally, the n_2 function of the optimal two-stage design is expected to be monotonously decreasing:


```
expect_true(
  all(diff(
    # get optimal two-stage design n2 pivots
    tbl_designs %>% filter(type == "two-stage") %>%
      {.[["optimal"]][[1]]$design@n2_pivots}
  ) < 0) )
```

5.3 Variant IV-2: Increase Power

5.3.1 Objective

The objective remains expected sample size under the alternative $\delta = 0.2$.

5.3.2 Constraints

The minimal required power is increased to 90%.

```
min_power_2 <- 0.9
pow_cnstr_2 <- Power(datadist, prior) >= min_power_2
```

5.3.3 Initial Design

For both flavours with two stages (group-sequential, generic two-stage) the initial design is created by `rpact` to fulfill the error rate constraints.

```
tbl_designs_9 <- tibble(
  type      = c("one-stage", "group-sequential", "two-stage"),
  initial = list(
    OneStageDesign(500, 2.0),
    rpact_design(datadist, 0.2, 0.025, 0.9, TRUE, order),
    TwoStageDesign(rpact_design(datadist, 0.2, 0.025, 0.9, TRUE, order))) )
```

5.3.4 Optimization

```
tbl_designs_9 <- tbl_designs_9 %>%
  mutate(
    optimal = purrr::map(initial, ~minimize(
      ess,
```

```

    subject_to(
      toer_cnstr,
      pow_cnstr_2
    ),

    initial_design = .,
    opts           = opts)) )

```

5.3.5 Test Cases

We start checking if the maximum number of iterations was not exceeded in all three cases.

```

tbl_designs_9 %>%
  transmute(
    type,
    iterations = purrr::map_int(tbl_designs_9$optimal,
                                ~.$nloptr_return$iterations) ) %>%
  {print(.); .} %>%
  {testthat::expect_true(all(.$iterations < opts$maxeval))}

```

```

## # A tibble: 3 x 2
##   type      iterations
##   <chr>         <int>
## 1 one-stage         30
## 2 group-sequential 1485
## 3 two-stage       3069

```

The type one error rate and power constraints are evaluated by simulation.

```

tbl_designs_9 %>%
  transmute(
    type,
    toer = purrr::map(tbl_designs_9$optimal,
                      ~sim_pr_reject(.[[1]], .0, datadist)$prob),
    power = purrr::map(tbl_designs_9$optimal,
                      ~sim_pr_reject(.[[1]], .2, datadist)$prob) ) %>%
  unnest(., cols = c(toer, power)) %>%
  {print(.); .} %>% {
    testthat::expect_true(all(.$toer <= alpha * (1 + tol)))
    testthat::expect_true(all(.$power >= min_power_2 * (1 - tol))) }

```

```

## # A tibble: 3 x 3

```

```
##   type           toer power
##   <chr>           <dbl> <dbl>
## 1 one-stage      0.0251 0.900
## 2 group-sequential 0.0249 0.900
## 3 two-stage      0.0250 0.900
```

Due to increasing degrees of freedom, the expected sample sizes under the alternative should be ordered as ‘one-stage > group-sequential > two-stage’. This is tested by simulation as well as by `evaluate()`.

```
tbl_designs_9 %>%
  mutate(
    ess      = map_dbl(optimal,
                       ~evaluate(ess, .$design) ),
    ess_sim  = map_dbl(optimal,
                       ~sim_n(.$design, .2, datadist)$n ) ) %>%
  {print(.); .} %>% {
    # sim/evaluate same under alternative?
    testthat::expect_equal(.$ess, .$ess_sim,
                           tolerance = tol_n,
                           scale = 1)
    # monotonicity with respect to degrees of freedom
    testthat::expect_true(all(diff(.$ess) < 0))
    testthat::expect_true(all(diff(.$ess_sim) < 0))}
  }
```

```
## # A tibble: 3 x 5
##   type           initial      optimal      ess ess_sim
##   <chr>           <list>      <list>      <dbl> <dbl>
## 1 one-stage      <OnStgDsg> <adptrOpR [3]> 525    525
## 2 group-sequential <GrpSqntD> <adptrOpR [3]> 405.    405.
## 3 two-stage      <TwStgDsg> <adptrOpR [3]> 397.    397.
```

Comparing with the inverse-normal based group-sequential design created by `rpact`, the optimal group-sequential design should show a lower expected sample size under the point alternative.

```
tbl_designs_9 %>%
  filter(type == "group-sequential") %>%
  { expect_lte(
    evaluate(ess, {.$[["optimal"]][[1]]$design}),
    evaluate(ess, {.$[["initial"]][[1]]})
  ) }
```

Since a point prior is regarded, the n_2 function of the optimal two-stage design is expected to be monotonously decreasing:

```
expect_true(
  all(diff(
    # get optimal two-stage design n2 pivots
    tbl_designs_9 %>% filter(type == "two-stage") %>%
    {.[["optimal"]][[1]]$design@n2_pivots}
  ) < 0) )
```

5.4 Variant IV-3: Increase Type One Error rate

5.4.1 Objective

As in variants IV.1 and IV-2, expected sample size under the point alternative is minimized.

5.4.2 Constraints

While the power is still lower bounded by 90% as in variant II, the maximal type one error rate is increased to 5%.

```
alpha_2      <- .05
toer_cnstr_2 <- Power(datadist, H_0) <= alpha_2
```

5.4.3 Initial Design

Again, a design computed by means of the package `rpact` to fulfill the updated error rate constraints is applied as initial design for the optimal group-sequential and generic two-stage designs.

```
tbl_designs_5 <- tibble(
  type      = c("one-stage", "group-sequential", "two-stage"),
  initial = list(
    OneStageDesign(500, 2.0),
    rpact_design(datadist, 0.2, 0.05, 0.9, TRUE, order),
    TwoStageDesign(rpact_design(datadist, 0.2, 0.05, 0.9, TRUE, order))) )
```

5.4.4 Optimization

```
tbl_designs_5 <- tbl_designs_5 %>%
  mutate(
    optimal = purrr::map(initial, ~minimize(
      ess,
      subject_to(
        toer_cnstr_2,
        pow_cnstr_2
      ),
      initial_design = .,
      opts = opts)) )
```

5.4.5 Test Cases

The convergence of the optimization algorithm is tested by checking if the maximum number of iterations was not exceeded.

```
tbl_designs_5 %>%
  transmute(
    type,
    iterations = purrr::map_int(tbl_designs_5$optimal,
      ~.$nloptr_return$iterations) ) %>%
  {print(.); .} %>%
  {testthat::expect_true(all(. $iterations < opts$maxeval))}
```

```
## # A tibble: 3 x 2
##   type          iterations
##   <chr>          <int>
## 1 one-stage         27
## 2 group-sequential 1127
## 3 two-stage        2338
```

By simulation, the constraints on the error rates (type one error and power) are tested.

```
tbl_designs_5 %>%
  transmute(
    type,
    toer = purrr::map(tbl_designs_5$optimal,
      ~sim_pr_reject(.[[1]], .0, datadist)$prob),
    power = purrr::map(tbl_designs_5$optimal,
      ~sim_pr_reject(.[[1]], .2, datadist)$prob) ) %>%
```

```
unnest(., cols = c(toer, power)) %>%
{print(.); .} %>% {
testthat::expect_true(all(.$toer <= alpha_2 * (1 + tol)))
testthat::expect_true(all(.$power >= min_power_2 * (1 - tol))) }
```

```
## # A tibble: 3 x 3
##   type          toer power
##   <chr>         <dbl> <dbl>
## 1 one-stage      0.0502 0.900
## 2 group-sequential 0.0500 0.900
## 3 two-stage      0.0502 0.900
```

Due to increasing degrees of freedom, the expected sample sizes under the alternative should be ordered as ‘one-stage > group-sequential > two-stage’. They are tested by simulation as well as by calling `evaluate()`.

```
tbl_designs_5 %>%
  mutate(
    ess = map_dbl(optimal,
                  ~evaluate(ess, .)$design ),
    ess_sim = map_dbl(optimal,
                      ~sim_n(.$design, .2, datadist)$n ) ) %>%
  {print(.); .} %>% {
    # sim/evaluate same under alternative?
    testthat::expect_equal(.$ess, .)$ess_sim,
                          tolerance = tol_n,
                          scale = 1)
    # monotonicity with respect to degrees of freedom
    testthat::expect_true(all(diff(.$ess) < 0)) }
```

```
## # A tibble: 3 x 5
##   type          initial    optimal          ess ess_sim
##   <chr>         <list>    <list>         <dbl> <dbl>
## 1 one-stage    <OnStgDsg> <adptrOpR [3]> 428    428
## 2 group-sequential <GrpSqntD> <adptrOpR [3]> 325.   325.
## 3 two-stage    <TwStgDsg> <adptrOpR [3]> 319.   319.
```

The expected sample size under the alternative that was used as objective criterion of the optimal group-sequential design should be lower than for the group-sequential design by `rpact` that is based on the inverse normal combination test.

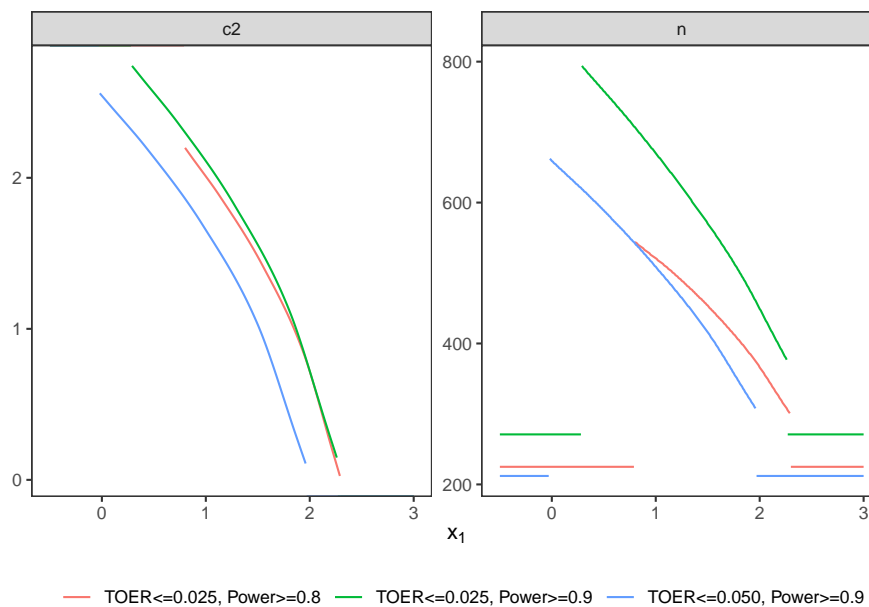
```
tbl_designs_5 %>%
  filter(type == "group-sequential") %>%
  { expect_lte(
    evaluate(ess, {.[["optimal"]][[1]]$design}),
    evaluate(ess, {.[["initial"]][[1]]})
  ) }
```

Also in this variant, the n_2 function of the optimal two-stage design is expected to be monotonously decreasing:

```
expect_true(
  all(diff(
    # get optimal two-stage design n2 pivots
    tbl_designs_5 %>% filter(type == "two-stage") %>%
      {.[["optimal"]][[1]]$design@n2_pivots}
  ) < 0) )
```

5.5 Plot Two-Stage Designs

The optimal two-stage designs stemming from the three different variants are plotted together.



Chapter 6

Scenario V: single-arm design, medium effect size

6.1 Details

In this scenario, again a point prior is analyzed. The null hypothesis is $\delta \leq 0$ and we assume an alternative effect size of $\delta = 0.3$. Type one error rate should be protected at 2.5% and the design's power should be at least 80%. Differently than in the previous scenarios, we are assuming a single-arm design throughout this scenario.

```
# data distribution and hypotheses
datadist  <- Normal(two_armed = FALSE)
H_0       <- PointMassPrior(.0, 1)
prior     <- PointMassPrior(.3, 1)

# define constraints
alpha     <- 0.025
min_power <- 0.8
toer_cnstr <- Power(datadist, H_0)  <= alpha
pow_cnstr  <- Power(datadist, prior) >= min_power
```

6.2 Variant V-1, sensitivity to integration order

In this variant, the sensitivity of the optimization with respect to the integration order is investigated. We apply three different integration orders: 5, 8, and 11.

6.2.1 Objective

Expected sample size under the alternative point mass prior $\delta = 0.3$ is minimized.

```
ess <- ExpectedSampleSize(datadist, prior)
```

6.2.2 Constraints

No additional constraints are considered in this variant.

6.2.3 Initial Design

In order to vary the initial design, `rpact` is not used in this variant. Instead, the following heuristical considerations are made. A fixed design for these parameters would require 176 subjects per group. We use the half of this as initial values for the sample sizes. The initial stop for futility is at $c_1^f = 0$, i.e., if the effect shows in the opponent direction to the alternative. The starting values for the efficacy stop and for c_2 is the $1 - \alpha$ -quantile of the normal distribution.

```
init_design <- function(order) {
  TwoStageDesign(
    n1 = ceiling(pwr::pwr.t.test(d = .3,
                                sig.level = .025,
                                power = .8,
                                alternative = "greater")$n) / 2,

    c1f = 0,
    c1e = qnorm(1 - 0.025),
    n2 = ceiling(pwr::pwr.t.test(d = .3,
                                sig.level = .025,
                                power = .8,
                                alternative = "greater")$n) / 2,

    c2 = qnorm(1 - 0.025),
    order = order
  )
}
```

6.2.4 Optimization

The optimal design is computed for three different integration orders: 5, 8, and 11.

```

opt_design <- function(order) {
  minimize(
    ess,
    subject_to(
      toer_cnstr,
      pow_cnstr
    ),
    initial_design = init_design(order),
    upper_boundary_design = TwoStageDesign(200, 2, 4, 200, 3, order),
    opts = opts
  )
}

opt <- tibble(
  order = c(5, 8, 11),
  design = lapply(c(5, 8, 11), function(x) opt_design(x))
)

```

6.2.5 Test cases

Check if the optimization algorithm converged in all cases.

```

opt %>%
  transmute(
    order,
    iterations = purrr::map_int(opt$design,
                                ~.$nloptr_return$iterations) ) %>%
  {print(.); .} %>%
  {testthat::expect_true(all(.$iterations < opts$maxeval))}

```

```

## # A tibble: 3 x 2
##   order iterations
##   <dbl>      <int>
## 1     5       2372
## 2     8       5378
## 3    11      10689

```

Test the constraints on type one error rate and power by simulation and compare the results to the outcome of `evaluate()`.

```

opt %>%
  transmute(
    order,

```

```

toer      = map_dbl(design,
                    ~evaluate(Power(datadist, PointMassPrior(.0, 1)), .$design),
toer_sim  = map_dbl(opt$design,
                    ~sim_pr_reject(.[[1]], .0, datadist)$prob),
power     = map_dbl(design,
                    ~evaluate(Power(datadist, PointMassPrior(.3, 1)), .$design),
power_sim = map_dbl(opt$design,
                    ~sim_pr_reject(.[[1]], .3, datadist)$prob),
ess       = map_dbl(design, ~evaluate(ess, .$design) ),
ess_sim   = map_dbl(opt$design, ~sim_n(.[[1]], .3, datadist)$n)
) %>%
unnest(., cols = c(toer, toer_sim, power, power_sim)) %>%
{print(.); .} %>% {
testthat::expect_true(all(.$toer      <= alpha * (1 + tol)))
testthat::expect_true(all(.$toer_sim  <= alpha * (1 + tol)))
testthat::expect_true(all(.$power     >= min_power * (1 - tol)))
testthat::expect_true(all(.$power_sim >= min_power * (1 - tol))) }

```

```

## # A tibble: 3 x 7
##   order  toer toer_sim power power_sim  ess ess_sim
##   <dbl> <dbl>   <dbl> <dbl>   <dbl> <dbl>   <dbl>
## 1     5 0.0250  0.0250 0.799    0.800  71.0   71.0
## 2     8 0.0250  0.0250 0.800    0.800  71.0   71.0
## 3    11 0.0250  0.0250 0.800    0.800  71.0   71.0

```

6.3 Variant V-2, utility maximization

6.3.1 Objective

In this variant, a utility function consisting of expected sample size and power is minimized. The parameter λ that is describing the ratio between expected sample size and power is varied.

```

pow <- Power(datadist, prior)
ess <- ExpectedSampleSize(datadist, prior)

obj <- function(lambda) {
  composite({ess - lambda * pow})
}

```

6.3.2 Constraints

The type one error rate is controlled at 0.025 on the boundary of the null hypothesis. Hence, the previous inequality can still be used. There is no constraint on power any more because power is part of the objective utility function.

6.3.3 Initial Design

The previous initial design with order 5 is applied.

6.3.4 Optimization

The optimal design is computed for two values of λ : 100 and 200.

```
opt_utility <- tibble(
  lambda = c(100, 200)
) %>%
  mutate(
    design = purrr::map(lambda, ~minimize(
      obj(.),
      subject_to(
        toer_cnstr
      ),
      initial_design = init_design(5),
      opts = opts))
  )
```

6.3.5 Test cases

Firstly, it is checked whether the maximum number of iterations was not exceeded in both flavours.

```
opt_utility %>%
  transmute(
    lambda,
    iterations = purrr::map_int(opt_utility$design,
      ~.$nloptr_return$iterations) ) %>%
  {print(.); .} %>%
  {testthat::expect_true(all(.$iterations < opts$maxeval))}
```

```
## # A tibble: 2 x 2
```

```
##   lambda iterations
##   <dbl>      <int>
## 1    100      3338
## 2    200      3154
```

Type one error rate control is tested for both designs by simulation and by `adoptr`'s function `evaluate`. In addition, it is tested if the design with larger λ (i.e., stronger focus on power), shows the larger overall power.

```
opt_utility %>%
  transmute(
    lambda,
    toer      = map_dbl(design,
                        ~evaluate(Power(datadist, PointMassPrior(.0, 1)), .$design)
    toer_sim  = purrr::map(opt_utility$design,
                        ~sim_pr_reject(.[[1]], .0, datadist)$prob),
    power     = map_dbl(design,
                        ~evaluate(Power(datadist, PointMassPrior(.3, 1)), .$design)
    power_sim = purrr::map(opt_utility$design,
                        ~sim_pr_reject(.[[1]], .3, datadist)$prob) ) %>%
  unnest(., c(toer, toer_sim, power, power_sim)) %>%
  {print(.); .} %>% {
    testthat::expect_true(all(.$toer      <= alpha * (1 + tol)))
    testthat::expect_true(all(.$toer_sim <= alpha * (1 + tol)))
    testthat::expect_lte(.$power[1], .$power[2]) }
}
```

```
## # A tibble: 2 x 5
##   lambda  toer toer_sim power power_sim
##   <dbl> <dbl>   <dbl> <dbl>   <dbl>
## 1    100 0.0250  0.0250 0.519   0.520
## 2    200 0.0251  0.0250 0.897   0.897
```

Finally, the three designs computed so far are plotted together to allow comparison.



6.4 Variant V-3, n1-penalty

In this variant, the influence of the regularization term $N1()$ is investigated.

6.4.1 Objective

In order to analyse the influence of $N1()$, a mixed criterion consisting of expected sample size under the point prior and $N1()$ is minimized.

```
N1 <- N1()

obj_n1 <- function(lambda) {
  composite({ess + lambda * N1})
}
```

6.4.2 Constraints

The inequalities from variant V.1 can still be used.

6.4.3 Initial Design

The previous initial design with order 5 is applied. This variant requires an upper bound on c_2 . Otherwise, very large values for c_2 and large n_2 -values would allow appear to reduce n_1 .

```
ub_design <- get_upper_boundary_design(init_design(5))
ub_design@c2_pivots <- rep(3, 5)
```

6.4.4 Optimization

The optimal design is computed for two values of λ : 0.05 and 0.2.

```
opt_n1 <- tibble(
  lambda = c(0.05, 0.2)
) %>%
  mutate(
    design = purrr::map(lambda, ~minimize(
      obj_n1(.),
      subject_to(
        toer_cnstr,
        pow_cnstr
      ),

      initial_design      = init_design(5),
      upper_boundary_design = ub_design,
      opts                = opts))
  )
```

6.4.5 Test cases

We start testing if the optimization algorithm converged in both cases

```
opt_n1 %>%
  transmute(
    lambda,
    iterations = purrr::map_int(opt_n1$design,
                                ~.$nloptr_return$iterations) ) %>%
  {print(.); .} %>%
  {testthat::expect_true(all(.$iterations < opts$maxeval))}
```

```
## # A tibble: 2 x 2
##   lambda iterations
```



```
##      <dbl>      <int>
## 1    0.05      3133
## 2    0.2       2921
```

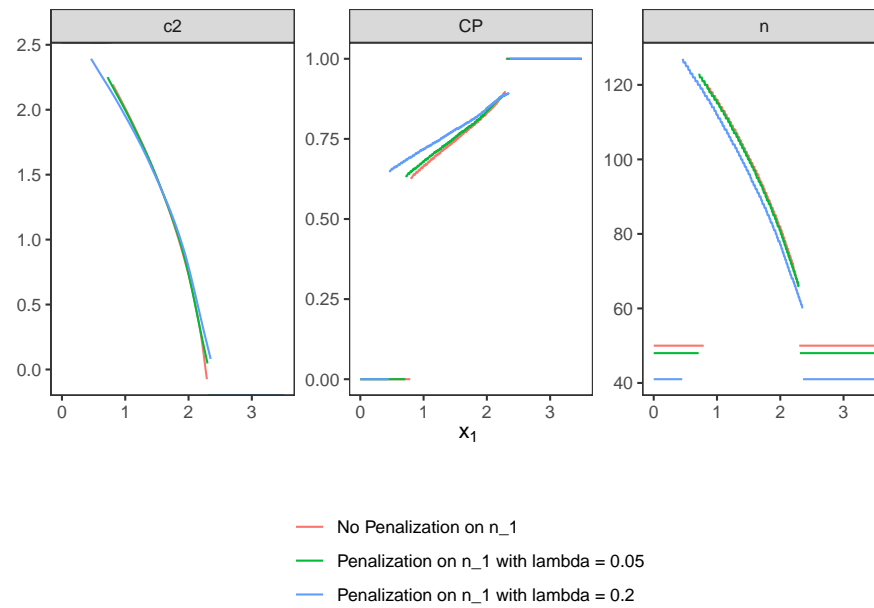
Next, the error rate constraints on type one error rate and power are both tested by simulation and by the `evaluate`-call.

```
opt_n1 %>%
  transmute(
    lambda,
    toer      = map_dbl(design,
                        ~evaluate(Power(datadist, PointMassPrior(.0, 1)), .)$design) ),
    toer_sim  = purrr::map(opt_n1$design,
                        ~sim_pr_reject(.[[1]], .0, datadist)$prob),
    power     = map_dbl(design,
                        ~evaluate(Power(datadist, PointMassPrior(.3, 1)), .)$design) ),
    power_sim = purrr::map(opt_n1$design,
                        ~sim_pr_reject(.[[1]], .3, datadist)$prob) ) %>%
  unnest(., cols = c(toer, toer_sim, power, power_sim)) %>%
  {print(.); .} %>% {
    testthat::expect_true(all(.$toer      <= alpha * (1 + tol)))
    testthat::expect_true(all(.$toer_sim  <= alpha * (1 + tol)))
    testthat::expect_true(all(.$power     >= min_power * (1 - tol)))
    testthat::expect_true(all(.$power_sim >= min_power * (1 - tol))) }

## # A tibble: 2 x 5
##   lambda  toer toer_sim power power_sim
##   <dbl> <dbl>   <dbl> <dbl>   <dbl>
## 1  0.05 0.0250  0.0250 0.801   0.801
## 2  0.2  0.0250  0.0250 0.800   0.800
```

Since n_1 is penalized in both flavours that are computed in this variant, we expect a lower n_1 value as larger λ . Furthermore, n_1 should be lower in both cases than in the unpenalized situation regarded in variant V.1. Finally, these three designs are plotted together to allow graphical comparison.

```
## # A tibble: 3 x 3
##   type                design      n_1
##   <chr>              <list>    <dbl>
## 1 No Penalization on n_1    <TwStgDsg>    50
## 2 Penalization on n_1 with lambda = 0.05 <TwStgDsg>    48
## 3 Penalization on n_1 with lambda = 0.2  <TwStgDsg>    41
```



6.5 Variant V-4, n_2 -penalty

Here, we alter the situation from variant V.3 by not penalizing n_1 , but the average stage-two sample size n_2 . This can be done by means of the function `AverageN2()`.

6.5.1 Objective

As in variant V.3, a mixed criterion is minimized. Here, it consists of expected sample size under the point prior and the average of n_2 .

```
avn2 <- AverageN2()

obj_n2 <- function(lambda) {
  composite({ess + lambda * avn2})
}
```

6.5.2 Constraints

The inequalities from variant V.1 can still be used.

6.5.3 Initial Design

The previous initial design with order 8 is applied. However, this case requires the definition of an upper-bound for c_2 . Otherwise, very small n_2 -values and very large c_2 -values would appear close to the early-futility-stop boundary in order to decrease the average n_2 .

```
ub_design <- get_upper_boundary_design(init_design(8))
ub_design@c2_pivots <- rep(2.5, 8)
```

6.5.4 Optimization

The optimal design is computed for two values of λ : 0.01 and 0.1.

```
opt_n2 <- tibble(
  lambda = c(0.01, 0.1)
) %>%
  mutate(
    design = purrr::map(lambda, ~minimize(
      obj_n2(.),
      subject_to(
        toer_cnstr,
        pow_cnstr
      ),
      initial_design = init_design(8),
      upper_boundary_design = ub_design,
      opts = opts))
  )
```

6.5.5 Test cases

As first step, we check if the maximum number of iterations was not exceeded in both cases.

```
opt_n2 %>%
  transmute(
    lambda,
    iterations = purrr::map_int(opt_n2$design,
                                ~.$nloptr_return$iterations) ) %>%
  {print(.); .} %>%
  {testthat::expect_true(all(. $iterations < opts$maxeval))}
```

```
## # A tibble: 2 x 2
##   lambda iterations
##   <dbl>      <int>
## 1  0.01     18398
## 2  0.1      11123
```

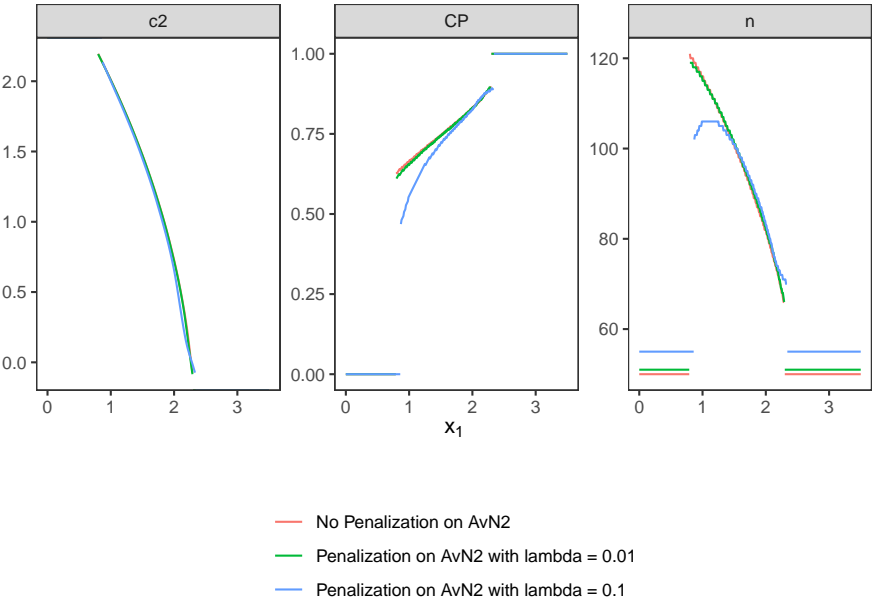
As second step, the type one error rate and power restrictions are tested by simulation and by calling `evaluate`.

```
opt_n2 %>%
  transmute(
    lambda,
    toer      = map_dbl(design,
                        ~evaluate(Power(datadist, PointMassPrior(.0, 1)), .$design)
    toer_sim  = purrr::map(opt_n2$design,
                        ~sim_pr_reject(.[[1]], .0, datadist)$prob),
    power     = map_dbl(design,
                        ~evaluate(Power(datadist, PointMassPrior(.3, 1)), .$design)
    power_sim = purrr::map(opt_n2$design,
                        ~sim_pr_reject(.[[1]], .3, datadist)$prob) ) %>%
  unnest(., c(toer, toer_sim, power, power_sim)) %>%
  {print(.); .} %>% {
    testthat::expect_true(all(.$toer      <= alpha * (1 + tol)))
    testthat::expect_true(all(.$toer_sim  <= alpha * (1 + tol)))
    testthat::expect_true(all(.$power     >= min_power * (1 - tol)))
    testthat::expect_true(all(.$power_sim >= min_power * (1 - tol))) }

## # A tibble: 2 x 5
##   lambda  toer toer_sim power power_sim
##   <dbl> <dbl>   <dbl> <dbl>   <dbl>
## 1  0.01 0.0250  0.0249 0.802   0.802
## 2  0.1  0.0250  0.0250 0.801   0.801
```

Due to increasing penalization, it is assumed that the optimal design computed in variant V.1 (no penalization) shows a larger average n_2 than the optimal penalized design with $\lambda = 0.01$ and this shows a larger average n_2 than the optimal design with $\lambda = 0.1$. Additionally, these three designs are depicted in a joint plot.

```
## # A tibble: 3 x 3
##   type                design  average_n2
##   <chr>              <list>      <dbl>
## 1 No Penalization on AvN2    <TwStgDsg>    47.6
## 2 Penalization on AvN2 with lambda = 0.01 <TwStgDsg>    46.6
## 3 Penalization on AvN2 with lambda = 0.1  <TwStgDsg>    38.9
```



Chapter 7

Scenario VI: binomial distribution, point prior

7.1 Details

In this scenario, the implemented normal approximation of the binomial distribution is evaluated. There are two treatment groups E (experimental) and C (control) and the outcome of interest is the event rate in both groups. The event rate in the control group is assumed to equal $p_C = 0.3$. Under the null hypothesis, the rate difference $p_E - p_C = 0$ is assumed. Under the alternative, the rate difference is assumed to equal $p_E - p_C = 0.2$. Type one error rate should be protected at 2.5% and the design's power should be at least 90%.

```
# data distribution and hypotheses
datadist  <- Binomial(rate_control = 0.3, two_armed = TRUE)
H_0       <- PointMassPrior(.0, 1)
prior     <- PointMassPrior(.2, 1)

# define constraints
alpha     <- 0.025
min_power <- 0.9
toer_cnstr <- Power(datadist, H_0)  <= alpha
pow_cnstr  <- Power(datadist, prior) >= min_power
```

7.2 Variant VI-1: Minimizing Expected Sample Size Under Point Prior

In this variant, it is evaluated whether the optimization leads to more efficient designs and is plausible with published results.

7.2.1 Objective

Expected sample size under the alternative point mass prior $\delta = 0.2$ is minimized.

```
ess <- ExpectedSampleSize(datadist, prior)
```

7.2.2 Constraints

No additional constraints are considered.

7.2.3 Initial Designs

For this example, the optimal one-stage, group-sequential, and generic two-stage designs are computed. The initial design for the one-stage case is determined heuristically and both the group sequential and the generic two-stage designs are optimized starting from the corresponding group-sequential design as computed by the `rpact` package.

```
order <- 7L
# data frame of initial designs
tbl_designs <- tibble(
  type = c("one-stage", "group-sequential", "two-stage"),
  initial = list(
    OneStageDesign(200, 2.0),
    rpact_design(datadist, 0.2, 0.025, 0.9, TRUE, order),
    TwoStageDesign(rpact_design(datadist, 0.2, 0.025, 0.9, TRUE, order))) )
```

The order of integration is set to 7.

7.2.4 Optimization

7.2. VARIANT VI-1: MINIMIZING EXPECTED SAMPLE SIZE UNDER POINT PRIOR73

```
tbl_designs <- tbl_designs %>%
  mutate(
    optimal = purrr::map(initial, ~minimize(
      ess,
      subject_to(
        toer_cnstr,
        pow_cnstr
      ),
      initial_design = .,
      opts = opts)) )
```

7.2.5 Test Cases

To avoid improper solutions, it is first verified that the maximum number of iterations was not exceeded in any of the three cases.

```
tbl_designs %>%
  transmute(
    type,
    iterations = purrr::map_int(tbl_designs$optimal,
                                ~.$nloptr_return$iterations) ) %>%
  {print(.); .} %>%
  {testthat::expect_true(all(.$iterations < opts$maxeval))}
```

```
## # A tibble: 3 x 2
##   type            iterations
##   <chr>              <int>
## 1 one-stage           28
## 2 group-sequential  1774
## 3 two-stage         4736
```

Next, the type one error rate and power constraints are verified for all three designs by simulation:

```
tbl_designs %>%
  transmute(
    type,
    toer = purrr::map(tbl_designs$optimal,
                      ~sim_pr_reject(.[[1]], .0, datadist)$prob),
    power = purrr::map(tbl_designs$optimal,
                      ~sim_pr_reject(.[[1]], .2, datadist)$prob) ) %>%
```

```
unnest(., cols = c(toer, power)) %>%
{print(.); .} %>% {
testthat::expect_true(all(.$toer <= alpha * (1 + tol)))
testthat::expect_true(all(.$power >= min_power * (1 - tol))) }
```

```
## # A tibble: 3 x 3
##   type      toer power
##   <chr>      <dbl> <dbl>
## 1 one-stage 0.0251 0.900
## 2 group-sequential 0.0249 0.900
## 3 two-stage 0.0249 0.901
```

Since the degrees of freedom of the three design classes are ordered as ‘two-stage’ > ‘group-sequential’ > ‘one-stage’, the expected sample sizes (under the alternative) should be ordered in reverse (‘two-stage’ smallest). Additionally, expected sample sizes under both null and alternative are computed both via `evaluate()` and simulation-based.

```
ess0 <- ExpectedSampleSize(datadist, H_0)
tbl_designs %>%
  mutate(
    ess      = map_dbl(optimal,
                      ~evaluate(ess, .$design) ),
    ess_sim  = map_dbl(optimal,
                      ~sim_n(.$design, .2, datadist)$n ),
    ess0     = map_dbl(optimal,
                      ~evaluate(ess0, .$design) ),
    ess0_sim = map_dbl(optimal,
                      ~sim_n(.$design, .0, datadist)$n ) ) %>%
  {print(.); .} %>% {
    # sim/evaluate same under alternative?
    testthat::expect_equal(.$ess, .$ess_sim,
                          tolerance = tol_n,
                          scale = 1)
    # sim/evaluate same under null?
    testthat::expect_equal(.$ess0, .$ess0_sim,
                          tolerance = tol_n,
                          scale = 1)
    # monotonicity with respect to degrees of freedom
    testthat::expect_true(all(diff(.$ess) < 0)) }
```

```
## # A tibble: 3 x 7
##   type      initial    optimal      ess ess_sim ess0 ess0_sim
##   <chr>      <list>      <list>      <dbl>  <dbl> <dbl>  <dbl>
```

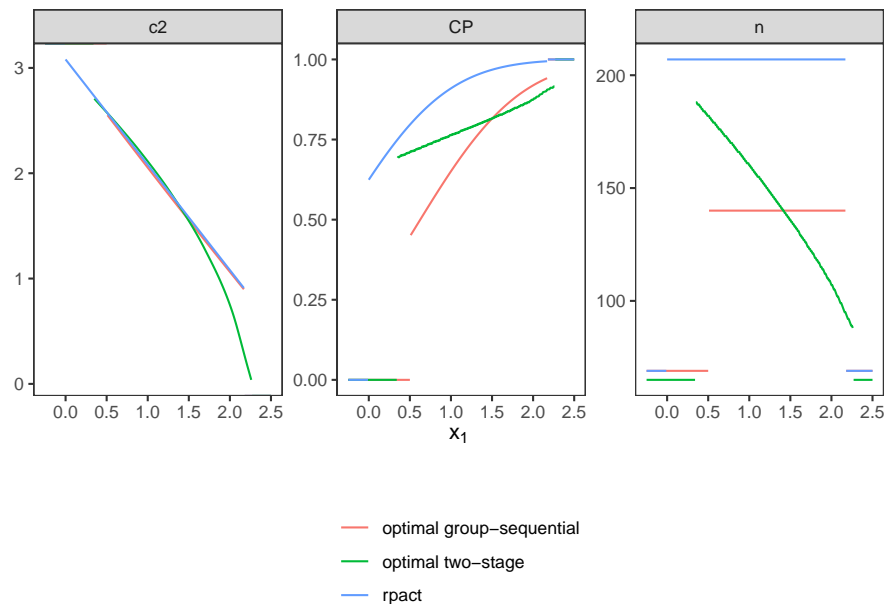
7.2. VARIANT VI-1: MINIMIZING EXPECTED SAMPLE SIZE UNDER POINT PRIOR⁷⁵

## 1 one-stage	<OnStgDsg>	<adptrOpR [3]>	124	124	124	124
## 2 group-sequential	<GrpSqntD>	<adptrOpR [3]>	96.2	96.2	89.7	89.8
## 3 two-stage	<TwStgDsg>	<adptrOpR [3]>	94.3	94.2	98.5	98.6

The expected sample size under the alternative must be lower or equal than the expected sample size of the initial **rpact** group-sequential design that is based on the inverse normal combination test.

```
testthat::expect_lte(
  evaluate(ess,
    tbl_designs %>%
      filter(type == "group-sequential") %>%
      pull(optimal) %>%
      .[[1]] %>%
      .$design ),
  evaluate(ess,
    tbl_designs %>%
      filter(type == "group-sequential") %>%
      pull(initial) %>%
      .[[1]] ) )
```

Finally, the **rpact** group-sequential design, the optimal group-sequential design, and the optimal generic two-stage design are plotted to allow visual inspection.



7.3 Variant VI-2: Minimizing Expected Sample Size under Null Hypothesis

7.3.1 Objective

Expected sample size under the null hypothesis is maximized.

7.3.2 Constraints

The constraints remain unchanged.

7.3.3 Initial design

Since optimization under the null favours an entirely different (monotonically increasing) sample size function, and thus also a different shape of the c_2 function, the `rpactinitial` design is a suboptimal starting point. Instead, we start with a constant c_2 function by heuristically setting it to 2 on the continuation area. Also, optimizing under the null favours extremely conservative boundaries for early efficacy stopping and we thus impose as fairly liberal upper bound of 3 for early efficacy stopping.

```
init_design_h0 <- tbl_designs %>%
  filter(type == "two-stage") %>%
  pull(initial) %>%
  .[[1]]
init_design_h0@c2_pivots <- rep(2, order)

ub_design <- TwoStageDesign(
  3 * init_design_h0@n1,
  2,
  3,
  rep(300, order),
  rep(3.0, order)
)
```

7.3.4 Optimization

The optimal two-stage design is computed.

```
opt_h0 <- minimize(
  ess0,
```

```

subject_to(
  toer_cnstr,
  pow_cnstr
),

initial_design      = init_design_h0,
upper_boundary_design = ub_design,
opts = opts )

```

7.3.5 Test cases

Make sure that the optimization algorithm converged within the set maximum number of iterations:

```

opt_h0$nlptr_return$iterations %>%
  {print(.); .} %>%
  {testthat::expect_true(. < opts$maxeval)}

```

```
## [1] 11351
```

The n_2 function of the optimal two-stage design is expected to be monotonously increasing.

```

expect_true(
  all(diff(opt_h0$design@n2_pivots) > 0) )

```

Next, the type one error rate and power constraints are tested.

```

tbl_performance <- tibble(
  delta = c(.0, .4) ) %>%
  mutate(
    power      = map(
      delta,
      ~evaluate(
        Power(datadist, PointMassPrior(., 1)),
        opt_h0$design) ),
    power_sim = map(
      delta,
      ~sim_pr_reject(opt_h0$design, ., datadist)$prob),
    ess        = map(
      delta,
      ~evaluate(ExpectedSampleSize(

```

```

      datadist,
      PointMassPrior(., 1) ),
      opt_h0$design) ),
  ess_sim = map(
    delta,
    ~sim_n(opt_h0$design, ., datadist)$n ) ) %>%
  unnest(., cols = c(power, power_sim, ess, ess_sim))

print(tbl_performance)

```

```

## # A tibble: 2 x 5
##   delta power power_sim  ess ess_sim
##   <dbl> <dbl>     <dbl> <dbl>   <dbl>
## 1    0  0.0250     0.0250  74.8    74.9
## 2   0.4  1.00        1.00   73.2    73.2

```

```

testthat::expect_lte(
  tbl_performance %>% filter(delta == 0) %>% pull(power_sim),
  alpha * (1 + tol) )

testthat::expect_gte(
  tbl_performance %>% filter(delta == 0.4) %>% pull(power_sim),
  min_power * (1 - tol) )

# make sure that evaluate() leads to same results
testthat::expect_equal(
  tbl_performance$power, tbl_performance$power_sim,
  tol = tol,
  scale = 1 )

testthat::expect_equal(
  tbl_performance$ess, tbl_performance$ess_sim,
  tol = tol_n,
  scale = 1 )

```

The expected sample size under the null must be lower or equal than the expected sample size of the initial `rpact` group-sequential design.

```

testthat::expect_gte(
  evaluate(ess0,
    tbl_designs %>%
      filter(type == "two-stage") %>%
      pull(initial) %>%
      .[[1]] ),
  evaluate(ess0, opt_h0$design) )

```

7.4 Variant VI-3: Conditional Power constraint

7.4.1 Objective

Same as in VI-1, the expected sample size under the alternative is minimized.

7.4.2 Constraints

Besides the previous global type one error rate and power constraints, an additional constraint on conditional power is imposed.

```
cp      <- ConditionalPower(datadist, prior)
cp_cnstr <- cp >= .85
```

7.4.3 Initial Design

The same initial (generic two-stage) design as in VI-1 is used.

7.4.4 Optimization

```
opt_cp <- minimize(
  ess,
  subject_to(
    toer_cnstr,
    pow_cnstr,
    cp_cnstr # new constraint
  ),
  initial_design = tbl_designs %>%
    filter(type == "two-stage") %>%
    pull(initial) %>%
    .[[1]],
  opts = opts )
```

7.4.5 Test Cases

Check if the optimization converged.

```

opt_cp$nlptr_return$iterations %>%
  {print(.); .} %>%
  {testthat::expect_true(. < opts$maxeval)}

```

```
## [1] 3409
```

Check constraints.

```

tbl_performance <- tibble(
  delta = c(.0, .2) ) %>%
  mutate(
    power = map(
      delta,
      ~evaluate(
        Power(datadist, PointMassPrior(., 1)),
        opt_cp$design) ),
    power_sim = map(
      delta,
      ~sim_pr_reject(opt_cp$design, ., datadist)$prob),
    ess = map(
      delta,
      ~evaluate(ExpectedSampleSize(
        datadist,
        PointMassPrior(., 1) ),
        opt_cp$design) ),
    ess_sim = map(
      delta,
      ~sim_n(opt_cp$design, ., datadist)$n ) ) %>%
  unnest(., cols = c(power, power_sim, ess, ess_sim))

print(tbl_performance)

```

```

## # A tibble: 2 x 5
##   delta power power_sim   ess ess_sim
##   <dbl> <dbl>   <dbl> <dbl>   <dbl>
## 1  0    0.0250   0.0249  91.6    91.6
## 2  0.2  0.899     0.899  94.5    94.5

```

```

testthat::expect_lte(
  tbl_performance %>% filter(delta == 0) %>% pull(power_sim),
  alpha * (1 + tol) )

testthat::expect_gte(

```



```
tbl_performance %>% filter(delta == 0.2) %>% pull(power_sim),
min_power * (1 - tol) )

# make sure that evaluate() leads to same results
testthat::expect_equal(
  tbl_performance$power, tbl_performance$power_sim,
  tol = tol,
  scale = 1 )

testthat::expect_equal(
  tbl_performance$ess, tbl_performance$ess_sim,
  tol = tol_n,
  scale = 1 )
```

The conditional power constraint is evaluated and tested on a grid over the continuation region (both simulated and via numerical integration).

```
tibble(
  x1 = seq(opt_cp$design@c1f, opt_cp$design@c1e, length.out = 25),
  cp = map_dbl(x1, ~evaluate(cp, opt_cp$design, .)),
  cp_sim = map_dbl(x1, function(x1) {
    x2 <- simulate(datadist, 10^6, n2(opt_cp$design, x1), .2, 42)
    rej <- ifelse(x2 > c2(opt_cp$design, x1), 1, 0)
    return(mean(rej))
  }) ) %>%
{print(.); .} %>% {
  testthat::expect_true(all(.$cp >= 0.85 * (1 - tol)))
  testthat::expect_true(all(.$cp_sim >= 0.85 * (1 - tol)))
  testthat::expect_true(all(abs(.$cp - .$cp_sim) <= tol)) }
```

```
## # A tibble: 25 x 3
##       x1      cp cp_sim
##   <dbl> <dbl> <dbl>
## 1 0.587 0.850 0.849
## 2 0.657 0.850 0.850
## 3 0.727 0.851 0.851
## 4 0.798 0.851 0.851
## 5 0.868 0.849 0.848
## 6 0.939 0.849 0.849
## 7 1.01  0.850 0.849
## 8 1.08  0.850 0.850
## 9 1.15  0.851 0.851
## 10 1.22  0.852 0.851
## # ... with 15 more rows
```

Finally, the expected sample size under the alternative prior should be larger than in the case without the constraint VI-1.

```
testthat::expect_gte(
  evaluate(ess, opt_cp$design),
  evaluate(
    ess,
    tbl_designs %>%
      filter(type == "two-stage") %>%
      pull(optimal) %>%
      .[[1]] %>%
      .$design ) )
```

#Scenario VII: binomial distribution, Gaussian prior {#scenarioVII}

In this scenario, we revisit the case from (#variantVII), but are not assuming a point prior anymore. Instead, a Gaussian prior with mean $\theta = 0.4$ and variance $\tau^2 = 0.2^2$ on the effect size is assumed.

Bibliography

Bauer, P., Bretz, F., Dragalin, V., König, F., and Wassmer, G. (2015). Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls. *Statistics in Medicine*, 35(3):325–347.

Pilz, M., Kunzmann, K., Herrmann, C., Rauch, G., and Kieser, M. (2019). A variational approach to optimal two-stage designs. *Statistics in Medicine*, 38(21):4159–4171.

Wassmer, G. and Brannath, W. (2016). *Group sequential and confirmatory adaptive designs in clinical trials*. Springer Series in Pharmaceutical Statistics -. Springer International Publishing.

Wassmer, G. and Pahlke, F. (2018). *rpact: Confirmatory Adaptive Clinical Trial Design and Analysis*. R package version 1.0.0.

Wickham, H., R Studio, and R Core Team (2018). *testthat: Unit Testing for R*. R package version 2.0.1.