Simulation of a trial with a binary endpoint and unblinded sample size re-calculation in rpact

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Summary

This R Markdown document provides examples for assessing trials with adaptive sample size re-calculation (SSR) using rpact. It also shows how to implement the promizing zone approach as proposed by Mehta and Pocock 2011 and further developed by Hsiao et al 2019 with rpact.

1 Introduction

rpact provides the functions `getSimulationMeans()` (continuous endpoints), `getSimulationRates()` (binary endpoints) and `getSimulationSurvival()` (time-to-event endpoints) for simulation of group-sequential trials with adaptive SSR.

For trials with adaptive SSR, the design can be created with the functions `getDesignInverseNormal()` or `getDesignFisher()`. The sample size is re-calculated based on the target conditional power (argument `conditionalPower`). Conditional power is by default evaluated at the observed parameters. If the evaluation of conditional power at other parameter values is desired, they can be provided as arguments `thetaH1` (for `getSimulationMeans()` and `getSimulationSurvival()`), or `pi1H1` and `pi2H1` (for `getSimulationRates()`). For continuous endpoints, by default, conditional power is evaluated at the standard deviation `stDev` under which the trial is simulated. In rpact 3.0, a variable 'stDevH1' can be entered to specify the standard deviation that is used for the sample size recalculation.

For the functions `getSimulationMeans()` and `getSimulationRates()` (but not in `getSimulationSurvival()`), the SSR function can be optionally modified using the argument `calcSubjectsFunction()` (see the respective help pages and the code below for details and examples).

In this vignette, we present an example of the use of these functions for a trial with a binary endpoint. For this, we will use the constraint promizing zone approach as described in Hsiao et al 2019.

For this vignette, additionally to `rpact` itself and `ggplot2`, we use the packages `ggpubr` and `dplyr`:

2 Assumptions and design options

- 1:1 randomized superiority trial with overall response rate (ORR) as the primary endpoint (binary)
- ORR in the control arm is known to be ~20%
- The novel treatment may increase ORR by 10%-13%

- 2.5% one-sided significance level

We first calculate the sample sizes (per treatment group) for the corresponding fixed designs with 90% power:

```
# fixed design powered for delta of 13%
ssMin <- getSampleSizeRates(pi1 = 0.33, pi2 = 0.2, alpha = 0.025, beta = 0.1)
( Nmin <- ceiling(c(ssMin$numberOfSubjects1)) )
```

```
## [1] 241
```

```
# fixed design powered for delta of 10%
ssMax <- getSampleSizeRates(pi1 = 0.30, pi2 = 0.2, alpha = 0.025, beta = 0.1)
( Nmax <- ceiling(c(ssMax$numberOfSubjects1)) )
```

```
## [1] 392
```

Assume that the sponsor is unwilling to make an up-front commitment for a trial with 392 subjects per treatment group but that they are willing to provide an up-front commitment for a trial with 241 subjects per group. If the results at an interim analysis with an unblinded SSR look "promising", the sponsor would then be willing to commit funding for up to 392 subjects per treatment group in total.

To help the sponsor, we investigate two designs with an interim analysis for SSR after 120 subjects per treatment group:

1. SSR based on conditional power: adjust sample size to achieve a conditional power of 90% assuming that the true response rates are 20% and 30% (if this is feasible within the given sample size range)
2. A constrained promising zone design (Hsiao et al. 2019) with $cp_{min} = 80$ and $cp_{max} = 90$.

To combine the two stages for both designs, we use a inverse-normal combination tests with optimal weights for the minimal final group size and no provision for early stopping for neither efficacy nor futility at interim:

```
# group size at interim
( n1 <- floor(Nmin/2) )
```

```
## [1] 120
```

```
# inverse normal design which possible rejection of H0 only at the final analysis
designIN <- getDesignInverseNormal(typeOfDesign = "asUser",
    informationRates = c(n1/Nmin, 1), userAlphaSpending = c(0.00, 0.025))
summary(designIN)
```

```
## Sequential analysis with a maximum of 2 looks
## (inverse normal combination test design)
##
## user defined alpha spending design, one-sided local significance level 2.5%,
## power 80%, undefined endpoint.
##
## Stage                                   1      2
## Information rate                    49.8%   100%
## Efficacy boundary (z-value scale)     Inf  1.960
## Cumulative alpha spent                  0 0.0250
## Overall power                           0 0.8000
## One-sided local significance level      0 0.0250
```

3 Design with SSR (SSR) based on conditional power

It is straightforward to simulate the test characteristics from this design using the function `getSimulationRates()`. `plannedSubjects` refers to the cumulated sample sizes over the two stages **in both treatment groups**. If `conditionalPower` is specified, `minNumberOfSubjectsPerStage` and `maxNumberOfSubjectsPerStage` must be specified. They refer to the minimum and maximum overall sample sizes **per stage** (the first element is the first stage sample size), respectively. If `pi1H1` and/or `pi2H1` are not specified, the observed (simulated) rates at interim are used for the SSR.

```
# Design with sample size re-estimated to get conditional power of 0.9 at
# pi1H1 = 0.3, pi2H1 = 0.2 [minimum effect size]
# (evaluate at most interesting values for pi1)
simCpower <- getSimulationRates(designIN, pi1 = c(0.2, 0.3, 0.33), pi2 = 0.2,
    plannedSubjects = 2*c(n1, Nmin),                # cumulative overall sample size
    conditionalPower = 0.9,
    minNumberOfSubjectsPerStage = 2*c(n1, (Nmin-n1)), # stage-wise minimal overall sample size
    maxNumberOfSubjectsPerStage = 2*c(n1, (Nmax-n1)), # stage-wise maximal overall sample size
    pi1H1 = 0.3, pi2H1 = 0.2,
    maxNumberOfIterations = 10000,
    seed = 12345)

simCpower$show(showStatistics = FALSE)
```

```
## Simulation of rates (inverse normal combination test design):
##
## Design parameters:
##   Information rates                          : 0.498, 1.000
##   Critical values                            : Inf, 1.96
##   Futility bounds (non-binding)              : -Inf
##   Cumulative alpha spending                  : 0.0000, 0.0250
##   Local one-sided significance levels        : 0.0000, 0.0250
##   Significance level                         : 0.0250
##   Type II error rate                         : 0.2000
##   Test                                       : one-sided
##
## User defined parameters:
##   Conditional power                          : 0.9
##   Maximum number of iterations               : 10000
##   Seed                                       : 12345
##   Planned cumulative subjects                : 240, 482
##   Minimum number of subjects per stage       : 240, 242
##   Maximum number of subjects per stage       : 240, 544
##   pi(1)                                      : 0.200, 0.300, 0.330
##   pi(2)                                      : 0.200
##   pi(1) under H1                             : 0.300
##
## Default parameters:
##   Planned allocation ratio                   : 1
##   Direction upper                            : TRUE
##   Calculate subjects function                 : default
##   Effect                                      : 0.00, 0.10, 0.13
##   Treatment groups                            : 2
##   Theta H0                                    : 0
##   Risk ratio                                  : FALSE
##   pi(2) under H1                              : 0.200
##   Normal approximation                        : TRUE
##
## Results:
##   Iterations [1]                              : 10000, 10000, 10000
##   Iterations [2]                              : 10000, 10000, 10000
##   Overall reject                              : 0.0229, 0.8617, 0.9731
##   Reject per stage [1]                        : 0.0000, 0.0000, 0.0000
##   Reject per stage [2]                        : 0.0229, 0.8617, 0.9731
##   Futility stop per stage                     : 0.0000, 0.0000, 0.0000
##   Futility stop                               : 0, 0, 0
##   Early stop                                  : 0.0000, 0.0000, 0.0000
##   Expected number of subjects                 : 771.1, 629.8, 574.2
##   Sample sizes [1]                            : 240.0, 240.0, 240.0
##   Sample sizes [2]                            : 531.1, 389.8, 334.2
##   Conditional power (achieved) [1]            : NA, NA, NA
##   Conditional power (achieved) [2]            : 0.4736, 0.8586, 0.9093
##
## Legend:
##   (i): values of treatment arm i
##   [k]: values at stage k
```

4 Constrained promising zone (CPZ) design

As described in Hsiao et al. 2019, this method chooses the sample size according to the following rules:

- Choose the second stage size N^* between $Nmin$ and $Nmax$ such that the conditional power is cp_{max} for the minimal effect size we want to detect (i.e., ORR of 20% vs. 30%). We chose $cp_{max} = 0.90$ here as in the original publication.
- If such a sample size N^* does not exist, then proceed as follows:
- If the conditional power cannot be boosted to at least cp_{min} by increasing the sample size to $Nmax$, i.e., if the interim result is not considered «promising», then do not increase the sample and set $N^* = Nmin$. We chose $cp_{min} = 0.80$ here as in the original publication.
- Otherwise: set $N^* = Nmax$

To simulate from the CPZ design in `rpact`, we can use the function `getSimulationRates()` again. However, the situation is more complicated because we need to re-define the sample size recalculation rule using the argument `calcSubjectsFunction` (see the help page `?getSimulationRates` for more information regarding `calcSubjectsFunction()`):

```
# CPZ design (evaluate at the most interesting values for pi1)
# home-made SSR function
myCPZSampleSizeCalculationFunction <- function(..., stage,
        plannedSubjects,
        conditionalPower,
        minNumberOfSubjectsPerStage,
        maxNumberOfSubjectsPerStage,
        conditionalCriticalValue,
        overallRate) {
  rateUnderH0 <- (overallRate[1] + overallRate[2]) / 2
```

```r
  # function adapted from example in ?getSimulationRates
  calculateStageSubjects <- function(cp) {
    2 * (max(0, conditionalCriticalValue *
    sqrt(2 * rateUnderH0 * (1 - rateUnderH0)) +
    stats::qnorm(cp) * sqrt(overallRate[1] *
    (1 - overallRate[1]) + overallRate[2] * (1 - overallRate[2]))))^2 /
    (max(1e-12, (overallRate[1] - overallRate[2])))^2
  }

  # Calculate sample size required to reach maximum desired conditional power
  # cp_max (provided as argument conditionalPower)
  stageSubjectsCPmax <- calculateStageSubjects(cp = conditionalPower)

  # Calculate sample size required to reach minimum desired conditional power
  # cp_min (**manually set for this example to 0.8**)
  stageSubjectsCPmin <- calculateStageSubjects(cp = 0.8)

  # Define stageSubjects
  stageSubjects <- ceiling(min(max(minNumberOfSubjectsPerStage[stage],
                 stageSubjectsCPmax), maxNumberOfSubjectsPerStage[stage]))

  # Set stageSubjects to minimal sample size in case minimum conditional power
  # cannot be reached with available sample size
  if (stageSubjectsCPmin > maxNumberOfSubjectsPerStage[stage]) {
    stageSubjects <- minNumberOfSubjectsPerStage[stage]
  }

  # return sample size
  return(stageSubjects)
}

# Now simulate from the CPZ design
simCPZ <- getSimulationRates(designIN, pi1  = c(0.2, 0.3, 0.33), pi2 = 0.2,
    plannedSubjects = 2*c(n1, Nmin),                 # cumulative overall sample size
    conditionalPower = 0.9,
    minNumberOfSubjectsPerStage = 2*c(n1, (Nmin-n1)),# stage-wise minimal overall sample size
    maxNumberOfSubjectsPerStage = 2*c(n1, (Nmax-n1)),# stage-wise maximal overall sample size
    pi1H1 = 0.3, pi2H1 = 0.2,
    calcSubjectsFunction = myCPZSampleSizeCalculationFunction,
    maxNumberOfIterations = 10000,
    seed = 12345)

simCPZ$show(showStatistics = FALSE)
```

```
## Simulation of rates (inverse normal combination test design):
##
## Design parameters:
##   Information rates                           : 0.498, 1.000
##   Critical values                             : Inf, 1.96
##   Futility bounds (non-binding)               : -Inf
##   Cumulative alpha spending                   : 0.0000, 0.0250
##   Local one-sided significance levels         : 0.0000, 0.0250
##   Significance level                          : 0.0250
##   Type II error rate                             : 0.2000
##   Test                                           : one-sided
##
## User defined parameters:
##   Conditional power                              : 0.9
##   Maximum number of iterations                   : 10000
##   Seed                                           : 12345
##   Planned cumulative subjects                    : 240, 482
##   Minimum number of subjects per stage           : 240, 242
##   Maximum number of subjects per stage           : 240, 544
##   Calculate subjects function                    : user defined
##   pi(1)                                          : 0.200, 0.300, 0.330
##   pi(2)                                          : 0.200
##   pi(1) under H1                                 : 0.300
##
## Default parameters:
##   Planned allocation ratio                       : 1
##   Direction upper                                : TRUE
##   Effect                                         : 0.00, 0.10, 0.13
##   Treatment groups                               : 2
##   Theta H0                                       : 0
##   Risk ratio                                     : FALSE
##   pi(2) under H1                                 : 0.200
##   Normal approximation                           : TRUE
##
## Results:
##   Iterations [1]                                 : 10000, 10000, 10000
##   Iterations [2]                                 : 10000, 10000, 10000
##   Overall reject                                 : 0.0243, 0.7981, 0.9418
##   Reject per stage [1]                           : 0.0000, 0.0000, 0.0000
##   Reject per stage [2]                           : 0.0243, 0.7981, 0.9418
##   Futility stop per stage                        : 0.0000, 0.0000, 0.0000
##   Futility stop                                  : 0, 0, 0
##   Early stop                                     : 0.0000, 0.0000, 0.0000
##   Expected number of subjects                    : 525.6, 573.3, 550.6
##   Sample sizes [1]                               : 240.0, 240.0, 240.0
##   Sample sizes [2]                               : 285.6, 333.3, 310.6
##   Conditional power (achieved) [1]               : NA, NA, NA
##   Conditional power (achieved) [2]               : 0.2887, 0.7970, 0.8820
##
## Legend:
##   (i): values of treatment arm i
##   [k]: values at stage k
```

5 Graphical comparison of the two designs

We first use the aggregated data from the two simulations to compare the dependence of the re-calculated sample size and the corresponding conditional power on the interim Z-score between the two designs. For this, we use the function `getData()`, the `summarize()` command of the dplyr package and plot it with `ggplot()`. Note that for this illustration we summaries over all values of `pi1`. This makes sense because we used a fixed `pi1H1` and `pi2H1` for both sample size simulation methods.

```
# aggregate data across simulation runs for both simulations and extract Z-score,
# conditionalPower, and totalSampleSize1 (per group)
```

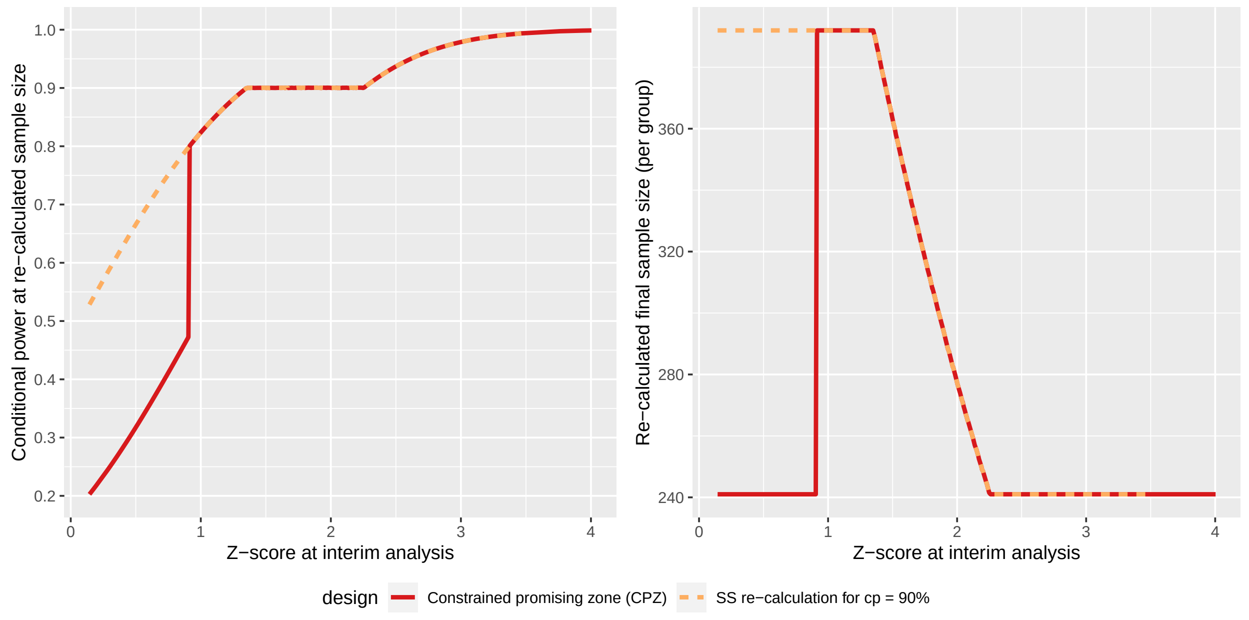
```r
aggSimCpower <- getData(simCpower)
sumCpower <- aggSimCpower %>% group_by(iterationNumber) %>%
    summarise(design = "SS re-calculation for cp = 90%",
        Z1 = testStatistic[1], conditionalPower = conditionalPowerAchieved[2],
        totalSampleSize1 = (numberOfSubjects[1]+numberOfSubjects[2])/2) %>%
        arrange(Z1) %>% filter(Z1> 0, Z1<5)
```

```
## `summarise()` ungrouping output (override with `.groups` argument)
```

```r
aggSimCPZ <- getData(simCPZ)
sumCPZ <- aggSimCPZ %>% group_by(iterationNumber) %>%
    summarise(design = "Constrained promising zone (CPZ)",
        Z1 = testStatistic[1], conditionalPower = conditionalPowerAchieved[2],
        totalSampleSize1 = (numberOfSubjects[1]+numberOfSubjects[2])/2) %>%
        arrange(Z1) %>% filter(Z1>0, Z1<5)
```

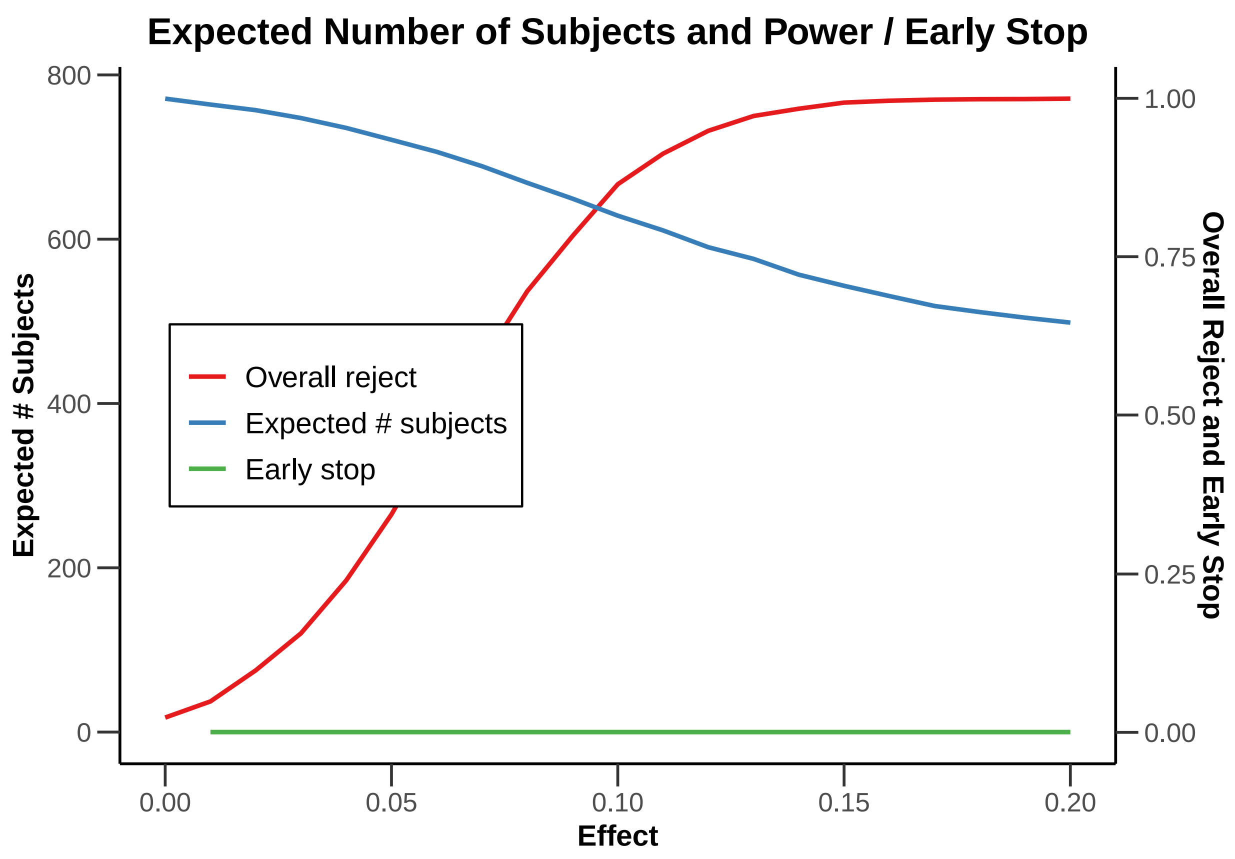
```
## `summarise()` ungrouping output (override with `.groups` argument)
```

```r
sumBoth <- rbind(sumCpower, sumCPZ)

# Plot it
plot1 <- ggplot(aes(Z1, conditionalPower, col = design, group = design), data = sumBoth)+
    geom_line(aes(linetype = design), lwd = 1.2)+
    scale_x_continuous(name = "Z-score at interim analysis")+
    scale_y_continuous(breaks = seq(0, 1, by = 0.1),
        name = "Conditional power at re-calculated sample size")+
    scale_color_manual(values = c("#d7191c", "#fdae61"))

plot2 <- ggplot(aes(Z1, totalSampleSize1, col = design, group = design), data = sumBoth)+
    geom_line(aes(linetype = design), lwd = 1.2)+
    scale_x_continuous(name = "Z-score at interim analysis")+
    scale_y_continuous(name = "Re-calculated final sample size (per group)")+
    scale_color_manual(values = c("#d7191c", "#fdae61"))

ggarrange(plot1, plot2, common.legend = TRUE, legend = "bottom")
```

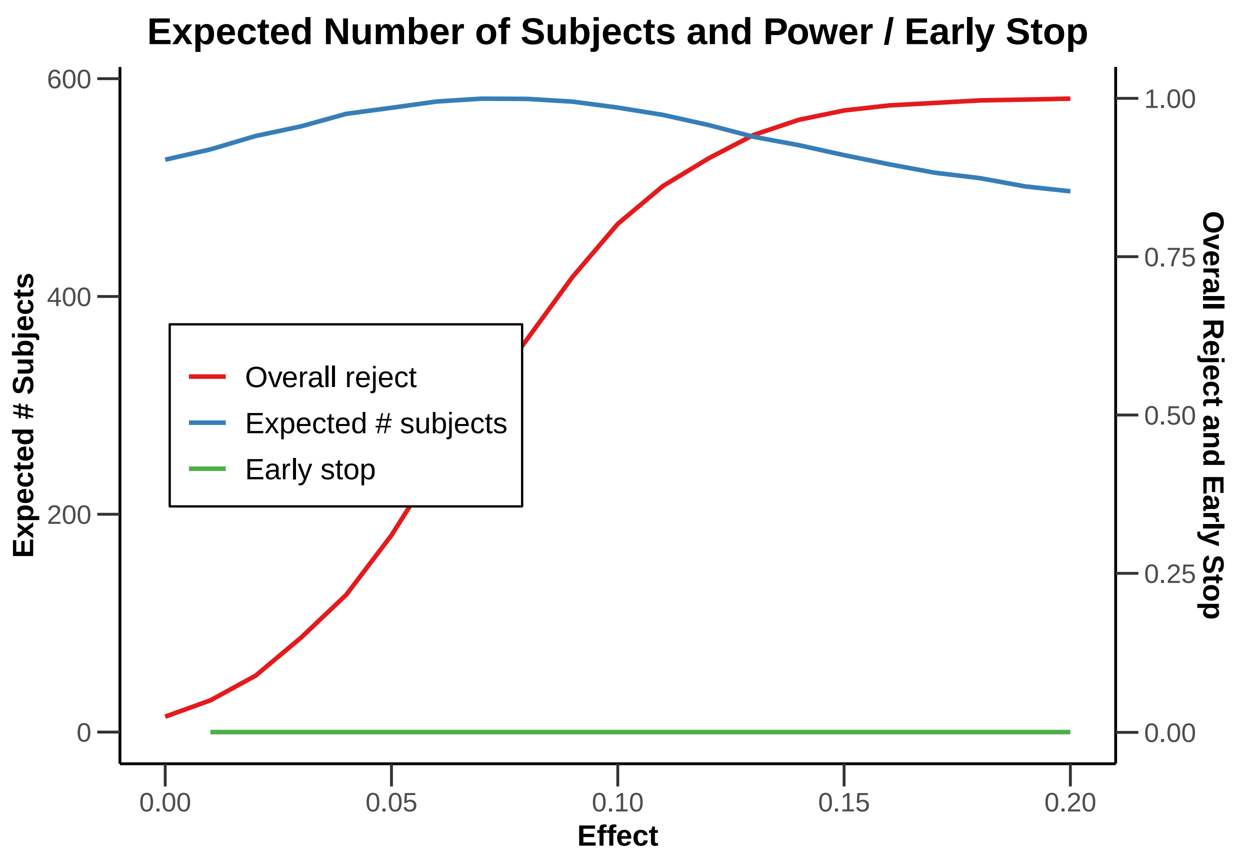


To compare the two designs across a wider range of parameters, we re-simulate the designs for a finer grid of assumed ORR in the intervention group and then visualize the results.

```r
# Simulate designs again over a range of parameters and plot them
pi1Seq <- seq(0.2, 0.4, by = 0.01)

simCpowerLong <- getSimulationRates(designIN, pi1 = pi1Seq, pi2 = 0.2,
    plannedSubjects = c(2*n1, 2*Nmin),
    conditionalPower = 0.9,
    minNumberOfSubjectsPerStage = c(2*n1, 2*(Nmin-n1)),
    maxNumberOfSubjectsPerStage = c(2*n1, 2*(Nmax-n1)),
    pi1H1 = 0.3, pi2H1 = 0.2,
    maxNumberOfIterations = 10000,
    seed = 12345)

plot(simCpowerLong, type = 6)
```

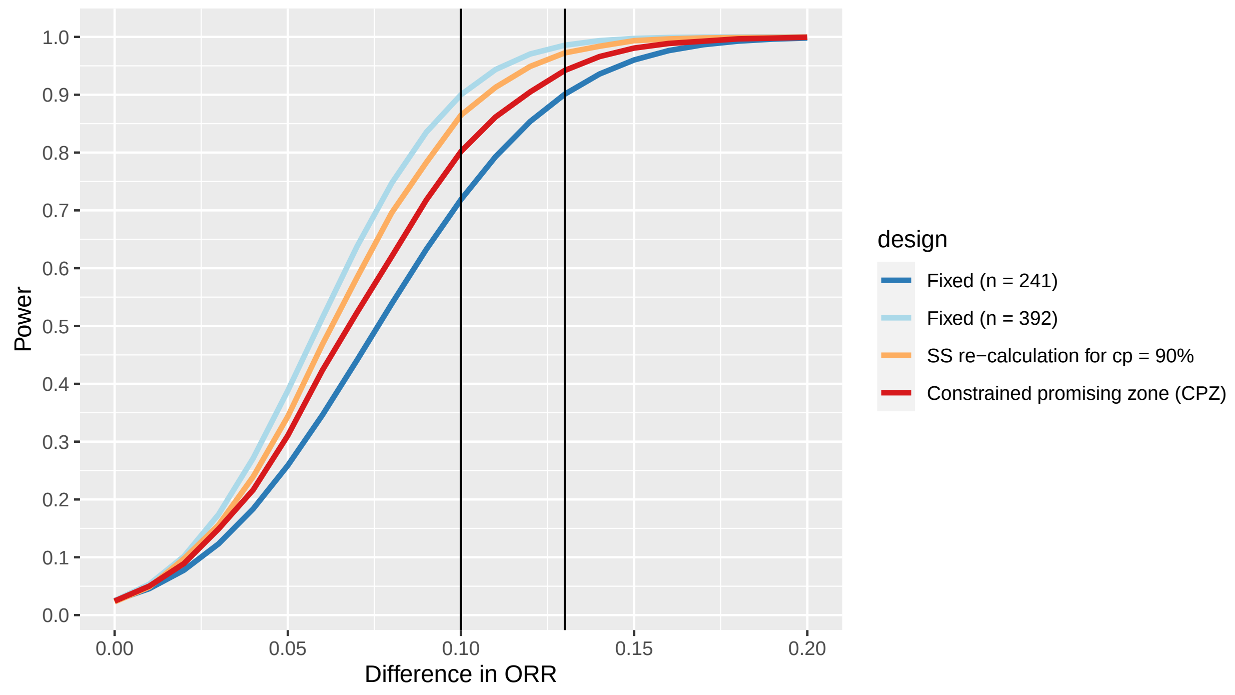


```r
simCPZLong <- getSimulationRates(designIN, pi1 = pi1Seq, pi2 = 0.2,
    plannedSubjects = 2*c(n1, Nmin),              # cumulative overall sample size
    conditionalPower = 0.9,
    minNumberOfSubjectsPerStage = 2*c(n1, (Nmin-n1)),# stage-wise minimal overall sample size
    maxNumberOfSubjectsPerStage = 2*c(n1, (Nmax-n1)),# stage-wise maximal overall sample size
    pi1H1 = 0.3, pi2H1 = 0.2,
    calcSubjectsFunction = myCPZSampleSizeCalculationFunction,
    maxNumberOfIterations = 10000,
    seed = 12345)

plot(simCPZLong, type = 6)
```

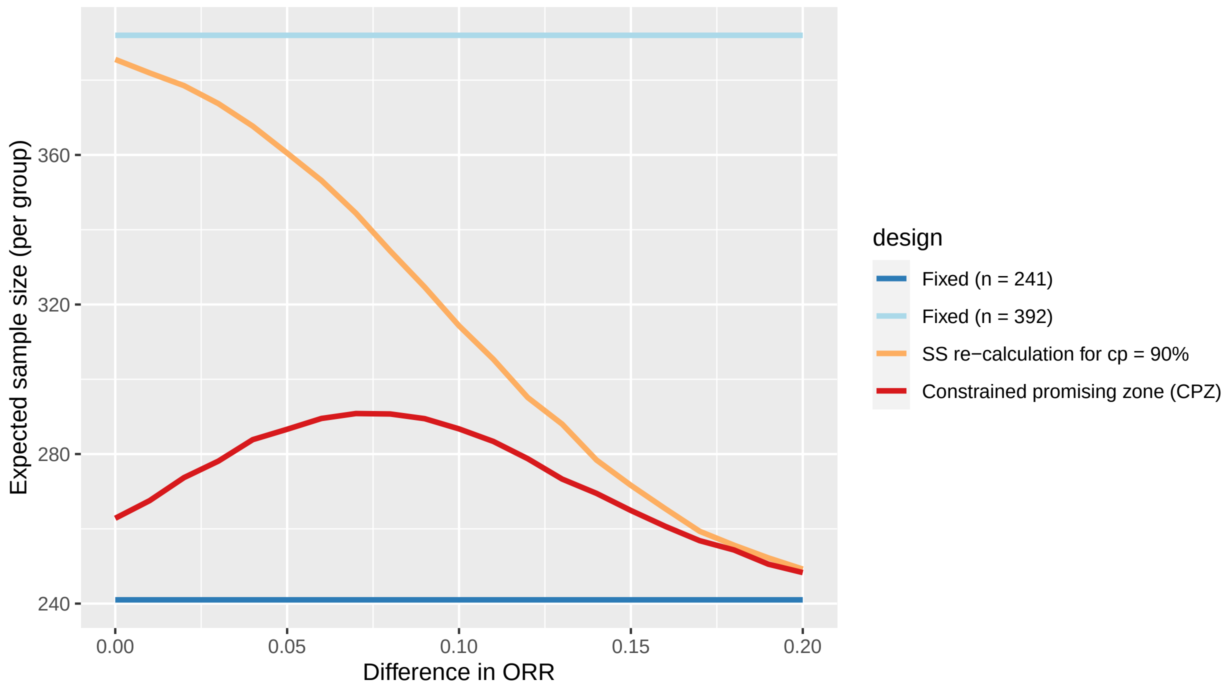


```
# Pool datasets from simulations (and fixed designs)
simCpowerData <- with(simCpowerLong,
    data.frame(design = "SS re-calculation for cp = 90%",
        pi1 = pi1, pi2 = pi2, effect = effect, power = overallReject,
        expectedNumberOfSubjects1 = expectedNumberOfSubjects/2),
        stringsAsFactors = F)

simCPZData <- with(simCPZLong,
    data.frame(design = "Constrained promising zone (CPZ)",
        pi1 = pi1, pi2 = pi2, effect = effect, power = overallReject,
        expectedNumberOfSubjects1 = expectedNumberOfSubjects/2),
        stringsAsFactors = F)

simFixed241 <- with(simCPZData,
    data.frame(design = "Fixed (n = 241)",
        pi1 = pi1, pi2 = pi2, effect = effect,
        power = getPowerRates(pi1 = pi1, pi2 = 0.2, maxNumberOfSubjects = 2*241,
            alpha = 0.025, sided = 1)$overallReject,
        expectedNumberOfSubjects1 = 241, stringsAsFactors = F))

simFixed392 <- with(simCPZData,
    data.frame(design = "Fixed (n = 392)",
        pi1 = pi1, pi2 = pi2, effect = effect,
        power = getPowerRates(pi1 = pi1, pi2 = 0.2, maxNumberOfSubjects = 2*392,
            alpha = 0.025, sided = 1)$overallReject,
        expectedNumberOfSubjects1 = 392, stringsAsFactors = F))
```

```r
simdata <- rbind(simCpowerData, simCPZData, simFixed241, simFixed392)
simdata$design <- factor(simdata$design,
  levels = c("Fixed (n = 241)", "Fixed (n = 392)",
  "SS re-calculation for cp = 90%", "Constrained promising zone (CPZ)"))

# Plot difference in ORR vs power
ggplot(aes(effect, power, col = design), data = simdata)+geom_line(lwd = 1.2)+
  scale_x_continuous(name = "Difference in ORR")+
  scale_y_continuous(breaks = seq(0, 1, by = 0.1), name = "Power")+
  geom_vline(xintercept = c(0.1, 0.13), color = "black")+
  scale_color_manual(values = c("#2c7bb6", "#abd9e9", "#fdae61", "#d7191c"))
```



```r
# Plot difference in ORR vs expected sample size
ggplot(aes(effect, expectedNumberOfSubjects1, col = design), data = simdata)+
  geom_line(lwd = 1.2)+
  scale_x_continuous(name = "Difference in ORR")+
  scale_y_continuous(name = "Expected sample size (per group)")+
  scale_color_manual(values = c("#2c7bb6", "#abd9e9", "#fdae61", "#d7191c"))
```



6 Conclusions for the example

- Targeting a fixed conditional power leads to the largest sample size increase if there is no treatment effect which is undesirable.
- In contrast, the CPZ design increases sample size only if the interim Z-score is “promising”. The corresponding increase in the expected sample size is small if there is no treatment effect or if the treatment effect is large.
- The CPZ design is a reasonable compromise between the two extreme fixed designs and has a power of approximately 80% for the smallest effect size of interest ($\delta = 10\%$).
- Caveat: This is just a toy example and the design could be refined further (e.g., by exploring other SSR rules, changing the timing of the interim, or adding the possibility for a futility stop) and should also be compared to group-sequential trial designs.

System: rpact 3.0.3, R version 4.0.3 (2020-10-10), platform: x86_64-w64-mingw32

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R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

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