example2-RPACT.R

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```r
# Using RPACT

# Install RPACT and GGPLOT2

library(rpact)
```

```
## Installation qualification for rpact 4.4.0 has not yet been performed.

## Please run testPackage() before using the package in GxP relevant environm
ents.
```

```r
# If necessary:
#
# install.packages("ggplot2")

# Example 2: Survival data
#
# Two-arm trial, new treatment vs control
#
# Observations follow a proportional hazards model with
# log hazard ratio theta, where
#
#    hazard ratio > 1 and theta > 0
#
# imply the new treatment is superior
#
# To test H_0: theta =< 0 vs theta > 0 with one-sided type I error
# probability alpha=0.025 and power 1-beta=0.8 at
#
#   theta = delta = 0.5 = log(1.65)

alpha=0.025
beta=0.2
delta=0.5
ifix=(qnorm(1-alpha)+qnorm(1-beta))^2/delta^2
ifix
```

```
## [1] 31.39552
```

```r
# Fixed sample size design
# We shall analyse data using the logrank statistic, assuming
# a normal approximation, so give the command
#   normalApproximation = TRUE
ss_mean <- getSampleSizeMeans(
  alpha = 0.025,
```

```
  beta = 0.2,
  sided = 1,
  alternative = 0.5,
  stDev = 1,
  normalApproximation = TRUE
)
summary(ss_mean)
```

Sample size calculation for a continuous endpoint

Fixed sample analysis, one-sided significance level 2.5%, power 80%. The results were calculated for a two-sample t-test (normal approximation), H0: mu(1) - mu(2) = 0, H1: effect = 0.5, standard deviation = 1.

Stage	Fixed
Stage level (one-sided)	0.0250
Efficacy boundary (z-value scale)	1.960
Efficacy boundary (t)	0.350
Number of subjects	125.6

Legend:

- *(t)*: treatment effect scale

```
ss_mean$maxNumberOfSubjects/4
```

```
## [1] 31.39552
```

```
# "Number of subjects=125.6" in a 2 treatment comparison with
# normal responses of variance 1 implies that the required
# information is 125.6/4 = 31.4
#
# For a logrank test, this corresponds, approximately,
# to 4*31.4 = 125.6 events

# Group sequential design

# Design a group sequential trial with 5 analyses
#
# Error spending design, non-binding futility boundary, rho-family
# error spending function, rho=2 for efficacy and futility boundaries
#
# In RPACT the rho-family is called the Kim and DeMets alpha
# spending function and must be specified for both the
# efficacy and the futility boundaries.
#
# Define a design object with 5 analyses and a parameter
# of 2 for the rho family
des_surviv <- getDesignGroupSequential(
```

```
  alpha = 0.025,
  beta = 0.2,
  sided = 1,
  kMax = 5,
  typeOfDesign = "asKD",
  typeBetaSpending = "bsKD",
  gammaA = 2,
  gammaB = 2
)
# See properties of this design, including efficacy
# and futility boundaries on the Z-scale
summary(des_surviv)
```

Sequential analysis with a maximum of 5 looks (group sequential design)

Kim & DeMets alpha spending design (gammaA = 2) and Kim & DeMets beta spending (gammaB = 2), non-binding futility, one-sided overall significance level 2.5%, power 80%, undefined endpoint, inflation factor 1.1333, ASN H1 0.7678, ASN H01 0.7942, ASN H0 0.5914.

Stage	1	2	3	4	5
Planned information rate	20%	40%	60%	80%	100%
Cumulative alpha spent	0.0010	0.0040	0.0090	0.0160	0.0250
Cumulative beta spent	0.0080	0.0320	0.0720	0.1280	0.2000
Stage levels (one-sided)	0.0010	0.0033	0.0067	0.0113	0.0173
Efficacy boundary (z-value scale)	3.090	2.714	2.473	2.280	2.114
Futility boundary (z-value scale)	-1.075	-0.023	0.758	1.429	
Cumulative power	0.0395	0.2108	0.4530	0.6692	0.8000
Futility probabilities under H1	0.008	0.024	0.040	0.056	

```
# These boundaries on the Z-scale apply to all cases with
# power 1-beta at the treatment effect under which type 2
# error is spent.
# We shall find the information needed to give power 1-beta
```

```r
# at our specified alternative theta=delta.
# Based on our group sequential design, we first find the
# sample size required in a 2 treatment comparison with
# normal responses of variance 1
ss_gsd <- getSampleSizeMeans(
  design = des_surviv,
  alternative = delta,
  stDev = 1,
  normalApproximation = T
)
ss_gsd$maxNumberOfSubjects
```

```
## [1] 142.3232
```

```r
# "Number of subjects=142.3" in a 2 treatment comparison with
# normal responses of variance 1 implies that the required
# information is 142.3/4 = 35.58
#
# For a logrank test, this corresponds, approximately,
# to 4*35.58 = 142.3 events

# Extract design characteristics to get inflation factor
# (and other information) for the group sequential design
dc_des_surviv <- getDesignCharacteristics(des_surviv)

dc_des_surviv$inflationFactor
```

```
## [1] 1.133308
```

```r
dc_des_surviv$.design$alphaSpent
```

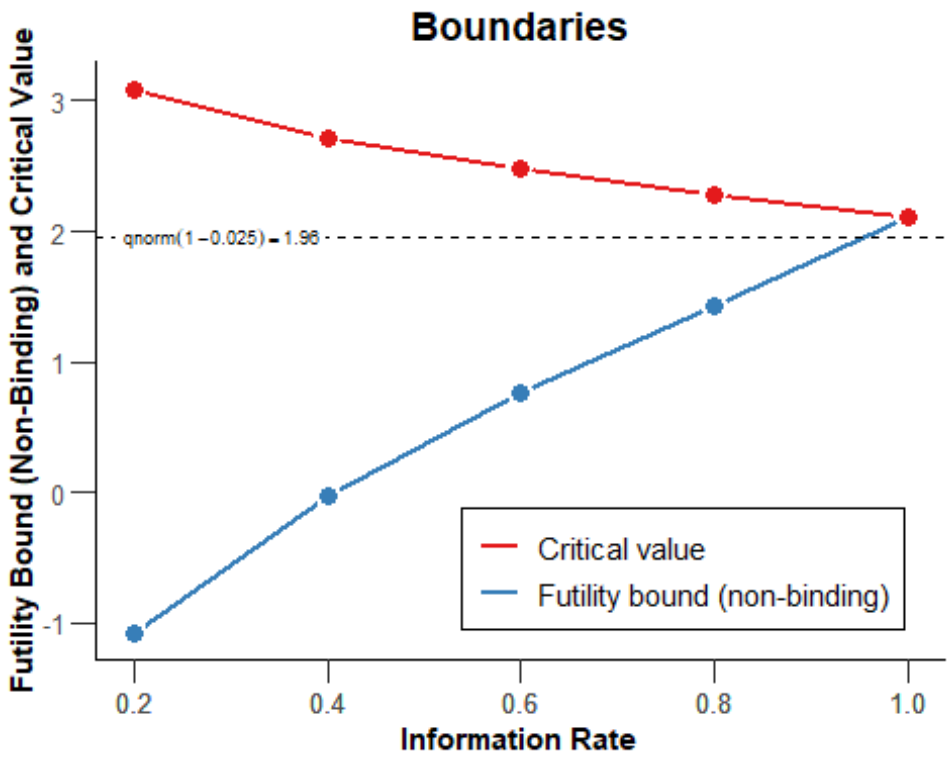
```
## [1] 0.001 0.004 0.009 0.016 0.025
```

```r
dc_des_surviv$.design$betaSpent
```

```
## [1] 0.008 0.032 0.072 0.128 0.200
```

```r
# Note the inflation factor is equal to the ratio of numbers
# of events in fixed and sequential designs
#  142.3/125.6 =  1.133

plot(des_surviv)
```




```r
# store the maximum information for this design
iMax <- ifix * dc_des_surviv$inflationFactor
iMax

## [1] 35.5808

# Under theta=0 (hazard ratio=1)
asn <- getPowerAndAverageSampleNumber(
  design = des_surviv,
  theta = 0,
  nMax = iMax
)
# Probabilities of rejecting the null hypothesis per stage
asn$rejectPerStage

##                   [,1]
## stage = 1 0.001000000
## stage = 2 0.002999985
## stage = 3 0.004995593
## stage = 4 0.006889910
## stage = 5 0.007304284

# Probabilities of stopping for futility per stage
asn$futilityPerStage

##                 [,1]
## stage = 1 0.1411630
## stage = 2 0.3601613
```

```
## stage = 3 0.2873594
## stage = 4 0.1409239

# overall probability of rejecting the null hypothesis
asn$calculatedPower

## [1] 0.02318977

# Note that, due to the no-binding futility boundary, the
# actual type 2 error rate is 0.0232



# Example data set

# We explore the consequences of observed sample sizes and
# observed information fractions that deviate from the
# originally planned design

# Suppose we have cumulative information levels

iobs=c(5.43,12.58,21.11,30.55,33.28)

# and treatment effect estimates

theta.hat=c(0.10,0.06,0.21,0.31)

# Efficacy boundary

# Analysis 1

# The observed information fraction is iobs[1]/35.58 = 5.43/35.58
#
# We need to state the information fractions for later
# analyses. We can just put in the values that were
# originally planned -- these will not affect the
# first boundary value
designUpdate1 <- getDesignGroupSequential(
  sided = 1,
  alpha = 0.025,
  beta = 0.2,
  informationRates = c(iobs[1]/35.58,0.4,0.6,0.8,1),
  typeOfDesign = "asKD",
  gammaA = 2
)
summary(designUpdate1)
```

Sequential analysis with a maximum of 5 looks (group sequential design)

Kim & DeMets alpha spending design (gammaA = 2), one-sided overall significance level 2.5%, power 80%, undefined endpoint, inflation factor 1.063, ASN H1 0.7896, ASN H01 0.9937, ASN H0 1.0567.

Stage	1	2	3	4	5
Planned information rate	15.3%	40%	60%	80%	100%
Cumulative alpha spent	0.0006	0.0040	0.0090	0.0160	0.0250
Stage levels (one-sided)	0.0006	0.0036	0.0068	0.0113	0.0173
Efficacy boundary (z-value scale)	3.247	2.690	2.470	2.279	2.114
Cumulative power	0.0170	0.1974	0.4258	0.6418	0.8000

```
# We see the first efficacy boundary point is at Z=3.247

# Continuing to the next analysis
# Now we give the observed information at analyses 1 and 2
designUpdate2 <- getDesignGroupSequential(
  sided = 1,
  alpha = 0.025,
  beta = 0.2,
  informationRates = c(iobs[c(1,2)]/35.58,0.6,0.8,1),
  typeOfDesign = "asKD",
  gammaA = 2
)
summary(designUpdate2)
```

Sequential analysis with a maximum of 5 looks (group sequential design)

Kim & DeMets alpha spending design (gammaA = 2), one-sided overall significance level 2.5%, power 80%, undefined endpoint, inflation factor 1.0626, ASN H1 0.7929, ASN H01 0.9941, ASN H0 1.0564.

Stage	1	2	3	4	5
Planned information rate	15.3%	35.4%	60%	80%	100%
Cumulative alpha spent	0.0006	0.0031	0.0090	0.0160	0.0250
Stage levels	0.0006	0.0027	0.0071	0.0114	0.0173

Stage	1	2	3	4	5
(one-sided)					
Efficacy boundary (z-value scale)	3.247	2.782	2.451	2.277	2.113
Cumulative power	0.0170	0.1475	0.4283	0.6421	0.8000

```
# We see the second efficacy boundary point is at Z=2.782

# Continuing to analysis 3
# Now we give the observed information at analyses 1, 2 and 3
designUpdate3 <- getDesignGroupSequential(
  sided = 1,
  alpha = 0.025,
  beta = 0.2,
  informationRates = c(iobs[c(1,2,3)]/35.58,0.8,1),
  typeOfDesign = "asKD",
  gammaA = 2
)
summary(designUpdate3)
```

Sequential analysis with a maximum of 5 looks (group sequential design)

Kim & DeMets alpha spending design (gammaA = 2), one-sided overall significance level 2.5%, power 80%, undefined endpoint, inflation factor 1.0625, ASN H1 0.7926, ASN H01 0.9941, ASN H0 1.0563.

Stage	1	2	3	4	5
Planned information rate	15.3%	35.4%	59.3%	80%	100%
Cumulative alpha spent	0.0006	0.0031	0.0088	0.0160	0.0250
Stage levels (one-sided)	0.0006	0.0027	0.0069	0.0115	0.0173
Efficacy boundary (z-value scale)	3.247	2.782	2.461	2.275	2.113
Cumulative power	0.0170	0.1475	0.4198	0.6423	0.8000

```
# We see the third efficacy boundary point is at Z=2.461

designUpdate4 <- getDesignGroupSequential(
  sided = 1,
```

```
  alpha = 0.025,
  beta = 0.2,
  informationRates = c(iobs[c(1,2,3,4)]/35.58,1),
  typeOfDesign = "asKD",
  gammaA = 2
)
summary(designUpdate4)
```

Sequential analysis with a maximum of 5 looks (group sequential design)

Kim & DeMets alpha spending design (gammaA = 2), one-sided overall significance level 2.5%, power 80%, undefined endpoint, inflation factor 1.065, ASN H1 0.7993, ASN H01 0.9972, ASN H0 1.0588.

Stage	1	2	3	4	5
Planned information rate	15.3%	35.4%	59.3%	85.9%	100%
Cumulative alpha spent	0.0006	0.0031	0.0088	0.0184	0.0250
Stage levels (one-sided)	0.0006	0.0027	0.0069	0.0139	0.0165
Efficacy boundary (z-value scale)	3.247	2.782	2.461	2.201	2.132
Cumulative power	0.0171	0.1479	0.4208	0.6995	0.8000

```
# The fourth efficacy boundary point is at Z=2.201

# The final analysis is handled differently to allow a
# final information level that differs from the target.
#
# In calculating the efficacy boundary, it is important that
# the RATIOS of information levels are correct. These ratios
# are preserved if we sample sizes by the final observed sample
# size to make the last value in informationRates equal to 1.
#
# However, we need to preserve the type I error probabilities
# already seen at earlier analyses and these depended on the
# observed sample sizes. This is achieved by adding the commands
#  typeOfDesign = "asUser",
#  userAlphaSpending = designUpdate4$alphaSpent
# Now, the remainder of alpha will be spent at the final analysis.
designUpdate5 <- getDesignGroupSequential(
  sided = 1,
  alpha = 0.025,
```

```
  beta = 0.2,
  informationRates = c(iobs[c(1,2,3,4,5)]/iobs[5]),
  typeOfDesign = "asUser",
  userAlphaSpending = designUpdate4$alphaSpent
)
summary(designUpdate5)
```

Sequential analysis with a maximum of 5 looks (group sequential design)

User defined alpha spending design (0.000582, 0.003125, 0.0088, 0.018431, 0.025), one-sided overall significance level 2.5%, power 80%, undefined endpoint, inflation factor 1.0465, ASN H1 0.8067, ASN H01 0.988, ASN H0 1.0413.

Stage	1	2	3	4	5
Planned information rate	16.3%	37.8%	63.4%	91.8%	100%
Cumulative alpha spent	0.0006	0.0031	0.0088	0.0184	0.0250
Stage levels (one-sided)	0.0006	0.0027	0.0069	0.0139	0.0184
Efficacy boundary (z-value scale)	3.247	2.782	2.461	2.201	2.088
Cumulative power	0.0183	0.1580	0.4424	0.7221	0.8000

```
# The final efficacy boundary point is at Z=2.088

designUpdate5$criticalValues

## [1] 3.247424 2.782192 2.460940 2.201259 2.087709

# These values agree very nicely with those from CJ's code

# Futility boundary

# RPACT does not yet provide an error spending FUTILITY
# boundary. Given the negative outcome of this trial, we
# would like to know the futility boundary values.
# From CJ's code, the futility boundary values are
#
#   -1.4351 -0.2322 0.7497 1.6382 2.0187

des_surv_1 <- getDesignGroupSequential(
  alpha = 0.025,
  beta = 0.2,
  sided = 1,
```

```
  kMax = 5,
  informationRates = c(iobs[1]/35.58,0.4,0.6,0.8,1),
  typeOfDesign = "asKD",
  typeBetaSpending = "bsKD",
  gammaA = 2,
  gammaB = 2
)
des_surv_1$futilityBounds
```

```
## [1] -1.435474442 -0.003099704  0.759645623  1.429025680
```

```
des_surv_2 <- getDesignGroupSequential(
  alpha = 0.025,
  beta = 0.2,
  sided = 1,
  kMax = 5,
  informationRates = c(iobs[1:2]/35.58,0.6,0.8,1),
  typeOfDesign = "asKD",
  typeBetaSpending = "bsKD",
  gammaA = 2,
  gammaB = 2
)
des_surv_2$futilityBounds
```

```
## [1] -1.4358736 -0.2333684  0.7744765  1.4295924
```

```
des_surv_3 <- getDesignGroupSequential(
  alpha = 0.025,
  beta = 0.2,
  sided = 1,
  kMax = 5,
  informationRates = c(iobs[1:3]/35.58,0.8,1),
  typeOfDesign = "asKD",
  typeBetaSpending = "bsKD",
  gammaA = 2,
  gammaB = 2
)
des_surv_3$futilityBounds
```

```
## [1] -1.4359524 -0.2334884  0.7480372  1.4313125
```

```
des_surv_4 <- getDesignGroupSequential(
  alpha = 0.025,
  beta = 0.2,
  sided = 1,
  kMax = 5,
  informationRates = c(iobs[1:4]/35.58,1),
  typeOfDesign = "asKD",
  typeBetaSpending = "bsKD",
  gammaA = 2,
  gammaB = 2
```

```
)
des_surv_4$futilityBounds

## [1] -1.4328123 -0.2287088  0.7542316  1.6438195

# Analysis of Cox model output

# The initial design is the same as for the logrank statistic.
# It is the observed information levels and Z-statistics that
# change.

# So, we repeat the above calculations with

iobs=c(4.11,10.89,19.23,28.10,30.96)

# Efficacy boundary

designUpdate1 <- getDesignGroupSequential(
  sided = 1,
  alpha = 0.025,
  beta = 0.2,
  informationRates = c(iobs[1]/35.58,0.4,0.6,0.8,1),
  typeOfDesign = "asKD",
  gammaA = 2
)
summary(designUpdate1)
```

Sequential analysis with a maximum of 5 looks (group sequential design)

Kim & DeMets alpha spending design (gammaA = 2), one-sided overall significance level 2.5%, power 80%, undefined endpoint, inflation factor 1.0627, ASN H1 0.7908, ASN H01 0.9935, ASN H0 1.0564.

Stage	1	2	3	4	5
Planned information rate	11.6%	40%	60%	80%	100%
Cumulative alpha spent	0.0003	0.0040	0.0090	0.0160	0.0250
Stage levels (one-sided)	0.0003	0.0037	0.0068	0.0114	0.0173
Efficacy boundary (z-value scale)	3.403	2.675	2.468	2.278	2.113
Cumulative power	0.0077	0.1998	0.4265	0.6419	0.8000

```r
# We see the efficacy boundary is at Z=3.403

designUpdate2 <- getDesignGroupSequential(
  sided = 1,
  alpha = 0.025,
  beta = 0.2,
  informationRates = c(iobs[c(1,2)]/35.58,0.6,0.8,1),
  typeOfDesign = "asKD",
  gammaA = 2
)
summary(designUpdate2)
```

Sequential analysis with a maximum of 5 looks (group sequential design)

Kim & DeMets alpha spending design (gammaA = 2), one-sided overall significance level 2.5%, power 80%, undefined endpoint, inflation factor 1.0617, ASN H1 0.7993, ASN H01 0.9946, ASN H0 1.0556.

Stage	1	2	3	4	5
Planned information rate	11.6%	30.6%	60%	80%	100%
Cumulative alpha spent	0.0003	0.0023	0.0090	0.0160	0.0250
Stage levels (one-sided)	0.0003	0.0021	0.0075	0.0115	0.0173
Efficacy boundary (z-value scale)	3.403	2.865	2.431	2.274	2.112
Cumulative power	0.0077	0.1047	0.4316	0.6428	0.8000

```r
# We see the second efficacy boundary point is at Z=2.865

designUpdate3 <- getDesignGroupSequential(
  sided = 1,
  alpha = 0.025,
  beta = 0.2,
  informationRates = c(iobs[c(1,2,3)]/35.58,0.8,1),
  typeOfDesign = "asKD",
  gammaA = 2
)
summary(designUpdate3)
```

Sequential analysis with a maximum of 5 looks (group sequential design)

Kim & DeMets alpha spending design (gammaA = 2), one-sided overall significance level 2.5%, power 80%, undefined endpoint, inflation factor 1.0608, ASN H1 0.7985, ASN H01 0.9946, ASN H0 1.0547.

Stage	1	2	3	4	5
Planned information rate	11.6%	30.6%	54%	80%	100%
Cumulative alpha spent	0.0003	0.0023	0.0073	0.0160	0.0250
Stage levels (one-sided)	0.0003	0.0021	0.0058	0.0121	0.0174
Efficacy boundary (z-value scale)	3.403	2.865	2.521	2.254	2.110
Cumulative power	0.0077	0.1045	0.3560	0.6445	0.8000

```
# We see the third efficacy boundary point is at Z=2.521

designUpdate4 <- getDesignGroupSequential(
  sided = 1,
  alpha = 0.025,
  beta = 0.2,
  informationRates = c(iobs[c(1,2,3,4)]/35.58,1),
  typeOfDesign = "asKD",
  gammaA = 2
)
summary(designUpdate4)
```

Sequential analysis with a maximum of 5 looks (group sequential design)

Kim & DeMets alpha spending design (gammaA = 2), one-sided overall significance level 2.5%, power 80%, undefined endpoint, inflation factor 1.0602, ASN H1 0.7974, ASN H01 0.9941, ASN H0 1.0542.

Stage	1	2	3	4	5
Planned information rate	11.6%	30.6%	54%	79%	100%
Cumulative alpha spent	0.0003	0.0023	0.0073	0.0156	0.0250
Stage levels (one-sided)	0.0003	0.0021	0.0058	0.0117	0.0176
Efficacy	3.403	2.865	2.521	2.267	2.107

Stage	1	2	3	4	5
boundary (z-value scale)					
Cumulative power	0.0077	0.1045	0.3558	0.6339	0.8000

```
# The fourth efficacy boundary point is at Z=2.267

designUpdate5 <- getDesignGroupSequential(
  sided = 1,
  alpha = 0.025,
  beta = 0.2,
  informationRates = c(iobs[c(1,2,3,4,5)]/iobs[5]),
  typeOfDesign = "asUser",
  userAlphaSpending = designUpdate4$alphaSpent
)
summary(designUpdate5)
```

Sequential analysis with a maximum of 5 looks (group sequential design)

User defined alpha spending design (0.000334, 0.002342, 0.007303, 0.015593, 0.025), one-sided overall significance level 2.5%, power 80%, undefined endpoint, inflation factor 1.0339, ASN H1 0.8128, ASN H01 0.9821, ASN H0 1.0295.

Stage	1	2	3	4	5
Planned information rate	13.3%	35.2%	62.1%	90.8%	100%
Cumulative alpha spent	0.0003	0.0023	0.0073	0.0156	0.0250
Stage levels (one-sided)	0.0003	0.0021	0.0058	0.0117	0.0202
Efficacy boundary (z-value scale)	3.403	2.865	2.521	2.267	2.049
Cumulative power	0.0090	0.1223	0.4026	0.6882	0.8000

```
# The final efficacy boundary point is at Z=2.049

designUpdate5$criticalValues

## [1] 3.402723 2.865456 2.521286 2.266749 2.048885

# Futility boundary

# RPACT does not yet provide an error spending FUTILITY
```

```r
# boundary. Given the negative outcome of this trial, we
# would like to know the futility boundary values.
# From CJ's code, the futility boundary values are
#
#   -1.7722 -0.4675 0.5546 1.4137 1.6138

# For an approximate answer, we can follow the approach
# illustrated in Example 1.

des_surv_1 <- getDesignGroupSequential(
  alpha = 0.025,
  beta = 0.2,
  sided = 1,
  kMax = 5,
  informationRates = c(iobs[1]/35.58,0.4,0.6,0.8,1),
  typeOfDesign = "asKD",
  typeBetaSpending = "bsKD",
  gammaA = 2,
  gammaB = 2
)
des_surv_1$futilityBounds
```

```
## [1] -1.77293652  0.01004924  0.76094322  1.42887785
```

```r
des_surv_2 <- getDesignGroupSequential(
  alpha = 0.025,
  beta = 0.2,
  sided = 1,
  kMax = 5,
  informationRates = c(iobs[1:2]/35.58,0.6,0.8,1),
  typeOfDesign = "asKD",
  typeBetaSpending = "bsKD",
  gammaA = 2,
  gammaB = 2
)
des_surv_2$futilityBounds
```

```
## [1] -1.7737664 -0.4699132  0.7887489  1.4298425
```

```r
des_surv_3 <- getDesignGroupSequential(
  alpha = 0.025,
  beta = 0.2,
  sided = 1,
  kMax = 5,
  informationRates = c(iobs[1:3]/35.58,0.8,1),
  typeOfDesign = "asKD",
  typeBetaSpending = "bsKD",
  gammaA = 2,
  gammaB = 2
```

```
)
des_surv_3$futilityBounds
```

```
## [1] -1.7745141 -0.4711302  0.5498144  1.4435530
```

```
des_surv_4 <- getDesignGroupSequential(
  alpha = 0.025,
  beta = 0.2,
  sided = 1,
  kMax = 5,
  informationRates = c(iobs[1:4]/35.58,1),
  typeOfDesign = "asKD",
  typeBetaSpending = "bsKD",
  gammaA = 2,
  gammaB = 2
)
des_surv_4$futilityBounds
```

```
## [1] -1.7751174 -0.4721123  0.5485091  1.4061923
```