Package ‘PlatformDesign’

June 13, 2022

Title Optimal Two-Period Multi-Arm Platform Design

Version 1.0.1

Description Design parameters can be calculated using this package based on the optimal two-period multi-arm platform design allowing pre-planned deferred arms to be added during the trial. More details about the design method can be found in the paper: Pan, H., Yuan, X. and Ye, J. (2022) ``An optimal two-period multi-
arm platform design with adding new arms''. Manuscript submitted for
publication. For additional references: Dunnett, C. W. (1955) <doi:10.2307/2281208>.

Imports mvtnorm, stats

License GPL (>= 3)

Encoding UTF-8

RoxygenNote 7.1.2

Suggests knitr, rmarkdown, ggplot2, testthat (>= 3.0.0)

VignetteBuilder knitr

Config/testthat/edition 3

NeedsCompilation no

Author Xiaomeng Yuan [aut, cre],
Haitao Pan [aut]

Maintainer Xiaomeng Yuan <xiaomeng.yuan@stjude.org>

Repository CRAN

Date/Publication 2022-06-13 06:40:08 UTC

R topics documented:

`admiss` *Find the admissible set in a two-period multi-arm platform design with delayed arms*

Description

Find the admissible set of the (n2, n0_2) pairs, given n1, n0_1, nt, ntrt and S.

Usage

```
admiss(n1, n0_1, nt, ntrt, S)
```

Arguments

`n1`	the sample size in each of the K experimental arms in the first period
`n0_1`	the sample size of the control for each of the K experimental arms in the first period
`nt`	the number of patients already enrolled on each of the K experimental arms in the first period at the time new arms are added
`ntrt`	the number of experimental arms in the K+M experimental arm trial, i.e, K+M
`S`	the upper limit of the total sample size for the K+M experimental arm trial. It usually takes the value of the sum of the sample size of two separate clinical trials (one with K and another with M experimental arm, each having one control arm). The total sample size of K (or M) experimental arm trial can be calculated using function one_stage_multiarm().

Details

Given n1, n0_1, nt, ntrt and S, using three constraints to find the admissible set of the (n2, n0_2) pairs. See the vignettes for details.

Value

a dataframe which contains all candidate values of n2 and n0_2 in the first and second column, respectively

Examples

```
admiss(n1=101, n0_1=143, nt=30, ntrt=4, S=690)
```

`cor.mat` *Calculate the correlation matrix of the z-statistics for in a two-period multi-arm platform design with delayed arms*

Description

Calculate the correlation matrix of the z-statistics in the two-period multi-arm platform design with delayed arms, given K, M, n, n0 and n0t.

Usage

```
cor.mat(K, M = 0, n, n0, n0t = NULL)
```

Arguments

`K`	the number of experimental arms in the first period in a two-period K+M trial
`M`	the number of delayed additional experimental arms added in the second period, default = 0 for calculating the correlation matrix of the Z-test statistics for a K-experimental arm trial in the first period
`n`	a positive integer, which is the sample size in each of the experimental arms
`n0`	a positive integer, which is the sample size of the control for each of the experimental arms
`n0t`	the number of patients already enrolled in the control arm when delayed experimental arms are added, default to NULL for calculating correlation matrix of the k-experimental arm trial in the first period

Details

Given K, M, n, n0 and n0t, calculate the correlation matrix of the z-statistics in the two-period K+M experimental arm trial with one common control arm.

Value

cormat, the correlation matrix of Z-test statistics in the two-period K+M experimental arm trial with one common control arm, or that in the k-experimental arm trial in the first period when M = 0

Examples

```
cor.mat(K = 2, M = 0, n = 101, n0 = 143)

#$cormat
#        [,1]      [,2]
#[1,] 1.0000000 0.4139344
#[2,] 0.4139344 1.0000000

#$cor1
#[1] 0.4139344
```

```
#$cor2
#NULL

 cor.mat(K = 2, M = 2, n = 107, n0 = 198, n0t = 43)

#$cormat
#      [,1]      [,2]      [,3]      [,4]
#[1,] 1.0000000 0.3508197 0.2746316 0.2746316
#[2,] 0.3508197 1.0000000 0.2746316 0.2746316
#[3,] 0.2746316 0.2746316 1.0000000 0.3508197
#[4,] 0.2746316 0.2746316 0.3508197 1.0000000

#$cor1
#[1] 0.3508197

#$cor2
#[1] 0.2746316
```

---

fwer_critical *Calculate the critical value and the marginal type-I error rate*

Description

Calculate the critical value and the marginal type-I error rate given the number of experimental arms, the family-wise type I error rate and the correlation matrix of the z-statistics.

Usage

```
fwer_critical(ntrt, fwer, corMat, seed = 123)
```

Arguments

`ntrt`	the number of experimental arms in the trial
`fwer`	the family-wise error rate (FWER) to be controlled, default to be the same throughout the trial
`corMat`	the correlation matrix of the Z-test statistics
`seed`	an integer for random number generation for numerically evaluating integration, default = 123

Details

Use the number of experimental arms, the family-wise type I error rate and the correlation matrix of the Z-test statistics to calculate the marginal type I error rate and the critical value.

Value

pairwise_alpha the marginal type-I error rate for the comparison between any of the experimental arm and its corresponding control

critical_val, the critical value for the comparison between any of the experimental arm and the corresponding controls

Other values returned are inputs.

Author(s)

Xiaomeng Yuan, Haitao Pan

References

Dunnett, C. W. (1955). A multiple comparison procedure for comparing several treatments with a control. Journal of the American Statistical Association, 50(272), 1096-1121.

Examples

```
corMat1 <- cor.mat(K=2, M = 2, n=107, n0=198, n0t = 43)$cormat
fwer_critical(ntrt=4, fwer=0.025, corMat=corMat1)

#$ntrt
#[1] 4

#$fwer
#[1] 0.025

#$corMat
#      [,1]      [,2]      [,3]      [,4]
#[1,] 1.0000000 0.3508197 0.2746316 0.2746316
#[2,] 0.3508197 1.0000000 0.2746316 0.2746316
#[3,] 0.2746316 0.2746316 1.0000000 0.3508197
#[4,] 0.2746316 0.2746316 0.3508197 1.0000000

#$pairwise_alpha
#[1] 0.006657461

#$critical_val
#[1] 2.475233
```

---

one_design — *Calculate other design parameters of a two-period multi-arm platform design given updated sample sizes*

Description

Provide other design parameters for a two-period K+M trial, given n2 and n0_2, nt, K, M, fwer and marginal power (of the the first period). This function serves for the purpose of spot-testing for any pre-specified n, n0_2 pair. Please use *platform_design()* for finding optimal values of n and n0_2.

Usage

```
one_design(n2, n0_2, nt, K, M, fwer, marginal.power, delta, seed = 123)
```

Arguments

n2	a positive integer, which is the sample size in each of the K+M experimental arms in the second period, n2 > nt
n0_2	a positive integer, which is the sample size of the concurrent control for each of the K+M experimental arms in the in the second period
nt	a positive integer, the number of patients already enrolled on each of the K experimental arms in the first period when the new arms are added
K	a positive integer, the number of experimental arms in the first period in a two-period K+M trial
M	a positive integer, the number of delayed (newly added) experimental arms added in the second period
fwer	the family-wise error rate (FWER) to be controlled, default to be the same throughout the trial
marginal.power	the marginal power to achieve in the first period in a two-period K+M trial
delta	the standardized clinical effect size expected to be detected in the trial
seed	an integer for random number generation for numerically evaluating integration, default = 123

Details

Given n2 and n0_2, nt, K, M, fwer and marginal power (of the first period), provide other design parameters for a two-period K+M trial.

Value

designs contains the calculated design parameters for period 1 and 2 including:

n1 and *n0_1*, the sample sizes of each of the K experimental arms and the control arm, respectively, in the first period

n2 and *n0_2*, the updated sample sizes of each of the K + M experimental arms and its corresponding concurrent control, respectively, after adding M experimental arms in the second period

nt and *n0t*, the number of patients already enrolled on each of the K experimental arms and the control arm, respectively, in the first period when the new arms are added

nc, the updated total sample size of the control arm after adding M experimental arms in the second period, i.e., the sum of concurrent (n0_2) and nonconcurrent (n0t) controls

N2, the total sample size of the two-period K+M experimental arm (and 1 control arm) platform trial

A1, the allocation ratio (control to experimental arm) before the M new experimental arms are added and after the initial K experimental arms end

A2, the allocation ratio after the M new experimental arms are added and before the initial K experimental arms end *cor1*, the correlation of Z statistics between any two of the K initially opened experimental arms (or between any two of the M delayed arms)

cor2, the correlation of Z statistics between any pair of one initially opened and one delayed experimental arm

critical_value1, the critical value for the comparison between any of the K experimental arms in the first period and the corresponding control

critical_value2, the critical value for the comparison between any of the K + M experimental arms in the second period and the corresponding control

marginal.power1 and *marginal.power2*, the marginal power for the first and second period, respectively

disjunctive.power1 and *disjunctive.power2*, the disjunctive power for the first and second period, respectively

effect_size, the standardized clinical effect size expected to be detected in the trial

Author(s)

Xiaomeng Yuan, Haitao Pan

References

Pan, H., Yuan, X. and Ye, J. (2022). An optimal two-period multi-arm confirmatory platform design with adding new arms. Manuscript submitted for publication.

Dunnett, C. W. (1955). A multiple comparison procedure for comparing several treatments with a control. Journal of the American Statistical Association, 50(272), 1096-1121.

Examples

```
one_design(n2 = 107, n0_2 = 198, nt = 30, K = 2, M = 2, fwer = 0.025,
           marginal.power = 0.8, delta = 0.4)

#$n1
#[1] 101

#$n0_1
#[1] 143

#$n2
#[1] 107

#$n0_2
#[1] 198

#$nt
#[1] 30

#$n0t
#[1] 43

#$nc
#[1] 241

#$N2
```

```
#[1] 669

#$A1
#[1] 1.414214

#$A2
#[1] 2.012987

#$cor1
#[1] 0.3508197

#$cor2
#[1] 0.2746316

#$critical_value1
#[1] 2.220604

#$critical_value2
#[1] 2.475233

#$marginal.power1
#[1] 0.8

#$marginal.power2
#[1] 0.80011

#$disjunctive.power1
#[1] 0.9222971

#$disjunctive.power2
#[1] 0.9853799

#$effect_size
#[1] 0.4
```

---

one_stage_multiarm *Calculate the sample size and other design parameters for an one-stage K-arm trial using the root-K rule for the allocation ratio*

Description

This design is to find the required sample sizes and the associated critical value to control the overall type I error rate (FWER) and achieve the user-specified marginal (i.e., experimental-wise or pairwise) power. Calculate required sample sizes for each of the experimental arm (n1), the control arm (n0_1), the total sample size (N1) and the critical value z_alpha1 in a K-arm trial setting (K experimental arms and 1 common control arm).

Usage

```
one_stage_multiarm(K, fwer, marginal.power, delta, seed = 123)
```

Arguments

`K`	the number of experimental arms
`fwer`	the family-wise type I error rate
`marginal.power`	the marginal power for each experimental-control comparison
`delta`	the standardized clinical effect size expected to be detected in the trial
`seed`	an integer for random number generation for numerically evaluating integration, default = 123

Details

Given the number of experimental arm (K), the family-wise type I error rate, the marginal power for each experimental-control comparison and the standardized effect size to calculate the sample size and other design parameters for the K-experimental arm trial with one control arm.

Value

n1 the sample size of each of the K experimental arms

n0_1 the sample size of the control arm

N1 the total sample size of a K-arm trial

z_alpha1 the critical value for the comparison between any of the K-experimental arm in the first period and its corresponding control

z_beta1 the value of the quantile function of the standard normal distribution with probability = marginal power of the K-arm trial

Power1 the disjunctive power of the K-arm trial defined as the probability of rejecting at least one of the K experimental arms under the alternative hypothesis

corMat1 the correlation matrix of the Z-test statistics

Author(s)

Xiaomeng Yuan, Haitao Pan

References

Pan, H., Yuan, X. and Ye, J. (2022). An optimal two-period multi-arm confirmatory platform design with adding new arms. Manuscript submitted for publication.

Dunnett, C. W. (1955). A multiple comparison procedure for comparing several treatments with a control. Journal of the American Statistical Association, 50(272), 1096-1121.

Examples

```
one_stage_multiarm(K = 2, fwer = 0.025, marginal.power = 0.8, delta = 0.4)
#$n1
#[1] 101

#$n0_1
#[1] 143
```

```
#$N1
#[1] 345

#$z_alpha1
#[1] 2.220604

#$z_beta1
#[1] 0.8416212

#$Power1
#[1] 0.9222971

#$corMat1
#[,1]      [,2]
#[1,] 1.0000000 0.4142136
#[2,] 0.4142136 1.0000000
```

`platform_design` *Design of an optimal two-period multi-arm platform trial with delayed arms*

Description

Find optimal design(s), provide the design parameters for a two-period K+M experimental arm platform trial

Usage

```
platform_design(
  nt,
  K,
  M,
  fwer,
  marginal.power,
  min.marginal.power = marginal.power,
  delta,
  seed = 123
)
```

Arguments

`nt`	the number of patients already enrolled on each of the K experimental arms in the first period at the time the new arms are added
`K`	the number of experimental arms in the first period in a two-period K+M trial
`M`	the number of delayed (newly added) experimental arms added in the second period

fwer	the family-wise error rate (FWER) to be controlled, default to be the same throughout the trial
marginal.power	the marginal power to achieve in the first period in a two-period K+M trial
min.marginal.power	the user-defined lower limit of the marginal power in the K+M trial (with K+M experimental arms and 1 common control arm), default to be the marginal power in the first period
delta	the standardized clinical effect size expected to be detected in the trial
seed	an integer for random number generation for numerically evaluating integration, default = 123

Details

Providing an optimized design in terms of minimizing the total sample size for adding M additional experimental arms in the middle of a clinical trial which originally (in the first period) have K experimental arms and 1 control arm, given user-defined FWER and marginal power.

Value

The function returns a list, including **designs**, **flag.dp**, **flag.mp**, and **flag.dpmp**.

designs contains the recommended optimal design parameters for periods 1 and 2 including:

n1 and *n0_1*, the sample sizes of each of the K experimental arms and the concurrent control, respectively, in the first period

n2 and *n0_2*, the updated sample sizes of each of the K + M experimental arms and its corresponding concurrent control, respectively, after adding M experimental arms in the second period

nt and *n0t*, the number of patients already enrolled on each of the K experimental arms and the control arm, respectively, in the first period at the time the M new arms are added

nc, the updated total sample size of the control arm after adding M experimental arms in the second period, i.e., the sum of concurrent (n0_2) and nonconcurrent (n0t) controls

N2, the total sample size of the two-period K+M experimental arm (and 1 control arm) platform trial

A1, the allocation ratio (control to experimental arm) before the M new experimental arms are added and after the initial K experimental arms end

A2, the allocation ratio after the M new experimental arms are added and before the initial K experimental arms end

cor1, the correlation of Z-test statistics between any two of the K initially opened experimental arms (or between any two of the M newly added arms)

cor2, the correlation of Z-test statistics between any pair of one initially opened and one newly added experimental arm

critical_value1, the critical value for the comparison between any of the K experimental arms in the first period and the corresponding control

critical_value2, the critical value for the comparison between any of the K + M experimental arms in the second period and the corresponding control

marginal.power1 and *marginal.power2*, the marginal power for the first and second period, respectively

disjunctive.power1 and *disjunctive.power2*, the disjunctive power for the first and second period, respectively *standardized_effect_size*, the standardized clinical effect size expected to be detected in the trial

flag.dp, **flag.mp**, and **flag.dpmp** indicate if the lower limit of disjunctive power, marginal power, and both of them has(have) met, respectively.

Author(s)

Xiaomeng Yuan, Haitao Pan

References

Pan, H., Yuan, X. and Ye, J. (2022). An optimal two-period multi-arm confirmatory platform design with adding new arms. Manuscript submitted for publication.

Dunnett, C. W. (1955). A multiple comparison procedure for comparing several treatments with a control. Journal of the American Statistical Association, 50(272), 1096-1121.

Examples

```
platform_design(nt = 30, K = 2, M = 2, fwer = 0.025, marginal.power = 0.8, delta = 0.4)

#flag.dpmp == 0, lower limits of marginal and disjunctive power are both met
#$designs
#      n1  n0_1  n2 n0_2 nt n0t  nc  N2
#15669 101  143 107  198 30  43 241 669
#15994 101  143 106  202 30  43 245 669
#16315 101  143 105  206 30  43 249 669
#16632 101  143 104  210 30  43 253 669

#        A1       A2       cor1      cor2        critical_value1 critical_value2
#15669 1.414214 2.012987 0.3508197 0.2746316        2.220604        2.475233
#15994 1.414214 2.092105 0.3441558 0.2708949        2.220604        2.475790
#16315 1.414214 2.173333 0.3376206 0.2671464        2.220604        2.476330
#16632 1.414214 2.256757 0.3312102 0.2633910        2.220604        2.476854

#          marginal.power1 marginal.power2 disjunctive.power1 disjunctive.power2
#15669             0.8       0.8001100          0.9222971          0.9853799
#15994             0.8       0.8003363          0.9222971          0.9857541
#16315             0.8       0.8003878          0.9222971          0.9860900
#16632             0.8       0.8002699          0.9222971          0.9863903

 #          standardized_effect_size
#15669          0.4
#15994          0.4
#16315          0.4
#16632          0.4

#$flag.dp
#[1] 0

#$flag.mp
#[1] 0
```

```
#$flag.dpmp
#[1] 0
```

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