

Package: OptimalGoldstandardDesigns (via r-universe)

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Type Package

Title Design Parameter Optimization for Gold-Standard Non-Inferiority Trials

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Description Methods to calculate optimal design parameters for one- and two-stage three-arm group-sequential gold-standard non-inferiority trial designs with or without binding or nonbinding futility boundaries, as described in Meis et al. (2023) <[doi:10.1002/sim.9630](https://doi.org/10.1002/sim.9630)>.

License GPL (>= 3)

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'pmv_upper_smaller_slower_fix.R'
'conditional_probability_functions.R'
'design_display_functions.R' 'global_constants.R'
'design_helper_functions.R' 'objective_functions.R'
'optimization_methods.R' 'table_format_functions.R'

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Repository <https://jan-imbi.r-universe.dev>

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Contents

calc_ASN	2
calc_ASNP	3
calc_c	3
calc_conditional_local_rejection_probs	4
calc_conditional_power	4
calc_cumc	5
calc_cumn	5
calc_final_state_probs	6
calc_gamma	6
calc_local_alphas	6
calc_local_rejection_boundaries	7
calc_mu_vec	7
calc_mu_wo_nT1	8
calc_nT1_wrt_bTC2e	8
calc_n_from_c	9
calc_prob_reject_both	9
calc_prob_reject_both_singlestage	10
calc_Sigma	10
calc_worst_type_I_error	11
conditional_mean	11
conditional_Sigma	12
objective_onestage	12
objective_twostage	13
OptimalGoldstandardDesigns	13
optimize_design_onestage	14
optimize_design_twostage	16
padd_whitespace	20
pmvnorm	21
pmvt	21
print.OneStageGoldStandardDesign	22
print.TwoStageGoldStandardDesign	23
Index	25

calc_ASN

Helper function to calculate the average sample size

Description

Helper function to calculate the average sample size

Usage

calc_ASN(D)

Arguments

D list containing all parameters of a the trial design.

calc_ASNP *Calculate the average placebo group sample size*

Description

Calculate the average placebo group sample size

Usage

calc_ASNP(D)

Arguments

D list containing all parameters of a the trial design.

calc_c *Helper function to calculate allocation ratios from stagewise sample sizes*

Description

Helper function to calculate allocation ratios from stagewise sample sizes

Usage

calc_c(D)

Arguments

D list containing all parameters of a the trial design.

calc_conditional_local_rejection_probs

Calculate the (local) conditional type I errors of both hypothesis given both interim test statistics.

Description

Calculate the (local) conditional type I errors of both hypothesis given both interim test statistics.

Usage

```
calc_conditional_local_rejection_probs(Z_TP1, Z_TC1, D, mu_vec = D$mu_vec$H0)
```

Arguments

Z_TP1	First stage Z-test statistic of the superiority test of treatment over placebo.
Z_TC1	First stage Z-test statistic of the non-inferiority test of treatment to the active control.
D	list containing all parameters of a the trial design.
mu_vec	vector of means of the test statistic $c(Z_TP1, Z_TP2, Z_TC1, Z_TC1)$.

Value

named numeric vector with both conditional type I errors.

calc_conditional_power

Calculate the conditional power to reject both hypothesis given both interim test statistics.

Description

Calculate the conditional power to reject both hypothesis given both interim test statistics.

Usage

```
calc_conditional_power(Z_TP1, Z_TC1, D)
```

Arguments

Z_TP1	First stage Z-test statistic of the superiority test of treatment over placebo.
Z_TC1	First stage Z-test statistic of the non-inferiority test of treatment to the active control.
D	list containing all parameters of a the trial design.

Value

numeric value of the conditional power.

calc_cumc	<i>Helper function to calculate "cumulative allocation ratio" from stage-wise allocation ratios</i>
-----------	---

Description

Helper function to calculate "cumulative allocation ratio" from stagewise allocation ratios

Usage

```
calc_cumc(D)
```

Arguments

D list containing all parameters of a the trial design.

calc_cumn	<i>Helper function to calculate cumulative sample sizes from stagewise sample sizes</i>
-----------	---

Description

Helper function to calculate cumulative sample sizes from stagewise sample sizes

Usage

```
calc_cumn(D)
```

Arguments

D list containing all parameters of a the trial design.

calc_final_state_probs

Helper function to calculate the final state probabilities

Description

Helper function to calculate the final state probabilities

Usage

```
calc_final_state_probs(hypothesis = "H0", D)
```

Arguments

hypothesis	string describing the hypothesis, either "H0" or "H1".
D	list containing all parameters of a the trial design.

calc_gamma

Helper function to calculate gamma factors from group variances and cumulative allocation ratios

Description

Helper function to calculate gamma factors from group variances and cumulative allocation ratios

Usage

```
calc_gamma(D)
```

Arguments

D	list containing all parameters of a the trial design.
---	---

calc_local_alphas

Helper function to calculate the local type I error rates of a Design

Description

Helper function to calculate the local type I error rates of a Design

Usage

```
calc_local_alphas(D)
```

Arguments

D	list containing all parameters of a the trial design.
---	---

`calc_local_rejection_boundaries`

Helper function to calculate the local rejection boundaries of group sequential testing procedure associated with the hypothesis belong to the groups argument

Description

Helper function to calculate the local rejection boundaries of group sequential testing procedure associated with the hypothesis belong to the groups argument

Usage

```
calc_local_rejection_boundaries(groups = "TP", D)
```

Arguments

groups	string describing the pair of groups. Either "TP" or "TC".
D	list containing all parameters of a the trial design.

`calc_mu_vec`

Helper function to calculate expected value of normal test statistic vector $c(Z_{TP1}, Z_{TP2}, Z_{TC1}, Z_{TP2})$ under the null and alternative hypothesis given $nT1$, γ and μ .

Description

Helper function to calculate expected value of normal test statistic vector $c(Z_{TP1}, Z_{TP2}, Z_{TC1}, Z_{TP2})$ under the null and alternative hypothesis given $nT1$, γ and μ .

Usage

```
calc_mu_vec(D)
```

Arguments

D	list containing all parameters of a the trial design.
---	---

calc_mu_wo_nT1	<i>Helper function to calculate expected value of normal test statistic vector $c(Z_{TP1}, Z_{TP2}, Z_{TC1}, Z_{TP2})$ under the null and alternative hypothesis given $nT1=1$, γ and μ.</i>
----------------	---

Description

This quantity is helpful when solving for the smallest n which fulfills a certain power constraint.

Usage

calc_mu_wo_nT1(D)

Arguments

D list containing all parameters of a the trial design.

calc_nT1_wrt_bTC2e	<i>Helper function to calculate the required sample size (of the stage 1 treatment group) to achieve the target power given the bTC2e</i>
--------------------	---

Description

Helper function to calculate the required sample size (of the stage 1 treatment group) to achieve the target power given the bTC2e

Usage

calc_nT1_wrt_bTC2e(bTC2e, D)

Arguments

bTC2e second stage critical value for the TC testing problem.
D list containing all parameters of a the trial design.

calc_n_from_c	<i>Helper function to calculate other n's given n₁,T and allocation ratios</i>
---------------	---

Description

Helper function to calculate other n's given n₁,T and allocation ratios

Usage

```
calc_n_from_c(nT1, D)
```

Arguments

nT1	first stage sample size of the treatment group.
D	list containing all parameters of a the trial design.

calc_prob_reject_both	<i>Helper function to calculate the probability to reject both hypotheses given the mean of the normal test statistic vector c(Z_TP1, Z_TP2, Z_TC1, Z_TC2).</i>
-----------------------	---

Description

Helper function to calculate the probability to reject both hypotheses given the mean of the normal test statistic vector c(Z_TP1, Z_TP2, Z_TC1, Z_TC2).

Usage

```
calc_prob_reject_both(mu_vec, D)
```

Arguments

mu_vec	vector of means of the test statistic c(Z_TP1, Z_TP2, Z_TC1, Z_TC1).
D	list containing all parameters of a the trial design.

calc_prob_reject_both_singlestage

Helper function to calculate the probability to reject both hypotheses given the mean of the normal test statistic vector $c(Z_{TP1}, Z_{TC1})$.

Description

Helper function to calculate the probability to reject both hypotheses given the mean of the normal test statistic vector $c(Z_{TP1}, Z_{TC1})$.

Usage

calc_prob_reject_both_singlestage(mu_vec, D)

Arguments

mu_vec vector of means of the test statistic $c(Z_{TP1}, Z_{TP2}, Z_{TC1}, Z_{TC1})$.
 D list containing all parameters of a the trial design.

calc_Sigma

Helper function to calculate the covariance matrix from the group variances, cumulative allocation ratios and gamma factors

Description

Helper function to calculate the covariance matrix from the group variances, cumulative allocation ratios and gamma factors

Usage

calc_Sigma(D)

Arguments

D list containing all parameters of a the trial design.

calc_worst_type_I_error

Helper function to calculate the maximal probability of rejecting the non-inferiority hypothesis in the testing procedure featuring nonsequential futility, given a point hypothesis for the superiority hypothesis.

Description

This is required in designs with nonsequential futility testing, as choosing locally valid designs is insufficient to guarantee type I error control.

Usage

```
calc_worst_type_I_error(bTC2e, D)
```

Arguments

bTC2e	second stage critical value for the TC testing problem.
D	list containing all parameters of a the trial design.

conditional_mean	<i>Calculate the conditional mean of a multivariate normal distribution</i>
------------------	---

Description

See e.g. Chapter 8.1.2 in [The Matrix Cookbook](#).

Usage

```
conditional_mean(x_a, mu_a, mu_b, Sigma)
```

Arguments

x_a	(Observed) first part of normally distributed vector.
mu_a	Mean of second part of normally distributed vector.
mu_b	Mean of first part of normally distributed vector.
Sigma	covariance matrix of test statistic vector $c(Z_{TP1}, Z_{TP2}, Z_{TC1}, Z_{TC2})$.

Value

numeric vector with the conditional mean

References

Petersen, K. B., & Pedersen, M. S. (2008). The matrix cookbook. Technical University of Denmark, 7(15), 510.

conditional_Sigma *Calculate the conditional mean of a multivariate normal distribution*

Description

See e.g. Chapter 8.1.2 in [The Matrix Cookbook](#).

Usage

```
conditional_Sigma(x_a, mu_a, mu_b, Sigma)
```

Arguments

x_a	(Observed) first part of normally distributed vector.
mu_a	Mean of second part of normally distributed vector.
mu_b	Mean of first part of normally distributed vector.
Sigma	covariance matrix of test statistic vector $c(Z_TP1, Z_TP2, Z_TC1, Z_TC2)$.

Value

numeric vector with the conditional covariance matrix

References

Petersen, K. B., & Pedersen, M. S. (2008). The matrix cookbook. Technical University of Denmark, 7(15), 510.

objective_onestage *Objective function for single-stage gold-standard designs*

Description

Objective function for single-stage gold-standard designs

Usage

```
objective_onestage(D)
```

Arguments

D	list containing all parameters of a the trial design.
---	---

objective_twostage *Objective function for two-stage gold-standard designs*

Description

Objective function for two-stage gold-standard designs

Usage

```
objective_twostage(D)
```

Arguments

D list containing all parameters of a the trial design.

OptimalGoldstandardDesigns
OptimalGoldstandardDesigns

Description

Methods to calculate optimal design parameters for one- and two-stage three-arm group-sequential gold-standard non-inferiority trial designs with or without binding or nonbinding futility boundaries, as described in (Meis et al. 2023).

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References

Meis J, Pilz M, Herrmann C, Bokelmann B, Rauch G, Kieser M (2023). “Optimization of the two-stage group sequential three-arm gold-standard design for non-inferiority trials.” *Statistics in Medicine*, **42**(4), 536-558. [doi:10.1002/sim.9630](https://doi.org/10.1002/sim.9630).

See Also

Useful links:

- <https://github.com/jan-imbi/OptimalGoldstandardDesigns>

```
optimize_design_onestage
```

Calculate optimal design parameters for a single-stage gold-standard design

Description

Calculate optimal design parameters for a single-stage gold-standard design

Usage

```
optimize_design_onestage(
  cP1 = NULL,
  cC1 = NULL,
  alpha = 0.025,
  beta = 0.2,
  alternative_TP = 0.4,
  alternative_TC = 0,
  Delta = 0.2,
  varT = 1,
  varP = 1,
  varC = 1,
  round_n = TRUE,
  kappa = 0,
  objective = quote(sum(unlist(n)) + kappa * n[[1]][["P"]]),
  inner_tol_objective = 1e-07,
  mvnorm_algorithm = mvtnorm::Miwa(steps = 4097, checkCorr = FALSE, maxval = 1000),
  nloptr_x0 = NULL,
  nloptr_lb = NULL,
  nloptr_ub = NULL,
  nloptr_opts = list(algorithm = "NLOPT_LN_SBPLX", ftol_rel = 1e-09, xtol_abs = 1e-08,
    xtol_rel = 1e-07, maxeval = 1000, print_level = 0),
  print_progress = TRUE,
  ...
)
```

Arguments

cP1	(numeric) allocation ratio n_{P1} / n_{T1} . Parameter to be optimized if left unspecified.
cC1	(numeric) allocation ratio n_{C1} / n_{T1} . Parameter to be optimized if left unspecified.
alpha	type I error rate.
beta	type II error rate.
alternative_TP	assumed difference between T and P under H1. Positive values favor T.

alternative_TC	assumed difference between T and C under H1. Positive values favor T.
Delta	non-inferiority margin for the test $X_T - X_C \leq -\Delta$ vs. $X_T - X_C > -\Delta$.
varT	variance of treatment group.
varP	variance of placebo group.
varC	variance of control group.
round_n	(logical) if TRUE, a design with integer valued sample sizes is returned.
kappa	(numeric) penalty factor for placebo patients in the default objective function.
objective	(expression) objective criterion.
inner_tol_objective	(numeric) used to determine the tolerances for integrals and nuisance optimization problems inside the objective function.
mvnorm_algorithm	algorithm for multivariate integration passed to pmvnorm .
nloptr_x0	(numeric vector) starting point for optimization.
nloptr_lb	(numeric vector) lower bound box for box constrained optimization.
nloptr_ub	(numeric vector) upper bound box for box constrained optimization.
nloptr_opts	(list) nloptr options. See nloptr .
print_progress	(logical) controls whether optimization progress should be visualized during the calculation.
...	additional arguments passed along.

Details

This function calculates optimal design parameters for a two-stage three-arm gold-standard non-inferiority trial. Run `vignette("Introduction", package = "OptimalGoldstandardDesigns")` to see some examples related to the associated paper (Meis et al. 2023).

Parameters which can be optimized are the allocation ratios for all groups and stages and the futility and efficacy boundaries of the first stage. The allocation ratios are $cT2 = nT2 / nT1$, $cP1 = nP1 / nT1$, $cP2 = nP2 / nT1$, $cC1 = nC1 / nT1$ and $cC2 = nC2 / nT1$. Here, $nT1$ denotes the sample size of the treatment group in the first stage, $nP2$ the sample size of the placebo group in the second stage, etc. The first stage efficacy boundaries are $bTP1e$ for the treatment vs placebo testing problem, and $bTC1e$ for the treatment vs control non-inferiority testing problem. The futility boundaries are denoted by $bTP1f$ and $bTC1f$.

If these parameters are left unspecified or set to NULL, they will be included into the optimization process, otherwise they will be considered boundary constraints. You may also supply quoted expressions as arguments for these parameters to solve a constrained optimization problem. For example, you can supply $cT2 = 1$, $cP2 = \text{quote}(cP1)$, $cC2 = \text{quote}(cC1)$ to ensure that the first and second stage allocation ratios are equal.

The design is optimized with respect to the objective criterion given by the parameter `objective`. By default, this is the overall sample size plus an optional penalty for the placebo group sample size, controlled by the parameter `kappa`.

Designs are calculated to fulfill the following constraints: the family-wise type I error rate is controlled at α under any combination of the two null hypotheses $\mu_T - \mu_P = 0$ and $\mu_T - \mu_C$

+ Delta = 0. The power to reject both hypothesis given both alternative hypotheses $\mu_T - \mu_P = \text{alternative_TP}$ and $\mu_T - \mu_C + \text{Delta} = \text{alternative_TC} + \text{Delta}$ is at least $1 - \text{beta}$. Variances are assumed to be given by varT , varP and varC .

If `binding_futility` is TRUE, type I error recycling is used. If `always_both_futility_tests` is TRUE, it is assumed that futility tests for both hypotheses are performed at interim, regardless of whether the treatment vs placebo null hypothesis was successfully rejected. If `always_both_futility_tests` is FALSE, the futility test for the treatment vs. control testing problem only needs to be done if the null for the treatment vs. placebo testing problem was rejected in the first stage.

Value

Design object (a list) with optimized design parameters.

References

Meis J, Pilz M, Herrmann C, Bokelmann B, Rauch G, Kieser M (2023). "Optimization of the two-stage group sequential three-arm gold-standard design for non-inferiority trials." *Statistics in Medicine*, **42**(4), 536-558. doi:10.1002/sim.9630.

Examples

```
# Should take about 2 second with the chosen accuracy
optimize_design_onestage(
  alpha = .025,
  beta = .2,
  alternative_TP = .4,
  alternative_TC = 0,
  Delta = .2,
  mvnorm_algorithm = mvtnorm::Miwa(steps = 512, checkCorr = FALSE, maxval = 1000),
  nloptr_opts = list(algorithm = "NLOPT_LN_SBPLX", ftol_rel = 1e-03, xtol_abs = 1e-08,
                    xtol_rel = 1e-07, maxeval = 1000, print_level = 0)
)
```

```
optimize_design_twostage
```

Calculate optimal design parameters for a two-stage gold-standard design

Description

Calculate optimal design parameters for a two-stage gold-standard design

Usage

```

optimize_design_twostage(
  cT2 = NULL,
  cP1 = NULL,
  cP2 = NULL,
  cC1 = NULL,
  cC2 = NULL,
  bTP1f = NULL,
  bTP1e = NULL,
  bTC1f = NULL,
  bTC1e = NULL,
  alpha = 0.025,
  beta = 0.2,
  alternative_TP = 0.4,
  alternative_TC = 0,
  Delta = 0.2,
  varT = 1,
  varP = 1,
  varC = 1,
  binding_futility = FALSE,
  always_both_futility_tests = TRUE,
  round_n = TRUE,
  lambda = 1,
  kappa = 0,
  eta = 0,
  objective = quote(sqrt(lambda)^2 * ASN[["H11"]] + (1 - sqrt(lambda)) * sqrt(lambda) *
    ASN[["H10"]] + (1 - sqrt(lambda)) * sqrt(lambda) * ASN[["H01"]] + (1 -
    sqrt(lambda))^2 * ASN[["H00"]] + kappa * (sqrt(lambda)^2 * ASNP[["H11"]] + (1 -
    sqrt(lambda)) * sqrt(lambda) * ASNP[["H10"]] + (1 - sqrt(lambda)) * sqrt(lambda) *
    ASNP[["H01"]] + (1 - sqrt(lambda))^2 * ASNP[["H00"]] + eta * cumn[[2]][["P"]]) + eta
    * (cumn[[2]][["T"]] + cumn[[2]][["P"]] + cumn[[2]][["C"]])),
  inner_tol_objective = .Machine$double.eps^0.25,
  mvnorm_algorithm = mvtnorm::Miwa(steps = 128, checkCorr = FALSE, maxval = 1000),
  nloptr_x0 = NULL,
  nloptr_lb = NULL,
  nloptr_ub = NULL,
  nloptr_opts = list(algorithm = "NLOPT_LN_SBPLX", ftol_rel = 1e-04, xtol_abs = 0.001,
    xtol_rel = 0.01, maxeval = 1000, print_level = 0),
  print_progress = TRUE,
  ...
)

```

Arguments

cT2	(numeric) allocation ratio $nT2 / nT1$. Parameter to be optimized if left unspecified.
cP1	(numeric) allocation ratio $nP1 / nT1$. Parameter to be optimized if left unspecified.

cP2	(numeric) allocation ratio n_{P2} / n_{T1} . Parameter to be optimized if left unspecified.
cC1	(numeric) allocation ratio n_{C1} / n_{T1} . Parameter to be optimized if left unspecified.
cC2	(numeric) allocation ratio n_{C2} / n_{T1} . Parameter to be optimized if left unspecified.
bTP1f	(numeric) first stage futility boundary for the T vs. P testing problem. Parameter to be optimized if left unspecified.
bTP1e	(numeric) first stage critical value for the T vs. P testing problem. Parameter to be optimized if left unspecified.
bTC1f	(numeric) first stage futility boundary for the T vs. C testing problem. Parameter to be optimized if left unspecified.
bTC1e	(numeric) first stage critical value for the T vs. C testing problem. Parameter to be optimized if left unspecified.
alpha	type I error rate.
beta	type II error rate.
alternative_TP	assumed difference between T and P under H1. Positive values favor T.
alternative_TC	assumed difference between T and C under H1. Positive values favor T.
Delta	non-inferiority margin for the test $X_T - X_C \leq -\Delta$ vs. $X_T - X_C > -\Delta$.
varT	variance of treatment group.
varP	variance of placebo group.
varC	variance of control group.
binding_futility	(logical) controls if futility boundaries are binding.
always_both_futility_tests	(logical) if true, both futility tests are performed after the first stage. If false, a 'completely sequential' testing procedure is employed (see Appendix of (Meis et al. 2023)).
round_n	(logical) if TRUE, a design with integer valued sample sizes is returned.
lambda	(numeric) weight of the alternative hypothesis in the default objective function. 1-lambda is the weight of the null hypothesis.
kappa	(numeric) penalty factor for placebo patients in the default objective function.
eta	(numeric) penalty factor for the maximum sample size in the default objective function.
objective	(expression) objective criterion.
inner_tol_objective	(numeric) used to determine the tolerances for integrals and nuisance optimization problems inside the objective function.
mvnorm_algorithm	algorithm for multivariate integration passed to pmvnorm .
nloptr_x0	(numeric vector) starting point for optimization.

nloptr_lb	(numeric vector) lower bound box for box constrained optimization.
nloptr_ub	(numeric vector) upper bound box for box constrained optimization.
nloptr_opts	(list) nloptr options. See nloptr .
print_progress	(logical) controls whether optimization progress should be visualized during the calculation.
...	additional arguments passed along.

Details

This function calculates optimal design parameters for a two-stage three-arm gold-standard non-inferiority trial. Run `vignette("Introduction", package = "OptimalGoldstandardDesigns")` to see some examples related to the associated paper (Meis et al. 2023).

Parameters which can be optimized are the allocation ratios for all groups and stages and the futility and efficacy boundaries of the first stage. The allocation ratios are $cT2 = nT2 / nT1$, $cP1 = nP1 / nT1$, $cP2 = nP2 / nT1$, $cC1 = nC1 / nT1$ and $cC2 = nC2 / nT1$. Here, $nT1$ denotes the sample size of the treatment group in the first stage, $nP2$ the sample size of the placebo group in the second stage, etc. The first stage efficacy boundaries are $bTP1e$ for the treatment vs placebo testing problem, and $bTC1e$ for the treatment vs control non-inferiority testing problem. The futility boundaries are denoted by $bTP1f$ and $bTC1f$.

If these parameters are left unspecified or set to NULL, they will be included into the optimization process, otherwise they will be considered boundary constraints. You may also supply quoted expressions as arguments for these parameters to solve a constrained optimization problem. For example, you can supply $cT2 = 1$, $cP2 = \text{quote}(cP1)$, $cC2 = \text{quote}(cC1)$ to ensure that the first and second stage allocation ratios are equal.

The design is optimized with respect to the objective criterion given by the parameter `objective`. The default objective function is described in the Subsection *Optimizing group sequential gold-standard designs* in Section 2 of (Meis et al. 2023). Additionally, this objective includes a term to penalize the maximum sample size of a trial, which can be controlled by the parameter `eta` (default is $\eta=0$).

Designs are calculated to fulfill the following constraints: the family-wise type I error rate is controlled at α under any combination of the two null hypotheses $\mu_T - \mu_P = 0$ and $\mu_T - \mu_C + \Delta = 0$. The power to reject both hypothesis given both alternative hypotheses $\mu_T - \mu_P = \text{alternative_TP}$ and $\mu_T - \mu_C + \Delta = \text{alternative_TC} + \Delta$ is at least $1 - \beta$. Variances are assumed to be given by var_T , var_P and var_C .

If `binding_futility` is TRUE, type I error recycling is used. If `always_both_futility_tests` is TRUE, it is assumed that futility tests for both hypotheses are performed at interim, regardless of whether the treatment vs placebo null hypothesis was successfully rejected. If `always_both_futility_tests` is FALSE, the futility test for the treatment vs. control testing problem only needs to be done if the null for the treatment vs. placebo testing problem was rejected in the first stage.

Value

Design object (a list) with optimized design parameters.

References

Meis J, Pilz M, Herrmann C, Bokelmann B, Rauch G, Kieser M (2023). “Optimization of the two-stage group sequential three-arm gold-standard design for non-inferiority trials.” *Statistics in Medicine*, **42**(4), 536-558. doi:10.1002/sim.9630.

Examples

```
# Should take about 15 seconds.

optimize_design_twostage(
  cT2 = 1,
  cP2 = quote(cP1),
  cC2 = quote(cC1),
  bTP1f = -Inf,
  bTC1f = -Inf,
  beta = 0.2,
  alternative_TP = 0.4,
  alternative_TC = 0,
  Delta = 0.2,
  binding_futility = TRUE,
  lambda = .9,
  kappa = 1,
  nloptr_opts = list(algorithm = "NLOPT_LN_SBPLX", ftol_rel = 1e-01)
)
```

padd_whitespace	<i>Add whitespace padding to string</i>
-----------------	---

Description

Add whitespace padding to string

Usage

```
padd_whitespace(str)
```

Arguments

str a character string

Value

string with whitespace padding until the full console width

pmvnorm_	<i>mvtnorm::pmvnorm, but returns 0 if any lower boundary is larger than any upper boundary</i>
----------	--

Description

mvtnorm::pmvnorm, but returns 0 if any lower boundary is larger than any upper boundary

Usage

```
pmvnorm_(upper, lower, ...)
```

Arguments

upper	the vector of upper limits of length n.
lower	the vector of lower limits of length n.
...	additional parameters passed to pmvnorm .

Value

The evaluated distribution function is returned, if `keepAttr` is true, with attributes

error	estimated absolute error
msg	status message(s).
algorithm	a character string with <code>class(algorithm)</code> .

See Also

[pmvnorm](#)

pmvt_	<i>mvtnorm::pmvt, but returns 0 if any lower boundary is larger than any upper boundary</i>
-------	---

Description

mvtnorm::pmvt, but returns 0 if any lower boundary is larger than any upper boundary

Usage

```
pmvt_(upper, lower, ...)
```

Arguments

upper	the vector of upper limits of length n.
lower	the vector of lower limits of length n.
...	additional parameters passed to pmvt .

Value

The evaluated distribution function is returned, if `keepAttr` is true, with attributes

error	estimated absolute error
msg	status message(s).
algorithm	a character string with <code>class(algorithm)</code> .

See Also

[pmvt](#)

```
print.OneStageGoldStandardDesign
```

Printing method for optimal single-stage goldstandard designs

Description

Printing method for optimal single-stage goldstandard designs

Usage

```
## S3 method for class 'OneStageGoldStandardDesign'
print(x, ...)
```

Arguments

x	An object of class <code>OneStageGoldStandardDesign</code>
...	additional parameters

Value

returns the input x invisibly. This functions is used for its side effects, i.e. printing design characteristics to the screen.

Examples

```
# Should take about 2 second with the chosen accuracy
optimize_design_onestage(
  alpha = .025,
  beta = .2,
  alternative_TP = .4,
  alternative_TC = 0,
  Delta = .2,
  mvnorm_algorithm = mvtnorm::Miwa(steps = 512, checkCorr = FALSE, maxval = 1000),
  nloptr_opts = list(algorithm = "NLOPT_LN_SBPLX", ftol_rel = 1e-03, xtol_abs = 1e-08,
                    xtol_rel = 1e-07, maxeval = 1000, print_level = 0)
)
```

```
print.TwoStageGoldStandardDesign
```

Printing method for optimal two-stage goldstandard designs

Description

Printing method for optimal two-stage goldstandard designs

Usage

```
## S3 method for class 'TwoStageGoldStandardDesign'
print(x, ...)
```

Arguments

x	An object of class TwoStageGoldStandardDesign
...	additional parameters

Value

returns the input x invisibly. This functions is used for its side effects, i.e. printing design characteristics to the screen.

Examples

```
# Should take about 15 seconds.
```

```
optimize_design_twostage(
  cT2 = 1,
  cP2 = quote(cP1),
  cC2 = quote(cC1),
  bTP1f = -Inf,
  bTC1f = -Inf,
  beta = 0.2,
```

```
alternative_TP = 0.4,  
alternative_TC = 0,  
Delta = 0.2,  
binding_futility = TRUE,  
lambda = .9,  
kappa = 1,  
nloptr_opts = list(algorithm = "NLOPT_LN_SBPLX", ftol_rel = 1e-01)  
)
```

Index

`calc_ASN`, [2](#)
`calc_ASNP`, [3](#)
`calc_c`, [3](#)
`calc_conditional_local_rejection_probs`,
[4](#)
`calc_conditional_power`, [4](#)
`calc_cumc`, [5](#)
`calc_cumn`, [5](#)
`calc_final_state_probs`, [6](#)
`calc_gamma`, [6](#)
`calc_local_alphas`, [6](#)
`calc_local_rejection_boundaries`, [7](#)
`calc_mu_vec`, [7](#)
`calc_mu_wo_nT1`, [8](#)
`calc_n_from_c`, [9](#)
`calc_nT1_wrt_bTC2e`, [8](#)
`calc_prob_reject_both`, [9](#)
`calc_prob_reject_both_singlestage`, [10](#)
`calc_Sigma`, [10](#)
`calc_worst_type_I_error`, [11](#)
`character`, [21](#), [22](#)
`conditional_mean`, [11](#)
`conditional_Sigma`, [12](#)

`nloptr`, [15](#), [19](#)

`objective_onestage`, [12](#)
`objective_twostage`, [13](#)
`OptimalGoldstandardDesigns`, [13](#)
`OptimalGoldstandardDesigns-package`
(`OptimalGoldstandardDesigns`),
[13](#)
`optimize_design_onestage`, [14](#)
`optimize_design_twostage`, [16](#)

`padd_whitespace`, [20](#)
`pmvnorm`, [15](#), [18](#), [21](#)
`pmvnorm_`, [21](#)
`pmvt`, [22](#)
`pmvt_`, [21](#)

`print.OneStageGoldStandardDesign`, [22](#)
`print.TwoStageGoldStandardDesign`, [23](#)