Package 'MAMS'

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Type Package

Title Designing Multi-Arm Multi-Stage Studies

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Depends mvtnorm, methods, future, future.apply

Description Designing multi-arm multi-stage studies with (asymptotically) normal endpoints and known variance.

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MAMS *Designing Multi-Arm Multi-Stage Studies*

Description

This package allows to design multi-arm multi-stage (MAMS) studies with asymptotically normal endpoints and known variance. It considers normal, binary, ordinal and time-to-event endpoints in which either the single best treatment or all promising treatments are continued at the interim analyses.

Details

Currently implemented functions are:

- `mams()`: a function allowing to design multi-arm multi-stage studies with normal endpoints,
- `new.bounds()`: a function allowing to update the lower and upper boundaries of a multi-arm multi-stage study, typically initally defined by `mams()`, based on observed sample sizes,
- `mams.sim()`: a function allowing to simulate multi-arm multi-stage studies given chosen boundaries and sample size, and estimates power and expected sample size,
- `stepdown.mams()`: a function allowing to find stopping boundaries for a 2- or 3-stage (step-down) multiple-comparisons-with-control test,
- `stepdown.update()`: a function allowing to update the stopping boundaries of a multi-arm multi-stage study, typically initally defined by `stepdown.mams()`, at an interim analysis as well as allowing for unplanned treatment selection and/or sample-size reassessment,
- `ordinal.mams()`: a function allowing to design multi-arm multi-stage studies with ordinal or binary endpoints,
- `tite.mams()`: a function allowing to design multi-arm multi-stage studies with time-to-event endpoints.

We refer to Jaki et al (2019) for an overview of the package as well as to Magirr et al (2012) and Magirr et al (2014) for theoretical details.

Parallelisation

Since version 2.0.0, **MAMS** relies on the package **future.apply** for parallel computation. The package **future.apply** is part of the **future** parallelisation framework that requires users to define their parallelisation strategy by means of the function `future::plan()`. This function takes several options like, for example, `sequential` (default strategy corresponding to a computation without parallelisation), `multicore` (using separate forked **R** processes, available to unix/osx users) and `multisession` (using separate **R** sessions, available to all users). We refer to Bengtsson H. (2022) for an overview of the **future** framework.

Note that, for the functions of **MAMS** to be available to workers defined by `future::plan()`, **MAMS** has to be installed at a location available under `.libPaths` (by default, **R** installs packages in the directory corresponding to the first element of `.libPaths`).

Reproducibility

Results of the **MAMS** package for studies involving more than 2 stages are seed-dependent (as the Gaussian quadrature integration of the multivariate normal distribution relies on probabilities estimated by means of the randomised Quasi-Monte-Carlo procedure of Genz and Bretz in `mvtnorm::pmvnorm()`).

Results are reproducible if a seed is set before the evaluation of a function of the **MAMS** package (typically by means of the function `set.seed`).

When `parallel=TRUE`, the **future** package assigns independent streams of L'Ecuyer pseudo-random numbers to each parallelised task, allowing results to be reproducible when a seed is set, even when using a different parallelisation strategy and/or a different number of workers. When `parallel=FALSE`, the random number generation is handled by base **R** directly instead of by the **future** package, so that, if the number of stages is larger than 2, evaluations using the same seed will not lead to the same exact results with `parallel=FALSE` and `parallel=TRUE`.

Author(s)

Thomas Jaki, Dominique-Laurent Couturier, Dominic Magirr and Philip Pallmann

Maintainer: Thomas Jaki <thomas.jaki@pm.me>.

References

Jaki T., Pallmann P. and Magirr D. (2019), *The R Package MAMS for Designing Multi-Arm Multi-Stage Clinical Trials*, **Journal of Statistical Software**, 88(4), 1-25. Link: doi: 10.18637/jss.v088.i04

Magirr D., Jaki T. and Whitehead J. (2012), *A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection*, **Biometrika**, 99(2), 494-501. Link: doi: 10.1093/biomet/ass002

Magirr D., Stallard N. and Jaki T. (2014), *Flexible sequential designs for multi-arm clinical trials*, **Statistics in Medicine**, 33(19), 3269-3279. Link: doi: 10.1002/sim.6183

Bengtsson H. (2022), *A Unifying Framework for Parallel and Distributed Processing in R using Futures*, to appear in **The R Journal**. Link: accepted version

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`mams` *Function to design multi-arm multi-stage studies with normal endpoints*

Description

The function determines the boundaries of a multi-arm multi-stage study for a given boundary shape and finds the required number of subjects.

Usage

```
mams(K=4, J=2, alpha=0.05, power=0.9, r=1:2, r0=1:2, p=0.75, p0=0.5,
     delta=NULL, delta0=NULL, sd=NULL, ushape="obf", lshape="fixed",
     ufix=NULL, lfix=0, nstart=1, nstop=NULL, sample.size=TRUE, N=20,
     type="normal", parallel=TRUE, print=TRUE)
```

Arguments

K	Number of experimental treatments (default=4).
J	Number of stages (default=2).
alpha	One-sided familywise error rate (default=0.05).
power	Desired power (default=0.9).
r	Vector of allocation ratios (default=1:2).
r0	Vector ratio on control (default=1:2).
p	Interesting treatment effect on the probability scale. See Details (default=0.75).
p0	Uninteresting treatment effect on the probability scale. See Details (default=0.5).
delta	Interesting treatment effect on the traditional scale. See Details (default=NULL).
delta0	Uninteresting treatment effect on the traditional scale. See Details (default=NULL).
sd	Standard deviation, assumed to be known. See Details (default=NULL).
ushape	Shape of upper boundary. Either a function specifying the shape or one of "pocock", "obf" (the default), "triangular" and "fixed". See details.
lshape	Shape of lower boundary. Either a function specifying the shape or one of "pocock", "obf", "triangular" and "fixed" (the default). See details.
ufix	Fixed upper boundary (default=NULL). Only used if shape="fixed".
lfix	Fixed lower boundary (default=0). Only used if shape="fixed".
nstart	Starting point for finding the sample size (default=1).
nstop	Stopping point for finding the sample size (default=NULL).
sample.size	Logical if sample size should be found as well (default=TRUE).
N	Number of quadrature points per dimension in the outer integral (default=20).
type	Will be changed automatically by the wrappers tite.mams() (to "tite") and ordinal.mams() (to "ordinal") to customise the output.
parallel	if TRUE (default), allows parallelisation of the computation via a user-defined strategy specified by means of the function future::plan(). If not set differently, the default strategy is sequential, which corresponds to a computation without parallelisation.
print	if TRUE (default), indicate at which stage the computation is.

Details

This function finds the boundaries and sample size of a multi-arm multi-stage study with K active treatments plus control in which all promising treatments are continued at interim analyses as described in Magirr et al (2012). At each interim analysis the test statistics are compared to the lower (futility) bound and any treatment whose corresponding test statistic falls below that bound is discontinued. Similarly if any test statistic exceeds the upper (efficacy) bound the null hypothesis corresponding to that treatment can be rejected and superiority of that treatment over control claimed. At the same time the study is stopped. If at least one test statistic exceeds the lower bound and none exceeds the upper bound the study is continued and further patients are recruited to all remaining experimental treatments plus control.

The design is found under the least favorable configuration, which requires an interesting treatment effect `p` that if present we would like to find with high probability and an uninteresting effect `p0`. Both `p` and `p0` are parameterized as $P(X_k > X_0) = p$, that is the probability of a randomly selected person on treatment k observing a better outcome than a random person on control. For `p=0.5` the experimental treatment and control perform equally well. The advantage of this paramterization is that no knowledge about the variance is required. To convert traditional effect sizes, δ to this format use $p = \Phi(\frac{\delta}{\sqrt{2}\sigma})$. Alternatively, the interesting and uninteresting effect size can also be specified directly on the traditional scale of `delta` and `delta` with an additional specification of the standard deviation `sd` assumed to be known.

The shape of the boundaries (`ushape`, `lshape`) are either using the predefined shapes following Pocock (1977), O'Brien & Fleming (1979) or the triangular Test (Whitehead, 1997) using options `"pocock"`, `"obf"` or `"triangular"` respectively, are constant (option `"fixed"`) or supplied in as a function. If a function is passed it should require exactly one argument specifying the number of stages and return a vector of the same length. The lower boundary shape is required to be non-decreasing while the upper boundary shape needs to be non-increasing. If a fixed lower boundary is used, `lfix` must be smaller than $\Phi^{-1}(1-\alpha)/2$ to ensure that it is smaller than the upper boundary.

The default starting point for finding the sample size is `nstart=1`, and the default point where the search is stopped (when `nstop=NULL`) is 3 times the sample size of the corresponding fixed single-stage design.

Computation of designs with more than four stages are very time consuming and not advised. The parameter `sample.size` controls whether the required sample size is computed as well. Setting to `FALSE` approximately halves the compuation time.

For designs with more than 2 stages, parallelisation of the computation by means of the packages `future` and `future.apply` lead to decreased computation times when choosing a parallelisation strategy like, for example, `multicore` (using separate forked **R** processes, available to unix/osx users) or `multisession` (using separate **R** sessions, available to all users) (refer to `future::plan()` for detail).

Value

An object of the class MAMS containing the following components:

`l`	Lower boundary.
`u`	Upper boundary.
`n`	Sample size on control in stage 1.
`N`	Maximum total sample size.
`K`	Number of experimental treatments.
`J`	Number of stages in the trial.
`alpha`	Familywise error rate.
`alpha.star`	Cumulative familywise error rate spent by each analysis.

power	Power under least favorable configuration.
rMat	Matrix of allocation ratios. First row corresponds to control while subsequent rows are for the experimental treatments.

Author(s)

Thomas Jaki, Dominic Magirr and Dominique-Laurent Couturier

References

Jaki T., Pallmann P. and Magirr D. (2019), *The R Package MAMS for Designing Multi-Arm Multi-Stage Clinical Trials*, **Journal of Statistical Software**, 88(4), 1-25. Link: doi: 10.18637/jss.v088.i04

Magirr D., Jaki T. and Whitehead J. (2012), *A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection*, **Biometrika**, 99(2), 494-501. Link: doi: 10.1093/biomet/ass002

Pocock S.J. (1977), *Group sequential methods in the design and analysis of clinical trials*, **Biometrika**, 64(2), 191-199.

O'Brien P.C., Fleming T.R. (1979), *A multiple testing procedure for clinical trials*, **Biometrics**, 35(3), 549-556.

Whitehead J. (1997), *The Design and Analysis of Sequential Clinical Trials*, **Wiley**: Chichester, UK.

See Also

print.MAMS, summary.MAMS, plot.MAMS, new.bounds, ordinal.mams, tite.mams, MAMS.

Examples

```
## A fixed sample (single stage) design specified on the p scale
mams(K=4, J=1, alpha=0.05, power=0.9, r=1, r0=1, p=0.65, p0=0.55)

## The same design specified on the delta scale
mams(K=4, J=1, alpha=0.05, power=0.9, r=1, r0=1, p=NULL, p0=NULL,
     delta=0.545, delta0=0.178, sd=1)

## An example in Table 1 of Magirr et al (2012)
# 2-stage design with O'Brien & Fleming efficacy and zero futility boundary
mams(K=4, J=2, alpha=0.05, power=0.9, r=1:2, r0=1:2, p=0.65, p0=0.55,
     ushape="obf", lshape="fixed", lfix=0, nstart=40)

# Note that these examples may take a few minutes to run

## 3-stage design with Triangular efficacy and futility boundary
mams(K=4, J=3, alpha=0.05, power=0.9, r=1:3, r0=1:3, p=0.65, p0=0.55,
     ushape="triangular", lshape="triangular", nstart=30)
```

```
## Example of a custom boundary function without sample size evaluation
mams(K=6, J=3, alpha=0.05, power=0.9, r=1:3, r0=1:3, p=0.7, p0=0.5,
     ushape=function(x)return(x:1), lshape="fixed", lfix=0,
     sample.size=FALSE)

## Different allocation ratios between control and experimental treatments.
## Twice as many patients are randomized to control at each stage.
mams(K=4, J=2, alpha=0.05, power=0.9, r=1:2, r0=c(2, 4), p=0.65, p0=0.55,
     ushape="obf", lshape="fixed", lfix=0, nstart=30)

##
## example considering different parallelisation strategies
##


# parallel = FALSE (future framework not used)
set.seed(1)
system.time(
print(mams(K=4, J=3, alpha=0.05, power=0.9, r=1:3, r0=1:3, p=0.65, p0=0.55,
     ushape="triangular", lshape="triangular", nstart=30, parallel = FALSE))
)
# parallel = TRUE (default) with default strategy (sequential computation)
plan(sequential)
set.seed(1)
system.time(
print(mams(K=4, J=3, alpha=0.05, power=0.9, r=1:3, r0=1:3, p=0.65, p0=0.55,
     ushape="triangular", lshape="triangular", nstart=30))
)
# parallel = TRUE(default) with multisession strategy (parallel computation)
plan(multisession)
set.seed(1)
system.time(
print(mams(K=4, J=3, alpha=0.05, power=0.9, r=1:3, r0=1:3, p=0.65, p0=0.55,
     ushape="triangular", lshape="triangular", nstart=30))
)
plan("default")
```

`mams.sim` *Simulating multi-arm multi-stage designs*

Description

The function simulates multi-arm multi-stage designs and estimates power and expected sample size.

Usage

```
mams.sim(nsim=10000, nMat=matrix(c(44, 88), nrow=2, ncol=5),
         u=c(3.068, 2.169), l=c(0.000, 2.169),
         pv=rep(0.5, 4), deltav=NULL, sd=NULL, ptest=1, parallel=TRUE)
```

Arguments

nsim	Number of simulations (default=10000).
nMat	Jx(K+1) dimensional matrix of observed/expected sample sizes. Rows correspond to stages and columns to arms. First column is control (default: 2x5 matrix with 44 subjects per stage and arm).
u	Vector of previously used upper boundaries (default=NULL).
l	Vector of previously used upper boundaries (default=NULL).
pv	Vector of size K of true treatment effects on the probability scale. See Details (default=rep(0.5, 4)).
deltav	Vector of size K of true treatment effects on the traditional scale. See Details (default=NULL).
sd	Standard deviation. See Details (default=NULL).
ptest	Vector of treatment numbers for determining power. For example, c(1, 2) will count rejections of one or both hypotheses for testing treatments 1 and 2 against control.
parallel	if TRUE (default), allows parallelisation of the computation via a user-defined strategy specified by means of the function future::plan(). If not set differently, the default strategy is sequential, which corresponds to a computation without parallelisation.

Details

This function simulates multi-arm multi-stage studies for a given matrix of sample sizes and boundaries given by the vectors u and l. The effect difference between each experimental treatment and control is given by pv and is parameterized as $P(X_k > X_0) = p$. That is the probability of a randomly selected person on treatment k observing a better outcome than a random person on control. For pv=rep(0.5,4 the experimental treatments and control perform equally well (i.e. the global null hypothesis is true). The advantage of this paramterization is that no knowledge about the variance is required. To convert traditional effect sizes, δ to this format use $p = \Phi(\frac{\delta}{\sqrt{2}\sigma})$. Alternatively, the effect size can also be specified directly on the traditional scale of deltav with an additional specification of the standard deviation sd.

The function returns the probability of rejecting any hypothesis (typeI), the power to reject the first hypothesis when the first treatment has the largest estimated effect, the proportion of rejections of the hypothesis specified by ptest (prop.rej) as well as the expected sample size.

Value

An object of the class MAMS.sim containing the following components:

```
res$typeI <- mean(unlist(reps["rej",]))

res$power <- mean(unlist(reps["pow",]))
```

```
res$prop.rej <- rej/nsim

res$exss <- mean(unlist(reps["ess",]))
```

`l`	Lower boundary.
`u`	Upper boundary.
`n`	Sample size on control in stage 1.
`N`	Maximum total sample size.
`K`	Number of experimental treatments.
`J`	Number of stages in the trial.
`rMat`	Matrix of allocation ratios. First row corresponds to control and second row to experimental treatments.
`nsim`	Number of simulation runs.
`typeI`	The proportion any hypothesis is rejected.
`power`	The proportion the first hypothesis is rejected and the corresponding test statistic is largest.
`ptest`	The vector `ptest`.
`prop.rej`	The proportion of times at least one of the hypothesis specified by `ptest` is rejected.
`exss`	The expected sample size.

Author(s)

Thomas Jaki, Dominic Magirr and Dominique-Laurent Couturier

References

Jaki T., Pallmann P. and Magirr D. (2019), *The R Package MAMS for Designing Multi-Arm Multi-Stage Clinical Trials*, **Journal of Statistical Software**, 88(4), 1-25. Link: doi: 10.18637/jss.v088.i04

Magirr D., Jaki T. and Whitehead J. (2012), *A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection*, **Biometrika**, 99(2), 494-501. Link: doi: 10.1093/biomet/ass002

See Also

`print.MAMS.sim`, `summary.MAMS.sim`, `mams`, `MAMS`.

Examples

```
# Note that some of these examples may take a few minutes to run

# 2-stage design with O'Brien & Fleming efficacy and zero futility boundary with
# equal sample size per arm and stage. Design can be found using
# mams(K=4, J=2, alpha=0.05, power=0.9, r=1:2, r0=1:2, ushape="obf", lshape="fixed",
#      lfix=0, p=0.65, p0=0.55)
```

```
# under global null hypothesis (using the pv scale)
mams.sim(nsim=10000, nMat=matrix(c(44, 88), nrow=2, ncol=5), u=c(3.068, 2.169),
         l=c(0.000, 2.169), pv=rep(0.5, 4), ptest=1)

# under global null hypothesis (using the deltav scale)
mams.sim(nsim=10000, nMat=matrix(c(44, 88), nrow=2, ncol=5), u=c(3.068, 2.169),
         l=c(0.000, 2.169), pv=NULL, deltav=rep(0, 4), sd=1, ptest=1)

# under LFC
mams.sim(nsim=10000, nMat=matrix(c(44, 88), nrow=2, ncol=5), u=c(3.068, 2.169),
         l=c(0.000, 2.169), pv=c(0.65, 0.55, 0.55, 0.55), ptest=1:2)

# when all treatments doing similarly well
mams.sim(nsim=10000, nMat=matrix(c(44, 88), nrow=2, ncol=5), u=c(3.068, 2.169),
         l=c(0.000, 2.169), pv=c(0.63, 0.62, 0.60, 0.61), ptest=4)

##
## example considering different parallelisation strategies
##

# parallel = FALSE (future framework not used)
set.seed(1)
system.time(
print(mams.sim(nsim=25000, nMat=matrix(c(44, 88), nrow=2, ncol=5), u=c(3.068, 2.169),
         l=c(0.000, 2.169), pv=c(0.65, 0.55, 0.55, 0.55), ptest=1:2, parallel=FALSE))
)
# parallel = TRUE (default) with default strategy (sequential computation)
plan(sequential)
set.seed(1)
system.time(
print(mams.sim(nsim=25000, nMat=matrix(c(44, 88), nrow=2, ncol=5), u=c(3.068, 2.169),
         l=c(0.000, 2.169), pv=c(0.65, 0.55, 0.55, 0.55), ptest=1:2))
)
# parallel = TRUE (default) with multisession strategy (parallel computation)
plan(multisession)
set.seed(1)
system.time(
print(mams.sim(nsim=25000, nMat=matrix(c(44, 88), nrow=2, ncol=5), u=c(3.068, 2.169),
         l=c(0.000, 2.169), pv=c(0.65, 0.55, 0.55, 0.55), ptest=1:2))
)
plan("default")
```

MAMSNews *Shows changes and news*

Description

Functions showing changes since previous versions.

Usage

```
MAMSNews()
```

Details

Displays the changes and news given in the NEWS file of the package.

Value

Screen output.

Author(s)

Thomas Jaki

Examples

```
MAMSNews()
```

---

new.bounds *Function to update boundaries based on observed sample sizes*

Description

The function determines updated boundaries of a multi-arm multi-stage study based on observed number of observations per arm.

Usage

```
new.bounds(K=3, J=2, alpha=0.05, nMat=matrix(c(10, 20), nrow=2, ncol=4),
           u=NULL, l=NULL, ushape="obf", lshape="fixed", ufix=NULL,
           lfix=0, N=20, parallel=TRUE, print=TRUE)
```

Arguments

K	Number of experimental treatments (default=3).
J	Number of stages (default=2).
alpha	One-sided familywise error rate (default=0.05).
nMat	Jx(K+1) dimensional matrix of observed/expected sample sizes. Rows correspond to stages and columns to arms. First column is control (default: 2x4 matrix with 10 subjects per stage and arm).
u	Vector of previously used upper boundaries (default=NULL).
l	Vector of previously used upper boundaries (default=NULL).
ushape	Shape of upper boundary. Either a function specifying the shape or one of "pocock", "obf" (the default), "triangular" and "fixed". See details.

lshape	Shape of lower boundary. Either a function specifying the shape or one of "pocock", "obf", "triangular" and "fixed" (the default). See details.
ufix	Fixed upper boundary (default=NULL). Only used if shape="fixed".
lfix	Fixed lower boundary (default=0). Only used if shape="fixed".
N	Number of quadrature points per dimension in the outer integral (default=20).
parallel	if TRUE (default), allows parallelisation of the computation via a user-defined strategy specified by means of the function future::plan(). If not set differently, the default strategy is sequential, which corresponds to a computation without parallelisation.
print	if TRUE (default), indicate at which stage the computation is.

Details

This function finds the boundaries for a given matrix of sample sizes in multi-arm multi-stage study with K active treatments plus control. The vectors u and l are the boundaries used so far while u.shape and l.shape specify the shape to the boundaries for the remaining analysis. By specifying u and l as NULL, a design using only the shapes given by ushape and lshape can be found for any sample sizes per stage and arm.

The shape of the boundaries (ushape, lshape) are either using the predefined shapes following Pocock (1977), O'Brien & Fleming (1979) or the triangular Test (Whitehead, 1997) using options "pocock", "obf" or "triangular" respectively, are constant (option "fixed") or supplied in as a function. If a function is passed it should require exactly one argument specifying the number of stages and return a vector of the same length. The lower boundary shape is required to be non-decreasing while the upper boundary shape needs to be non-increasing. If a fixed lower boundary is used, lfix must be smaller than $\Phi^{-1}(1-\alpha)/2$ to ensure that it is smaller than the upper boundary.

Value

An object of the class MAMS containing the following components:

l	Lower boundary.
u	Upper boundary.
n	Sample size on control in stage 1.
N	Maximum total sample size.
K	Number of experimental treatments.
J	Number of stages in the trial.
alpha	Familywise error rate.
power	Power under least favorable configuration.
rMat	Matrix of allocation ratios. First row corresponds to control and second row to experimental treatments.

Author(s)

Thomas Jaki, Dominic Magirr and Dominique-Laurent Couturier

References

Jaki T., Pallmann P. and Magirr D. (2019), *The R Package MAMS for Designing Multi-Arm Multi-Stage Clinical Trials*, **Journal of Statistical Software**, 88(4), 1-25. Link: doi: 10.18637/jss.v088.i04

Magirr D., Jaki T. and Whitehead J. (2012), *A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection*, **Biometrika**, 99(2), 494-501. Link: doi: 10.1093/biomet/ass002

Magirr D., Stallard N. and Jaki T. (2014), *Flexible sequential designs for multi-arm clinical trials*, **Statistics in Medicine**, 33(19), 3269-3279. Link: doi: 10.1002/sim.6183

Pocock S.J. (1977), *Group sequential methods in the design and analysis of clinical trials*, **Biometrika**, 64(2), 191-199.

O'Brien P.C., Fleming T.R. (1979), *A multiple testing procedure for clinical trials*, **Biometrics**, 35(3), 549-556.

Whitehead J. (1997), *The Design and Analysis of Sequential Clinical Trials*, **Wiley**: Chichester, UK.

See Also

`print.MAMS`, `summary.MAMS`, `plot.MAMS`, `mams`, `MAMS`.

Examples

```
# Note that some of these examples may take a few minutes to run

# 2-stage design with O'Brien & Fleming efficacy and zero futility boundary with
# equal sample size per arm and stage. Results are equivalent to using
# mams(K=4, J=2, alpha=0.05, power=0.9, r=1:2, r0=1:2, ushape="obf", lshape="fixed",
#      lfix=0, sample.size=FALSE)

new.bounds(K=4, J=2, alpha=0.05, nMat=matrix(c(10, 20), nrow=2, ncol=5), u=NULL, l=NULL,
           ushape="obf", lshape="fixed", lfix=0)

# A 2-stage design that was designed to use an O'Brien & Fleming efficacy and
# zero futility boundary with equal sample size per arm and stage (n=14).
# The observed sample size after stage one are 10, 10, 18, 10, 13 for each arm
# while the original upper bounds used are (3.068, 2.169) for stage 1.
# The updated bounds are (3.068, 2.167).

new.bounds(K=4, J=2, alpha=0.05,
           nMat=matrix(c(10, 28, 10, 28, 18, 28, 10, 28, 13, 28), nrow=2, ncol=5),
           u=3.068, l=0, ushape="obf", lshape="fixed", lfix=0)

# same using parallelisation via separate R sessions running in the background
```

```
future::plan(multisession)
new.bounds(K=4, J=2, alpha=0.05,
           nMat=matrix(c(10, 28, 10, 28, 18, 28, 10, 28, 13, 28), nrow=2, ncol=5),
           u=3.068, l=0, ushape="obf", lshape="fixed", lfix=0)
future::plan("default")
```

`ordinal.mams` *Function to design multi-arm multi-stage studies with ordinal or binary endpoints*

Description

The function determines (approximately) the boundaries of a multi-arm multi-stage study with ordinal or binary endpoints for a given boundary shape and finds the required number of subjects.

Usage

```
ordinal.mams(prob=c(0.35, 0.4, 0.25), or=2, or0=1.2, K=4, J=2, alpha=0.05,
     power=0.9, r=1:2, r0=1:2, ushape="obf", lshape="fixed", ufix=NULL,
     lfix=0, nstart=1, nstop=NULL, sample.size=TRUE, N=20,
     parallel=TRUE, print=TRUE)
```

Arguments

`prob`	Vector of expected probabilities of falling into each category under control conditions. The elements must sum up to one (default=`c(0.35, 0.4, 0.25)`).
`or`	Interesting treatment effect on the scale of odds ratios (default=`2`).
`or0`	Uninteresting treatment effect on the scale of odds ratios (default=`1.2`).
`K`	Number of experimental treatments (default=`4`).
`J`	Number of stages (default=`2`).
`alpha`	One-sided familywise error rate (default=`0.05`).
`power`	Desired power (default=`0.9`).
`r`	Vector of allocation ratios (default=`1:2`).
`r0`	Vector ratio on control (default=`1:2`).
`ushape`	Shape of upper boundary. Either a function specifying the shape or one of `"pocock"`, `"obf"` (the default), `"triangular"` and `"fixed"`.
`lshape`	Shape of lower boundary. Either a function specifying the shape or one of `"pocock"`, `"obf"`, `"triangular"` and `"fixed"` (the default).
`ufix`	Fixed upper boundary (default=`NULL`). Only used if `shape="fixed"`.
`lfix`	Fixed lower boundary (default=`0`). Only used if `shape="fixed"`.
`nstart`	Starting point for finding the sample size (default=`1`).
`nstop`	Stopping point for finding the sample size (default=`NULL`).

sample.size	Logical if sample size should be found as well (default=TRUE).
N	Number of quadrature points per dimension in the outer integral (default=20).
parallel	if TRUE (default), allows parallelisation of the computation via a user-defined strategy specified by means of the function future::plan(). If not set differently, the default strategy is sequential, which corresponds to a computation without parallelisation.
print	if TRUE (default), indicate at which stage the computation is.

Details

This function finds the (approximate) boundaries and sample size of a multi-arm multi-stage study with ordinal or binary endpoints with K active treatments plus control in which all promising treatments are continued at interim analyses as described in Magirr et al (2012). It is a wrapper around the basic mams function to facilitate its use with ordinal and binary endpoints, following ideas of Whitehead & Jaki (2009) and Jaki & Magirr (2013). For a binary endpoint the vector prob has only two elements (success/failure, yes/no, etc.). See mams for further details on the basic methodology.

Value

An object of the class MAMS containing the following components:

l	Lower boundary.
u	Upper boundary.
n	Sample size on control in stage 1.
N	Maximum total sample size.
K	Number of experimental treatments.
J	Number of stages in the trial.
alpha	Familywise error rate.
alpha.star	Cumulative familywise error rate spent by each analysis.
power	Power under least favorable configuration.
rMat	Matrix of allocation ratios. First row corresponds to control while subsequent rows are for the experimental treatments.

Author(s)

Philip Pallmann

References

Jaki T., Pallmann P. and Magirr D. (2019), *The R Package MAMS for Designing Multi-Arm Multi-Stage Clinical Trials*, **Journal of Statistical Software**, 88(4), 1-25. Link: doi: 10.18637/jss.v088.i04

Magirr D., Jaki T. and Whitehead J. (2012), *A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection*, **Biometrika**, 99(2), 494-501. Link: doi: 10.1093/biomet/ass002

Magirr D., Stallard N. and Jaki T. (2014), *Flexible sequential designs for multi-arm clinical trials*, **Statistics in Medicine**, 33(19), 3269-3279. Link: doi: 10.1002/sim.6183

Pocock S.J. (1977), *Group sequential methods in the design and analysis of clinical trials*, **Biometrika**, 64(2), 191-199.

O'Brien P.C., Fleming T.R. (1979), *A multiple testing procedure for clinical trials*, **Biometrics**, 35(3), 549-556.

Whitehead J. (1997), *The Design and Analysis of Sequential Clinical Trials*, **Wiley**: Chichester, UK.

See Also

print.MAMS, summary.MAMS, plot.MAMS, mams, MAMS.

Examples

```
## An example based on the example in Whitehead & Jaki (2009)
# 2-stage design with triangular efficacy and futility boundaries
prob <- c(0.075, 0.182, 0.319, 0.243, 0.015, 0.166)
ordinal.mams(prob=prob, or=3.06, or0=1.32, K=3, J=2, alpha=0.05,
                 power=0.9, r=1:2, r0=1:2, ushape="triangular",
                 lshape="triangular")
# same example with parallelisation via separate R sessions running in the background
future::plan(multisession)
ordinal.mams(prob=prob, or=3.06, or0=1.32, K=3, J=2, alpha=0.05,
                 power=0.9, r=1:2, r0=1:2, ushape="triangular",
                 lshape="triangular", parallel=TRUE)
future::plan("default")
```

---

plot *Different generic functions for class MAMS.*

Description

Generic functions for summarizing an object of class MAMS.

Usage

```
## S3 method for class 'MAMS'
print(x, digits=max(3, getOption("digits") - 4), ...)

## S3 method for class 'MAMS'
summary(object, digits=max(3, getOption("digits") - 4), ...)

## S3 method for class 'MAMS'
```

```
plot(x, col=NULL, pch=NULL, lty=NULL, main=NULL, xlab="Analysis",
     ylab="Test statistic", ylim=NULL, type=NULL, las=1, ...)

## S3 method for class 'MAMS.sim'
print(x, digits=max(3, getOption("digits") - 4), ...)

## S3 method for class 'MAMS.sim'
summary(object, digits=max(3, getOption("digits") - 4), ...)

## S3 method for class 'MAMS.stepdown'
print(x, digits=max(3, getOption("digits") - 4), ...)

## S3 method for class 'MAMS.stepdown'
summary(object, digits=max(3, getOption("digits") - 4), ...)

## S3 method for class 'MAMS.stepdown'
plot(x, col=NULL, pch=NULL, lty=NULL, main=NULL, xlab="Analysis",
     ylab="Test statistic", ylim=NULL, type=NULL, bty="n", las=1, ...)
```

Arguments

x	An output object of class MAMS.
digits	Number of significant digits to be printed.
object	An output object of class MAMS.
col	A specification for the default plotting color (default=NULL). See par for more details.
pch	Either an integer specifying a symbol or a single character to be used as the default in plotting points (default=NULL). See par for more details.
lty	A specification for the default line type to be used between analyses (default=NULL). Setting to zero supresses ploting of the lines. See par for more details.
main	An overall title for the plot (default=NULL).
xlab	A title for the x axis (default="Analysis").
ylab	A title for the y axis (default="Test statistic").
ylim	Numeric vector of length 2, giving the y coordinates range (default=NULL).
type	Type of plot to be used (default=NULL). See plot for more details.
bty	Should a box be drawn around the legend? The default "n" does not draw a box, the alternative option "o" does.
las	A specification of the axis labeling style. The default 1 ensures the labels are always horizontal. See ?par for details.
...	Further (graphical) arguments to be passed to methods.

Details

print.MAMS produces a summary of an object from class MAMS including boundaries and requires sample size if initially requested.

`summary.MAMS` produces same output as `print.MAMS`.

`plot.MAMS` produces as plot of the boundaries.

`print.MAMS.sim` produces a summary of an object from class MAMS.sim including type-I-error and expected sample size.

`summary.MAMS.sim` produces same output as `print.MAMS.sim`.

`print.MAMS.stepdown` produces a summary of an object from class MAMS including boundaries and requires sample size if initially requested.

`summary.MAMS.stepdown` produces same output as `print.stepdown.mams`.

`plot.MAMS.stepdown` produces a plot of the boundaries. When used with `stepdown.update`, pluses indicate observed values of test statistics.

Value

Screen or graphics output.

Author(s)

Thomas Jaki, Dominic Magirr, Philip Pallmann

References

Magirr D, Jaki T, Whitehead J (2012) A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection. Biometrika, 99(2), 494-501.

Stallard N, Todd S (2003) Sequential designs for phase III clinical trials incorporating treatment selection. Statistics in Medicine, 22(5), 689-703.

Magirr D, Stallard N, Jaki T (2014) Flexible sequential designs for multi-arm clinical trials. Statistics in Medicine, 33(19), 3269-3279.

See Also

`mams`, `stepdown.mams`, `MAMS`.

Examples

```
# 2-stage design with triangular boundaries
res <- mams(K=4, J=2, alpha=0.05, power=0.9, r=1:2, r0=1:2, p=0.65, p0=0.55,
            ushape="triangular", lshape="triangular", nstart=30)

print(res)
summary(res)
```

```
plot(res)

res <- mams.sim(nsim=10000, nMat=matrix(c(44, 88), nrow=2, ncol=5), u=c(3.068, 2.169),
                l=c(0.000, 2.169), pv=c(0.65, 0.55, 0.55, 0.55), ptest=c(1:2, 4))

print(res)

# 2-stage 3-treatments versus control design, all promising treatments are selected:
res <- stepdown.mams(nMat=matrix(c(10, 20), nrow=2, ncol=4),
                     alpha.star=c(0.01, 0.05), lb=0,
                     selection="all.promising")

print(res)
summary(res)
plot(res)
```

`stepdown.mams` *Function to find stopping boundaries for a 2- or 3-stage (step-down) multiple-comparisons-with-control test.*

Description

The function determines stopping boundaries for all intersection hypothesis tests in a multi-arm multi-stage study, given the amount of alpha (familywise error rate) to be spent at each analysis.

Usage

```
stepdown.mams(nMat=matrix(c(10, 20), nrow=2, ncol=4),
              alpha.star=c(0.01, 0.025), lb=0,
              selection="all.promising")
```

Arguments

`nMat`	Matrix containing the cumulative sample sizes in each treatment arm (columns: control, trt 1, . . . , trt K), at each analysis (rows). The number of analyses must be either 2 or 3 (default=matrix(c(10, 20), nrow=2, ncol=4)).
`alpha.star`	Cumulative familywise error rate to be spent at each analysis (default=c(0.01, 0.025)).
`lb`	Fixed lower boundary (default=0).
`selection`	How are treatments selected for the next stage? Using the default "all.promising" method, all treatments with a test statistic exceeding the lower boundary are taken forward to the next stage. If "select.best", only the treatment with the largest statistic may be selected for future stages. (default="all.promising").

Details

The function implements the methods described in Magirr et al (2014) to find individual boundaries for all intersection hypotheses.

Value

An object of the class MAMS.stepdown containing the following components:

`l`	Lower boundaries.
`u`	Upper boundaries.
`nMat`	Cumulative sample sizes on each treatment arm.
`K`	Number of experimental treatments.
`J`	Number of stages in the trial.
`alpha.star`	Cumulative familywise error rate spent at each analysis.
`selection`	Pre-specified method of treatment selection.
`zscores`	A list containing the observed test statistics at analyses so far (at the design stage this is NULL).
`selected.trts`	A list containing the treatments selected for each stage.

Author(s)

Dominic Magirr

References

Jaki T., Pallmann P. and Magirr D. (2019), *The R Package MAMS for Designing Multi-Arm Multi-Stage Clinical Trials*, **Journal of Statistical Software**, 88(4), 1-25. Link: doi: 10.18637/jss.v088.i04

Magirr D., Jaki T. and Whitehead J. (2012), *A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection*, **Biometrika**, 99(2), 494-501. Link: doi: 10.1093/biomet/ass002

Magirr D., Stallard N. and Jaki T. (2014), *Flexible sequential designs for multi-arm clinical trials*, **Statistics in Medicine**, 33(19), 3269-3279. Link: doi: 10.1002/sim.6183

Stallard N. and Todd S. (2003), *Sequential designs for phase III clinical trials incorporating treatment selection*, **Statistics in Medicine**, 22(5), 689-703.

See Also

`print.MAMS.stepdown`, `summary.MAMS.stepdown`, `plot.MAMS.stepdown`, `stepdown.update`, `MAMS`.

Examples

```
# Note that some of these examples may take a few minutes to run

# 2-stage 3-treatments versus control design, all promising treatments are selected:
stepdown.mams(nMat=matrix(c(10, 20), nrow=2, ncol=4),
              alpha.star=c(0.01, 0.05), lb=0,
              selection="all.promising")
```

```
# select the best treatment after the first stage:
stepdown.mams(nMat=matrix(c(10, 20), nrow=2, ncol=4),
              alpha.star=c(0.01, 0.05), lb=0,
              selection="select.best")

# 3 stages and unequal randomization:
stepdown.mams(nMat=matrix(c(20, 40, 60, rep(c(10, 20, 30), 3)), nrow=3, ncol=4),
              alpha.star=c(0.01, 0.025, 0.05), lb=c(0, 0.75),
              selection="all.promising")
```

`stepdown.update` *Update the stopping boundaries of multi-arm multi-stage study at an interim analysis, allowing for unplanned treatment selection and/or sample-size reassessment.*

Description

Function to update a planned multi-arm multi-stage design to account for unplanned adaptations.

Usage

```
stepdown.update(current.mams=stepdown.mams(), nobs=NULL,
                zscores=NULL, selected.trts=NULL, nfuture=NULL)
```

Arguments

`current.mams`	The planned step-down MAMS design prior to the current interim analysis (=`defaultstepdown.mams()`).
`nobs`	Cumulative sample sizes observed on each treatment arm up to and including the current interim analysis.
`zscores`	Observed vector of test statistics at the current interim analysis.
`selected.trts`	The set of experimental treatments to be taken forward to the next stage of testing. This argument should be omitted at the final analysis.
`nfuture`	A matrix of future cumulative sample sizes. The number of rows must be equal to the originally planned number of stages (2 or 3) minus the number of stages already observed. The number of columns must be equal to the number of treatment arms (default=`NULL`).

Details

The function implements the ideas described in Magirr et al. (2014) to update a design according to unplanned design modifications. It takes as input the planned multi-arm multi-stage design prior to the interim analysis, together with the actually observed cumulative sample sizes and test statistics. Treatments to be included in future stages, as well as future sample sizes, can be chosen without following pre-specified rules. The output is a new multi-arm multi-stage design for the remaining stages such that the familywise error remains controlled at the pre-specified level.

Value

An object of the class MAMS.stepdown containing the following components:

`l`	Lower boundaries.
`u`	Upper boundaries.
`sample.sizes`	Cumulative sample sizes on each treatment arm.
`K`	Number of experimental treatments.
`J`	Number of stages in the trial.
`alpha.star`	Cumulative familywise error rate spent at each analysis, conditional on results so far.
`selection`	Pre-specified method of treatment selection.
`zscores`	A list containing the observed test statistics at analyses so far (at the design stage this is NULL).
`selected.trts`	A list containing the treatments selected for each stage.

Author(s)

Dominic Magirr

References

Jaki T., Pallmann P. and Magirr D. (2019), *The R Package MAMS for Designing Multi-Arm Multi-Stage Clinical Trials*, **Journal of Statistical Software**, 88(4), 1-25. Link: doi: 10.18637/jss.v088.i04

Magirr D., Jaki T. and Whitehead J. (2012), *A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection*, **Biometrika**, 99(2), 494-501. Link: doi: 10.1093/biomet/ass002

Magirr D., Stallard N. and Jaki T. (2014), *Flexible sequential designs for multi-arm clinical trials*, **Statistics in Medicine**, 33(19), 3269-3279. Link: doi: 10.1002/sim.6183

Stallard N. and Todd S. (2003), *Sequential designs for phase III clinical trials incorporating treatment selection*, **Statistics in Medicine**, 22(5), 689-703.

See Also

`print.MAMS.stepdown`, `summary.MAMS.stepdown`, `plot.MAMS.stepdown`, `stepdown.mams`, `MAMS`.

Examples

```
# 2-stage 3-treatments versus control design
# all promising treatments are selected:
orig_mams <- stepdown.mams(nMat=matrix(c(10, 20), nrow=2, ncol=4),
                           alpha.star=c(0.01, 0.05), lb=0,
                           selection="all.promising")
```

```
# make adjustment for the observed sample sizes
# not being exactly as planned:
stepdown.update(orig_mams, nobs=c(9, 8, 13, 11), zscores=c(1.1, -0.5, 0.2),
                selected.trts=1:3, nfuture=NULL)

# make adjustment for the observed sample sizes
# not being exactly as planned. In addition, drop treatment 2:
stepdown.update(orig_mams, nobs=c(9, 8, 13, 11), zscores=c(1.1, -0.5, 0.2),
                selected.trts=c(1, 3), nfuture=NULL)

# make adjustment for the observed sample sizes not being
# exactly as planned. In addition, drop treatment 2. In addition,
# double the planed cumulative second stage sample sizes:
updated_mams <- stepdown.update(orig_mams, nobs=c(9, 8, 13, 11),
                                zscores=c(1.1, -0.5, 0.2), selected.trts=c(1, 3),
                                nfuture=matrix(c(40, 40, 13, 40), nrow=1, ncol=4))

# Account for the observed second stage sample sizes:
stepdown.update(updated_mams, nobs=c(38, 41, 13, 36), zscores=c(1.9, -Inf, 1.2),
                selected.trts=NULL)

# 'select.best' design. Account for actually observed sample sizes
# in first stage, and drop treatment 2:
orig_mams <- stepdown.mams(nMat=matrix(c(10, 20), nrow=2, ncol=4),
                           alpha.star=c(0.01, 0.05), lb=0, selection="select.best")

stepdown.update(orig_mams, nobs=c(9, 8, 13, 11), zscores=c(1.1, -0.5, 0.2),
                selected.trts=c(1, 3), nfuture=NULL)
```

`tite.mams` *Function to design multi-arm multi-stage studies with time-to-event endpoints*

Description

The function determines (approximately) the boundaries of a multi-arm multi-stage study with time-to-event endpoints for a given boundary shape and finds the required number of events.

Usage

```
tite.mams(hr=1.5, hr0=1.1, K=4, J=2, alpha=0.05, power=0.9,
          r=1:2, r0=1:2, ushape="obf", lshape="fixed", ufix=NULL,
          lfix=0, nstart=1, nstop=NULL, sample.size=TRUE, N=20,
          parallel=TRUE, print=TRUE)
```

Arguments

`hr`	Interesting treatment effect on the scale of hazard ratios (default=2).
`hr0`	Uninteresting treatment effect on the scale of hazard ratios (default=1.2).

K	Number of experimental treatments (default=4).
J	Number of stages (default=2).
alpha	One-sided familywise error rate (default=0.05).
power	Desired power (default=0.9).
r	Vector of allocation ratios (default=1:2).
r0	Vector ratio on control (default=1:2).
ushape	Shape of upper boundary. Either a function specifying the shape or one of "pocock", "obf" (the default), "triangular" and "fixed".
lshape	Shape of lower boundary. Either a function specifying the shape or one of "pocock", "obf", "triangular" and "fixed" (the default).
ufix	Fixed upper boundary (default=NULL). Only used if shape="fixed".
lfix	Fixed lower boundary (default=0). Only used if shape="fixed".
nstart	Starting point for finding the sample size (default=1).
nstop	Stopping point for finding the sample size (default=NULL).
sample.size	Logical if sample size should be found as well (default=TRUE).
N	Number of quadrature points per dimension in the outer integral (default=20).
parallel	if TRUE (default), allows parallelisation of the computation via a user-defined strategy specified by means of the function future::plan(). If not set differently, the default strategy is sequential, which corresponds to a computation without parallelisation.
print	if TRUE (default), indicate at which stage the computation is.

Details

This function finds the (approximate) boundaries and sample size of a multi-arm multi-stage study with time-to-event endpoints with K active treatments plus control in which all promising treatments are continued at interim analyses as described in Magirr et al (2012). It is a wrapper around the basic mams function to facilitate its use with time-to-event endpoints, following ideas of Jaki & Magirr (2013). Note that the sample size is calculated as the required number of events, from which the total sample size can be estimated (e.g., Whitehead 2001). See ?mams for further details on the basic methodology.

Value

An object of the class MAMS containing the following components:

l	Lower boundary.
u	Upper boundary.
n	Sample size on control in stage 1.
N	Maximum total sample size.
K	Number of experimental treatments.

J	Number of stages in the trial.
alpha	Familywise error rate.
alpha.star	Cumulative familywise error rate spent by each analysis.
power	Power under least favorable configuration.
rMat	Matrix of allocation ratios. First row corresponds to control while subsequent rows are for the experimental treatments.

Author(s)

Philip Pallmann, Dominic Magirr

References

Jaki T. and Magirr D. (2013), *Considerations on covariates and endpoints in multi-arm multi-stage clinical trials selecting all promising treatments*, **Statistics in Medicine**, 32(7), 1150-1163. Link: doi: 10.1002/sim.5669

Jaki T., Pallmann P. and Magirr D. (2019), *The R Package MAMS for Designing Multi-Arm Multi-Stage Clinical Trials*, **Journal of Statistical Software**, 88(4), 1-25. Link: doi: 10.18637/jss.v088.i04

Magirr D., Jaki T. and Whitehead J. (2012), *A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection*, **Biometrika**, 99(2), 494-501. Link: doi: 10.1093/biomet/ass002

Whitehead J. (2001), *Predicting the duration of sequential survival studies*, **Drug Information Journal**, 35(4), 1387-1400.

See Also

print.MAMS, summary.MAMS, plot.MAMS, mams, MAMS.

Examples

```
## An example 2-stage design with triangular efficacy and futility boundaries
tite.mams(hr=2, hr0=1.5, K=3, J=2, alpha=0.05, power=0.9,
          r=1:2, r0=1:2, ushape="triangular", lshape="triangular")
```

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