

Package ‘MAMS’

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Type Package

Title Designing Multi-Arm Multi-Stage Studies

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

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R topics documented:

mams	2
mams.sim	5
MAMSNews	7
new.bounds	8
ordinal.mams	10
plot	12
stepdown.mams	15
stepdown.update	17
tite.mams	19

Index	22
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mams	<i>Function to design multi-arm multi-stage studies with normal end-points</i>
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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")
```

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 <code>tite.mams</code> (to "tite") and <code>ordinal.mams</code> (to "ordinal") to customise the output.

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 p_0 . Both p and p_0 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 parameterization 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 `delta0` 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, `fix` 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 computation time.

Value

An object of the class MAMS containing the following components:

<code>l</code>	Lower boundary.
<code>u</code>	Upper boundary.
<code>n</code>	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 and Dominic Magirr

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.

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

O'Brien PC, Fleming TR (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.

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)
```

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=1000, 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)
```

Arguments

nsim	Number of simulations (default=1000).
nMat	$J \times (K+1)$ dimensional matrix of observed/expected sample sizes. Rows correspond to stages and columns to arms. First column is control (default: 2×5 matrix with 44 subjects per stage and arm).
u	Vector of previously used upper boundaries (default=NULL).
l	Vector of previously used lower 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.

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 parameterization 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 `pctest` (`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",]))
```

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

Author(s)

Thomas Jaki and Dominic Magirr

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.

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)
```

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)
```

Arguments

K	Number of experimental treatments (default=3).
J	Number of stages (default=2).
alpha	One-sided familywise error rate (default=0.05).
nMat	$J \times (K+1)$ dimensional matrix of observed/expected sample sizes. Rows correspond to stages and columns to arms. First column is control (default: 2×4 matrix with 10 subjects per stage and arm).
u	Vector of previously used upper boundaries (default=NULL).
l	Vector of previously used lower 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).

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, `lfixed` 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:

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

Author(s)

Thomas Jaki and Dominic Magirr

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.

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

O'Brien PC, Fleming TR (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.

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)
```

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)
```

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).

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

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.

Jaki T, 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.

Whitehead J, Jaki T (2009) One- and two-stage design proposals for a phase II trial comparing three active treatments with control using an ordered categorical endpoint. *Statistics in Medicine*, 28(5), 828-847.

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")
```

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

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

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	<i>Function to find stopping boundaries for a 2- or 3-stage (step-down) multiple-comparisons-with-control test.</i>
---------------	---

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:

1	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

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.

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	<i>Update the stopping boundaries of multi-arm multi-stage study at an interim analysis, allowing for unplanned treatment selection and/or sample-size reassessment.</i>
-----------------	--

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 (default=stepdown.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

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.

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 planned cumulative second stage sample sizes:
updated_mams1 <- 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_mams1, 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	<i>Function to design multi-arm multi-stage studies with time-to-event endpoints</i>
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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)

```

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).

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

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.

Jaki T, 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.

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

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")
```

Index

*Topic **classes**

plot, [12](#)

*Topic **design**

mams, [2](#)

mams.sim, [5](#)

new.bounds, [8](#)

ordinal.mams, [10](#)

stepdown.mams, [15](#)

stepdown.update, [17](#)

tite.mams, [19](#)

*Topic **misc**

MAMSNews, [7](#)

mams, [2](#)

mams.sim, [5](#)

MAMSNews, [7](#)

new.bounds, [8](#)

ordinal.mams, [10](#)

plot, [12](#)

print.MAMS (plot), [12](#)

stepdown.mams, [15](#)

stepdown.update, [17](#)

summary.MAMS (plot), [12](#)

tite.mams, [19](#)