Package ‘MAMS’

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Type Package

Title Designing Multi-Arm Multi-Stage Studies

Version 1.2

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Depends mvtnorm, methods

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

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mams

Function to design multi-arm multi-stage studies with normal end-points

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

```r
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 tite.mams (to "tite") and ordinal.mams (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, \( \delta \) 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 \( \sigma \) assumed to be known.

The shape of the boundaries (\( lshape, ushape \)) 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 computation time.

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 and Dominic Magirr

References


Examples

```r
## 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

```r
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.

```r
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**

```r
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), deltat=NA, sd=NA, ptest=1)
```

**Arguments**

- **nsim**
  Number of simulations (default=1000).

- **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)).

- **deltat**
  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 $p v$ 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 $p v = \text{rep}(0.5, 4)$ 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, $\delta$ to this format use $p = \Phi\left(\frac{\delta}{\sqrt{2} \sigma}\right)$. Alternatively, the effect size can also be specified directly on the traditional scale of $\text{delta} \text{avg}$ with an additional specification of the standard deviation $sd$.

The function returns the probability of rejecting any hypothesis ($\text{typeI}$), 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 $\text{ptest}$ ($\text{prop.rej}$) as well as the expected sample size.

Value

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

```r
res$typeI <- mean(unlist(reps["rej",])) res$power <- mean(unlist(reps["pow",])) res$prop.rej <- rej/nsim res$exss <- mean(unlist(reps["ess",]))
```

<table>
<thead>
<tr>
<th>1</th>
<th>Lower boundary.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$u$</td>
<td>Upper boundary.</td>
</tr>
<tr>
<td>$n$</td>
<td>Sample size on control in stage 1.</td>
</tr>
<tr>
<td>$N$</td>
<td>Maximum total sample size.</td>
</tr>
<tr>
<td>$K$</td>
<td>Number of experimental treatments.</td>
</tr>
<tr>
<td>$J$</td>
<td>Number of stages in the trial.</td>
</tr>
<tr>
<td>$r\text{Mat}$</td>
<td>Matrix of allocation ratios. First row corresponds to control and second row to experimental treatments.</td>
</tr>
<tr>
<td>$\text{nsim}$</td>
<td>Number of simulation runs.</td>
</tr>
<tr>
<td>$\text{typeI}$</td>
<td>The proportion any hypothesis is rejected.</td>
</tr>
<tr>
<td>$\text{power}$</td>
<td>The proportion the first hypothesis is rejected and the corresponding test statistic is largest.</td>
</tr>
<tr>
<td>$\text{ptest}$</td>
<td>The vector $\text{ptest}$.</td>
</tr>
<tr>
<td>$\text{prop.rej}$</td>
<td>The proportion of times at least one of the hypothesis specified by $\text{ptest}$ is rejected.</td>
</tr>
<tr>
<td>$\text{exss}$</td>
<td>The expected sample size.</td>
</tr>
</tbody>
</table>

Author(s)

Thomas Jaki and Dominic Magirr
References

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

```r
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", uf=fix=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**  
  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).
new.bounds

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 u.shape and l.shape can be found for any sample sizes per stage and arm.

The shape of the boundaries (u.shape, l.shape) 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:

- **u** 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 and Dominic Magirr

References


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",
# 1fix=0, sample.size=FALSE)

new.bounds(K=4, J=2, alpha=0.05, nMat=matrix(c(10, 28), nrow=2, ncol=5), u=NULL, l=NULL,
   ushape="obf", lshape="fixed", 1fix=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, 10, 28, 13, 28), nrow=2, ncol=5),
   u=3.068, l=0, ushape="obf", lshape="fixed", 1fix=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

```r
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", 1fix=NULL,
   1fix=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).
alp  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 treat-
ments 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.
alp  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


Examples

```r
## 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")
```

Different generic functions for class MAMS.

Description
Generic functions for summarizing an object of class MAMS.

Usage

```r
## 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 plotting 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**


**Examples**

```r
# 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:
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

```r
stepdown.mams(nMat=matrix(c(10, 20), nrow=2, ncol=4),
               alpha.star=c(0.01, 0.05), 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


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(currentNmams=stepdownNmams(), nobs=NULL, zscores=NULL, selectedNtrts=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.
stepdown.update

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


Examples

# 2-stage 3-treatments versus control design
# all promising treatments are selected:
orig_mams <- stepdown.mams(nMat=matrix(c(10L 20L), nrow=1L, ncol=4L),
  alpha.star=c(0.01L, 0.05L), lb=0L,
  selection="all.promising")

# make adjustment for the observed sample sizes not being exactly as planned:
stepdown.update(orig_mams, nobs=c(9L, 8L, 13L, 11L), zscores=c(1.1L, -0.5L, 0.2L),
  selected.trts=1:3L, 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(9L, 8L, 13L, 11L), zscores=c(1.1L, -0.5L, 0.2L),
  selected.trts=c(1L, 3L), 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(9L, 8L, 13L, 11L),
  zscores=c(1.1L, -0.5L, 0.2L), selected.trts=c(1L, 3L),
  nfuture=matrix(c(40L, 40L, 13L, 40L), nrow=1L, ncol=4L))
# 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

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)

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


Examples

```r
## 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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