Advancing Adaptive Multi-Arm Multi-Stage Clinical Trials with the MAMS R Package

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INTRODUCTION

Multi-Arm Multi-Stage (MAMS) trials are innovative designs that allow the comparison of multiple treatments against a common control across several stages. These trials incorporate adaptations such as stopping for futility or efficacy at either the arm or trial level, enhancing efficiency in identifying promising interventions. Despite the existence of some specialised MAMS software, these tools are often limited in scope and usability. Our project addresses this gap by developing the MAMS R package, which is designed to be flexible, user-friendly, and accessible to users with minimal programming experience.

METHODS

The MAMS R package employs a modular approach, enabling easy integration of various methods for trial adaptation. Currently, the package implements three key methods: Simultaneous stopping, Drop-the-losers design, and separate stopping rule for platform trials.

The modular design ensures that new methods can be seamlessly incorporated into the package as they are developed. This approach enhances the package's adaptability and broadens its applicability to a wide range of MAMS (platform) trial designs.

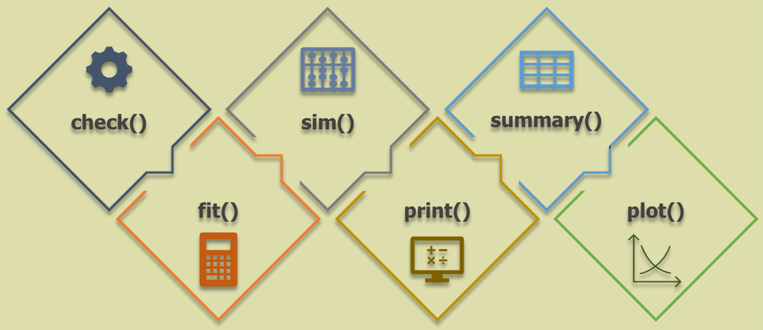
STRUCTURE

Main MAMS package function

mams(method = "module_name", ...)

method = "simultaneous"	method = "dtl"	method = "sep"
Simultaneous stopping rules	Drop the losers	Separate stopping rules

MAMS module



EXAMPLE APPLICATION

R call: **> mams(method = "dtl")**

Design	Function call	Description
Investigation of 4 experimental treatments in 2 stages with normal endpoints.	K = 4	Number of experimental treatments
	J = 2	Number of stages
One-sided familywise error rate of 0.05 and desired power of 0.9.	alpha = 0.05	One-sided familywise error rate
	power = 0.9	Desired power
Allocation ratios: r = 1:2 for experimental treatments, r0 = 1:2 for control.	r = 1:2	Vector of allocation ratios
	r0 = 1:2	Vector ratio on control
Effect size parameters	p = 0.75	Interesting treatment effect on probability scale
	p0 = 0.5	Uninteresting treatment effect on probability scale
	delta = NULL	Interesting treatment effect on traditional scale
	delta0 = NULL	Uninteresting treatment effect on traditional scale
	sd = NULL	Standard deviation
Fixed lower boundary with shape "obf" for upper boundary.	ushape = obf	Shape of upper boundary
	lshape = fixed	Shape of lower boundary
	ufix = NULL	Fixed upper boundary
	lfix = 0	Fixed lower boundary
Sample Size and Computational Settings	nstart = 1	Starting point for sample size
	nstop = NULL	Stopping point for sample size
	sample.size = TRUE	Find sample size
	Q = 20	Number of quadrature points
Simulations using 50,000 iterations, considering H0 = True.	nsim = 50000	Number of simulations
	H0 = TRUE	Consider case with all effect sizes set to 0

OUTPUT

```
-- MAMS design ---------------------------------------------
-- Design characteristics --

* Normally distributed endpoint
* Drop the losers
* 2 stages
* 4 treatment arms
* 5% overall type I error
* 90% power of detecting Treatment 1 as the best arm
* Assumed effect sizes per treatment arm:

                  | Under H1            | Under H0
              abbr | cohen.d prob.scale | cohen.d prob.scale
  Treatment 1   T1 |   0.954       0.75 |       0         0.5
  Treatment 2   T2 |   0.000       0.50 |       0         0.5
  Treatment 3   T3 |   0.000       0.50 |       0         0.5
  Treatment 4   T4 |   0.000       0.50 |       0         0.5


-- Arms allocation per stage --

           Stage 1 | Stage 2
Control        1   |    1
Treatment      4   |    1

-- Limits --

             Stage 1 Stage 2 shape
Upper bounds      NA   2.055   dtl
Lower bounds      NA   2.055   dtl

-- Sample sizes --
                          | Expected (§)
            Cumulative    | Under H1          | Under H0
            Stage 1 Stage 2† | low    mid high | low    mid high
Control          13      26 |  26 26.000   26 |  26 26.000   26
Treatment 1      13      26 |  26 25.735   26 |  13 16.300   26
Treatment 2      13      26 |  13 13.083   13 |  13 16.263   26
Treatment 3      13      26 |  13 13.093   13 |  13 16.214   26
Treatment 4      13      26 |  13 13.090   13 |  13 16.223   26
TOTAL‡           65      91 |     91.000      |     91.000
† Max cumulative size per arm
‡ Based on arms allocation at each stage
-- Futility cumulated probabilities (§) --
            Under H1          | Under H0
            Stage 1 Stage 2   | Stage 1 Stage 2
Treatment 1       0   0.077 |       0   0.241
Treatment 2       0   0.005 |       0   0.238
Treatment 3       0   0.006 |       0   0.235
Treatment 4       0   0.006 |       0   0.236
ANY               0   0.095 |       0   0.950
ALL               0   0.000 |       0   0.000
-- Efficacy cumulated probabilities (§) --
            Under H1          | Under H0
            Stage 1 Stage 2   | Stage 1 Stage 2
Treatment 1       0   0.902 |       0   0.013
Treatment 2       0   0.001 |       0   0.013
Treatment 3       0   0.001 |       0   0.012
Treatment 4       0   0.001 |       0   0.012
ANY               0   0.905 |       0   0.050
T1 IS BEST        0   0.902 |       0   0.013
ALL               0   0.000 |       0   0.000

* Estimated T1 related power (§) = 90.218%, [89.956, 90.478] 95% CI
* Estimated overall type I error (§) = 5.012%, [4.822, 5.204] 95% CI

(§) Operating characteristics estimated by a simulation
    considering 50000 Monte Carlo samples
```

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REFERENCES

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