Multi-Arm Multi-Stage Designs (MAMS)

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Defining a multi-stage trial

We now consider splitting the trial over J stages

In the first stage of the trial, patients are recruited to all treatments $T_1, \ldots, T_K$

After each trial stage $j = 1, \ldots, J$, treatments may be dropped either for futility or for efficacy.

If the trial is not stopped at an interim analysis, we recruit patients for the shared control group and remaining treatment arms at the next stage.

Sampling scheme in a 2-stage case

In stage 1, we recruit patients to all of the treatments

We then conduct an interim analysis to choose which treatments to continue recruiting from

This may be extended to many stages conducting interim analyses between each stage of the trial

Different types of MAMS designs

Different MAMS designs can be defined based on:

- stopping rules
  - per arm
    - early futility stopping or not
    - early efficacy stopping or not
  - for the trial
    - simultaneous stop:
      trial stops as soon as at least one treatment is found efficacious
    - separate stop:
      trial continues as long as at least one treatment is 'promising'
- on the maximum number of arms allowing to reach the jth stage
  - unlimited
  - only 1

Two-stage selection screens

Suppose that responses to the kth treatment,
$Y_{ki} \sim N(\mu_k, \sigma^2),\ k = 0, 1, \ldots, K$

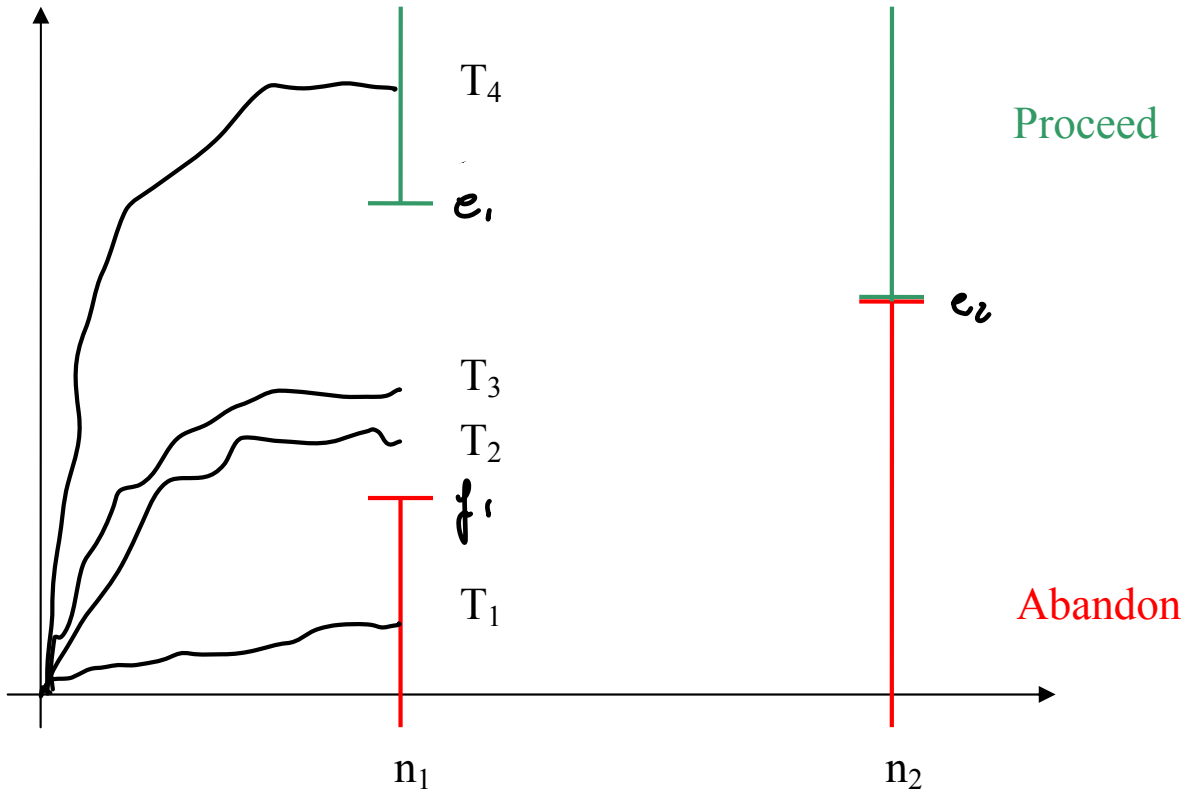
In Stage 1, n_{1k} patients are treated on T_k, with mean response $\bar{y}_{1k}$ with test statistic (where n_{jk} denote the sample size of T_k at stage j)

$$Z_{1k} = \frac{\bar{y}_{1k} - \bar{y}_{10}}{\sqrt{\frac{\sigma^2}{n_{1k}} + \frac{\sigma^2}{n_{10}}}}$$

After Stage 1, an interim analysis is conducted

- If $Z_{1k} < f_1$, then T_k will be dropped
- If $Z_{1k^*} = \max(Z_{11}, \ldots, Z_{1K}) > e_1$, then T_{k^*} will be selected

Early stopping : Visualisation



- T_1 eliminated and T_4 selected at interim

Only the best treatment moved forward to stage 2

(e.g. Stallard & Todd, 2003; Whitehead & Jaki 2009)

If no treatment is selected after Stage 1, and not all treatments are dropped, then

- n_{20} further patients are treated on the control
- n_{2k^*} on treatment T_{k^*}, the best remaining active treatment

At the end of Stage 2, the statistic of the remaining treatment is given by

$$Z_{2k^*} = \frac{\bar{y}_{2k^*} - \bar{y}_{20}}{\sqrt{\frac{\sigma^2}{n_{.k^*}} + \frac{\sigma^2}{n_{.0}}}},$$

where $\bar{y}_{2k^*}$ denotes the mean response in group k^* defined over the $n_{.k^*} = \sum_{j=1}^{2} n_{jk^*}$ patients.

If $Z_{2k^*} > e_2$, then T_{k^*} will be selected (declared efficacious).

All promising treatments moved forward to stage 2

(Magirr et al, 2012)

If no treatment is selected after Stage 1, and not all treatments are dropped, then

- n_{20} further patients are treated on the control
- n_{2k} on treatment T_k for all k so that $Z_{1k} > f_1$

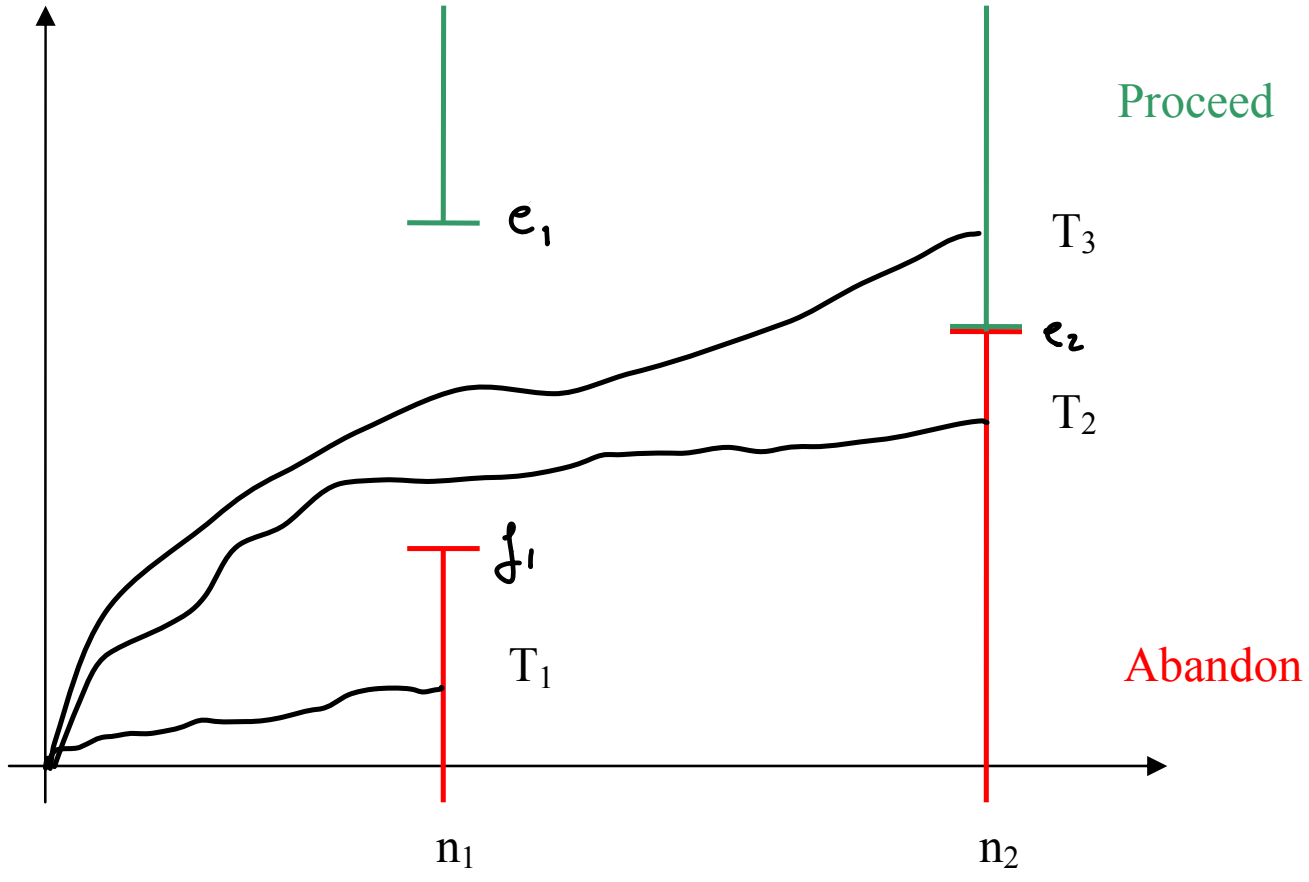
At the end of Stage 2, the statistics of the kth treatment is given by

$$Z_{2k} = \frac{\bar{y}_{2k} - \bar{y}_{20}}{\sqrt{\frac{\sigma^2}{n_{.k}} + \frac{\sigma^2}{n_{.0}}}},$$

where $\bar{y}_{2k}$ denotes the mean response in group k defined over the $n_{.k} = \sum_{j=1}^{2} n_{jk}$ patients.

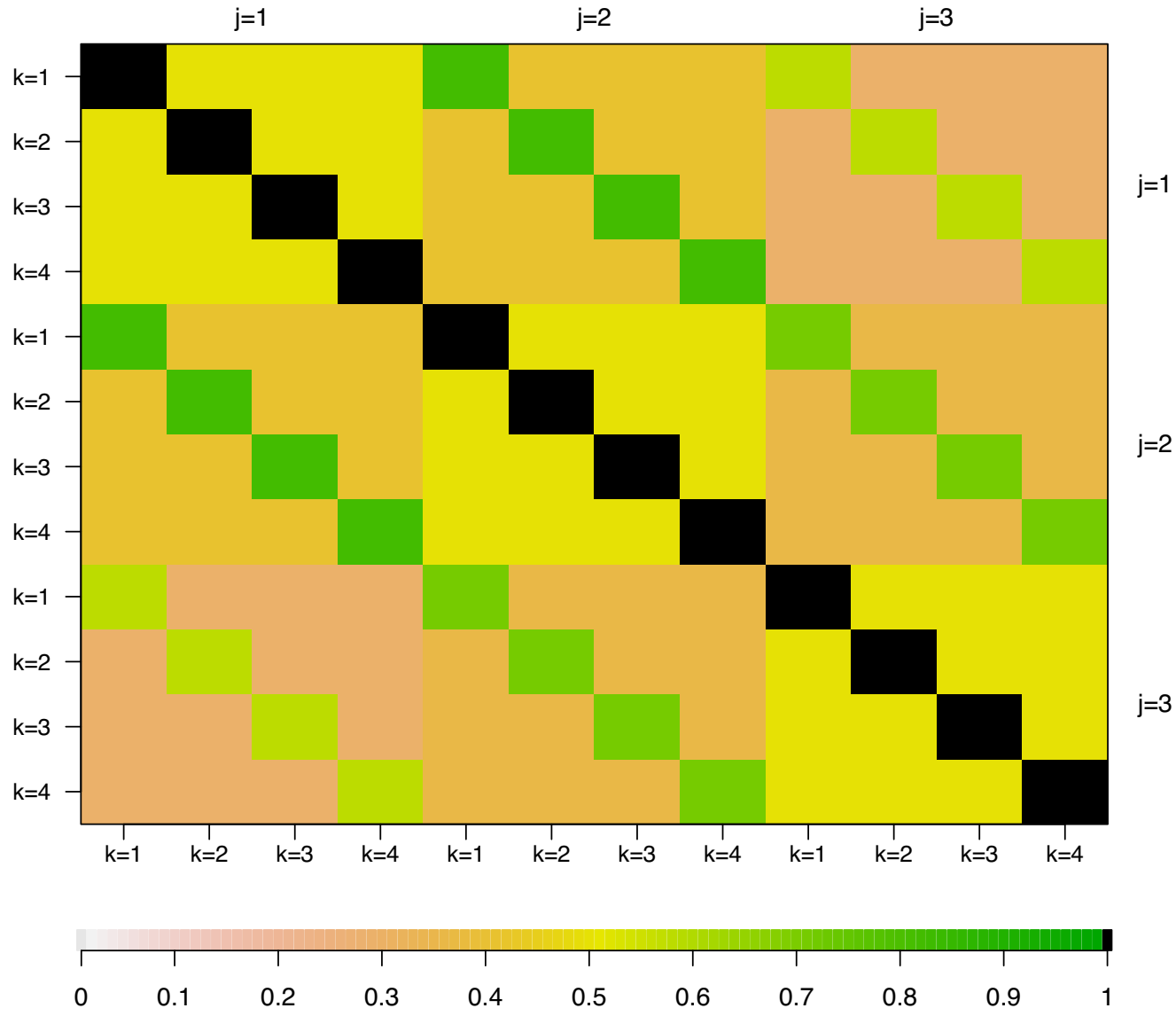
If $Z_{2k^*} = \max(Z_{21}, \ldots, Z_{2K}) > e_2$, then T_{k^*} will be selected.

Conclusion at stage 2: Visualisation



- T_1 eliminated at interim and T_3 selected at final analysis

Within/between 'Stage and treatment arm' dependence



Constraints for finding a design

Under the global null:

$$\nu = P(\text{select a treatment} \mid \mu_0 = \mu_1 = \cdots = \mu_K)$$

Under the alternative:

$$\begin{aligned} 1 - \eta \quad = \quad & P(\text{select } T_K \mid \mu_K = \mu_0 + \delta \text{ and} \\ & \qquad \mu_k = \mu_0 + \delta_0,\ k = 1, \ldots, K-1). \end{aligned}$$

- Given the sample size ratios $r_k = n_{\cdot k}/n_{\cdot 0}$ $\Rightarrow$ find f_1, f_2, e_2 and n_{0j}
- Further constraints can be set, such as
  - (i) $f_1 = 0, e_1 = \infty$
  - (ii) $f_1 = 0, e_1 = \frac{4}{3} e_2$
  - (iii) $f_1 = 0$ and e_1, e_2 defined via O'Brien-Fleming rule

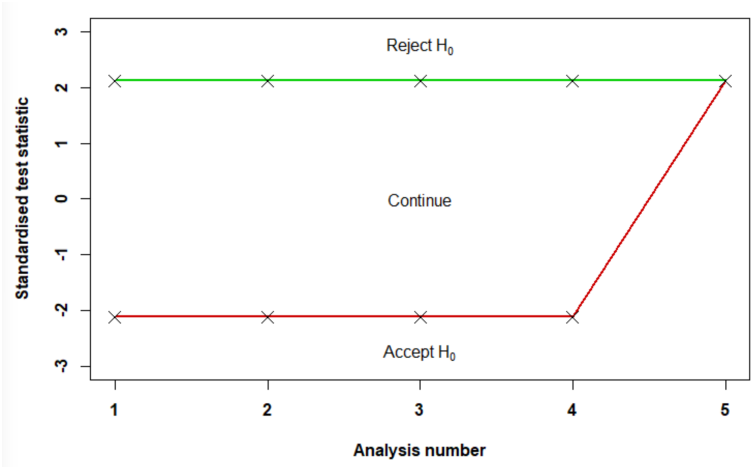
  and a solution can be computed and evaluated

Efficacy and futility bounds:

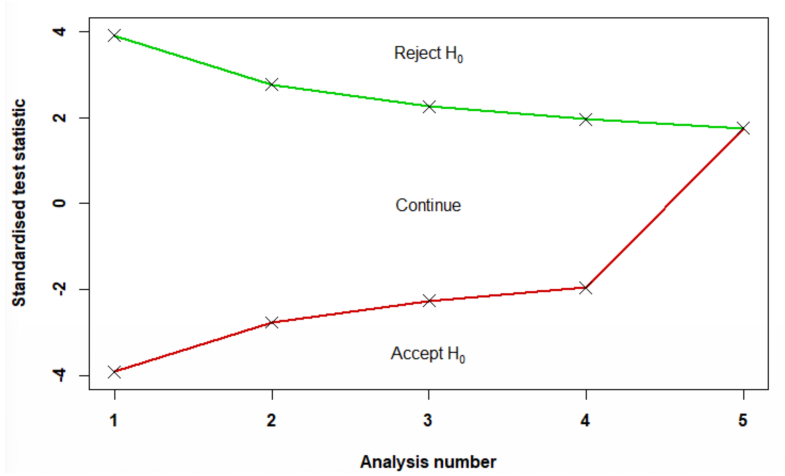
- The shape of the stopping boundaries will determine the ESS and MSS.
- Two main ways to choose between the infinite number of possible shapes:
  - Use some 'fixed' boundary shape (specified through a simple functional form)
  - Search for an optimal design to minimise a criterion for some δ (ESS).
- First method is much quicker, but second method allows greater control over the ESS properties of the design.
- Common boundary shapes to choose from:
  - Pocock
  - O'Brien-Fleming
  - Triangular test

Efficacy and futility bounds: Visualisation

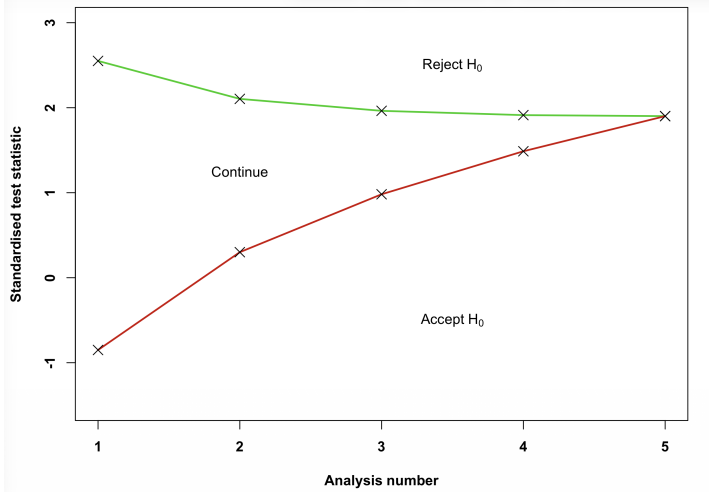
Pocock



O'Brien & Fleming



Triangular



Application – the `MAMS::mams()` function

The `mams()` function of the `MAMS` package allows to design studies with asymptotically normal endpoints and known variance. It considers

- normal, binary, ordinal and time-to-event endpoints
- different arm/trial stopping rules
  - `method="simultaneous"` (default):
    - all promising arms of stage $j-1$ are moved forward to stage $j \leq J$,
    - both efficacy and/or futility early stopping are possible,
    - the trial stops as soon as one treatment is found efficacious.
  - `method="dtl"` (drop-the loser):
    - at each stage, a pre-defined number of treatment arms if moved to the next stage
    - neither efficacy and futility early stopping are possible,
    - efficacy can only be claim for the only treatment considered at stage J
  - `method="sep"` (separate):
    - all promising arms of stage $j-1$ are moved forward to stage $j \leq J$,
    - both efficacy and/or futility early stopping are possible,
    - the trial keeps going as long as at least one 'promising' treatment remains.

Application – the trial TREADON

Let us consider a variant of the TREADON trial with two stages and two treatment arms and let's assume that

- assumed effect sizes and uncertainty: $\delta = 0.8,\ \delta_0 = 0,\ \sigma = 2.7$
- target type I and type II errors: $\nu = 0.05,\ 1 - \eta = 0.9$
- allocation ratios: same sample size for each group at each stage
- efficacy stopping rules: O'Brien-Fleming
- futility stopping rules: fixed value equal to 0

```
> library(MAMS)
> design1 = mams(K=2, J=2, alpha=0.05, power=0.9, r=1:2, r0=1:2,
                 delta=0.8, delta0=0, sd=2.7,
                 ushape="obf", lshape="fixed", lfix=0,
                 method="simultaneous",
                 type="normal", parallel=TRUE)
```

Application – the trial TREADON

Some results ('simultaneous' stopping rule)

f_1	e_1	e_2	n_{10}	N	$E_0(N)$	$E_{LFC}(N)$
0	∞	1.910	118	708	550	646
0	$-\frac{4c}{3}$	1.945	120	720	556	532
0	2.731	1.931	119	714	555	546

N is the maximum sample size

$E_0(N)$ and $E_{LFC}(N)$ = expected total sample size under the null and least favourable configuration respectively.

Where simulation can help

- Estimating the ESS (practical 2, task 4)
- Investigating the effect of drop-out scenarios (practical 2, task 5)
- Estimating the probability of reversed conclusions (practical 2, task 6)
- Estimating the probability of reversed conclusions (practical 2, task 6)
- Estimating biases related to early/late stopping (practical 2, task 7)
- Estimating the duration of the study (practical 2, task 8)
- Delay in observing endpoint/overrun (practical 2, task 8)
- ...

References

- Dunnett, C. (1955). A Multiple Comparison Procedure for Comparing Several Treatments with a Control. *Journal of the American Statistical Association*, **50(272)**, 1096-1121.
- 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 and Todd S (2003) Sequential Designs for Phase III Clinical Trials Incorporating Treatment Selection. *Statistics in Medicine*. **22**:689-703.