

MRC

Clinical
Trials
Unit

Smarter Studies
Global Impact
Better Health



UCL

Software for Design in stage

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Hubs for Trials
Methodology Research

London Hub

Background

- Adaptive designs can require complex sample size calculations and estimation of operating characteristics
- Software should make this easy for others to carry out and to encourage adoption of methods
- Freely available non-commercial software is needed

Outline

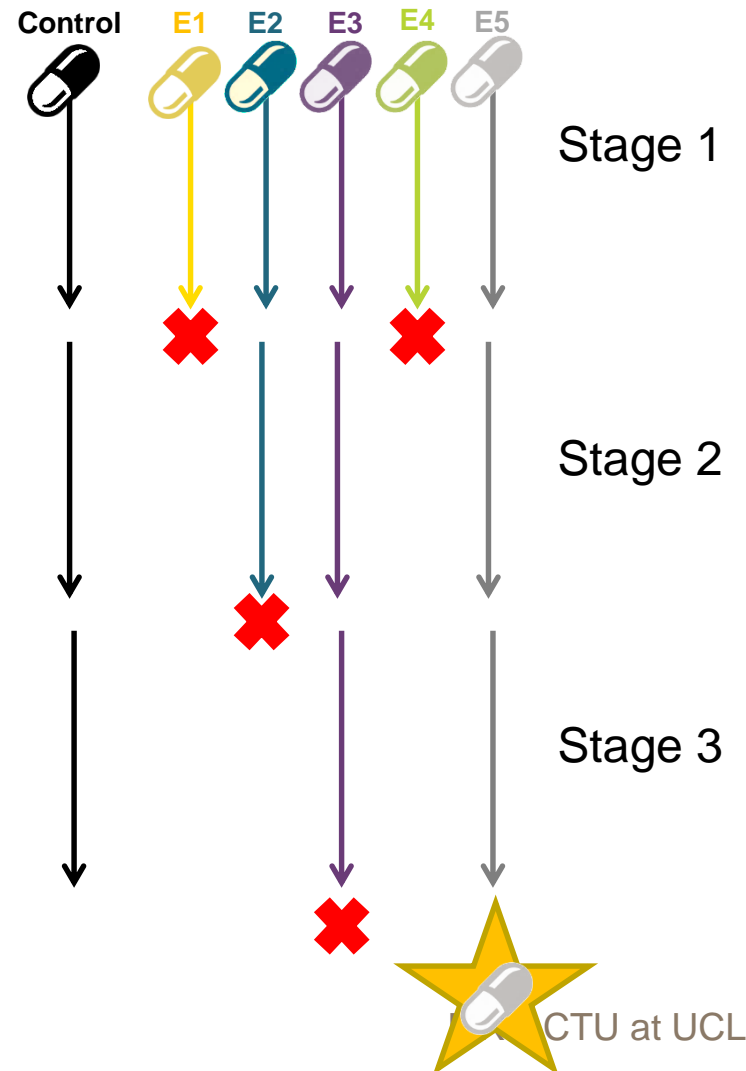
- Intro to `nstage`
- Recent software developments
- Alternative software

Outline

- **Intro to nstage**
- Recent software developments
- Alternative software

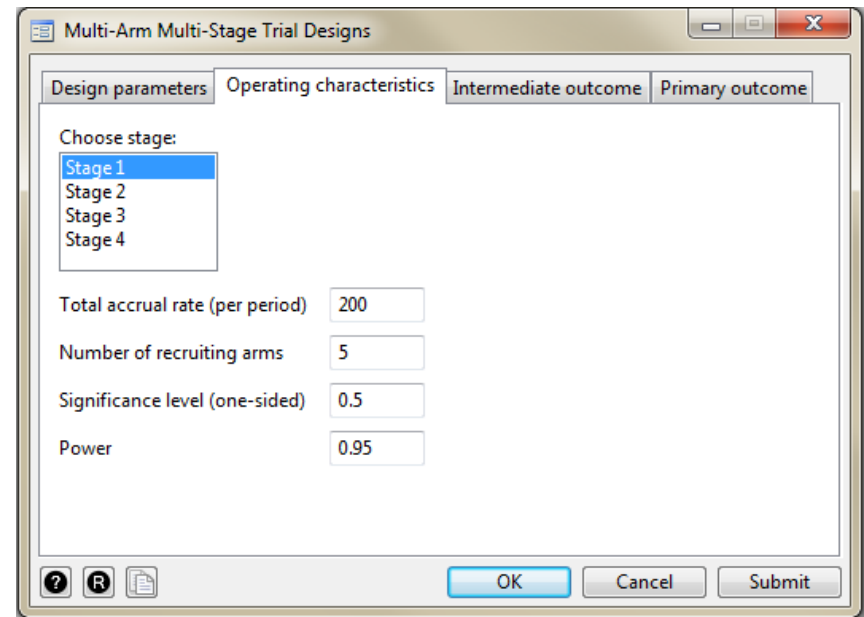
MAMS design

- **Multi-Arm Multi-Stage (MAMS)**
- Methods by Royston et al (2003,2011)
- For time-to-event outcomes
 - Extended to binary
- Phase III
- Multiple research arms, 1 common control arm
- Uses intermediate outcome observable before definitive outcome for early assessment of lack-of-benefit



nstage

- Stata program developed for designing MAMS trials (Barthel & Royston, 2009; Bratton et al 2015)
- Menu-driven approach
- Calculates:
 - Sample size requirements
 - Operating characteristics
 - Expected timings of stages



Input parameters

- Experimental arms & allocation ratio
- Stages/number of interim analyses
- Expected recruitment rate
- Significance levels and power for each interim and final analysis
- Treatment effect in control arm
- Targeted treatment effect in research arms
- Use of an intermediate outcome for interim analyses (& correlation with primary outcome)

Outputs

- Overall power
- Overall type I error (pairwise error rate and familywise error rate)
- Sample size required for each analysis
- Expected timing of analyses

Operating characteristics

	Alpha (1S)	Power	HR H0	HR H1	Crit.HR	Length*	Time*
Stage 1	0.1000	0.950	1.000	0.750	0.883	7.445	7.445
Stage 2	0.0250	0.901	1.000	0.750	0.842	1.179	8.624
Pairwise	0.0239	0.895				8.624	
Familywise (SE)	0.0750	(0.0005)					

Sample size and number of events

	Stage 1			Stage 2		
	Overall	Control	Exper.	Overall	Control	Exper.
Arms	5	1	4	5	1	4
Acc. rate	200	40	160	200	40	160
Patients*	1489	298	1191	1725	345	1380
Events**	982	214	768	1204	260	944

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Aim of updates

- Extend the methods of the design to enable early assessment of efficacy
- Enable design of a trial which strongly controls the familywise error rate to meet regulations
- Allow flexibility of software with respect to assumptions made on how trial is carried out
- Calculate additional operating characteristics for different trial objectives

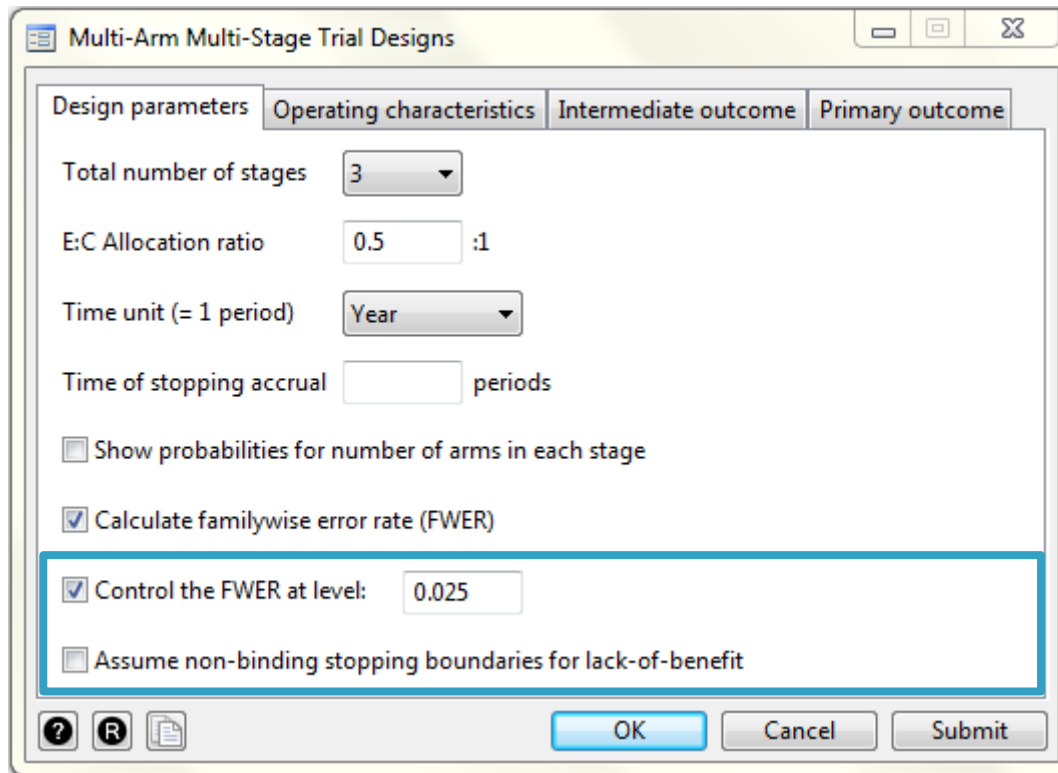
New option: Specifying efficacy stopping boundaries

The screenshot shows a software window titled "Multi-Arm Multi-Stage Trial Designs" with four tabs: "Design parameters", "Operating characteristics", "Intermediate outcome", and "Primary outcome". The "Primary outcome" tab is active, showing "Design Parameters for Primary Outcome" with input fields for "Survival probability" (0.5), "Survival time (periods)" (1.5), "Hazard ratio under H0" (1), and "Hazard ratio under H1" (0.75). Below this, the "Efficacy stopping rules (one-sided)" section is highlighted with a blue border and contains the following options:

- Assess primary outcome for efficacy at interim stage analyses
- Efficacy stopping rule: Haybittle-Peto (dropdown menu)
- p-values: 0.0005 (input field)
- Stop trial once any arm is dropped for efficacy

At the bottom of the window are icons for help, refresh, and save, along with "OK", "Cancel", and "Submit" buttons.

New option: Control the FWER



Multi-Arm Multi-Stage Trial Designs

Design parameters | Operating characteristics | Intermediate outcome | Primary outcome

Total number of stages: 3

E:C Allocation ratio: 0.5 :1

Time unit (= 1 period): Year

Time of stopping accrual: _____ periods

Show probabilities for number of arms in each stage

Calculate familywise error rate (FWER)

Control the FWER at level: 0.025

Assume non-binding stopping boundaries for lack-of-benefit

? R [] OK Cancel Submit

Additional outputs

Additional estimates available from return list command

- Alternative measures of power for multi-arm trials
- p-values generated for efficacy stopping boundary
- Expected number of events on primary outcome measure when efficacy is assessed early

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Alternative software

- Commercial
 - EAST
 - ADDPLAN
- Open-source
 - MAMS (package in R)
 - ASD (package in R)

References

- Barthel, F. M.-S., & Royston, P. (2009). A menu-driven facility for sample-size calculation in novel multiarm, multistage randomized controlled trials with a time-to-event outcome. *Stata Journal*, 9(4), 505523. <https://doi.org/10.1177/152695230934523>
- Bratton, D. J., & Choodari-Oskooei, B. (2015). A menu-driven facility for sample-size calculation in multiarm, multistage randomized controlled trials with time-to-event outcomes: Update. *Stata Journal*, 15(2), 350368.
- Blenkinsop, A., & Choodari-Oskooei, B. (2018), Multi-arm, multi-stage randomized controlled trials with stopping boundaries for efficacy and lack-of-benefit: An update to nstage, *Stata Journal* (to be submitted)