MRC Clinical Trials Unit

Smarter Studies
Global Impact
Better Health

UCL

Software for Design

`nstage`

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MRC 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

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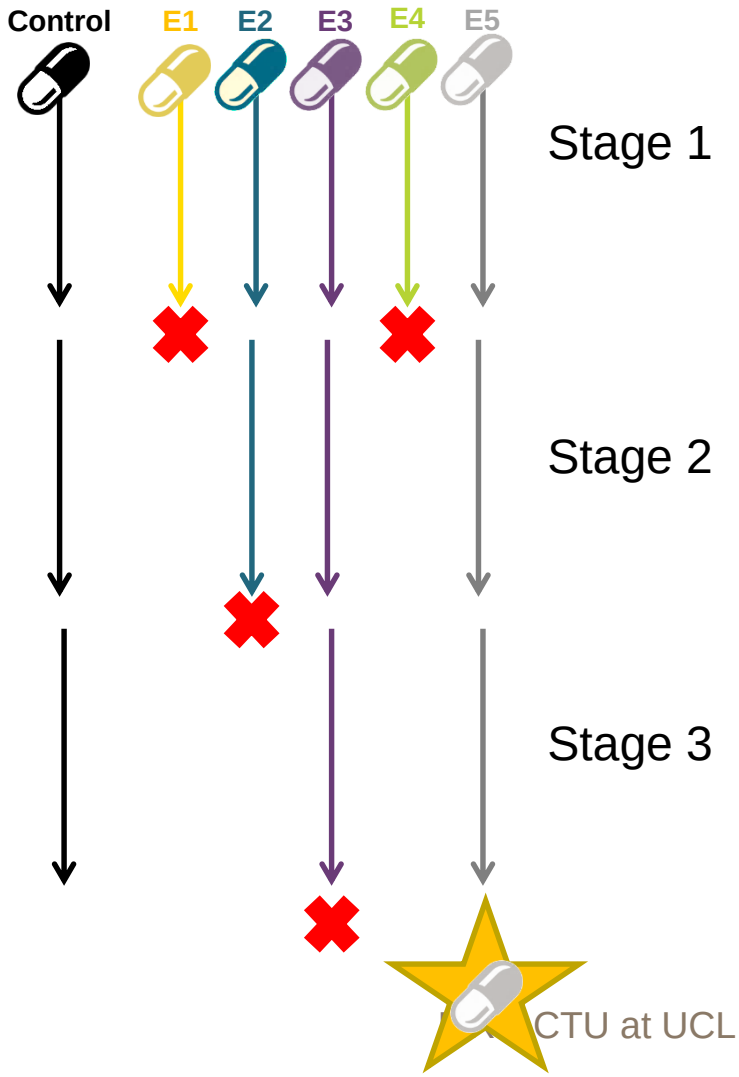
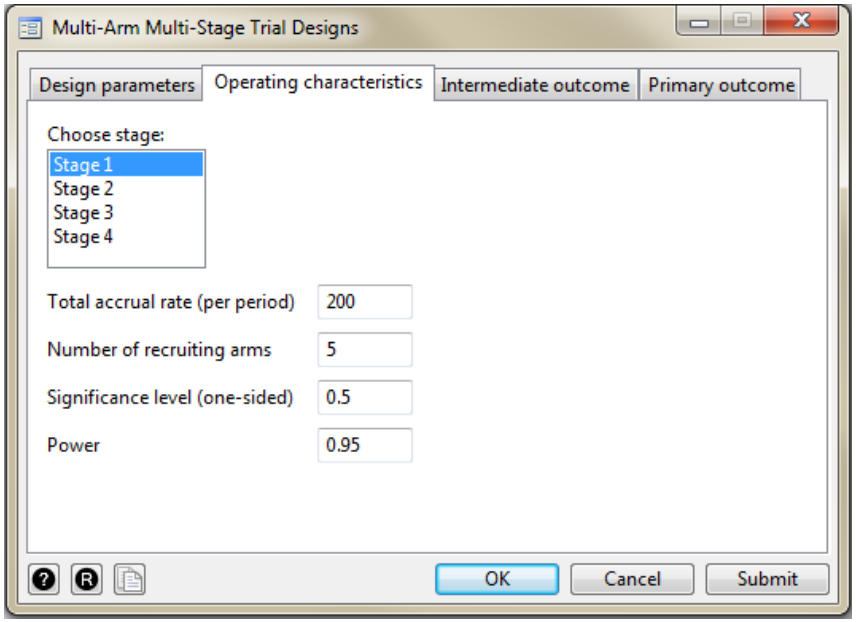
MAMS design

- **M**ulti-**A**rm **M**ulti-**S**tage (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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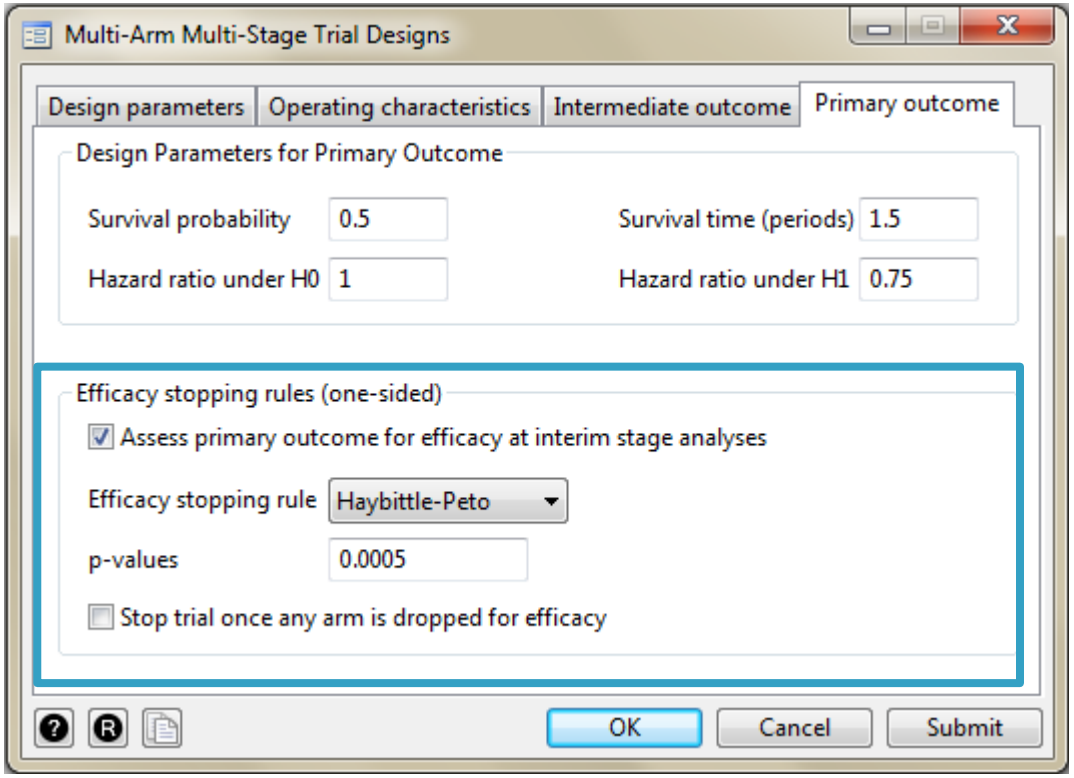
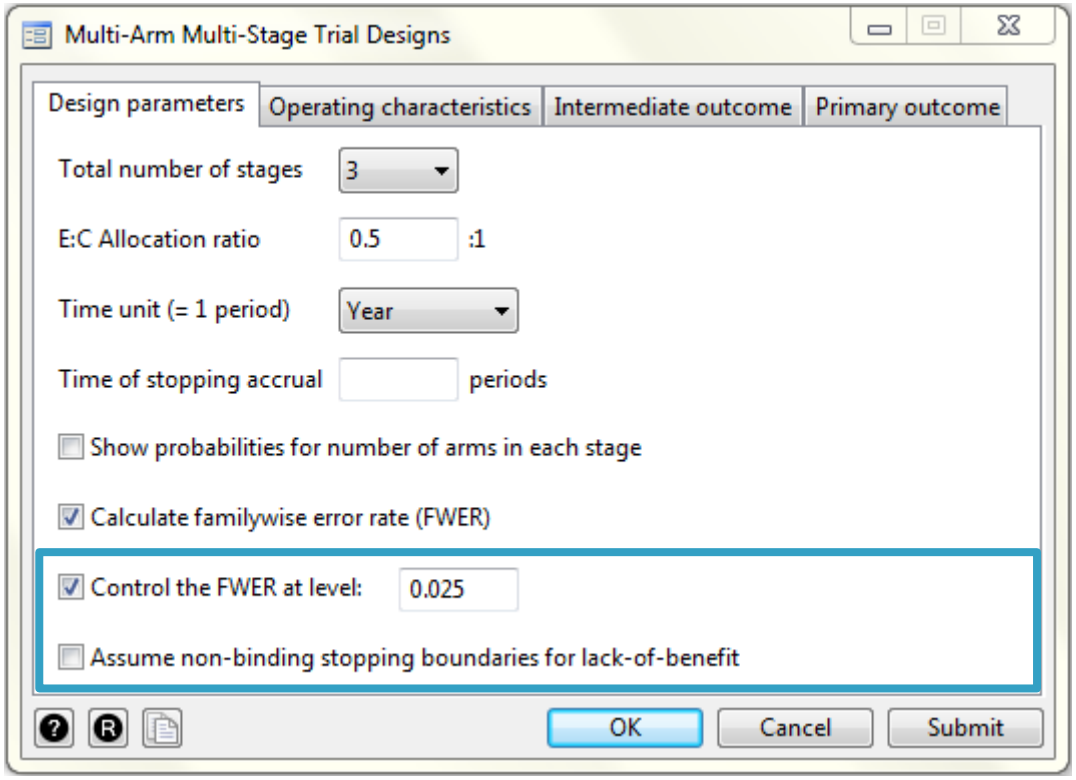
Aim of updates

- 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



New option: Control the FWER



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/The Stata Journal
- 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)