Software for Design
nstage

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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

- **Multi-Arm Multi-Stage** (MAMS)
- 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

<table>
<thead>
<tr>
<th></th>
<th>Alpha(1S)</th>
<th>Power</th>
<th>HR</th>
<th>H0</th>
<th>HR</th>
<th>H1</th>
<th>Crit.HR</th>
<th>Length*</th>
<th>Time*</th>
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<tbody>
<tr>
<td>Stage 1</td>
<td>0.1000</td>
<td>0.950</td>
<td>1.000</td>
<td>0.750</td>
<td>0.883</td>
<td>7.445</td>
<td>7.445</td>
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<tr>
<td>Stage 2</td>
<td>0.0250</td>
<td>0.901</td>
<td>1.000</td>
<td>0.750</td>
<td>0.842</td>
<td>1.179</td>
<td>8.624</td>
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<td>Pairwise</td>
<td>0.0239</td>
<td>0.895</td>
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<td>8.624</td>
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<tr>
<td>Familywise(SE)</td>
<td>0.0750</td>
<td>(0.0005)</td>
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</tbody>
</table>

### Sample size and number of events

<table>
<thead>
<tr>
<th></th>
<th>Stage 1</th>
<th></th>
<th>Stage 2</th>
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<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Control</td>
<td>Exper.</td>
<td>Overall</td>
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<tr>
<td>Arms</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>5</td>
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<td>Acc. rate</td>
<td>200</td>
<td>40</td>
<td>160</td>
<td>200</td>
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<tr>
<td>Patients*</td>
<td>1489</td>
<td>298</td>
<td>1191</td>
<td>1725</td>
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<tr>
<td>Events**</td>
<td>982</td>
<td>214</td>
<td>768</td>
<td>1204</td>
</tr>
</tbody>
</table>
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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

![Image of software interface showing design parameters and efficacy stopping rules](image-url)
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


• 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)