Evaluating the Impact of Increasing the Sample Size in the Secondary Prevention of Small Subcortical Strokes (SPS3) Study: Hindsight is 20/20

Leslie Ain McClure, PhD
Associate Professor of Biostatistics
University of Alabama at Birmingham
Sample size re-estimation is a commonly used procedure in which nuisance parameters are reassessed mid-study to help ensure study goals are met with sufficient power.

Much research has been done to determine the impact of sample size re-estimation on the operating characteristics of the study:

- Little impact on the Type I error rate in large RCTs.
- Post-hoc examinations of the impact of sample size re-estimation on study results have been few.
SPS3 was a multi-national, multi-center randomized clinical trials, with goals of assessing whether:

- The combination of aspirin + clopidogrel is more effective at reducing the risk of recurrent stroke than aspirin alone, and
- The risk of recurrent stroke will differ for those randomized to blood pressure lowering within a “higher” target range (SBP 130-144 mmHg) compared to those randomized to blood pressure lowering within a “lower” target range (SBP < 130 mmHg)

Patients were randomized in a 2x2 factorial design to the four combinations of levels of treatment.
The SPS3 Design

- The sample size \( n=2500 \) for SPS3 was determined assuming:
  - 7% annual event rate in aspirin group
  - 10% loss to follow-up
  - 2 planned interim analyses
  - Average of 3-years of follow-up
  - 90% power to detect 25% relative risk reduction attributable to combination therapy
  - 80% power to detect 20% relative risk reduction attributable to combination therapy

- Similar calculations were made for the BP arm
March, 2003: Recruitment began

March, 2009: An unplanned study modification was made after 2081 patients were randomized
  - Increase the sample size from 2500 to 3000
  - Follow patients an additional 1 year after the last patient was randomized

November, 2010: Patient 2500 was randomized

April, 2011: Last patient randomized to SPS3 (n=3020)

August, 2011: SPS3 DSMB terminated the antiplatelet arm due to safety concerns, coupled with apparent lack of efficacy
  - BP arm continued

April, 2012: Follow-up ended for BP arm
Methods

- We examined what might have happened in SPS3, given the original study assumptions.
  - Patient 2500 was randomized on 11/11/2009.
  - One year of follow-up after the last patient randomized.
    - Follow-up was “ended” on 11/11/2010.

- Analyses for both efficacy and safety were performed under the original design assumptions.
  - Primary efficacy endpoint: composite of ischemic & hemorrhagic strokes.
  - Primary safety endpoints: major bleeds, deaths.

- We compared the results obtained with 3020 patients to what “might have been” with 2500.
Comparison of results between the original design and the modified design: Primary outcome, AP arm

<table>
<thead>
<tr>
<th></th>
<th>2500 Patients</th>
<th>3020 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin + Clopidogel (n=1253)</td>
<td>Aspirin + Placebo (n=1247)</td>
</tr>
<tr>
<td># Events</td>
<td>108</td>
<td>107</td>
</tr>
<tr>
<td>Average FU (years)</td>
<td>3.3 (1.8)</td>
<td>3.4 (1.8)</td>
</tr>
<tr>
<td>Event Rate</td>
<td>2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.0 (0.78, 1.3)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.86</td>
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Results: Efficacy

Comparison of results between the original design and the modified design: Primary outcome, BP arm

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<tr>
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<th>2500 Patients</th>
<th>3020 Patients</th>
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<tbody>
<tr>
<td></td>
<td>&lt; 130 (n=1249)</td>
<td>130-149 (n=1251)</td>
</tr>
<tr>
<td># Events</td>
<td>102</td>
<td>113</td>
</tr>
<tr>
<td>Average FU (years)</td>
<td>3.4 (1.8)</td>
<td>3.3 (1.8)</td>
</tr>
<tr>
<td>Event Rate</td>
<td>2.4</td>
<td>2.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.89 (0.68, 1.2)</td>
<td>0.81 (0.63, 1.0)</td>
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<tr>
<td>p-value</td>
<td>0.40</td>
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Few differences were found between the safety results for the original 2500 and the 3200

<table>
<thead>
<tr>
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<th>2500 Patients HR (95% CI)</th>
<th>3020 Patients HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td><strong>AP Arm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Bleeds</td>
<td>2.1 (1.5, 3.0)</td>
<td>2.0 (1.4, 2.7)</td>
</tr>
<tr>
<td>Death</td>
<td>1.4 (1.0, 1.9)</td>
<td>1.5 (1.1, 2.0)</td>
</tr>
<tr>
<td><strong>BP Arm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Bleeds</td>
<td>1.2 (0.84, 1.6)</td>
<td>1.1 (0.80, 1.5)</td>
</tr>
<tr>
<td>Death</td>
<td>1.2 (0.84, 1.6)</td>
<td>1.0 (0.79, 1.4)</td>
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</tbody>
</table>
What was the impact of increasing the sample size?

- Antiplatelet results did not change appreciably with the addition of the 520 patients
  - Still no difference on the primary endpoint
  - Still large differences in safety outcomes

- These results are highly confounded by the early closure of the antiplatelet arm
  - However, given the actual treatment difference observed, it is still unlikely that we would have observed a statistically significant difference
What was the impact of increasing the sample size?

Blood pressure efficacy results trended towards significance at the end of the study.

Had we stopped at planned study end, we would have missed an interesting result.

Results would have been interpreted as a clearly “negative” trial.

Blood pressure safety results were not impacted by the study modification.
Study adaptation, including sample size re-estimation is a popular trend in clinical trials.

- Allows reassessment of initial study assumptions, which may not be correct.
- Post-hoc review of the impact of the modification is important to help assess the costs and benefits of adaptation.
- In SPS3, the sample size re-estimation helped to provide a clearer answer as to which level of SBP control was more effective in preventing recurrent stroke.
Acknowledgements

- Dr. Christopher Coffey
- Dr. Jeff Szychowski
- Dr. Oscar Benavente
- Dr. Robert Hart

- Members of the SPS3 Steering Committee
- Members of the SPS3 DSMB
- NIH/NINDS U01 NS0385929