THE IMPACT OF VARYING CLUSTER SIZE ON PRECISION IN CROSS-SECTIONAL STEPPED-WEDGE CLUSTER RANDOMISED TRIALS

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Objectives:

- Discuss a method for estimating power in a SW-CRT with unequal clusters sizes in which the sizes are known
- Present a method for estimating power in a SW-CRT with unequal clusters sizes in which the sizes are not known
- Explore the extent to which a SW-CRT is affected by varying cluster size
  - Highlight design characteristics which are most influential
  - Investigate which of a SW-CRT and a parallel CRT is most affected by varying cluster size
Background

Stepped-wedge cluster trial:

- If clusters are equal in size – number of observations under control and intervention condition are equal
- If clusters are not equal in size – number of observations in control and intervention condition depends on randomisation
Motivating Example

- SW-CRT with four general practices randomised over four sequences.

- The clusters sizes are known pre-trial and are unequal—the cluster-period sizes are: 10, 50, 100, and 500 (mean = 165, cv = 0.73).

- The SW-CRT is designed, such that the target difference \( = 0.25 \) (SD: 2); type 1 error = 5%.

- Power can be calculated for each randomisation order:

<table>
<thead>
<tr>
<th>Randomisation Order</th>
<th>A B C D</th>
<th>A B D C</th>
<th>A C B D</th>
<th>A C D B</th>
<th>A D B C</th>
<th>A D C B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82.37%</td>
<td>78.45%</td>
<td>86.30%</td>
<td>78.33%</td>
<td>85.71%</td>
<td>81.52%</td>
</tr>
<tr>
<td>2</td>
<td>83.16%</td>
<td>82.45%</td>
<td>88.98%</td>
<td>81.52%</td>
<td>86.37%</td>
<td>78.33%</td>
</tr>
<tr>
<td>3</td>
<td>87.02%</td>
<td>86.37%</td>
<td>89.04%</td>
<td>85.71%</td>
<td>82.45%</td>
<td>78.45%</td>
</tr>
<tr>
<td>4</td>
<td>89.04%</td>
<td>88.98%</td>
<td>87.02%</td>
<td>86.30%</td>
<td>83.16%</td>
<td>82.37%</td>
</tr>
</tbody>
</table>
## Practical Example – ACS QUIK

- Acute coronary syndrome quality improvement
- 60 clusters over a 2 year period with 5 sequences
- 14,760 patients (246 per cluster – 41 per cluster period)
- High variation of cluster size (CV = 1.64)
- ICC = 0.05, standardised effect size = 0.09

### Power

<table>
<thead>
<tr>
<th>CV</th>
<th>Parallel CRCT using Conventional Methods</th>
<th>SW-CRCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>29.2%</td>
<td>85.4%</td>
</tr>
<tr>
<td>1.64</td>
<td>11.4%</td>
<td>??</td>
</tr>
</tbody>
</table>
Method to estimate power in a SW-CRT when cluster sizes vary (exact sizes unknown)

- Specify:
  - Average cluster size at one time point
  - CV (or variance)
- The cluster sizes are then simulated

- Assumptions
  - Exact cluster sizes are unknown
  - Cluster sizes vary across clusters by a gamma distribution
  - Individual clusters sizes don’t vary over time
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<thead>
<tr>
<th>CV</th>
<th>Parallel CRCT using Conventional Methods</th>
<th>Parallel CRCT using simulation</th>
<th>SW-CRCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>29.2%</td>
<td>29.2%</td>
<td>85.4%</td>
</tr>
<tr>
<td>1.64</td>
<td>11.4%</td>
<td>21.8%</td>
<td>83.3%</td>
</tr>
</tbody>
</table>
Simulation study to explore the impact of design characteristics on precision in a SW-CRT with varying cluster size

Outcome of interest: Relative Efficiency (RE)

\[ RE = \frac{\text{Precision}_{\text{unequal}}}{\text{Precision}_{\text{equal}}} \]

Math formula: \[ R = \frac{M \times \rho}{1 + (M - 1)\rho} \]

\( M = \) Cluster size, \( \rho = \) ICC

Two steps

Twelve steps

Number of clusters | 12, 24, 48, 96
---|---
Number of sequences | 2, 3, 4, 6, 12
CV | 0, 0.5, 0.75, 1.0, 1.25, 1.5
Cluster mean correlation (R) | 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0
Number of simulations | 4000
Relative efficiency of a SW-CRT

A SW-CRT with 12 clusters and 12 sequences

- As cv increases, the relative loss in precision increases (on average)
- As cv increases, the variation in the possible precision increases
- The relative efficiency can be greater than 1
Increasing the number of steps

**SW-CRT with 12 clusters, and \( cv = 1.5 \)**

**Small number of sequences (2)**
- RE upper limit at 1
- Little variation in top 50%

**Large number of sequences (12)**
- RE can be > 1
- Lower average RE
Increasing the number of clusters

- Lower likelihood of imbalance in the number of control and intervention observations
- On average, the relative efficiency increases
- Potential gains or losses become minimised

SW-CRT with 12 sequences, and cv = 1.5
Comparison of a SW-CRT to a parallel CRT (12 clusters, 12 sequences)

- SW-CRT has higher relative efficiency, on average
- More variability in the possible relative efficiency in a SW-CRT
The randomisation order of clusters in a SW-CRT with unequal cluster sizes will affect the power.

How a SW-CRT is impacted by varying cluster size is influenced by the design characteristics.

On average, a SW-CRT is affected less by varying cluster size than a P-CRT.

Potentially, a SW-CRT can offer a more efficient design with unequal cluster sizes than equal cluster sizes – which is impossible in a P-CRT.

Trials should ensure sample size/power calculations acknowledge the variation of cluster size – stratified randomisation may need to be used when possible.
Future work

- Consider impact of varying cluster size in a framework that allows for an alternative correlation structure

- Create a shiny app to allow trialists to see the effects of unequal cluster sizes in their study

- Restricted randomisation method
References
