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

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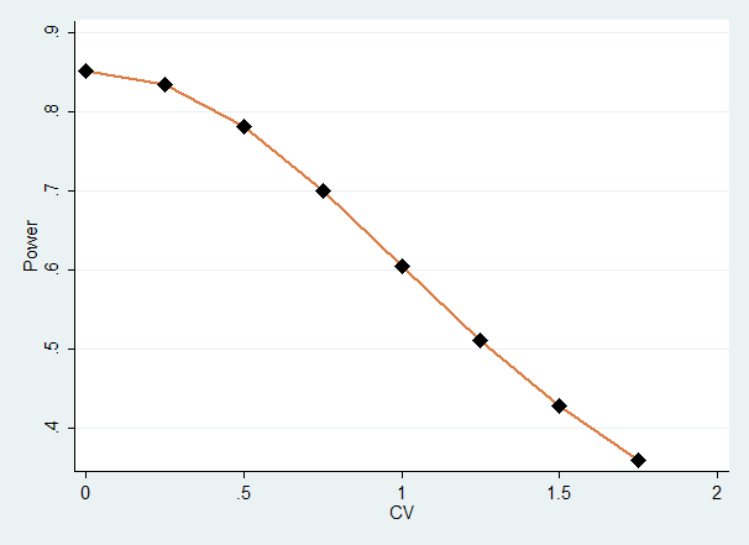
Objectives:

- 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

Parallel Cluster Trial



40 clusters, cluster size = 90, ICC = 0.05, effect size = 0.24

Stepped-wedge Cluster Trial

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

A B C D	A B D C	A C B D	A C D B	A D B C	A D C B
82.37%	*78.45%*	*86.30%*	*78.33%*	*85.71%*	*81.52%*
B A C D	B A D C	B C A D	B C D A	B D A C	B D C A
83.16%	82.45%	88.98%	81.52%	86.37%	78.33%
C A B D	C A D B	C B A D	C B D A	C D A B	C D B A
87.02%	86.37%	89.04%	85.71%	82.45%	78.45%
D A B C	D A C B	D B A C	D B C A	D C A B	D C B A
89.04%	88.98%	87.02%	86.30%	83.16%	82.37%

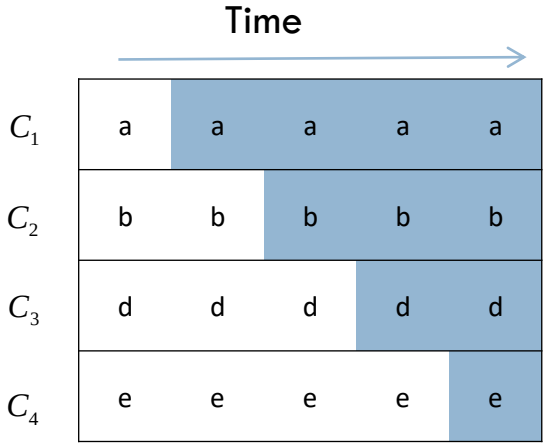
Practical Example – ACS QUIK

- 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	
CV	Parallel CRCT using Conventional Methods	SW-CRCT
0	29.2%	85.4%
1.64	11.4%	??

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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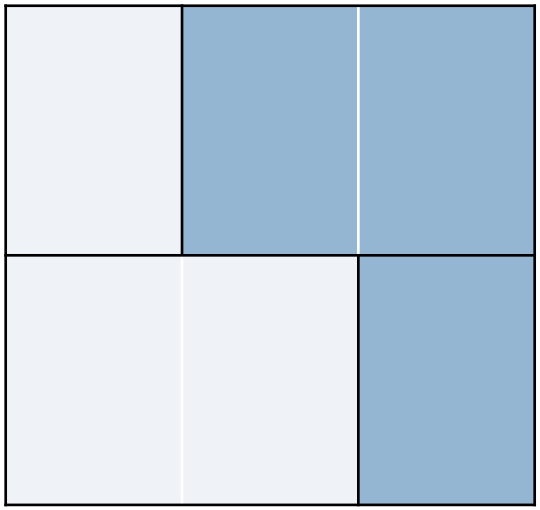
	Power		
CV	Parallel CRCT using Conventional Methods	Parallel CRCT using simulation	SW-CRCT
0	29.2%	29.2%	85.4%
1.64	11.4%	21.8%	83.3%

Simulation study to explore the impact of design characteristics on precision in a SW-CRT with varying cluster size

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



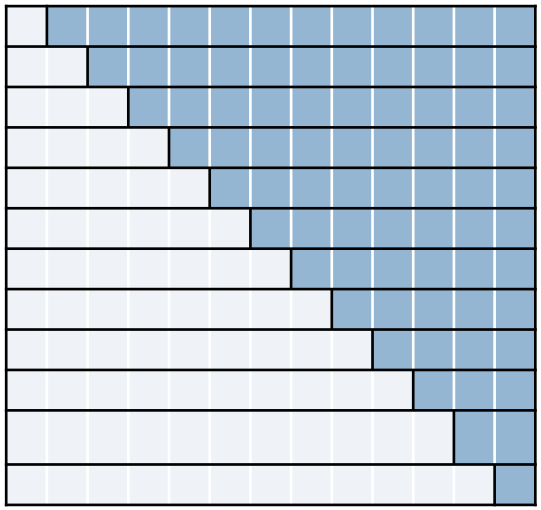
Two steps

$$R = \frac{M \times \rho}{1 + (M - 1)\rho}$$

M = Cluster size, ρ = ICC

Outcome of interest:
Relative Efficiency (RE)

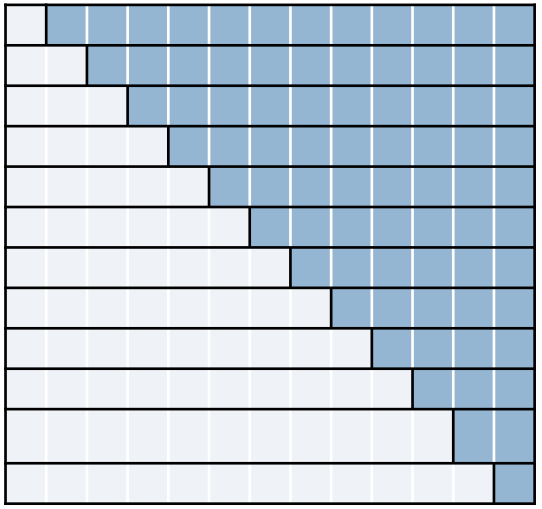
$$RE = \frac{Precision_{unequal}}{Precision_{equal}}$$

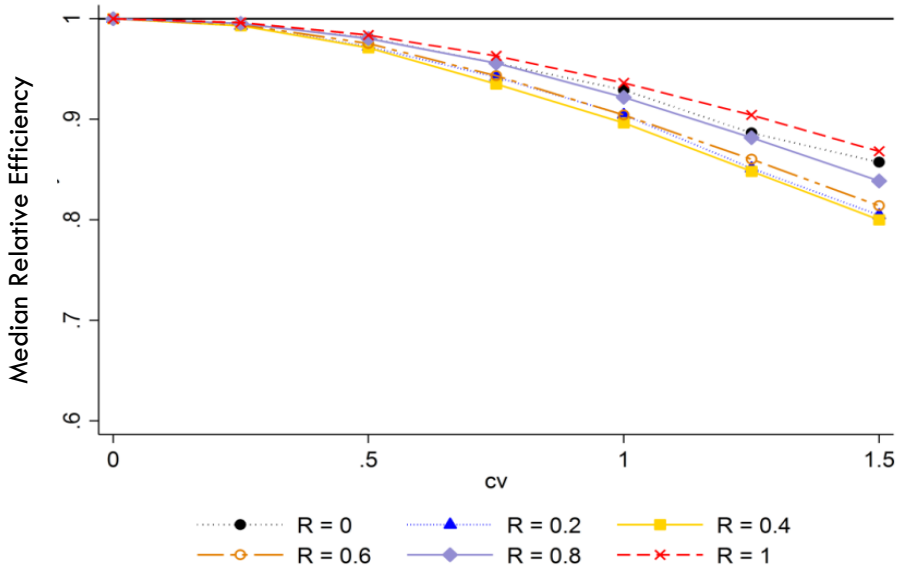


Twelve steps

Relative efficiency of a SW-CRT

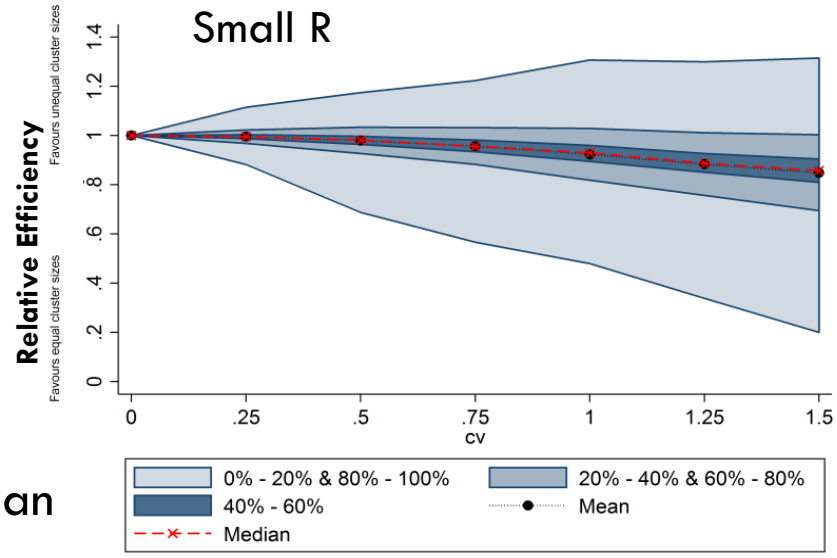
A SW-CRT with 12 clusters and 12 sequences





- 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

Small R

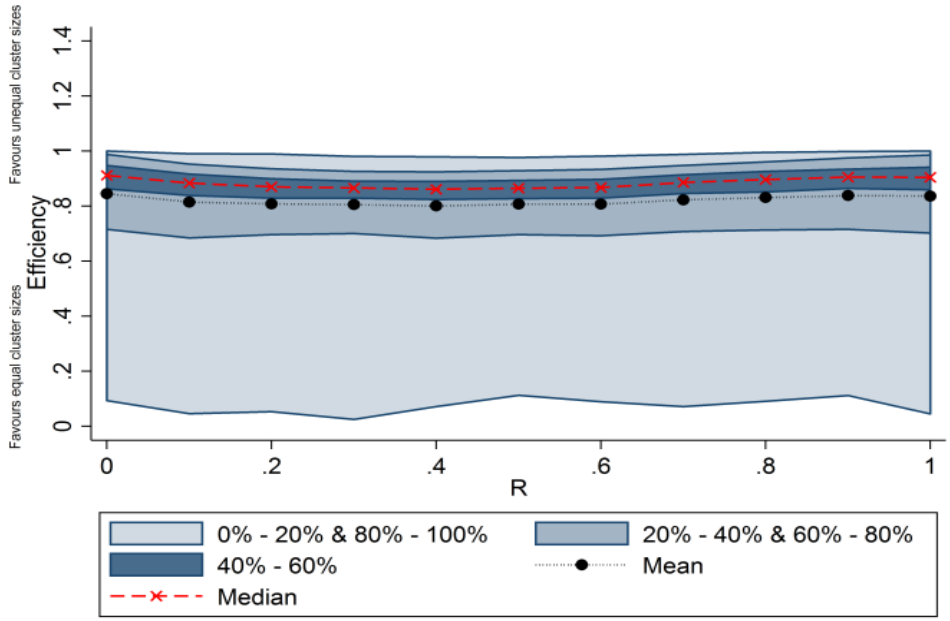


Increasing the number of steps

SW-CRT with 12 clusters, and cv = 1.5

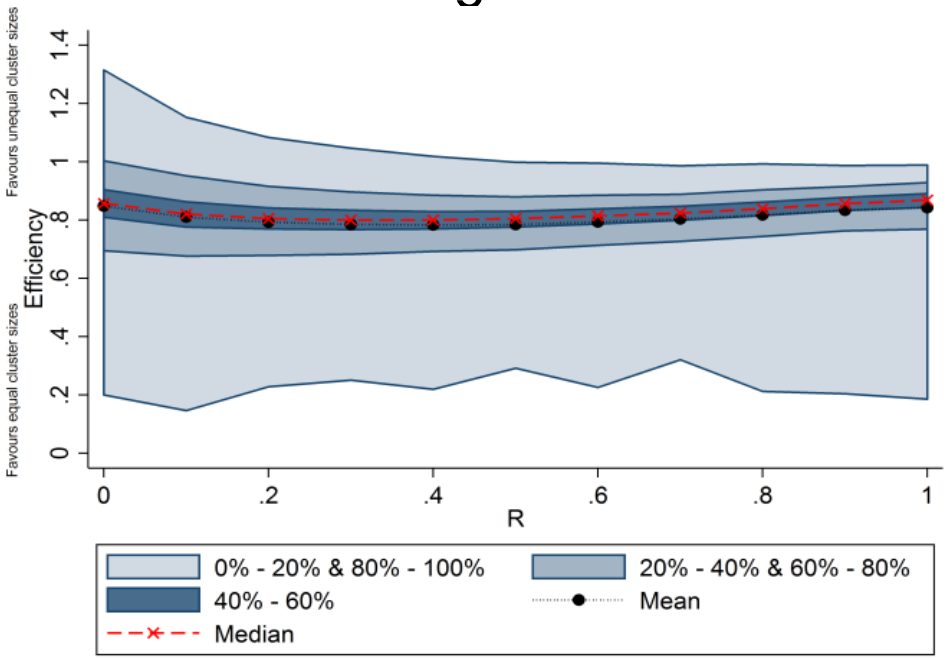
Small number of sequences (2)

- RE upper limit at 1
- Little variation in top 50%

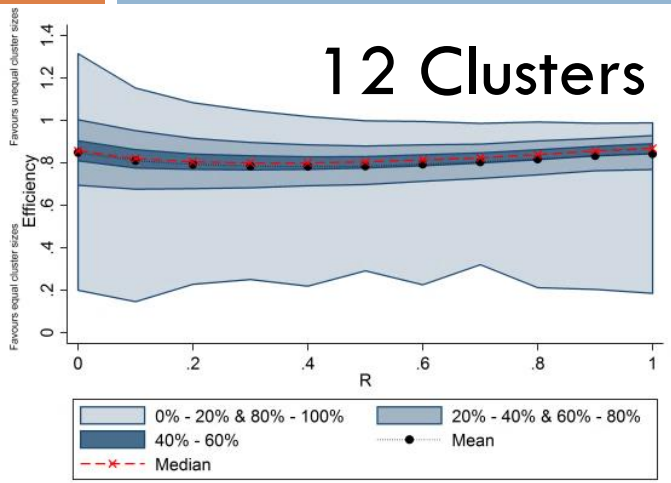


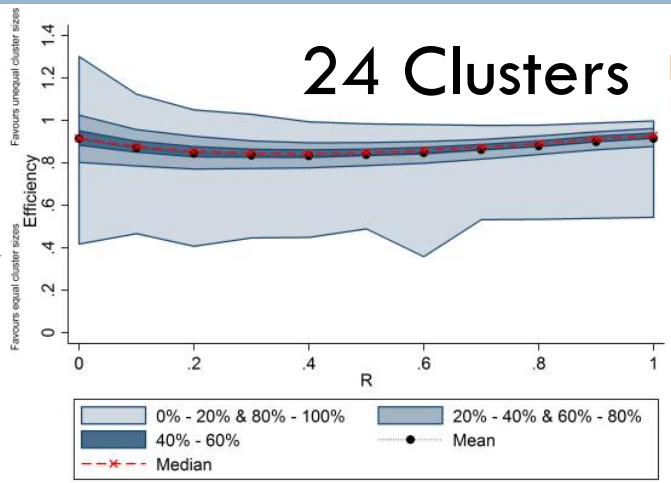
Large number of sequences (12)

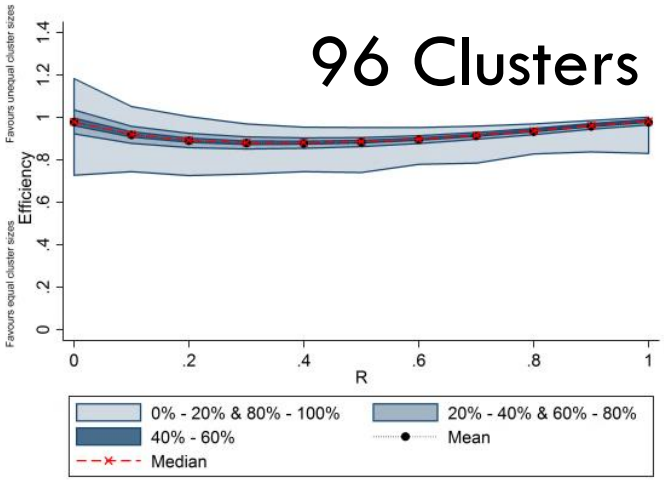
- RE can be > 1
- Lower average RE

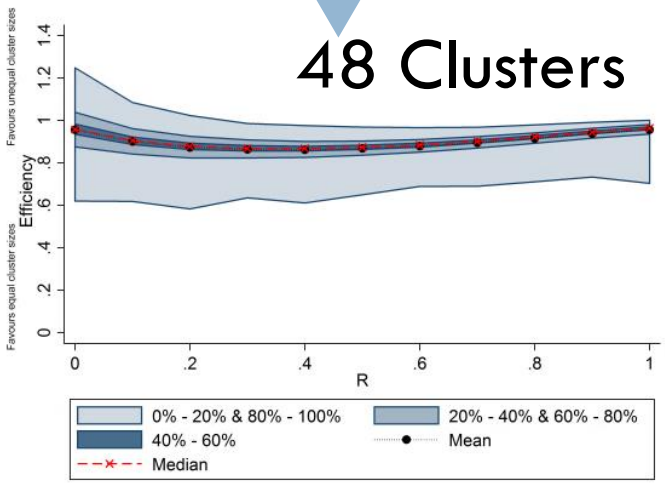


Increasing the number of clusters





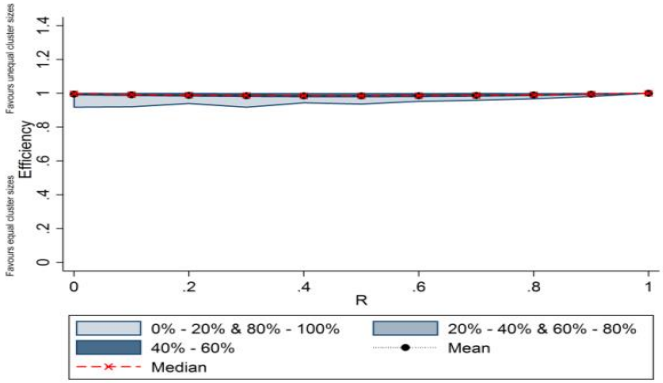
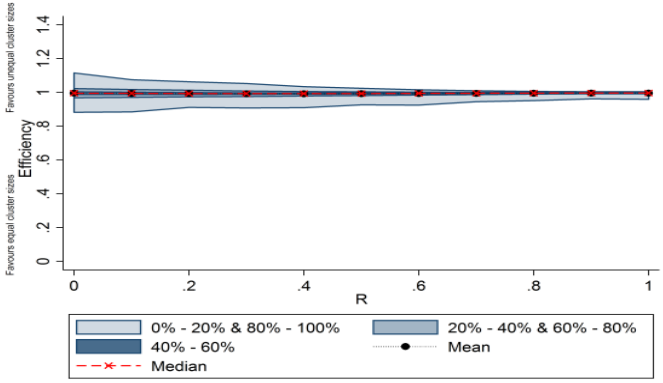
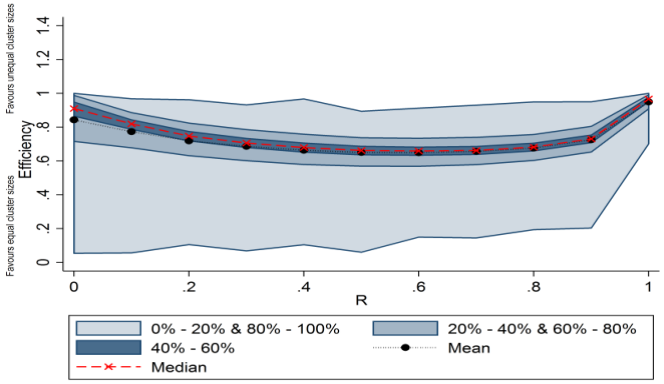
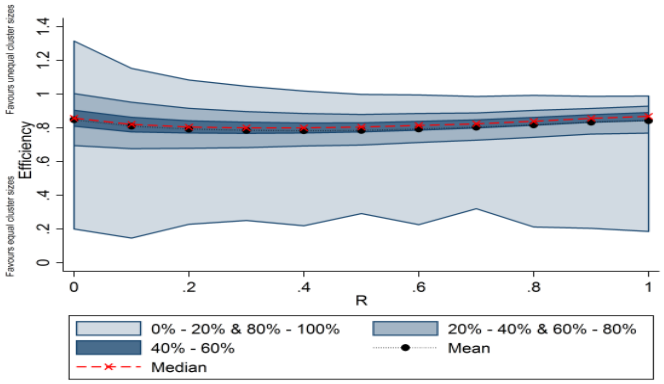




- Lower likelihood of imbalance in the number of control and intervention observations
- On average, the relative efficiency increases
- Potential gains or losses become minimised

SW-CRT with 12 sequences, and cv = 1.5

Comparison of a SW-CRT to a parallel CRT (12 clusters, 12 sequences)

cv	Parallel cluster trial	Stepped-wedge cluster trial
Small		
High		

- SW-CRT has higher relative efficiency, on average
- More variability in the possible relative efficiency in a SW-CRT

Conclusion

- 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 there study
- Restricted randomisation method

References

- M.A Hussey and J.P Hughes, Design and analysis of stepped wedge cluster randomized trials. (2007) Contemporary Clinical Trials, 28 (2), pp. 182-191

- Eldridge,SM, Ashby,D, Kerry,S: Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method. Int J Epidemiol 35:1292-1300, 2006