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Evaluation of a covariate-constrained randomization procedure in stepped wedge cluster randomized trials

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Overview

In stepped wedge (SW) designs, differing cluster-level characteristics or individual-level covariate distributions that differ by cluster can lead to imbalance by treatment arm and potential confounding of the treatment effect.

Adapting a method used in cluster-randomized trials, we propose a covariate-constrained randomization (CCR) method to be used in SW designs. In CCR, the study randomization scheme is chosen from a subset of randomizations with adequate covariate balance by treatment arm. We provide a balance metric for use in SW, guidance for CCR implementation, and recommendations for statistical inference following study data collection.

Stepped wedge design

Stepped wedge (SW) design

- Type of cluster randomized trial (CRT)
- All clusters experience both control/intervention conditions
- Begin on control, then switch over to intervention
- Order that clusters switch to intervention is randomized
- Statistical model is a linear mixed model (1)

Stepped wedge designs are used because:

- Limited number of clusters available (can be more efficient than CRT since each cluster can act as its own control)
- Easier to implement intervention one cluster at a time
- Clusters may be more readily enrolled if they know they will all receive the intervention at a certain point

Covariate imbalance in SW

Rand. A	Time period					Characteristic X % by cluster
Cluster	1	2	3	4	5	
1	0	1	1	1	1	44%
2	0	0	1	1	1	29%
3	0	0	0	1	1	17%
4	0	0	0	0	1	0%

Rand. B	Time period					Characteristic X % by cluster
Cluster	1	2	3	4	5	
3	0	1	1	1	1	17%
4	0	0	1	1	1	0%
1	0	0	0	1	1	44%
2	0	0	0	0	1	29%

0-Control | 1-Intervention

- Two possible randomizations of cluster order: **A** and **B**
- Covariate imbalance by treatment arm likely in randomization **A**: higher proportion of participants with characteristic X in the intervention arm
- Would prefer a randomization with better balance, i.e. **B**

Aims and Methods

AIMS: Develop and evaluate a covariate-constrained randomization (CCR) procedure for use in SW designs.

1) Define a balance metric for use in SW
2) Provide recommendations for CCR procedure use, including:
   (a) candidate set size from balance metric, and
   (b) analysis/inference methods

EVALUATION METHODS: Evaluate the CCR procedure in SW with various design features, types of confounding

- Compare statistical properties of treatment effect estimation bias, power, and type I error
- Analysis with linear mixed models – (a) unadjusted and (b) adjusted for the potential confounders

Results

			Analysis	
Balance[a]	Outcome	Covariate type	Unadjusted	Adjusted for covariates
Good $B_{SW} \leq$ P90	Bias	Cluster-level	Unbiased	Unbiased
		Individual-level	Potential for bias	Unbiased
	Power	Cluster-level	Low (small I/K/ICC[b])	Acceptable
		Individual-level	Low	Acceptable
	Type I error	Cluster-level	Nominal level	Nominal level
		Individual-level	Nominal level	Nominal level

			Analysis	
Balance[a]	Outcome	Covariate type	Unadjusted	Adjusted for covariates
Worst B_{SW} > P90	Bias	Cluster-level	Potential for substantial bias	Bias elevated (small ICC[b])
		Individual-level	Potential for substantial bias	Unbiased
	Power	Cluster-level	Low (small K and ICC[b])	Low (small K and/or ICC[b])
		Individual-level	Low	Low (smallest I/K/ICC[b])
	Type I error	Cluster-level	Elevated (small I/K/ICC[b])	Nominal level
		Individual-level	Elevated (small I/K/ICC[b])	Nominal level

[a]See right panel on definitions of B_{SW} and good/worst balance.
[b]Abbreviations: I = number of clusters, K = number of participants per cluster-period, ICC = intra-class correlation

Discussion and Conclusions

- Covariate-constrained randomization is beneficial in SW
  - In worst balance conditions, potential for biased treatment effect estimates, low power, and elevated type I error
- Researchers should consider potential confounders early in the design phase – determine if CCR is needed
- Recommendation: use B_{SW} metric to define a relatively large candidate set (P80 or P90)
  - Potential concerns for being "over-constrained" if candidate set is too small relative to the number of possible randomizations
- Analyses adjusted for the potential confounders had best properties

Covariate-constrained randomization (CCR)

CCR Steps

1) Assemble information on covariates that vary by cluster and summarize for each cluster (ex: urban/rural site, mean age at site)
2) Generate all possible randomizations and calculate level of covariate balance (B_{SW}) for each one
3) Using the distribution of B_{SW}, define a smaller ***candidate set*** of randomizations where there is an acceptable level of balance
4) Randomly select one cluster randomization scheme from this candidate set for use in study

SW Balance Metric: B_{SW}

Account for the proportion of participants each cluster would contribute to treatment group depending on randomized order

Define z_{il} as a z-score for cluster i and covariate l

Define $p_{i(t=0)}$ as the proportion of participants in cluster i in the control group ($t = 1$, treatment group)

$$B_{SW} = \sum_l w_l \left(\sum_i p_{i(t=0)} z_{il} - \sum_i p_{i(t=1)} z_{il} \right)^2$$

Can use weights (w_l) to signify relative importance of covariate in the balancing

Use B_{SW} to select candidate set

- Smaller values of B_{SW} indicate better balance.
- A common method is to select candidate set based on percentiles (P) of the distribution of B_{SW}.
- We compared the candidate sets defined by the 90th percentile (P90):
  Good balance: $B_{SW} \leq$ P90
  Worst balance: B_{SW} > P90

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