Analysis of the stepped wedge cluster randomized trial with small number of clusters:

An empirical assessment of available methods for a binary outcome

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Outline

- Introduction
- Outline of methods
    - Correlation structure
    - Individual level methods
    - Cluster level methods
- Overview of the Register Now Trial
- Results
- Discussion and complications
- Next steps

Introduction

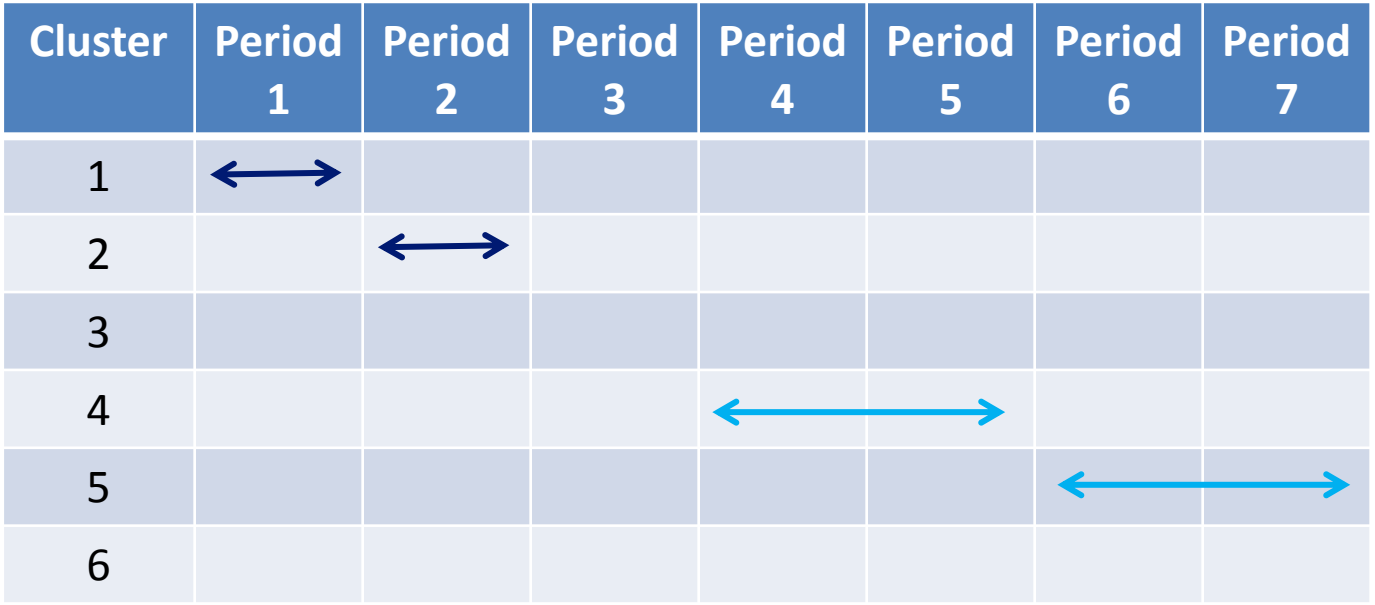
Empirical assessment of Cluster and Individual level analyses:

	Cluster Level	Individual Level
Advantages	Often robust and considered computationally simpler	Can be more efficient with varying cluster sizes
Adjustment	Requires a two stage approach for individual level covariates	Straightforward for individual and cluster-level adjustments
Correlation	Cluster level summaries used	Complex correlation structure needs to be defined and often unknown (within and between-period)
Disadvantages	May be less powerful with varying cluster sizes	Not robust with small sample sizes Computational challenges

- Models can include different effect estimates: mean differences, odds ratios, relative risks
- For non-linear links, the fundamental estimate is different for a cluster level analysis and an individual level analysis.

Outline of methods

- **5 Individual-level methods**
- **Estimating the correlation structure -** Two types of correlations to be specified:
  1. Within-period correlations
  2. Between-period correlations



- **3 Cluster-level methods**

Individual level methods

Method	Fixed effects	Random effects	Correlation
Hussey and Hughes model[1]	Intervention Categorical period	Intercept for cluster	Constant within and between-period
Hooper/Girling model[2]	Intervention Categorical period	Intercept for cluster Random categorical time effect for cluster	Constant between-period (i.e., no decay)
Kasza and Forbes model[3]	Intervention Categorical period	Random categorical time effect for cluster	Exponential decay between-period: AR(1) structure
Random coefficients model	Intervention Continuous period	Intercept for cluster Random slope for continuous time	Flexible correlation structure
Fixed-effects model	Intervention Categorical period Cluster		

1. Hughes et al (2015): Current issues in the design and analysis of stepped wedge trials. Contemporary Clinical Trials 45(PtA): 55
2. Hooper et al (2016): Sample size calculation for stepped wedge and other longitudinal cluster randomised trials. Stat in Med. 35(26):4718
3. Kasza et al (2017): Impact of non-uniform correlation structure on sample size and power in multiple-period cluster randomised trials. Stat Methods Med Res.

Estimated Correlation Structure

Constant ICC over time:

Within-period ICC = **Between-period ICC**

Used in Hussey and Hughes model – does not allow for decay over time

	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7
Period 1	ρ	ρ	ρ	ρ	ρ	ρ	ρ
Period 2		ρ	ρ	ρ	ρ	ρ	ρ
Period 3			ρ	ρ	ρ	ρ	ρ
Period 4				ρ	ρ	ρ	ρ
Period 5					ρ	ρ	ρ
Period 6						ρ	ρ
Period 7							ρ

Estimated Correlation Structure

Fixed between-period ICC and:

Within-period ICC > **Between-period ICC**

Used in Hooper/Girling model – allows for a different within-correlation from between-correlation, which is not allowed to decay over time

	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7
Period 1	ρ	$r\rho$	$r\rho$	$r\rho$	$r\rho$	$r\rho$	$r\rho$
Period 2		ρ	$r\rho$	$r\rho$	$r\rho$	$r\rho$	$r\rho$
Period 3			ρ	$r\rho$	$r\rho$	$r\rho$	$r\rho$
Period 4				ρ	$r\rho$	$r\rho$	$r\rho$
Period 5					ρ	$r\rho$	$r\rho$
Period 6						ρ	$r\rho$
Period 7							ρ

Estimated Correlation Structure

Between ICCs decay exponentially over time:

Within-period ICC **>** **Between-period ICC**

Used in Kasza and Forbes model – allows for an exponential decay over time

	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7
Period 1	ρ	$r\rho$	$r^2\rho$	$r^3\rho$	$r^4\rho$	$r^5\rho$	$r^6\rho$
Period 2		ρ	$r\rho$	$r^2\rho$	$r^3\rho$	$r^4\rho$	$r^5\rho$
Period 3			ρ	$r\rho$	$r^2\rho$	$r^3\rho$	$r^4\rho$
Period 4				ρ	$r\rho$	$r^2\rho$	$r^3\rho$
Period 5					ρ	$r\rho$	$r^2\rho$
Period 6						ρ	$r\rho$
Period 7							ρ

Cluster level methods

Method	Type	Details
Linear mixed-effects regression of cluster-period proportions [1,2]	Parametric	Account for over-time correlation using standard longitudinal methods
A non-parametric within-period method (Thompson et al., 2018) [3]	Non-parametric	1. Calculate within-period differences using only periods 2. Combined across periods using IPW 3. Randomly permute assignment of clusters to sequences 10,000 times and repeat steps
A design-based analysis permutation method [4] (Hughes et al., TBD)	Non-parametric	1. Compute intervention effect for each permutation 2. Compare observed intervention effect to permutation distribution

1. Hussey and Hughes (2007): Design and analysis of stepped wedge cluster randomized trials. Contemporary Clinical Trials 28:182
2. Morgan et al. (2017): Choosing appropriate analysis methods for cluster randomised cross-over trials with binary outcome. Stats in Med. 30:36(2):318
3. Thompson et al. (2018): Robust analysis of stepped wedge trials using cluster-level summaries within periods. Stats in Med. 1-14
4. Hughes et al. (TBD). Robust Inference for stepped wedge designs.

Cluster level methods

Including individual level adjustments in cluster level analyses - Two stage process (Hayes and Moulton)**:**

Stage 1: Obtain covariate adjusted residuals

1. Run regression analysis for the outcome of interest with all covariates except intervention (ignoring clustering)

   output out=<output_dataset> pred = <predicted values>

2. Obtain the observed (d_{ij}) and predicted (e_{ij}) values for the j^{th} cluster and i^{th} treatment arm
3. Obtain the cluster residuals
   1. Ratio-residual: $R_{ij} = \frac{d_{ij}}{e_{ij}}$
   2. Difference-residual: $R_{ij} = \frac{d_{ij} - e_{ij}}{y_{ij}}$, where y_{ij} is total number of individuals

Cluster level methods

Including individual level adjustments in cluster level analyses - Two stage process (Hayes and Moulton)**:**

Stage 1: Obtain covariate adjusted residuals

1. Run regression analysis for the outcome of interest with all covariates except intervention (ignoring clustering **and period effect**)

   output out=<output_dataset> pred = <predicted values>

2. Obtain the observed (d_{ijk}) and predicted (e_{ijk}) values for the j^{th} cluster and i^{th} treatment arm, **and the k^{th} period**
3. Obtain the **cluster-period residuals**
   1. Ratio-residual: $R_{ijk} = \frac{d_{ijk}}{e_{ijk}}$
   2. Difference-residual: $R_{ijk} = \frac{d_{ijk} - e_{ijk}}{y_{ijk}}$, where y_{ijk} is total number of individuals

Cluster level methods

Including individual level adjustments in cluster level analyses - Two stage process (Hayes and Moulton)**:**

Stage 2: Compare adjusted residuals between treatment arms

1. Identify the appropriate methods to evaluate intervention effect
2. Analyze the covariate-adjusted residuals in place of the cluster level summaries
3. Adjust the degrees of freedom: $df = c_1 + c_0 - 2 - p$, where
   - c_i is number of clusters in the intervention arms
   - p is the number of cluster level covariates

Cluster level methods

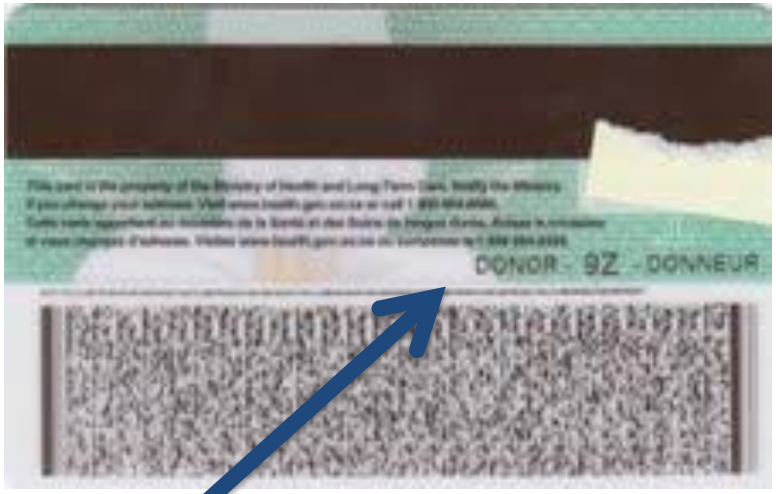
Including individual level adjustments in cluster level analyses - Two stage process (Hayes and Moulton)**:**

Stage 2: Compare adjusted residuals between treatment arms

1. Identify the appropriate methods to evaluate intervention effect
2. Analyze the covariate-adjusted residuals in place of the **cluster-period level** summaries
3. Adjust the degrees of freedom: $\boldsymbol{df = KENWARD\ ROGERS}$,
   - Further exploration needed for the df
   - Alternative option:
     - $C \times P - C - P = 6 \times 7 - 6 - 7 = 29$
     - Where C is the number of clusters and P is the number of periods
   - Would also need to subtract any cluster-period level covariates

Register Now Trial

Current Issue: Not enough organs and current approach (i.e., Service Ontario) may not be appropriate



Register Now Trial

The Organ Donor Registration Collaborative:

The Ottawa Hospital RESEARCH INSTITUTE | L'Hôpital d'Ottawa INSTITUT DE RECHERCHE

LAWSON HEALTH RESEARCH INSTITUTE

Trillium Gift Of Life Network
Ontario's Organ and Tissue Donation Agency

Register Now Trial

The Register Now intervention - 3 key components :

Case finding: Practice reception staff check back of health card for donor status and provides leaflet addressing barriers and enablers and point to iPad

Leaflet: Addresses identified barriers with specific behaviour change techniques

Immediate opportunity to register: iPad in waiting room to register while they wait

Register Now Trial

Period = 2 week interval

UP = Usual Practice

INT = Intervention

Cluster	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7
1	UP	INT	INT	INT	INT	INT	INT
2	UP	UP	INT	INT	INT	INT	INT
3	UP	UP	UP	INT	INT	INT	INT
4	UP	UP	UP	UP	INT	INT	INT
5	UP	UP	UP	UP	UP	INT	INT
6	UP	UP	UP	UP	UP	UP	INT

Li et al (2018). Promoting deceased organ and tissue donation registration in family physician waiting rooms (RegisterNow-1 trial): study protocol for a pragmatic, stepped-wedge cluster randomized controlled registry. *Trials* 21:18(1):610

Register Now Trial

Current Issue: Not enough organs and current approach (i.e., Service Ontario) may not be appropriate

Objective: To promote registration for organ donation in 6 family physician offices

Outcome: Proportion of patients who registered for organ donation within 7 days of their visit

- Effect size: absolute difference in prevalent rates between exposed and unexposed
- Primary analysis: adjusted for age, sex and income quintile

Register Now Trial - Results

Randomized Registry Trial:

- Data routinely collected
  - Organ Donor Registration Dataset
  - Ontario Health Insurance Plan Claims Database
  - Registered Persons Database
- Datasets were linked using unique encoded identifiers and analyzed at ICES.

Population:

- 19,443 patient visits in total
- Average cluster period size: 586 patient visits

Discussion and complications

- **All methods provided similar estimates and interpretation**
  - Minimal difference in the intervention effect

- **Cluster level methods:**
  - Mixed model using cluster level variables allowed for all clusters to contribute to the analysis but can be sensitive to the mis-specification of the correlation for the period effect
  - Thompson et al.’s method only used a portion of the data
    - 3 periods vs. 7
    - 18 cluster-periods vs 42.
  - Hughes et al.'s method assumes variance structure is same for each cluster

Discussion and complications

- **All methods provided similar estimates and interpretation**
  - Minimal difference in the intervention effect

- **Individual level methods:**
  - Consistent message in individual level methods
  - Use of Kenward-Rogers small sample correction was not possible due to excessive computation time
  - Hooper/Girling model had computational issues in unadjusted model
  - Kasza and Forbes model required lengthy computation time

Future work

Cluster level methods:

- Explore two-stage models for the adjustment in cluster-level analyses through a simulation study
- Requires small sample adjustment and a better understanding of the appropriate degrees of freedom
- Unclear the how to apply the CI for Thompson et al., 2017
  - Percentile of the permutations
  - Bootstrap confidence intervals

Individual level methods:

- A robust Poisson regression model using GEE
- Explore random coefficient model with splines for the days of trial (99 days)

Future work

Additional:

- *"Repeated measurements are taken from mostly different individuals in each period; it is possible that a very small proportion of individuals will have repeat visits to their family doctors but because no identifying information will be collected, such individuals will be included in the analysis as independent individuals"*

    - Explore extensions to the proposed models to control for correlation at the individual level
        - The model for closed cohort described in Hopper et al 2016
        - Incorporating a sandwich estimator for repeated measures on individuals

Thank You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