Sample size considerations for stepped wedge designs with subclusters

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What is a Cluster Randomized Trial?

In a cluster randomized trial (CRT) the unit of randomization is a *cluster* instead of an *individual* in a randomized controlled trial (RCT).

One might choose a CRT over a RCT if:

1. There is a high risk of contamination.
2. The goal is evaluate how a practice-wide change affects patient outcomes.

What is a Stepped Wedge Cluster Randomized Trial?

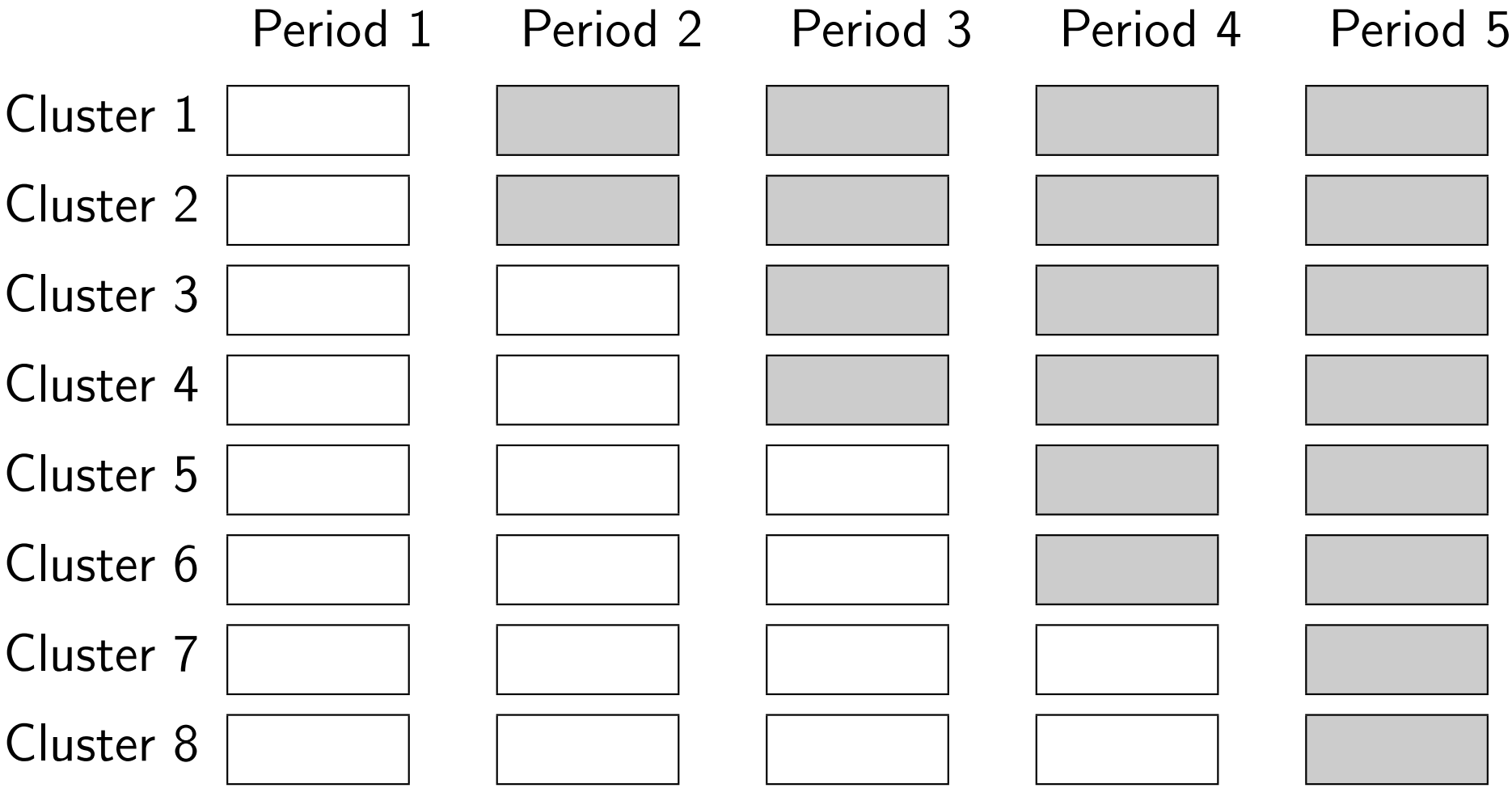
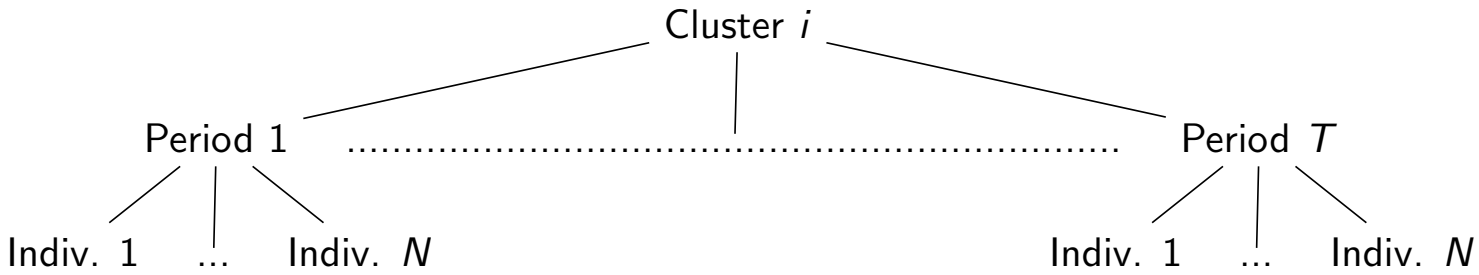


Figure: A schematic illustration of a stepped wedge cluster randomized trial with 8 clusters and 5 periods. Each white cell indicates a cluster-period under the control condition and each gray cell indicates a cluster-period under the intervention condition.

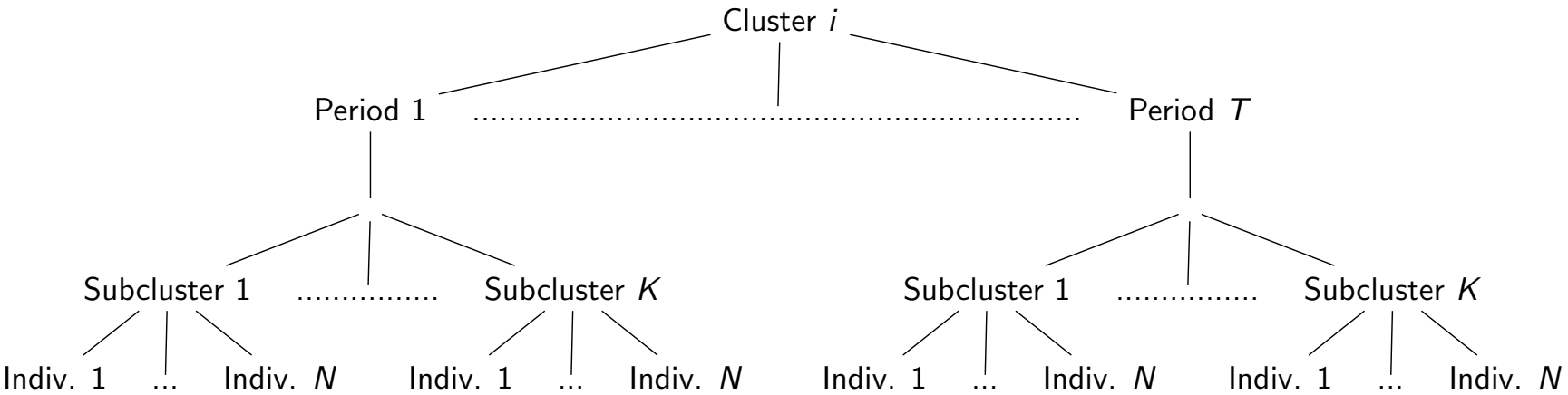
Example of Multilevel SW-CRT

SW-CRT without multiple levels of clustering:



Example: Individuals are nested in hospitals (cluster).

SW-CRT with multiple levels of clustering:



Example: Individuals are nested in primary care providers (subcluster) which are nested in hospitals (cluster).

Motivating Studies: LIRE & EPT Trials

The Lumbar Imaging with Reporting of Epidemiology (LIRE) trial (Jarvik et al., 2015).

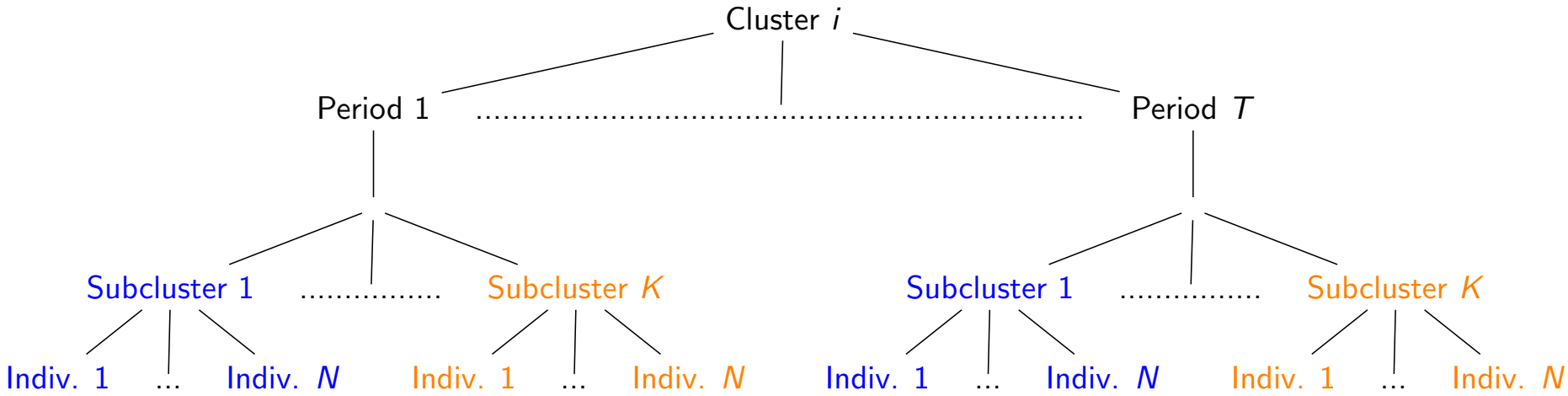
- Randomized clinics consisting of primary care providers.
- Outcome of interest was a composite measure of back pain (Gaussian).

The Washington Expedited Partner Therapy (EPT) trial (Golden et al., 2015).

- Randomized local health jurisdictions containing clinics.
- Outcome of interest was chlamydia reinfection (Binary).

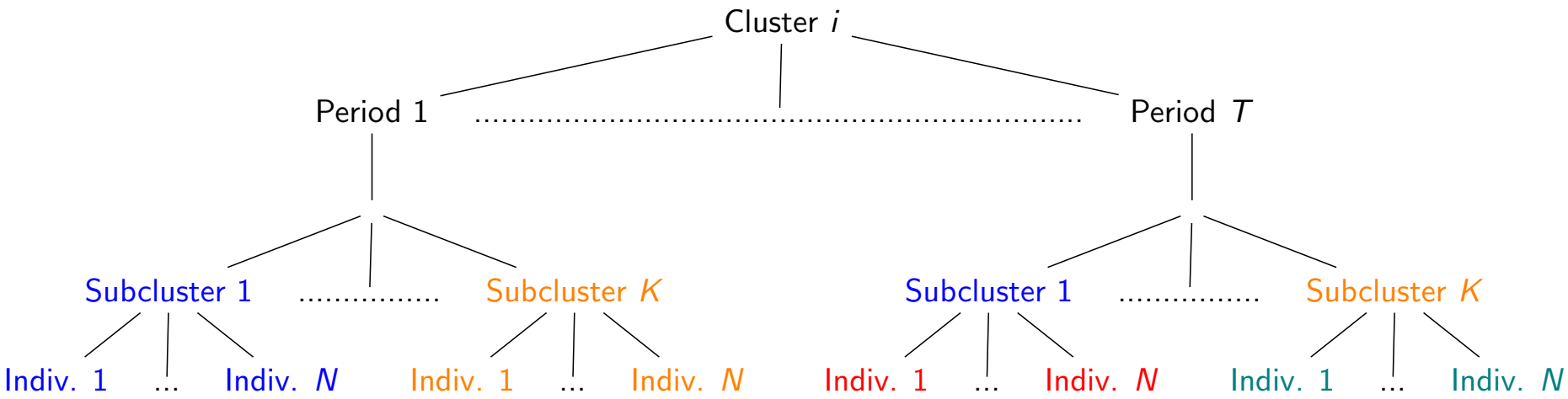
Design Variants under Multilevel Clustering

(A) Closed-cohort design at both the subcluster and subject level



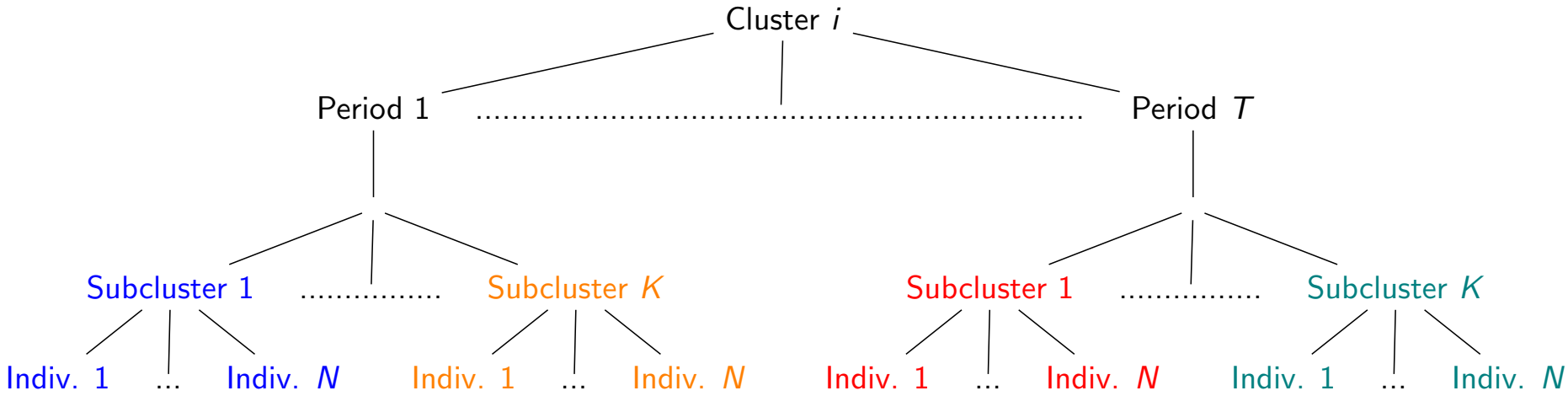
Design Variants under Multilevel Clustering

(B) Closed-cohort design on the subcluster level but a cross-sectional design at the subject level



Design Variants under Multilevel Clustering

(C) Cross-sectional design at both the subcluster and subject level



Current Methods

We want to analyze a trial where participant l is nested in subcluster k sampled at time period j within cluster i.

- Hussey and Hughes (2007) used a linear mixed model (LMM) to take into account correlations within a cluster using a single random effect.

$$Y_{ijkl} = \beta_j + X_{ij}\delta + b_i + \epsilon_{ijkl}$$

- To differentiate the within- and between-period correlations Hooper et al. (2016) extended the LMM (Hussey and Hughes, 2007).

$$Y_{ijkl} = \beta_j + X_{ij}\delta + b_i + s_{ij} + \epsilon_{ijkl}$$

- To take into account multiple levels of clustering Teerenstra et al. (2019) extended the LMM (Hussey and Hughes, 2007).

$$Y_{ijkl} = \beta_j + X_{ij}\delta + b_i + c_{ik} + \epsilon_{ijkl}$$

Gap in Knowledge

Key problem:

- Current methods available are too simplistic. Differentiating the within and between-period correlations are necessary to avoid underpowered trials in SW-CRTs (Taljaard et al., 2016).
- Extensive simulation studies are required in order to explore power estimates across various possible correlation parameters.

Key point of this talk:

- We provide a closed-form variance expression for Gaussian outcomes thus eliminating the need for extensive simulations studies.

Statistical Model

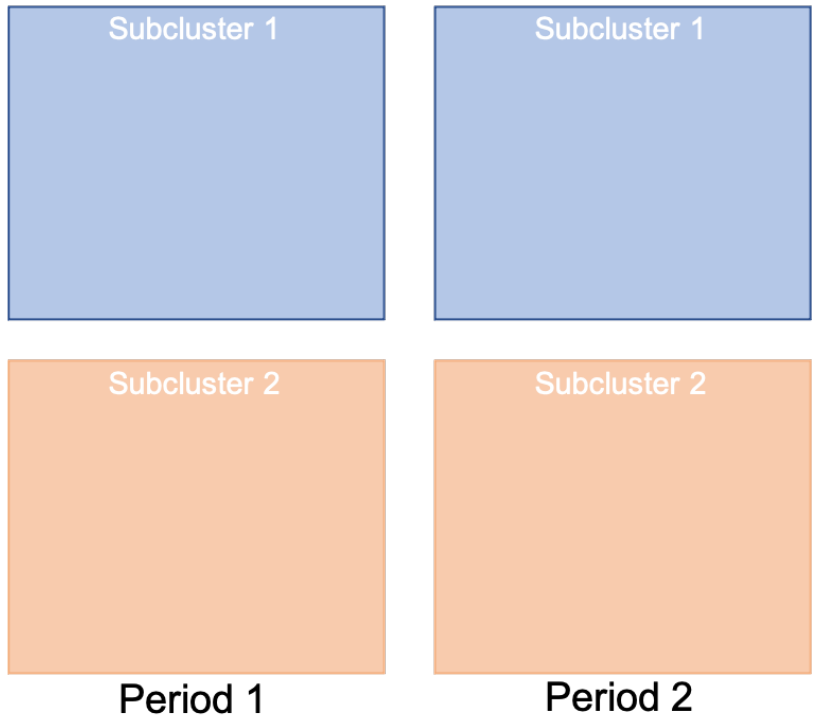
Given our outcome of interest, Y_{ijkl}, for individual $l = 1, ..., N$ nested in subcluster $k = 1, ..., K$ nested in period $j = 1, ..., T$ and cluster $i = 1, ..., I$. We are interested in the following model,

$$\text{LMM: } Y_{ijkl} = \beta_j + X_{ij}\delta + \underbrace{b_i + c_{ik}}_{\text{(sub)cluster}} + \underbrace{s_{ij} + \pi_{ijk}}_{\text{period interactions}} + \underbrace{\gamma_{ikl}}_{\text{within-person}} + \epsilon_{ijkl}$$

β_j is the effect of period j (time effect).
X_{ij} is the intervention indicator for cluster i at period j.
δ is the intervention effect.
$b_i \sim \text{Normal}(0, \sigma_b^2)$ is the random cluster effect.
$c_{ik} \sim \text{Normal}(0, \sigma_c^2)$ is the random subcluster effect.
$s_{ij} \sim \text{Normal}(0, \sigma_s^2)$ is the random cluster-by-period effect.
$\pi_{ijk} \sim \text{Normal}(0, \sigma_\pi^2)$ is the random subcluster-by-period effect.
$\gamma_{ikl} \sim \text{Normal}(0, \sigma_\gamma^2)$ is the random participant effect (if closed-cohort).
$\epsilon_{ijkl} \sim \text{Normal}(0, \sigma_\epsilon^2)$ is the error.

ICCs under Statistical Model

Under this model we have the following intracluster correlation coefficients (ICC),



where the total variance is $\sigma^2 = \sigma_b^2 + \sigma_c^2 + \sigma_s^2 + \sigma_\pi^2 + \sigma_\gamma^2 + \sigma_\epsilon^2$.

Calculating Power

The power to detect a treatment effect $\delta \neq 0$ with nominal type I error rate α is

$$\text{power} \approx \Phi_t \left(t_{\alpha/2,\text{DoF}}; \text{DoF}, |\delta| / \sqrt{\text{var}(\hat{\delta})} \right),$$

where $\Phi_t(t; \text{DoF}, \Lambda)$ is the cumulative t-distribution function with DoF degrees of freedom and noncentrality parameter Λ and $t_{\alpha/2,\text{DoF}}$ is the upper $\alpha/2$th quantile of the central t-distribution.

We used $DoF = I - 2$ which has been found to control type I error rate well (Ford and Westgate, 2020).

We assume an equal number of subclusters and participants across all clusters at all time periods such that $K_{ij} = K$ and $N_{ijk} = N$.

Variance of Intervention Effect

We can generate the variance of our intervention effect, var($\hat{\delta}$), using the feasible generalized least squares (FGLS) estimator

$$\sigma^2(\Sigma_{i=1}^{I} \boldsymbol{Z}_i' \boldsymbol{R}_i^{-1} \boldsymbol{Z}_i)^{-1},$$

where $\boldsymbol{Z}_i$ is the design matrix and $\boldsymbol{R}_i$ is the induced correlation matrix for cluster i.

Given our correlation parameters we can express our extended block exchangeable correlation matrix, $\boldsymbol{R}_i$, as $\boldsymbol{R}_i = \boldsymbol{I}_T \otimes (\boldsymbol{B} - \boldsymbol{C}) + \boldsymbol{J}_T \otimes \boldsymbol{C}$ where

$$\boldsymbol{B} = (1 - \alpha_0)\boldsymbol{I}_{KN} + (\alpha_0 - \rho_0)\boldsymbol{I}_K \otimes \boldsymbol{J}_N + \rho_0 \boldsymbol{J}_{KN}$$
$$\boldsymbol{C} = (\alpha_2 - \alpha_1)\boldsymbol{I}_{KN} + (\alpha_1 - \rho_1)\boldsymbol{I}_K \otimes \boldsymbol{J}_N + \rho_1 \boldsymbol{J}_{KN}$$

Variance of Intervention Effect

$\boldsymbol{R}_i$ has six eigenvalues Graybill (1983),

$$\lambda_1 = 1 - \alpha_0 - \alpha_2 + \alpha_1$$
$$\lambda_2 = 1 - \alpha_0 - \alpha_2 + \alpha_1 + N(\alpha_0 - \alpha_1 - \rho_0 + \rho_1)$$
$$\lambda_3 = 1 - \alpha_0 - \alpha_2 + \alpha_1 + N(\alpha_0 - \alpha_1 + (K-1)(\rho_0 - \rho_1))$$
$$\lambda_4 = 1 - \alpha_0 + (T-1)(\alpha_2 - \alpha_1)$$
$$\lambda_5 = 1 - \alpha_0 + (T-1)(\alpha_2 - \alpha_1) + N(\alpha_0 - \rho_0 + (T-1)(\alpha_1 - \rho_1))$$
$$\lambda_6 = 1 - \alpha_0 + (T-1)(\alpha_2 - \alpha_1) + N(\alpha_0 + (T-1)\alpha_1 + (K-1)(\rho_0 + (T-1)\rho_1))$$

Using Leiva (2007) we can generate a closed-form expression of $\boldsymbol{R}_i^{-1}$

$$\boldsymbol{R}_i^{-1} = \frac{1}{\lambda_1}\boldsymbol{I}_{TKN} - \frac{\lambda_2 - \lambda_1}{N\lambda_1\lambda_2}\boldsymbol{I}_{TK} \otimes \boldsymbol{J}_N + \frac{\lambda_2 - \lambda_3}{KN\lambda_2\lambda_3}\boldsymbol{I}_T \otimes \boldsymbol{J}_{KN} + \frac{1}{T}\left(\frac{1}{\lambda_4} - \frac{1}{\lambda_1}\right)\boldsymbol{J}_T \otimes \boldsymbol{I}_{KN}$$
$$+ \frac{1}{T}\left(\frac{\lambda_2 - \lambda_1}{N\lambda_1\lambda_2} - \frac{\lambda_5 - \lambda_4}{N\lambda_4\lambda_5}\right)\boldsymbol{J}_T \otimes \boldsymbol{I}_K \otimes \boldsymbol{J}_N + \frac{1}{TK}\left(\frac{\lambda_5 - \lambda_6}{N\lambda_5\lambda_6} - \frac{\lambda_2 - \lambda_3}{N\lambda_2\lambda_3}\right)\boldsymbol{J}_{TKN}.$$

Variance of Intervention Effect

Using $\boldsymbol{R}_i^{-1}$ we can derive a closed-form expression for the variance of the intervention effect

$$\text{var}(\hat{\delta}) = \frac{(\sigma^2/KN)IT\lambda_6\lambda_3}{(U^2 + ITU - TW - IV)\lambda_6 - (U^2 - IV)\lambda_3},$$

where $U = \sum_{i=1}^{I}\sum_{j=1}^{T} X_{ij}$, $V = \sum_{i=1}^{I}(\sum_{j=1}^{T} X_{ij})^2$, and $W = \sum_{j=1}^{T}(\sum_{i=1}^{I} X_{ij})^2$ are the same design constants used by Hussey and Hughes (2007) and others.

$$\lambda_3 = 1 - \alpha_0 - \alpha_2 + \alpha_1 + N(\alpha_0 - \alpha_1 + (K-1)(\rho_0 - \rho_1))$$
$$\lambda_6 = 1 - \alpha_0 + (T-1)(\alpha_2 - \alpha_1) + N(\alpha_0 + (T-1)\alpha_1 + (K-1)(\rho_0 + (T-1)\rho_1))$$

Connection to other design variants:

1. Closed-cohort on subcluster level and cross-sectional on participant level ($\alpha_2 = \alpha_1$)
2. Cross-sectional on subcluster (and participant) level ($\alpha_2 = \alpha_1 = \rho_1$)

This expression can be used for each of the three design variants and any type of longitudinal CRT (parallel or crossover designs).

Design Effect

The variance ratio under a multilevel cluster randomized trial design to individual randomization is

$$\text{design effect} = \frac{I^2 T \lambda_6 \lambda_3}{4(U^2 + ITU - TW - IV)\lambda_6 - 4(U^2 - IV)\lambda_3}.$$

$$\lambda_3 = 1 - \alpha_0 - \alpha_2 + \alpha_1 + N(\alpha_0 - \alpha_1 + (K-1)(\rho_0 - \rho_1))$$
$$\lambda_6 = 1 - \alpha_0 + (T-1)(\alpha_2 - \alpha_1) + N(\alpha_0 + (T-1)\alpha_1 + (K-1)(\rho_0 + (T-1)\rho_1))$$

- Design effect increases with increasing within-period ICCs (α_0 and ρ_0).
- Design effect *typically* increases with decreasing between-period ICCs (α_1, ρ_1, and α_2).

Simulation Study: Overview

To validate our sample size methodology we conducted a simulation study. We assumed design variant (B), closed-cohort on the subcluster level and cross-sectional at the individual level ($\alpha_1 = \alpha_2$).

- Number of clusters, I, varied between 8 and 30.
- Number of subclusters, K, varied between 2 and 6.
- Subcluster sizes, N, up to 15.
- Number of periods, T, varied between 4 and 7.
- Standardized effect sizes, δ/σ, ranged between 0.1 and 0.5 (for Gaussian outcomes).
- Three sets of ICCs representing small and large correlations.

Simulation Study: Results (n=1000)

δ/σ	α_0	α_1	ρ_0	ρ_1	I	K	N	T	Test Size	Empirical	Predicted
0.1	0.03	0.015	0.0075	0.00375	24	6	15	7	3.6	88.2	85.3
0.1	0.01	0.005	0.0025	0.00125	30	6	15	4	4.3	82.5	82.2
0.2	0.1	0.05	0.025	0.0125	24	6	10	4	4.5	85.4	83.3
0.2	0.03	0.015	0.0075	0.00375	15	3	10	6	4.0	81.1	80.9
0.2	0.01	0.005	0.0025	0.00125	10	4	10	6	2.7	79.4	80.2
0.25	0.1	0.05	0.025	0.0125	21	4	10	4	5.2	83.7	84.6
0.25	0.03	0.015	0.0075	0.00375	12	2	10	7	3.5	81.0	80.3
0.25	0.01	0.005	0.0025	0.00125	24	2	8	4	4.1	83.7	84.3
0.35	0.1	0.05	0.025	0.0125	10	3	8	6	1.9	83.6	83.1
0.35	0.03	0.015	0.0075	0.00375	9	3	12	4	2.4	84.3	83.8
0.35	0.01	0.005	0.0025	0.00125	8	3	7	5	1.7	77.7	80.4
0.4	0.1	0.05	0.025	0.0125	18	2	7	4	3.2	87.9	86.2
0.4	0.03	0.015	0.0075	0.00375	8	3	7	5	1.1	84.3	83.9
0.4	0.01	0.005	0.0025	0.00125	15	2	5	4	3.3	81.2	83.3
0.5	0.1	0.05	0.025	0.0125	12	2	4	5	3.2	84.3	82.6
0.5	0.03	0.015	0.0075	0.00375	9	2	8	4	1.8	87.4	85.8

Time effect used in simulation: $\beta_1 = 0$ with $\beta_{j+1} - \beta_j = 0.1 \times (0.5)^{j-1}$ for $j \geq 1$.

Application to LIRE Trial

The LIRE trial (Jarvik et al., 2015) randomized 100 clinics consisting of a total of 1700 primary care providers (PCP) over 6 periods.

- Assuming an equal number of PCPs per clinic we have: $I = 100$, $K = 17$, and $T = 6$.

The outcome of interest was spine-related RVUs, a composite measure of back pain. Assuming an effect size of -0.1 and total variance of 2.5, we are interested in calculating the required number of patients per PCP, N, to achieve at least 80% power at the 5% nominal test size.

- Using the ICC estimates from the study design, we assume the following: $\alpha_0 = 0.046$, $\alpha_1 = 0.023$, $\rho_0 = 0.040$, $\rho_1 = 0.020$.
- Using our closed-form expression for $\text{var}(\hat{\delta})$ and the power formula we found that having 77 participants per PCP, $N = 77$, produced 87.5% power.

Additional & Future Work

Additional extensions include:

- Non-Gaussian outcomes under a GLMM.
- Unequal cluster sizes.

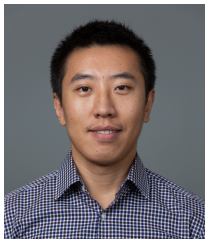
This work was recently published in *Biometrics Methodology* and is available online: `https://onlinelibrary.wiley.com/doi/10.1111/biom.13596`.

Future work in this area includes:

- Extending the current methodology to accommodate a decaying correlation structure.
- Open enrollment.

Collaborators & Funding Source

Thank you to my collaborators:



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Thank you!