

# Stepped Wedge Cluster Randomized Trials

STAT 548 Qualifying Paper

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**Abstract.** TODO

## 1 Introduction

The work of Hussey and Hughes (2007) can be viewed as an entry-point to the study of stepped wedge cluster randomized trials (SW-CRT), which is a type of experimental design that is particularly pragmatic compared to alternative designs that may also be used in similar contexts. In this report, we review the paper by Hussey and Hughes. We summarize the main ideas while filling in missing details, replicate one of the empirical studies with a slight modification, and provide a critique of the paper. We also discuss how the literature on SW-CRTs has developed since the paper was published, and highlight some of the common extensions to the standard model presented in the paper.

This report is organized as follows: Section 2 summarizes the paper and provides additional details where necessary; Section 3 discusses our view and critique of the paper; Section 4 describes modern common extensions to the standard SW-CRT model; and Section 5 concludes this report with a discussion. Appendix A includes some of the longer derivations from Section 2 to avoid disrupting the flow of the summary.

## 2 Summary and additional details

In this section, we summarize the main ideas of the paper by Hussey and Hughes (2007) and provide additional details that we feel are missing from the paper.

### 2.1 Context and motivation

Cluster randomized trials (CRT) are characterized by the randomization to interventions being done at the group or cluster-level rather than at the individual-level, and it is typically assumed that the individuals within a cluster are correlated. CRTs are considered when it is not convenient or not appropriate to administer an intervention to single individuals. Hussey and Hughes (2007) claim that the majority of CRT designs studied and employed (at the time of the paper) featured parallel designs where approximately half of the clusters are simultaneously given one intervention and the other half are simultaneously given another. While these parallel CRTs are convenient analytically, they may present problems in practice if, for example, there are logistical constraints that make delivering the intervention simultaneously across multiple clusters difficult. Other potential issues of parallel designs include ethical concerns where if there is an expectation that a new intervention improves on an existing one, then withholding the new intervention from certain clusters is problematic. Therefore, the main objective of Hussey and Hughes's work is to showcase the

stepped wedge CRT design as an alternative that addresses the potential issues of the parallel design, and to explain how the data collected from such a design are analyzed. In addition, Hussey and Hughes also examine certain statistical considerations of SW-CRT designs, such as power and efficacy of estimators, and how these properties are affected by model assumptions and design parameters.

## 2.2 SW-CRT design

The SW-CRT design is a type of crossover design. However, unlike in standard crossover CRTs where clusters start with possibly different treatments and switches treatments at a determined time point, SW-CRT are characterized by

1. the crossover being unidirectional where all clusters start with the same treatment (the control or an existing treatment) and end with the same treatment (the intervention), and
2. the staggered times at which each cluster switches to the intervention (with the times being randomized across clusters).

Figure 1 from the paper clearly illustrates the differences between the discussed CRT designs.

Parallel		Time	Crossover		Time	Stepped wedge		Time				
		1			1 2			1	2	3	4	5
Cluster	1	1	Cluster	1	1 0	Cluster	1	0	1	1	1	1
	2	1		2	1 0		2	0	0	1	1	1
	3	0		3	0 1		3	0	0	0	1	1
	4	0		4	0 1		4	0	0	0	0	1

Figure 1: Example treatment schedules for parallel, crossover, and stepped wedge CRT designs. The control/existing treatment and the intervention are denoted 0 and 1, respectively. Figure slightly modified from (Hussey & Hughes, 2007).

From Figure 1, it can be seen how the SW-CRT design addresses the practical issues of the parallel design. Rather than simultaneously delivering the intervention to multiple groups, SW-CRTs stagger the delivery to clusters across different times, potentially alleviating logistical concerns. Furthermore, all clusters eventually obtain the intervention, which avoids the problem of withholding the intervention from certain clusters. The SW-CRT design is not without its own complications, however. The staggered times generally means that the duration of the study is elongated relative to the parallel and crossover designs. The unidirectional crossover also implies that time may be correlated with the effect of the intervention, which may lead to issues in estimation of the intervention effect when analyzing the data.

Beyond the general characteristics of SW-CRTs described above, other considerations and design parameters (e.g., cluster sizes, number of clusters crossing over at each time point, new individuals in a cluster across time, etc.) will depend on the context of the specific study. Hussey and Hughes examine the model for a SW-CRT in detail under a specific setting. How the model changes to varying study contexts are only briefly mentioned or, in the case of some variations, not discussed at all. We return to this point in our critique of the paper in Section 3 and again when we discuss model extensions in Section 4.

## 2.3 Assumed setting and SW-CRT model

The SW-CRT model that Hussey and Hughes (2007) examine in their paper can be considered the “basic” or “standard” model and is based on a particular example trial.

### 2.3.1 Expedited Partner Treatment trial

The primary SW-CRT setting that Hussey and Hughes work under is based on the context of the 2012 *Washington State Community Expedited Partner Treatment (EPT) Trial*. The hypothesis of interest in this study was whether a public health program that increases the use of EPT decreases the prevalence of chlamydia in young women and the incidence of gonorrhea in WA state. The intervention—promotion of EPT and targeted provision of partner services—was instituted in 23 WA state local health jurisdictions (LHJ) across four waves separated by 6–9 months. Each wave included approximately six LHJs, and the order in which LHJs initiated the intervention were randomly assigned. The measured primary outcomes in the study included the prevalence of chlamydia in women aged 15–25 who tested positive in participating clinics and the incidence of gonorrhea in women as ascertained through public health reporting.

One of the key design aspects to consider for modeling is how the clusters and the individuals are defined. For example, in the chlamydia study of the EPT trial, the individual LHJs are the clusters, and the individuals in a cluster are the women who were tested in a participating clinic during a particular timeframe. It is also important to note that the women within a single cluster likely differ at different time points over the trial (i.e., the study uses a cross-sectional CRT). While the number of women who were tested likely varied between LHJs and across time within a single LHJ, there were likely more than enough women tested that only a sample of women for each time point and for each LHJ were sufficient for fitting a reasonable model. In this scenario, it is analytically more convenient to take samples of equal sizes across LHJs and across time.

Another aspect to consider is the form of the outcome. In the EPT trial, the measured outcomes are prevalence of chlamydia and incidence of gonorrhea, both of which are continuous measures. Thus, based on the EPT trial, Hussey and Hughes examine a continuous outcome SW-CRT model that assumes a cross-sectional design and fixed cluster sizes.

### 2.3.2 SW-CRT model

A linear mixed effects model (LMM) can be used to model the SW-CRT design described under the setting in the previous section. Assuming that there are  $I$  clusters,  $T$  time points, and  $N$  individuals in each cluster at each time point, we can define the mean for cluster  $i$  at time  $j$  as

$$\mu_{ij} = \mu + \alpha_i + \beta_j + X_{ij}\theta$$

where

- $\mu$  is the overall mean across clusters and time,
- $\alpha_i \sim N(0, \tau^2)$  is a random effect for cluster  $i \in \{1, \dots, I\}$  that captures the correlation between individuals,
- $\beta_j$  is a fixed effect for time point  $j \in \{1, \dots, T-1\}$  (assuming  $\beta_T = 0$  for identifiability),
- $X_{ij}$  is a treatment indicator for cluster  $i$  at time  $j$  with 1 denoting the intervention, and
- $\theta$  is the treatment effect of interest.

Using a slightly different notation from Hussey and Hughes, a model at the individual-level is then given by

$$Y_{ijk} = \mu_{ij} + e_{ijk}$$

where  $e_{ijk} \sim N(0, \sigma^2)$  are i.i.d. noise, and a model at the cluster-level is then given by

$$\bar{Y}_{ij} = \mu_{ij} + \frac{1}{N} \sum_{k=1}^N e_{ijk}.$$

As mentioned, this model can be considered the standard model for a SW-CRT design as the assumptions it makes are fairly basic. The model can be extended many ways depending on the setting of the specific study. We revisit this point in Section 4.

Aside from the model itself, two other quantities obtained from the model are also commonly referred to in the CRT literature. These two quantities are the intraclass correlation (ICC)  $\rho = \frac{\tau^2}{\tau^2 + \sigma^2}$  (and its induced variation inflation factor  $1 + (N - 1)\rho$ ) and the coefficient of variation (CV)  $\frac{\tau}{\mu}$ . These quantities characterize the effect of the within-cluster correlation on the cluster mean variance and are often the parameters being adjusted in CRT simulation studies. We provide some additional intuition for these quantities in Appendix A.1.

## 2.4 Methods and analysis

Hussey and Hughes (2007) discuss several ideas related to estimation and analysis of the statistical model for a SW-CRT. We highlight the key points in this section. Note that when discussing an estimator or one its statistical properties, Hussey and Hughes provide only the result in most cases and exclude the explanation or derivation from the paper. We fill in the missing details for the key points of discussion in Appendix A.

### 2.4.1 Estimation of the treatment effect

The general objective when analyzing data from a SW-CRT is to estimate and test the treatment effect  $\theta$ . When the variance components  $\tau^2$  and  $\sigma^2$  are known, a cluster-level estimation of  $\theta$  is possible using weighted least squares (WLS). While this approach is useful for conducting a pre-trial power analysis, it is generally the case in practice that  $\tau^2$  and  $\sigma^2$  are unknown. When the variance components are unknown, an individual-level analysis using generalized linear mixed effects models (GLMM) or generalized estimating equations (GEE) will likely be the preferred approach. Hussey and Hughes caution that the LMM, GLMM, and GEE approaches all rely on asymptotic results, and so an analysis of a SW-CRT involving few clusters or time points may produce misleading findings.

Hussey and Hughes note that when there are no time effects on the outcome (i.e., when  $\beta_j = 0$  for all  $j$ ), estimation of the treatment effect  $\theta$  can be done using a within-cluster analysis (an analysis based on comparing the control and intervention time periods for each cluster). This case also allows testing of the treatment effect using a paired t-test where the two groups correspond to the control and the intervention time periods. However, if it is incorrectly assumed that the time effects are trivial, the estimator for  $\theta$  will be biased. We provide additional details about the estimator and the bias in Appendix A.2.

Hussey and Hughes also discuss the relative efficiency of the WLS estimator of the treatment effect compared to the within-cluster estimator. When there are no time effects, the WLS estimator is always more efficient than the within-cluster estimator (unless  $\tau^2 = 0$ ). When there are time effects, the within-cluster estimator is more efficient (but likely biased). We provide further details for these statements in Appendix A.3.

### 2.4.2 Power and relevant factors

To test the hypothesis  $H_0 : \theta = 0$  against a simple alternative  $H_a : \theta = \theta_a$  in the general case, Hussey and Hughes (2007) prescribe using a Wald test with the test statistic

$$Z = \frac{\hat{\theta}}{\sqrt{\text{Var}(\hat{\theta})}}.$$

The power for a two-tailed test of size  $\alpha$  is then

$$\text{power} \approx \Phi \left( \frac{\theta_a}{\sqrt{\text{Var}(\hat{\theta})}} - Z_{1-\frac{\alpha}{2}} \right)$$

where  $\Phi$  is the cumulative distribution function of the standard normal and  $Z_{1-\frac{\alpha}{2}}$  is the  $(1 - \frac{\alpha}{2})$ -quantile of the standard normal. We provide additional details about the Wald test and the power calculation in Appendix A.4.

Hussey and Hughes also discuss how the power decreases with fewer measured time points and with delays in the treatment effect. Both of these factors are more of a concern when there are constraints on the duration of the trial. The decrease in power can be mitigated by allowing for more time points (i.e., fewer clusters randomized to each time point) and by increasing the length of each time interval to allow for the treatment effect to realize over fewer time points. We provide an explanation for these statements in Appendix A.5.

## 2.5 Simulation study of analysis methods

Hussey and Hughes (2007) performed a simulation study to compare the power of the test  $H_0 : \theta = 0$  versus  $H_a : \theta \neq 0$  in a SW-CRT analysis using LMM, GEE, and GLMM. The case of equal cluster sizes and the case of unequal cluster sizes were both investigated. Their results suggest that LMM has greater power than the other two methods when the cluster sizes are equal, and otherwise GEE and GLMM have greater power. They explain that when the cluster sizes are unequal, the clusters need to be weighted in LMM, but the weights will depend on the true (unknown) variance components.

## 3 Critical appraisal

TODO

## 4 Extensions of the standard model

TODO

- cluster sizes
- delayed treatment effect
- cluster-time random effects
- non-normal response
- cross-sectional vs cohort
- bayesian

## 5 Discussion

## References

- Hussey, M. A., & Hughes, J. P. (2007). Design and analysis of stepped wedge cluster randomized trials. *Contemporary clinical trials*, 28(2), 182–191.

## A Appendix

TODO

### A.1 ICC and CV

### A.2 Within-cluster estimator for treatment effect

Let  $t_i \in \{1, \dots, T-1\}$  be the last time point at which cluster  $i$  receives the control/existing intervention. When there are no time effects on the outcome, the within-cluster estimator for the treatment effect given by Hussey and Hughes (2007) is

$$\tilde{\theta} = \frac{1}{I} \sum_{i=1}^I \left( \frac{\sum_{j=t_i+1}^T \bar{Y}_{ij.}}{T-t_i} - \frac{\sum_{j=1}^{t_i} \bar{Y}_{ij.}}{t_i} \right).$$

Each term in the sum corresponds to a particular cluster, and each term calculates the difference in the mean outcome between the intervention and the control periods of that cluster. Note that the estimator is only unbiased when there are no time effects, as

$$\begin{aligned} \mathbb{E}[\tilde{\theta}] &= \frac{1}{I} \sum_{i=1}^I \left( \frac{\sum_{j=t_i+1}^T \mathbb{E}[\bar{Y}_{ij.}]}{T-t_i} - \frac{\sum_{j=1}^{t_i} \mathbb{E}[\bar{Y}_{ij.}]}{t_i} \right) \\ &= \frac{1}{I} \sum_{i=1}^I \left( \frac{\sum_{j=t_i+1}^T (\mu + \alpha_i + \beta_j + \theta)}{T-t_i} - \frac{\sum_{j=1}^{t_i} (\mu + \alpha_i + \beta_j)}{t_i} \right) \\ &= \frac{1}{I} \sum_{i=1}^I \left( \frac{\sum_{j=t_i+1}^T (\mu + \alpha_i + \theta)}{T-t_i} - \frac{\sum_{j=1}^{t_i} (\mu + \alpha_i)}{t_i} \right) \quad (*) \\ &= \frac{1}{I} \sum_{i=1}^I (\mu + \alpha_i + \theta - \mu - \alpha_i) \\ &= \theta \end{aligned}$$

where the line (\*) follows from the assumption of no time effects. When there are time effects, the estimator is biased with the bias being

$$\begin{aligned} \text{bias}(\tilde{\theta}, \theta) &= \mathbb{E}[\tilde{\theta}] - \theta \\ &= \frac{1}{I} \sum_{i=1}^I \left( \frac{\sum_{j=t_i+1}^T (\mu + \alpha_i + \beta_j + \theta)}{T-t_i} - \frac{\sum_{j=1}^{t_i} (\mu + \alpha_i + \beta_j)}{t_i} \right) - \theta \\ &= \frac{1}{I} \sum_{i=1}^I \left( \frac{\sum_{j=t_i+1}^T \beta_j}{T-t_i} + \theta - \frac{\sum_{j=1}^{t_i} \beta_j}{t_i} \right) - \theta \\ &= \frac{1}{I} \sum_{i=1}^I \left( \frac{\sum_{j=1}^T \beta_j X_{ij}}{T-t_i} - \frac{\sum_{j=1}^T \beta_j (1-X_{ij})}{t_i} \right) \\ &= \frac{1}{I} \sum_{j=1}^T \beta_j \sum_{i=1}^I \frac{t_i X_{ij} - (T-t_i)(1-X_{ij})}{t_i(T-t_i)} \\ &= \sum_{j=1}^T \beta_j \sum_{i=1}^I \frac{t_i - T(1-X_{ij})}{It_i(T-t_i)}, \end{aligned}$$

which is the form given by Hussey and Hughes.

### A.3 Relative efficiency of WLS and within-cluster estimator

Let  $\hat{\theta}$  denote the WLS estimator of  $\theta$ , that is, for the WLS solution

$$\hat{\eta} = (\hat{\mu}, \hat{\beta}_1, \dots, \hat{\beta}_{T-1}, \hat{\theta}) = (\mathbf{X}^T \mathbf{W}^{-1} \mathbf{X})^{-1} \mathbf{X}^T \mathbf{W}^{-1} \mathbf{y}$$

where  $\mathbf{X}$  is the  $IT \times (T+1)$  design matrix,  $\mathbf{y}$  is the vector of cluster means of length  $IT$ , and  $\mathbf{W} = \text{Var}(\mathbf{y})$  is the  $IT \times IT$  block diagonal matrix with each  $T \times T$  block describing the correlation structure of a cluster over time given by

$$\begin{bmatrix} \tau^2 + \frac{\sigma^2}{N} & \tau^2 & \dots & \tau^2 \\ \tau^2 & \ddots & & \vdots \\ \tau^2 & & \ddots & \tau^2 \\ \tau^2 & \dots & \tau^2 & \tau^2 + \frac{\sigma^2}{N} \end{bmatrix}.$$

Let  $\mathbf{e}_i$  represent the unit column vector with a 1 in the  $i$ -th position. The variance of  $\hat{\theta}$  is given by

$$\begin{aligned} \text{Var}(\hat{\theta}) &= \mathbf{e}_{T+1}^T (\mathbf{X}^T \mathbf{W}^{-1} \mathbf{X})^{-1} \mathbf{X}^T \mathbf{W}^{-1} \text{Var}(\mathbf{y}) \mathbf{W}^{-1} \mathbf{X}^T (\mathbf{X}^T \mathbf{W}^{-1} \mathbf{X})^{-1} \mathbf{e}_{T+1} \\ &= \mathbf{e}_{T+1}^T (\mathbf{X}^T \mathbf{W}^{-1} \mathbf{X})^{-1} \mathbf{e}_{T+1} \end{aligned}$$

and the variance is given by

$$\text{Var}(\tilde{\theta}) = \frac{\sigma^2}{NI^2} \sum_i \left( \frac{1}{t_i} + \frac{1}{T-t_i} \right)$$

The relative efficacy of the WLS estimator  $\hat{\theta}$  versus the within-cluster estimator  $\tilde{\theta}$  is given by the inverse ratio of the variances. If there are no time effects, the ratio is

$$\text{efficiency}(\hat{\theta}, \tilde{\theta}) = \frac{\sum_i \left( \frac{1}{t_i} + \frac{1}{T-t_i} \right) \left( ITU - U^2 \right) \frac{\sigma^2}{N} + IT(TU - V)\tau^2}{I^3 \left( \frac{\sigma^2}{N} + T\tau^2 \right)}$$

When there are no time effects, the WLS estimator is more efficient than the within-cluster estimate unless  $\tau^2 = 0$ . If there are time effects, the WLS estimator is less efficient but the within-cluster estimator is likely biased.

Note:  $\text{Var}(\hat{\theta})$  is not the one given above as it is assumed there are no time effects.

$$\begin{aligned} \text{efficacy}(\hat{\theta}, \tilde{\theta}) &= \frac{\text{Var}(\tilde{\theta})}{\text{Var}(\hat{\theta})} \\ &= \frac{\left( \frac{\sigma^2}{NI^2} \sum_i \left( \frac{1}{t_i} + \frac{1}{T-t_i} \right) \right)}{\left( \frac{I\sigma^2 \left( \frac{\sigma^2}{N} + T\tau^2 \right)}{(IU-W)\sigma^2 + N(U^2 + ITU - TW - IV)\tau^2} \right)} \\ &= \frac{\sum_i \left( \frac{1}{t_i} + \frac{1}{T-t_i} \right) ((IU - W)\sigma^2 + N(U^2 + ITU - TW - IV)\tau^2)}{NI^3 \left( \frac{\sigma^2}{N} + T\tau^2 \right)} \\ &= \frac{\sum_i \left( \frac{1}{t_i} + \frac{1}{T-t_i} \right) \left( (IU - W) \frac{\sigma^2}{N} + (U^2 + ITU - TW - IV)\tau^2 \right)}{I^3 \left( \frac{\sigma^2}{N} + T\tau^2 \right)} \end{aligned}$$

### A.4 Wald test and power

### A.5 Measured time points and delayed treatment effect on power

### A.6 Introduction

- In cluster randomized trials (CRTs), randomization of interventions are done at the level of groups rather than individuals. This is most useful when intervention can only be administered at the



community-level, when contamination may be an issue, or for other reasons. The individual units within a cluster are correlated.

- In parallel CRTs, clusters are all assigned an intervention at a single time point. If cluster sizes are equal, t-tests/ANOVA may be used to compare cluster-level mean responses. Clusters may also be matched for a paired setup. When cluster sizes vary, individual level analyses such as generalized estimating equations (GEE) or random effects models may be used.
- In crossover CRTs, each interventions is applied to a cluster at different time points (with a possible “washout” period in between). The order of the interventions is randomized for each cluster. Crossover designs are less commonly used in CRTs due to extending the period of the study. Crossover CRTs usually use paired t-tests to make within-cluster comparisons.
- In a stepped wedge CRT, clusters cross from one intervention to another at different time points (typically all starting from the control intervention and all ending with the treatment intervention). The time at which each cluster crosses over is randomized. The stepped wedge CRT is useful when there are limited resources for applying the intervention. The key features of the stepped wedge CRT is that the crossover is unidirectional and that the intervention is never removed once implemented. The unidirectionality does complicate the analysis as the treatment effect cannot be estimated from only within-cluster comparisons.

## A.7 Model

- For a design with  $I$  clusters,  $T$  time points,  $N$  individuals sampled per cluster per time interval, define the cluster means

$$\mu_{ij} = \mu + \alpha_i + \beta_j + \theta X_{ij}$$

where

- $\alpha_i \sim N(0, \tau^2)$  is a random effect for cluster  $i \in \{1, \dots, I\}$
- $\beta_j$  is a fixed effect for time interval  $j \in \{1, \dots, T-1\}$  (with  $\beta_T = 0$  for identifiability)
- $X_{ij}$  is the intervention indicator in cluster  $i$  at time  $j$  (with 1 denoting intervention)
- $\theta$  is the treatment effect.

- Individual level responses are modelled as

$$Y_{ijk} = \mu_{ij} + \epsilon_{ijk}$$

where  $\epsilon_{ijk} \stackrel{iid}{\sim} N(0, \sigma^2)$ . Cluster means are modelled as

$$\bar{Y}_{ij.} = \mu_{ij} + \bar{\epsilon}_{ij.}$$

where  $\bar{\epsilon}_{ij.} = \frac{\sum_k \epsilon_{ijk}}{N}$ . Assume that  $\epsilon_{ijk}$  are independent of  $\alpha_i$ .

- The variance of the individual-level response is

$$\text{Var}(Y_{ijk}) = \tau^2 + \sigma^2$$

The variance of the cluster-level response is

$$\text{Var}(\bar{Y}_{ij.}) = \tau^2 + \frac{\sigma^2}{N} = \left( \frac{\tau^2 + \sigma^2}{N} \right) (1 + (N-1)\rho)$$

where  $(1 + (N - 1)\rho)$  is the “variance inflation factor” and  $\rho = \frac{\tau^2}{\tau^2 + \sigma^2}$  is the intraclass correlation. Note:

$$\begin{aligned} \left( \frac{\tau^2 + \sigma^2}{N} \right) (1 + (N - 1)\rho) &= \left( \frac{\tau^2 + \sigma^2}{N} \right) \left( 1 + \frac{(N - 1)\tau^2}{\tau^2 + \sigma^2} \right) \\ &= \frac{\tau^2 + \sigma^2}{N} + \frac{N\tau^2(\tau^2 + \sigma^2)}{N(\tau^2 + \sigma^2)} - \frac{(\tau^2 + \sigma^2)\tau^2}{N(\tau^2 + \sigma^2)} \\ &= \frac{\tau^2 + \sigma^2}{N} + \tau^2 - \frac{\tau^2}{N} \\ &= \tau^2 + \frac{\sigma^2}{N} \end{aligned}$$

- Some characterize the cluster effect on the variance using the coefficient of variation (CV)  $\frac{\tau}{\mu}$ .
- If the individual level responses are binary, then the cluster-level response  $\bar{Y}_{ij}$  is a proportion and it is assumed  $\sigma^2 = \mu(1 - \mu)$ .
- For varying-sized clusters, replace  $N$  with  $N_{ij}$ .

## A.8 Data analysis

### A.8.1 $\tau^2$ and $\sigma^2$ known

If the variances  $\tau^2$  and  $\sigma^2$  are known, then estimates of the fixed effects can be estimated using weighted least squares (WLS) at the cluster-level. Let  $\mathbf{X}$  be the  $IT \times (T + 1)$  design matrix of cluster-time means corresponding to parameter vector  $\eta = (\mu, \beta_1, \dots, \beta_{T-1}, \theta)$ . Let  $\mathbf{W}$  be a  $IT \times IT$  block diagonal matrix where each  $T \times T$  block of  $\mathbf{W}$  describes the correlation structure between the repeated cluster means over time and has the structure

$$\begin{bmatrix} \tau^2 + \frac{\sigma^2}{N} & \tau^2 & \dots & \tau^2 \\ \tau^2 & \ddots & & \vdots \\ \tau^2 & & \ddots & \tau^2 \\ \tau^2 & \dots & \tau^2 & \tau^2 + \frac{\sigma^2}{N} \end{bmatrix}$$

Then the fixed effect estimates are given by

$$\hat{\eta} = (\mathbf{X}^T \mathbf{W}^{-1} \mathbf{X})^{-1} \mathbf{X}^T \mathbf{W}^{-1} \mathbf{y}$$

### A.8.2 $\tau^2$ and $\sigma^2$ unknown

- When the response is continuous and normally distributed, an empirical Bayes approach at the cluster-level is possible to estimate the fixed effects in the LMM. This approach also works for non-normal individual-level data when the cluster sizes are approximately equal.
- If the responses are non-normal and the cluster sizes vary, then analysis at the individual-level using GLMM or GEE is preferred.

## A.9 Power analysis

Consider testing the hypothesis  $H_0 : \theta = 0$  versus  $H_a : \theta = \theta_a$ . A Wald test may be based on  $Z = \frac{\hat{\theta}}{\sqrt{\text{Var}(\hat{\theta})}}$  where  $\hat{\theta}$  is from  $\hat{\eta}$ . The approximate power for a two-tailed test of size  $\alpha$  is

$$\text{power} = \Phi \left( \frac{\theta_a}{\sqrt{\text{Var}(\hat{\theta})}} - Z_{1-\alpha/2} \right)$$

where  $\Phi$  is the cumulative standard normal distribution and  $Z_{1-\alpha/2}$  is the  $(1 - \alpha/2)$ -th quantile of the standard normal distribution.  $\text{Var}(\hat{\theta})$  is an element of  $(\mathbf{X}^T \mathbf{W}^{-1} \mathbf{X})^{-1}$  but may be possible to express in the closed form

$$\text{Var}(\hat{\theta}) = \frac{I\sigma^2 \left( \frac{\sigma^2}{N} + T\tau^2 \right)}{(IU - W)\sigma^2 + N(U^2 + ITU - TW - IV)\tau^2}$$

where

$$\begin{aligned} U &= \sum_{ij} X_{ij} \\ W &= \sum_j \left( \sum_i X_{ij} \right)^2 \\ V &= \sum_i \left( \sum_j X_{ij} \right)^2 \end{aligned}$$

Note: under  $H_a$ ,

$$Z - \frac{\theta_a}{\sqrt{\text{Var}(\hat{\theta})}} \sim N(0, 1) \rightarrow Z \sim N \left( \frac{\theta_a}{\sqrt{\text{Var}(\hat{\theta})}}, 1 \right)$$

and so

$$\begin{aligned} \text{power} &= P(Z > Z_{1-\alpha/2}) \\ &= P \left( Z - \frac{\theta_a}{\sqrt{\text{Var}(\hat{\theta})}} > Z_{1-\alpha/2} - \frac{\theta_a}{\sqrt{\text{Var}(\hat{\theta})}} \right) \\ &= 1 - \Phi \left( Z_{1-\alpha/2} - \frac{\theta_a}{\sqrt{\text{Var}(\hat{\theta})}} \right) \\ &= \Phi \left( \frac{\theta_a}{\sqrt{\text{Var}(\hat{\theta})}} - Z_{1-\alpha/2} \right) \end{aligned}$$

## A.10 Effect of number of steps

Optimal power is achieved when a single cluster crosses over to the intervention at each time. The loss of power is primarily due to the loss of measurement times rather than due to the loss of randomization times. The loss of power is also relatively independent of the CV.

## A.11 Delayed treatment effect

If effect of intervention only reaches full effect  $\theta$  after some time, then power is reduced. The delay may be modelled by allowing  $X_{ij}$  to be fractional (although the given  $\text{Var}(\hat{\theta})$  is not valid in this case). Power is increased by adding additional measurement periods at the end of the trial or by increasing the time intervals.

## A.12 Simulation results

Compared power of test for LMM, GEE and GLMM for varying levels of relative risk. In equal cluster size case,  $\text{LMM} > \text{GEE} > \text{GLMM}$ . In unequal cluster size case,  $\text{GEE} \approx \text{GLMM} > \text{LMM}$ . When cluster sizes vary

significantly, it is suggested to do individual-level analyses. A jackknife estimate of the variance is suggested to maintain the size of the test in GEE/GLMM analyses.