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Optimal allocation of clusters in cohort stepped wedge designs

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ABSTRACT

We study optimal allocation of clusters for a fixed number of periods in cohort stepped wedge cluster randomized trials. The optimal design turns more clusters into treatment during the second and final periods, and depends on values of correlation parameters.

1. Introduction

Cluster randomized trials are designed to randomize intact clusters of individuals to treated conditions, with measurements taken on members of the clusters (Murray, 1998; Turner et al., 2017a, b). Common reasons for conducting such trials include minimizing contamination and logistical convenience (Donner and Klar, 2000). Stepped wedge (SW) cluster randomized trials are a class of unidirectional crossover designs that have received increasing attention over the past decade (Mdege et al., 2011). Under such designs, each cluster starts from the control condition and switches to treatment from some period onwards, until all clusters are treated. While standard SW designs dictate that an equal number of clusters be switched to treatment at each period, optimal cross-sectional stepped wedge designs have been shown to depend on the intraclass correlation (Lawrie et al., 2015). However, the previous result is limited to the Hussey and Hughes model (Hussey and Hughes, 2007) with a single random cluster effect and does not consider cohort designs with additional correlation parameters. Recent reviews of stepped wedge cluster randomized trials indicate that cohort designs are common in practice (Barker et al., 2016; Martin et al., 2016), so it is important to understand the optimal allocation of clusters in cohort SW designs in order to maximize efficiency. Girling and Hemming (2016) considered optimal cohort SW designs, but they discussed a larger class of designs that includes hybrid designs having both parallel and stepped wedge components. Since there are occasions where the stepped wedge design is of interest to encourage cluster participation or due to ethical reasons, we focus solely on the stepped wedge design and obtain its optimal form for cohort studies, extending the previous result (Lawrie et al., 2015). The conditions where the current results differ from the previous results are also discussed.

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2. Cohort stepped wedge designs

2.1. Characterizing the class of designs

We focus on complete cohort stepped wedge designs with T periods, where I clusters are allocated to $T-1$ distinct treatment sequences. We assume a closed cohort of N individuals are identified in each cluster and that measurements are taken for each individual during each period. Denote X_{ij} as the treatment indicator that equals 1 if cluster i receives treatment in period j, and zero otherwise. Following Lawrie et al. (2015), the class of stepped wedge designs are characterized by the following conditions: (i) the number of periods is at least 3 ($T \geq 3$); (ii) each cluster starts from the control condition and ends in the treated condition ($X_{i1} = 0$ and $X_{iT} = 1$ for all $i = 1, \ldots, I$); (iii) each cluster switches from control to treatment exactly once, and the period at which the switch occurs is random. We write the treatment sequence for cluster i as $\boldsymbol{X}_i' = (X_{i1}, \ldots, X_{iT})$, which contains t ones preceded by $T-t$ zeros for some $t \in \{1, \ldots, T-1\}$. Clearly, there are at most $T-1$ distinct treatment sequences to choose from, which are defined by the step, or period, when a cluster or group of clusters switch to the treated condition. The standard SW design assigns $I/(T-1)$ clusters to each possible treatment sequence, however, this design is not the optimal design under the Hussey and Hughes model except when $T = 3$ (Lawrie et al., 2015). We show below that the standard SW design is also not necessarily efficient for cohort stepped wedge cluster randomized trials.

2.2. The statistical model

We consider the following linear mixed model used for cohort stepped wedge designs, as discussed in Girling and Hemming (2016) and Hooper et al. (2016):

$$Y_{ijk} = \beta_j + \delta X_{ij} + c_i + \pi_{ij} + s_{ik} + \epsilon_{ijk}, \tag{1}$$

where Y_{ijk} is the response of individual k ($k = 1, \ldots, N$) from cluster i ($i = 1, \ldots, I$) in period j ($j = 1, \ldots, T$), X_{ij} is the treatment indicator introduced previously, δ is the treatment effect, β_j is the jth fixed period effect, c_i is the random cluster effect distributed by $N(0, \sigma_c^2)$, π_{ij} is the random cluster-by-period interaction distributed by $N(0, \sigma_\pi^2)$, s_{ik} is the random effect for repeated measures within the same individual distributed by $N(0, \sigma_s^2)$ and ϵ_{ijk} is the $N(0, \sigma_\epsilon^2)$ residual error. We assume c_i, π_{ij}, s_{ik} and ϵ_{ijk} are independent of each other, and denote the total variance of response Y_{ijk} by the sum of all the variance components $\sigma^2 = \sigma_c^2 + \sigma_\pi^2 + \sigma_s^2 + \sigma_\epsilon^2$. We further assume that $\sigma_\pi^2, \sigma_s^2 \geq 0$ and $\sigma_c^2, \sigma_\epsilon^2 > 0$. Notice that in a cross-sectional design where different sets of individuals are assessed in different periods, the between-individual variance component is usually assumed to be zero, $\sigma_s^2 = 0$. The Hussey and Hughes model is obtained by further assuming no random cluster-by-period interaction so that $\sigma_\pi^2 = 0$.

For a cohort stepped wedge design, we recognize the following three correlation parameters to describe the individual responses, following the notations in Preisser et al. (2003). The within-period correlation is defined as the correlation between the responses of two distinct individuals in the same cluster within the same period, $\alpha_0 = Corr(Y_{ijk}, Y_{ijk'}) = (\sigma_c^2 + \sigma_\pi^2)/\sigma^2$; the inter-period correlation is defined as the correlation between the responses of two distinct individuals in the same cluster at two distinct periods, $\alpha_1 = Corr(Y_{ijk}, Y_{ij'k'}) = \sigma_c^2/\sigma^2$; the individual auto-correlation is defined as the correlation between the responses of same individual at two distinct periods, $\alpha_2 = Corr(Y_{ijk}, Y_{ij'k}) = (\sigma_c^2 + \sigma_s^2)/\sigma^2$. Since σ_c^2 and σ_ϵ^2 are assumed to be strictly positive, two natural constraints for the correlation parameters are $0 < \alpha_1 \leq \alpha_0 < 1$ and $0 < \alpha_1 \leq \alpha_2 < 1$.

Following Hussey and Hughes (2007), we can write the mean response for each cluster-period as

$$Y_{ij} = \frac{1}{N}\sum_{k=1}^{N} Y_{ijk} = \beta_j + \delta X_{ij} + c_i + \pi_{ij} + \bar{s}_{i\cdot} + \bar{\epsilon}_{ij\cdot}, \tag{2}$$

where $\bar{s}_{i\cdot} = \sum_{k=1}^{N} s_{ik}/N$ and $\bar{\epsilon}_{ij\cdot} = \sum_{k=1}^{N} \epsilon_{ijk}/N$. If the variance components are known, the generalized least square solution $\hat{\delta}$ is used to estimate the treatment effect. The variance of $\hat{\delta}$ is given by the $(T+1, T+1)$th element of the covariance matrix $N\sigma^2(\sum_{i=1}^{I} \boldsymbol{Z}_i' \boldsymbol{R}_i^{-1} \boldsymbol{Z}_i)^{-1}$, where $\boldsymbol{Z}_i$ is the $T \times (T+1)$ fixed-effects design matrix for cluster i, namely $\boldsymbol{Z}_i = (\boldsymbol{I}_T, \boldsymbol{X}_i)$ with $\boldsymbol{I}_T$ the $T \times T$ identity matrix, and $\boldsymbol{R}_i$ is proportional to the correlation structure of the cluster-period means, and could be written as $\boldsymbol{R}_i = \psi \boldsymbol{I}_T + \xi \boldsymbol{J}_T$, where $\boldsymbol{J}_T$ is a matrix of ones, $\psi = 1 + (N-1)\alpha_0 - (N-1)\alpha_1 - \alpha_2$ and $\xi = (N-1)\alpha_1 + \alpha_2$. Since $\boldsymbol{R}_i$ is compound symmetric, the inverse can be analytically calculated as $\boldsymbol{R}_i^{-1} = \boldsymbol{I}_T/\psi - \xi \boldsymbol{J}_T/(\gamma\psi)$ where $\gamma = \psi + T\xi = 1 + (N-1)\alpha_0 + (T-1)(N-1)\alpha_1 + (T-1)\alpha_2$. It follows from block matrix inversion and some simplification algebra that the variance of $\hat{\delta}$ is

$$Var(\hat{\delta}) = \frac{IN^{-1}\sigma^2\gamma\psi}{(IU - W)\gamma + (U^2 - IV)\xi}, \tag{3}$$

where $U = \sum_{i=1}^{I}\sum_{j=1}^{T} X_{ij}$, $W = \sum_{j=1}^{T}(\sum_{i=1}^{I} X_{ij})^2$ and $V = \sum_{i=1}^{I}(\sum_{j=1}^{T} X_{ij})^2$ are design constants depending on the treatment sequence for each cluster. In cross-sectional studies without random cluster-by-period interaction and without random individual effects, i.e. $\sigma_\pi^2 = \sigma_s^2 = 0$, variance (3) reduces to the well-known Hussey and Hughes formulae (Hussey and Hughes, 2007). An alternative derivation of an equivalent expression to (3) using the cluster mean correlation $T\xi/\gamma$ is given in Girling and Hemming (2016).

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