Optimal allocation of subjects in a cluster randomized trial with fixed number of clusters when the ICCs or costs are heterogeneous over clusters

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Abstract

The intra-cluster correlation coefficient (ICC) plays an important role while designing the cluster randomized trials (CRTs). Often optimal CRTs are designed assuming that the magnitude of the ICC is constant across the clusters. However, this assumption is hardly satisfied. In some applications, the precise information about the cluster specific correlation is known in advance. In this article, we propose an optimal design with non-constant ICC across the clusters. Also in many situations, the cost of sampling of an observation from a particular cluster may differ from that of some other cluster. An optimal design in those scenarios is also obtained assuming unequal costs of sampling from different clusters. The theoretical findings are supplemented by thorough numerical examples.

Keywords: Cluster randomized trials, Cost function, Intra-cluster correlation coefficient, Optimal design.

1. Introduction

CRTs are widely used in various applications including social and education surveys, health research community, behavioral and bio-medical science (Donner and Klar (2000)). In CLTs, often the data structure is hierarchical in which individuals are nested within clusters. Differing from complete randomized design, in CRTs, the randomization is done at the cluster level. Though CRTs require a larger sample size compared to a completely randomized design, they are still extensively used from the ethical, cost and contamination
point of views. There is a vast literature available on optimally designing CRTs (Raudenbush (1997); Heo and Leon (2008); Konstantopoulos (2009)).

The individuals within a cluster share similarities due to the cluster effect, which is measured by the ICC. Designing a CRT depends on the value of the ICC, which is unknown prior to the experiments. In usual practice, an overall estimate of the ICC based on the combined information of all the clusters is used to design a CRT. The aforementioned estimate of the ICC is based on the assumption of homogeneity of the clusters which is hardly satisfied in practice. It is evident from many studies that the ICC varies over clusters with a significant amount of differences. One of the reason is when clusters with different base line variables are included. In educational trials, Hedges and Hedberg (2007) reported that in educational achievements the clusters can be divided into three categories (grades) based on ICCs. Similarly, in CRTs related to the science achievements the ICC varies over subjects (science, reading and mathematics) (Westine et al. (2013)) and districts (Hedberg and Hedges (2014)). ICCs derived from the Medical Research Council Trial of the Assessment and Management of Older People in the Community are reported in Smeeth and Ng (2002). In there, it is shown that the ICCs are differ based on the variables such as social variables, daily activities and alcohol and smoking. Kul et al. (2014) reported ICCs for demographical and outcome variables from cluster randomized trials of heart failure patients in UC and care pathways. The ICCs are shown variations depending on the baseline characteristics. Another reason for different ICC across the clusters may be the cluster effect itself even the baseline variable is same (Crespi et al. (2009), Wang et al. (2014) and Staples et al. (2015)).

Designing an optimal CRT is always challenging due to the lack of information about the ICC. A possible approach for taking into account the variability of ICC among the clusters is to consider it as a random quantity and assign some distribution, which leads to a Bayesian approach recently proposed by Singh and Mukhopadhyay (2016b). This approach provides an average weighted optimal design with respect to the specific weights, which are the prior probability chosen for the ICC. However, Bayesian designs are sensitive to the choice of the priors assigned for the ICC. Knowing the information of cluster specific correlations, it seems reasonable that the clusters with higher ICC and with lower ICC should have different sizes. Optimal CRTs with unequal cluster sizes are rarely available in the literature.
Due to subject dropouts or non-response, cluster sizes show variation and may lead to an experiment with unequal cluster sizes. The relative efficiency of CRTs with unequal cluster size compared to those with equal cluster size is investigated by Van Breukelen et al. (2007) and You et al. (2011) using some suitable design selection criterion function (functions of the variance of the estimates of variance components). However, in these papers an overall estimate of the ICC for all the clusters is used. It is shown that the loss in the efficiency assuming equal cluster sizes can be compensated by increasing the number of clusters. If there is some restriction on the number of clusters, the efficiency can be increased by adding more subjects to the clusters. The trade–off between the number of clusters and the cluster size to achieve a pre–specified power of the associated test is discussed in Singh et al. (2015) for thee–level CRTs.

In many applications cost is an important factor when limited resources are available. Flynn et al. (2002) reported that the factors such as staff costs, data collection costs, travel costs and management costs can cause variation in sampling units across clusters. When there is a variability in the cost, equal allocation is insufficient as illustrated in Moussa (1985). In case of limited resources, planning an optimal experiment is not a simple task (Marcoulides (1993)). Consequently, experimental groups having different costs, or there are some cost constraints, induce another problem for experimenters.

In this article, we propose an optimal CRT design with unequal cluster sizes based on clusters specific ICCs. The number of clusters in each arm (treatment versus control) is assumed to be fixed. A generalized estimating equation (GEE) approach is used to estimate the model parameters. The dependency among the subjects within a cluster is measured by a compound symmetric correlation structure. The variance of the estimate of the treatment effect is considered as a design selection criterion. We also propose optimal design under cost constraint assuming varying sampling costs across clusters.

This article is organized as follows. In Section 2 we define the model and discuss the GEE approach used for the estimation of the model parameters. The design selection criterion function is proposed in Section 3. In Section 4 optimal designs for unequal ICCs and unequal sampling costs among the clusters are proposed. Section 5 illustrates the proposed optimal design numerically using some real data examples. Concluding remarks and some
open research problems are provided in Section 6. For convenience, all proofs are provided in the Appendix.

2. Model

Consider a two-level cluster model with two treatment groups having \( m \) clusters in each group with varying cluster sizes. The observations from the same cluster are assumed to be correlated. The \( k \)th response denoted as \( y_{ijk} \) from the \( j \)th cluster nested in the \( i \)th group is marginally distributed with the exponential family distribution defined as:

\[
    f(y_{ijk}|\phi_{ijk}, \psi) = \exp\left\{ y_{ijk}\phi_{ijk} - b(\phi_{ijk}) + c(y_{ijk}) \right\} \tau + d(y_{ijk}, \tau),
\]

where \( i = 1, 2, j = 1, 2, \ldots, m, \) and \( k = 1, 2, \ldots, n_{ij} \), \( \phi_{ijk} \) is a function of the model parameters, \( b(\cdot), c(\cdot) \) and \( d(\cdot) \) are known functions and \( \tau \) is the dispersion parameter. The defining components of (1) are:

1. The linear predictor

\[
    \eta_{ijk} = \alpha + \beta x_{ij},
\]

where \( \alpha \) is the fixed unknown parameter, \( \beta \) is the group effect and \( x_{ij} = 1 \) if \( i = 1 \) and 0 otherwise.

2. The mean of \( y_{ijk} \) denoted by \( \mu_{ijk} \) is related to the linear predictor through a link function \( h \) such that \( h(\mu_{ijk}) = \eta_{ijk} \) and the inverse of \( h \) exists.

Some useful relations used later in this article are: (1) \( \text{E}(y_{ijk}) = \mu_{ijk} = \frac{db(\phi_{ijk})}{d\phi_{ijk}} / \tau \)

\[
    \text{Var}(y_{ijk}) = \frac{(d^2b(\phi_{ijk})/d\phi_{ijk}^2)}{\tau} \text{ (see Singh and Mukhopadhyay (2016a) for details)}.
\]

Remark 1. The model defined in Section 2 can also be fully specified as follows for the normal responses:

\[
    y^*_{ij} = \mu \mathbf{1}_{n_j} + \beta x_{ij} \mathbf{1}_{n_j} + \epsilon^*_{ij},
\]
where terms common in (3) have the same interpretation as in the model (2), \(1_{n_j}\) is the vector of all ones of length \(n_j\), \(y_{ij}^{*T} = (y_{ij1}, \ldots, y_{ijn})\), \(\epsilon_{ij}^{*T} = (\epsilon_{ij1}, \ldots, \epsilon_{ijn})\), for \(i = 1, 2\), and \(j = 1, \ldots, k\). The vector \(\epsilon_{ij}^{*T}\) follows a multivariate normal distribution with the zero mean vector and the variance matrix \(\sigma_{\epsilon}^2 W_{ij}(\rho_j)\) defined later in (10).

2.1. Estimation

In cluster trials, the subjects within a cluster share similarities and hence are likely to be correlated. This dependency can be explained by a “working correlation matrix” \(W_{ij}(\rho)\), characterized by \(\rho\) which is a vector of parameters as a measure of correlation. The working correlation structure was introduced in the analysis of longitudinal data by Liang and Zeger (1986). When \(W_{ij}(\rho)\) is the true correlation matrix for all \(i\) and \(j\), the covariance of \(Y_{ij} = (y_{ij1}, \ldots, y_{ijn})\) is

\[
V_{ij} = A_{ij}^{1/2} W_{ij}(\rho) A_{ij}^{1/2}, \quad (4)
\]

where \(A_{ij} = \text{diag}(\text{Var}(y_{ij1}), \ldots, \text{Var}(y_{ijn}))\). The vector of regression parameters \(\theta = (\alpha, \beta)\) is estimated using the generalized estimating equation approach (see Liang and Zeger (1986)). The asymptotic variance of the estimate \(\hat{\theta}\) of \(\theta\) is

\[
\text{Var}(\hat{\theta}) = \left[ \sum_{i=1}^{2} \sum_{j=1}^{m} \frac{\partial \mu_{ij}^{T}}{\partial \theta} V_{ij}^{-1}(\rho) \frac{\partial \mu_{ij}}{\partial \theta} \right]^{-1}, \quad (5)
\]

where \(\mu_{ij}^{T} = (\mu_{ij1}, \ldots, \mu_{ijn})\) and \(\theta^{T} = (\alpha, \beta)\) in our settings. Often the ICC is positive and we assume throughout this article that the components of \(\rho\) are positive.

3. Design criterion

In our formulation, we assume that there are \(m\) number of clusters fixed in each of the two treatment groups. We further assume that clusters in the first treatment group are identical to those of the second treatment group. More specifically, \(n_{ij} = n_j\) and \(\rho_{ij} = \rho_j\) for \(i = 1, 2\) and \(j = 1, \ldots, m\), where \(\rho_{ij}\) is the ICC of the \(j\)th cluster nested in the \(i\)th treatment group. Suppose there are \(N\) experimental units available to each treatment group. The problem is
to allocate these $N$ subjects to $m$ clusters so that the design selection criterion which we shall define soon is optimized. The design space is defined as $\mathcal{N} = \{(n_1, \ldots, n_m) : n_i \geq 0, \sum_{i=1}^{m} n_i = N\}$. Every such permutation of $N$ subjects is called an exact design. Finding an exact optimal design may be mathematically intractable. Instead we seek approximate design $\xi \in \Xi$, where $\Xi = \{ (\xi_1, \ldots, \xi_m) : 0 \leq \xi_i \leq 1, \sum_{i=1}^{m} \xi_i = 1\}$ is the unit simplex. In other words, $\xi_i = n_i/N$ is the ratio of the $i$th cluster size to the total experimental units. It can be observed that the variance of the estimate $\theta$ given in (5) is a function of the design $\xi$, the vector of ICCs $\rho$, and the model parameter $\theta$ involved in the linear predictor. Thus, we can re-express (5) as

$$\psi(\xi; \rho, \theta) = \text{Var}(\hat{\theta}).$$

(6)

Our primary interest is in estimating the treatment effect. For this purpose, we seek a design that minimizes the variance of the estimate of the treatment effect. The variance can be obtained from (6) as follows

$$\psi_{\beta}(\xi; \rho, \theta) = e^T \text{Var}(\hat{\theta}) e,$$

(7)

where $e^T = (0, 1)$. Therefore, a design which minimizes (7), i.e.,

$$\xi_{opt} = \arg \min_{\xi \in \Xi} \psi_{\beta}(\xi; \rho, \theta)$$

(8)

is called an optimal design.

Note that the optimal design $\xi_{opt}$ is an $A_\beta$-optimal design. The performance of a design $\xi$ compared to any other design $\eta$ can be measured by the efficiency function defined as

$$Eff(\xi, \eta) = \frac{\psi_{\beta}(\xi; \rho, \theta)}{\psi_{\beta}(\eta; \rho, \theta)}.$$  

(9)

The condition $Eff(\xi, \eta) < 1$ implies that $\xi$ is better compared to $\eta$, while $Eff(\xi, \eta) = 1$ implies that both designs are equally efficient.

4. Design evaluation

In this section, we consider a particular case in which the response marginally follows a normal distribution. Under the defined linear predictor and the assumption of a fixed
number of clusters, optimal designs are the same for all the responses which are marginally distributed as exponential family distribution (see Section 2). It can be shown that the variance of the estimate of the treatment effect of the responses marginally belonging to the exponentially family distribution is proportional to that of the normal case. Thus, we shall focus only on the marginally normally distributed responses.

4.1. Optimal cluster design with unequal ICCs

There are various structural forms of the working correlation matrix, which should be chosen carefully depending on the experiment under study. The estimates obtained using the GEE approach are consistent even if the correlation structure is misspecified. If the responses are uncorrelated, an independent structure is used. For longitudinal studies, exchangeable and auto-regressive structures are used. If there is no evidence of any structural form, unstructured forms are used. In cluster trials, it is reasonable to assume an exchangeable correlation structure. Optimal designs obtained in this article are based on the exchangeable correlation structure as the working structure given by

\[ W_{ij}(\rho_j) = (1 - \rho_j)I + \rho_jJ, \]

where \( W_{ij}(\rho_j) \) is the correlation matrix corresponding to the \( j \)th cluster nested in the \( i \)th treatment group with correlation \( \rho_j \), \( I \) is the identity matrix and \( J \) is the matrix of all ones of order \( n_{ij} \times n_{ij} \) for \( i = 1, 2 \) and \( j = 1, \ldots, m \).

If \( y_{ijk} \sim N(\mu_{ijk}, \sigma^2_\epsilon) \), comparing with (1) gives \( \mathbb{E}(y_{ijk}) = \mu_{ijk} \) and \( \text{Var}(y_{ijk}) = \sigma^2_\epsilon \). The variance of the estimate of the treatment effect defined in (7) can be calculated as (see appendix for details)

\[ \psi_\beta(\xi; \rho) = \sigma^2_\epsilon \left[ \sum_{i=1}^{m} \frac{\xi_i}{(1/N)(1 - \rho_i) + \xi_i \rho_i} \right]^{-1}. \]  

Note that when \( \rho_i = \rho \) and \( n_i = n \) for all \( i = 1, \ldots, m \), we get

\[ \psi_\beta(\xi; \rho) = \sigma^2_\epsilon \left[ \frac{mn}{1 + (n - 1)\rho} \right]^{-1}. \]
which is equal to the variance of the estimate of $\beta$ given in Singh and Mukhopadhyay (2016b). Following Singh and Mukhopadhyay (2016b), a standardized variance $\psi_{\beta}(\xi; \rho)/\sigma^2_\varepsilon$ can be used to find the design. It can be observed that $\sigma^2_\varepsilon$ does not affect an optimal design. Without loss of generality, we can assume that $\sigma^2_\varepsilon = 1$. In the following theorem, we give an optimal design based on the formula (8).

Theorem 4.1. An optimal design is given by $\xi_{opt} = (\xi^*_1, \ldots, \xi^*_m)$, where

$$\xi^*_i = \sqrt{1 - \rho_i} \left(1 - (1/N)(a\sqrt{1 - \rho_i} - b)\right) / a\rho_i$$

for $i = 1, \ldots, m$, \hspace{1cm} (12)

and $a = \sum_{i=1}^m \sqrt{1 - \rho_i} / \rho_i$, $b = \sum_{i=1}^m (1 - \rho_i) / \rho_i$.

It is clear from (12) that if $\rho_i = \rho_j$, then $\xi^*_i = \xi^*_j$, i.e., clusters with equal ICCs should be of the same size. Moreover, the following corollary suggest that a cluster with high ICC requires fewer subjects compared to a cluster with low ICC.

Corollary 4.1.1. If $\rho_i \leq \rho_j$ then $\xi^*_i \geq \xi^*_j$.

An optimal design depends on ICCs and the total sample size $N$. For large sample size, the limiting optimal design is $\xi^*_i \rightarrow \sqrt{1 - \rho_i} / a\rho_i$ as $N \rightarrow \infty$. The sensitivity of an optimal design with respect to ICCs and $N$ is studied in the numerical section.

4.2. Cost effective optimal cluster design

Often the cost of a CRT is fixed prior to the experiment. In this scenario, the CRT should be designed optimally within budget constraints. For equal cluster size given a cost constraint, the methods for the analysis and optimal designs for CRTs exist in the literature (Raudenbush (1997); Berger and Wong (2009); Van Breukelen and Candel (2012); Singh and Mukhopadhyay (2016b)). In most of those studies, it is assumed that the cost of observing a unit from a cluster is equal for all the clusters. However, there are various factors that may affect the cost of including a cluster in the study, which lead to clusters with different costs. Flynn et al. (2002) reported factors which can cause variation in sampling units from clusters such as staff costs, data collection costs, travel costs and management costs. Sample size determination when the cost of the treatment group is different than
that of the control group is discussed in Liu (2003). Design with unequal costs across the clusters are proposed in Guo and Luh (2013) which is optimal for testing of hypothesis of the treatment difference. To the best of our knowledge, we are not aware of any optimal CRT which takes into account the discrepancy of the costs among the clusters from the estimation point of view.

For a fixed number of clusters (\(m\)), let \(T\) be the total cost of selecting individuals from \(m\) clusters and \(c_j\) be the cost of observing an individual from the \(j\)th cluster. Since it is assumed that the clusters in both the treatment groups are equivalent, we can write

\[
T = \sum_{j=1}^{m} c_j n_j,
\]

(13)

where \(c_j n_j\) is the cost of selecting \(n_j\) individuals from the \(j\)th cluster. Note that the total sample size is already bounded by the cost function (13) so that we can relax the condition \(\sum_{i=1}^{m} n_i = N\). The design space in this case is \(\mathcal{N} = \{(n_1, \ldots, n_m) : n_i \geq 0, \sum_{j=1}^{m} c_j n_j = T\}\).

Unlike in Section 4.1, we assume equal ICCs for each cluster, i.e., \(\rho_j = \rho\) for \(j = 1, \ldots, m\). This assumption may produce an efficient design if a reasonable estimate or a guess value is available for ICC prior to the experiment. Taking the sample size \(n_i\) as a continuous variable Van Breukelen and Candel (2015) an optimal design using formula (8) is given in the following theorem.

**Theorem 4.2.** An optimal design is given by \(n_{opt} = \{\tilde{n}_1, \ldots, \tilde{n}_m\}\) with

\[
\tilde{n}_i = \frac{T - (1-\rho)(x\sqrt{c_i} - y)}{x\sqrt{c_i}} \quad \text{for } i = 1, \ldots, m,
\]

(14)

where \(x = \sum_{i=1}^{m} \sqrt{c_i}\) and \(y = \sum_{i=1}^{m} c_i\).

In this case, an optimal design may not be consist of integer components. However, it can be rounded off to integers efficiently (Kiefer (1971)). It is reasonable to sample more subjects from the cluster with a low sampling cost. The following corollary establishes this relationship.

**Corollary 4.2.1.** If \(c_i \leq c_j\) then \(\tilde{n}_i \geq \tilde{n}_j\).
The proof of Corollary 4.2.1 is simple and hence omitted. In the next section, we present some numerical studies illustrating the proposed methodology.

5. Numerical studies

Designing an optimal CRT requires information about the ICCs prior to the experiment. These values can be estimated using the pilot data based on similar studies or the values suggested by experts. We illustrate the proposed methodology to obtain an optimal CRT based on the data available in the literature.

5.1. Unequal ICCs

5.1.1. Example 1:

In this example, clusters with different baseline variables are considered. Consider the study by Kul et al. (2014) in which ICCs based on demographical and outcome variables from cluster randomized trials of heart failure patients in UC and care pathways are reported. ICCs for the baseline variables Age, Disease Severity at Admission (NHYA), Admitted from Home or Referred by GP, Co-morbidities and Hypertension are 0.025, 0.046, 0.058, 0.025 and 0.043 respectively. Let us assume to design a CRT in which the clusters are consist of individuals based on different baseline variables given above. Both of the treatment arms will have m = 5 clusters and ρ = (0.025, 0.046, 0.058, 0.025, 0.043) and N = 500. Suppose the overall estimate of the ICC ρ ∈ (0.025, 0.058). We are interested to check the performance of the proposed optimal design (ξopt) given in Theorem 4.1 compared to the balanced design for a fixed value of ρ. A balanced design nbal = (N/m, . . . , N/m) assigns equal subjects to each cluster. Based on the various values of ρ ∈ (0.025, 0.058), the efficiency is plotted in Figure 1. From the figure it is clear that for too small values of ρ, balanced perform better, but as ρ increases nbal is more efficient. It suggest that when within cluster variation is too small, a balanced design can be used.

5.1.2. Example 2: An extreme case

In many CRTs, ICC can vary in a wide range such as from 0 to 0.5 (Campbell et al. (2005)). A precise information about the ICCs of the associated clusters can significantly improve the design performance. To illustrate, suppose there are m = 6 clusters in each
treatment arm. Assume that $\rho_1 = (0.01, 0.1, 0.2, 0.3, 0.4, 0.5)$, i.e., ICCs are equispaced. We compare the optimal design given in Theorem 4.11 to the commonly used balanced design. The results are presented in Table 1. For various values of $N \in \{100, \ldots, 300\}$, the efficiency lies between 0.563 to 0.613. This shows that the optimal design performs much better compared to the balanced design. As proved in Corollary 4.1.1, clusters with lower ICCs require more samples compared to the clusters with higher ICCs. For large $N$, the optimal design converges to the limiting design $(0.832, 0.079, 0.037, 0.023, 0.016, 0.012)$.

5.1.3. Example 3: CRTs for academic achievements

In Example 2, an extreme scenario is considered in which ICCs among the clusters differ drastically. Usually in CRTs, homogeneous clusters consisting of similar ICCs are considered. In those scenarios, the performance of an optimal design should also be investigated. For this purpose, we have considered the academic achievement CRT reported in Hedges and Hedberg (2007). In particular, for low-achievement schools (Hedges and Hedberg (2007)) the ICC varies over the students of different grades. In mathematics, the ICC at kindergarten to Grade 4 ranges from 0.09 to 0.13, in Grades 5-7 from 0.05 to 0.08, and in Grades 8-12 from 0.075 to 0.085. In reading achievement, the ICC ranges from 0.10 to 0.14, 0.06 to 0.07, and about 0.05 for the groups K-4, 5-8 and 10-12 respectively. In this example, the baseline variable is same (reading achievement), however the clusters vary across the grades. A more precise cluster specific estimates of ICC can be obtained by the method given in Crespi et al. (2009). Now consider designing a CRT for the comparison of academic achievements with two methods of teaching (treatments), which is based on the information of the aforementioned clusters. There are $m = 6$ clusters (3 for mathematics and 3 for reading) in each arm. Using a pseudo-Bayesian approach, design and corresponding efficiency is reported in Table 2. The pseudo-Bayesian approach is as follows: 10,000 random samples of $\rho$ assuming $\rho_i \in (a_i, b_i)$ are generated and based on each sample, the optimal design and its efficiency with respect to the balanced design is calculated. Then the average of these 10,000 designs and efficiency are calculated. The interval $(a_i, b_i)$ of $\rho_i$ is the range of the ICC associated with the $i$th cluster for $i = 1, \ldots, m$. The results are similar to those in Example 1. However, due to less variation in the ranges of ICCs among the clusters, the
optimal design utilizes proportions ($\xi_i$)'s with less variation in all the clusters. Clusters with lower range of ICCs such as $\rho_2 \in (0.05, 0.08)$, $\rho_5 \in (0.06, 0.07)$ and $\rho_6 = 0.05$ require higher proportions compared to the clusters with higher ICCs as expected from Corollary 4.1.1. Compared to the optimal design, the performance of the balanced design ($\xi_{bal}$) is inferior as expected with efficiency in the range 0.978 to 0.986 for various sample sizes ($N$). Moreover, as $N$ increases the efficiency increases and implies that for large $N$, the balanced design is close to the optimal design in terms of efficiency.

5.2. Cost effective optimal design

5.2.1. Example 4:

This example is based on the study conducted by University of Michigan in partnership with the Consortium for Policy Research in Education. The aim of the study was to determine the impact of various comprehensive school reform (CSR) programs on instruction and student achievement in high poverty elementary schools. Further details of this study can be found in Singh and Mukhopadhyay (2016b). To compare the two reform programs namely Americas Choice and Success for All, there were $m = 4$ clusters (schools) from which students were selected. Basically a balanced design is used. Based on the data, the ANOVA estimate of $\rho$ is computed to be 0.05. Suppose the cost of selecting an individual form the $j$th cluster is $c_j = j$ for $j = 1 \ldots, 4$. Using Theorem 4.2, optimal designs for various choices of total costs are given in Table 3. From Table 3, it can be observed that as the total cost increases, each cluster has more samples. For example when $N = 500$, we get $n_{opt} = (94.7, 58.7, 46.7, 36.9)$ while for $N = 800$, we have $n_{opt} = (151.6, 88.3, 71.1, 64.6)$. The affect of the ICC on optimal design can be seen from Table 4 where the sample size $N$ decreases as $\rho$ increases when cost is fixed ($T = 500$). These findings are consistent with those reported in Raudenbush (1997). Finally, a cluster with lower sampling cost has more individuals compared to a cluster with higher sampling cost as expected from Corollary 4.2.1.

6. Summary and discussion

The ICC plays an important role in designing CRTs optimally. Prior to the experiment, the value of the ICC is unknown and an estimate obtained from related pilot data or sugges-
tions from experts can be used. Often an overall estimate of the ICC based on the data of all the clusters is used. This is because while defining the model, it is assumed that the cluster effect is identically and independently distributed. However, in practice the assumption of identical distribution hardly holds. In this article, we assume that the variances within the clusters can vary, which suggests using different ICCs associated to with each cluster. Assuming varying ICCs among the clusters, an optimal design for CRT is proposed. We proposed designs for CRTs in which the response is marginally distributed as an exponential family distribution. Later, it is found that optimal designs for an exponential family distribution coincide with normal responses under our assumptions. A generalized estimating equation approach is used. Optimal designs are obtained by minimizing the variance of the estimate of the treatment effect, which is referred to as an $A_s$-optimal design in the literature. An optimal design assigns more observations to the cluster with a lower ICC compared to the cluster with a higher ICC. Based on numerical studies, it is found that the proposed design is more efficient than the commonly used balanced design. In usual practice, an overall estimate of an ICC is used to design a CRT. In Example 3, we have shown that the optimal design based on the cluster level estimates of the ICCs is more efficient than a commonly used balanced design based on overall estimate of the ICC. One of the main feature of the proposed design is that it has flexibility to include non-homogeneous clusters in the experiments. The applications of the proposed methodology is limited. However, the methodology is suited for the matched pair cluster randomized trials where clusters in two arms are suppose to be identical in nature. The relevant CRTs in which our methods are applicable not commonly used because of the lack of the designing tools. We hope that the proposed designs shall convince the applied statisticians to design such CRTs.

Utilizing the methodology used to obtained optimal design for unequal ICCs, we also proposed an optimal design under the cost constraint. We assumed that the sampling cost of an individual from a cluster can be different from that of the other cluster. However, in this case the assumption of unequal ICCs is relaxed. It is found that in an optimal design, the cluster with a lower sampling cost uses more samples compared to the cluster with a higher sampling cost. A very sleek solution of an optimal design is obtained. Further, the theoretical findings are supported by the numerical studies.
We have considered an exponential family distribution to include a wider class of CRTs with non-normal response. In our settings, it is found that the optimal design for the normal responses is the same for other distributions belonging to the exponential family. However, this is not the case when covariates or other effects are added to the model. Optimal designs in these scenarios need to be explored. There are some limitations of optimal designs proposed in this article. We assumed that the clusters in the two arms (control versus treatment) are equivalent. Further, these designs are obtained when the number of clusters is fixed in advance. Optimal designs relaxing these assumptions can be obtained using the methodology proposed here. Moreover, designs for higher level CRTs (three or higher level) may also be of interest.

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Appendix

Derivation of the formula (11):

Consider the formula (5) for the variance of the estimate of $\theta$. For the case of normal response, $E(y_{ijk}) = \mu_{ijk}$ and the link function is the identity function, i.e., $h(\mu_{ijk}) = \mu_{ijk}$. Therefore, $\partial\mu_{ij}^T/\partial\theta = \partial(1, x_{ij})\theta/\partial\theta = (1, x_{ij}1)^T$, where 1 is the vector of all ones of length $n_j$ for $j = 1, \ldots, m$. The variance Var$(y_{ijk}) = \sigma^2$ implies $A_j = \sigma^2 I$, in the formula (4). Also

$$W_{ij}^{-1}(\rho_j) = \frac{1}{1-\rho_j}I - \frac{\rho_j}{(1-\rho_j)(1+(n_j-1)\rho_j)}J. \quad (15)$$

Note that we assume $n_{ij} = n_j$ for $i = 1, 2$. Using the expressions of $A_j$, $W_{ij}^{-1}(\rho_j)$ and transforming $\xi_j = n_j/N$, we get (11).
Proof of Theorem 4.1

We provide a sketch of the proof.

Proof. Without loss of generality, we assume that \( \sigma_i^2 = 1 \). The minimization of \( \psi_\beta(\xi; \rho) \) defined in (11) is equivalent to maximization of \( [\psi_\beta(\xi; \rho)]^{-1} \). The Lagrangian of this problem is

\[
L(\xi; \rho) = [\psi_\beta(\xi; \rho)]^{-1} + \alpha (\sum_{i=1}^{m} \xi_i - 1)
\]

and the solution satisfies the system

\[
\frac{\partial L(\xi; \rho)}{\partial \xi_i} = \frac{(1/N)(1 - \rho_i)}{\{(1/N)(1 - \rho_i) + \xi_i \rho_i\}^2} + \alpha = 0, \quad \text{for } i = 1, \ldots, m \tag{16}
\]

\[
\frac{\partial L(\xi; \rho)}{\partial \alpha} = \sum_{i=1}^{m} \xi_i = 1. \tag{17}
\]

After a little calculation, equations (16) and (17) together can be written in the following matrix form:

\[
A\xi = b, \tag{18}
\]

where

\[
A = \begin{bmatrix}
T \\ u \\ v^T \\ 1
\end{bmatrix},
\]

\[
T = \begin{bmatrix}
\rho_1 & -\rho_2 \sqrt{\frac{1-\rho_1}{1-\rho_2}} & 0 & 0 & \cdots & 0 \\
0 & \rho_2 & -\rho_3 \sqrt{\frac{1-\rho_2}{1-\rho_3}} & 0 & \cdots & 0 \\
\vdots & \ddots & \ddots & \ddots & \cdots & \vdots \\
0 & \cdots & \rho_i & -\rho_{i+1} \sqrt{\frac{1-\rho_i}{1-\rho_{i+1}}} & \cdots & 0 \\
\vdots & \vdots & \cdots & \cdots & \ddots & \cdots \\
0 & \cdots & \cdots & \cdots & \cdots & -\rho_{m-1} \sqrt{\frac{1-\rho_{m-1}}{1-\rho_m}} \\
0 & \cdots & \cdots & \cdots & \cdots & \rho_{m-1}
\end{bmatrix},
\]

\[
v^T = (1, \ldots, 1), \quad u = (0, \ldots, 0, -\rho_m \sqrt{(1-\rho_{m-1})(1-\rho_m)})^T \quad \text{and the } i\text{th entry of } b \text{ is } \frac{1}{N} \sqrt{1-\rho_i} (\sqrt{1-\rho_{i+1}} - \sqrt{1-\rho_m})^T\]
The inverse of the matrix $A$ can be given by

$$A^{-1} = \begin{bmatrix}
T^{-1} + T^{-1}u s^{-1}v^T T^{-1} & -s^{-1} T^{-1}u \\
-s^{-1}v^T T^{-1} & s^{-1}
\end{bmatrix},$$

where $s = 1 - v^T T^{-1}u$.

The matrix $T$ is a tridiagonal matrix and its inverse can be calculated by the formulas given in El-Mikkawy and Karawia (2006). After a tedious but not so difficult calculation, solving $\xi_{opt} = A^{-1}b$ gives the desired solution given in (12). This completes the proof. □

**Proof of Corollary 4.1.1**

**Proof.** Let us assume that $\rho_i \leq \rho_j$. From (12), we have

$$\xi_i^* - \xi_j^* = \frac{\sqrt{1 - \rho_i}}{\rho_i} [1 - (1/N)(a\sqrt{1 - \rho_i} - b)] - \frac{\sqrt{1 - \rho_j}}{\rho_j} [1 - (1/N)(a\sqrt{1 - \rho_j} - b)]$$

$$= (b/N + 1)\left(\frac{\sqrt{1 - \rho_i}}{\rho_i} - \frac{\sqrt{1 - \rho_j}}{\rho_j}\right) + (1/N)\frac{(\rho_i - \rho_j)}{\rho_i \rho_j}$$

$$\geq (b/N + 1)\left(\frac{1 - \rho_i}{\rho_i} - \frac{1 - \rho_j}{\rho_j}\right) + (1/N)\frac{(\rho_i - \rho_j)}{\rho_i \rho_j} \geq 0,$$

where the inequality in (20) follows from the fact that $(\sqrt{1 - x} - 1)/x \geq (\sqrt{1 - y} - 1)/y$ for $0 < x \leq y \leq 1$, and the last inequality in (21) follows from $\rho_i \leq \rho_j$. Hence the result follows. □

**Proof of Theorem 4.2**

We will outline the proof.

**Proof.** Without loss of generality, assume that $\sigma^2 = 1$. Re-transforming $n_i = N\xi_i$ for $i = 1, \ldots, m$, (11) reduces to

$$\psi_\beta(n; \rho) = \left[\sum_{i=1}^{m} \frac{n_i}{1 + (n_i - 1)\rho}\right]^{-1}$$

(22)
The minimization of $\psi_\beta(n; \rho)$ defined in (22) is equivalent to maximization of $[\psi_\beta(n; \rho)]^{-1}$. Using the cost constraint defined in (13), the Lagrangian of this problem is

$$L(n; \rho) = [\psi_\beta(n; \rho)]^{-1} + \alpha(\sum_{i=1}^{m} c_i n_i - T).$$

Assuming $n_i$’s as continuous variables, the solution satisfies the system

$$\frac{\partial L(\xi; \rho)}{\partial n_i} = \frac{(1 - \rho_i)}{(1 + (n_i - 1)\rho_i)^2} + \alpha c_i = 0, \quad \text{for } i = 1, \ldots, m \quad (23)$$

$$\frac{\partial L(\xi; \rho)}{\partial \alpha} = \sum_{i=1}^{m} c_i n_i - T = 0. \quad (24)$$

After a little calculation, equations (23) and (24) together can be written in the following matrix form:

$$A \xi = b, \quad (25)$$

where

$$A = \begin{bmatrix} T & u \\ v^T & c_m \end{bmatrix}, \quad (26)$$

$T$ is the tridiagonal matrix with diagonal entries $t_{ii} = n_{i+1} \sqrt{c_{i+1}/c_i}$, upper diagonal $t_{i,i+1} = -1$ for $i = 1, \ldots, m-1$ and all other entries are zero, $u = (0, \ldots, 0, -1)^T$, $v = (c_1, \ldots, c_{m-1})$. The $i$th entry of $b$ is $((1 - \rho)/\rho)(1 - \sqrt{c_{i+1}/c_i})$ for $i = 1, \ldots, m-1$ and $b_m = T$. The rest of the proof follows on the same lines as in Theorem 4.1.

**Remark 2.** In the proofs of Theorems 4.1 and 4.2, obtaining solutions from (18) and (25) is tedious. Readers are advised to verify the proposed solutions by putting them in equations (18) and (25).
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Table 1: Optimal design and corresponding efficiency for Example 2

| $N$   | $\xi_{opt}$       | $Eff(\xi_{opt}, \xi_{bal})$ |
|-------|-------------------|-----------------------------|
| 100   | (0.813, 0.082, 0.041, 0.027, 0.020, 0.016) | 0.563                      |
| 150   | (0.820, 0.081, 0.040, 0.026, 0.019, 0.014) | 0.566                      |
| 200   | (0.823, 0.081, 0.039, 0.025, 0.018, 0.014) | 0.579                      |
| 250   | (0.824, 0.080, 0.039, 0.025, 0.018, 0.013) | 0.595                      |
| 300   | (0.826, 0.080, 0.039, 0.025, 0.018, 0.013) | 0.613                      |

Figure 1: Efficiency plot for Example 1
Table 2: Average of optimal design and corresponding efficiency for Example 3. The parameter spaces for ICCs are $\rho_1 \in (0.09, 0.13), \rho_2 \in (0.05, 0.08), \rho_3 \in (0.075, 0.085), \rho_4 \in (0.10, 0.14), \rho_5 \in (0.06, 0.07), \rho_6 = 0.05$.

| $N$ | Average $\xi_{opt}$ | $Eff(\xi_{opt}, \xi_{bal})$ |
|-----|---------------------|-----------------------------|
| 50  | (0.114, 0.192, 0.155, 0.105, 0.189, 0.245) | 0.978 |
| 100 | (0.113, 0.193, 0.154, 0.103, 0.190, 0.247) | 0.977 |
| 150 | (0.112, 0.193, 0.154, 0.102, 0.191, 0.248) | 0.979 |
| 200 | (0.112, 0.193, 0.154, 0.102, 0.191, 0.249) | 0.981 |
| 250 | (0.112, 0.193, 0.154, 0.102, 0.191, 0.249) | 0.983 |
| 300 | (0.112, 0.193, 0.154, 0.102, 0.191, 0.249) | 0.984 |
| 350 | (0.111, 0.193, 0.154, 0.102, 0.191, 0.249) | 0.986 |

Table 3: Optimal designs for Example 4

| $T$  | $n_{opt}$ | $\psi_\beta(\xi; \rho, \theta)$ |
|------|-----------|-----------------------------|
| 500  | (94.711, 58.748, 46.726, 36.904) | 0.017 |
| 600  | (111.427, 69.636, 56.236, 45.148) | 0.016 |
| 700  | (135.422, 78.207, 62.034, 55.515) | 0.016 |
| 800  | (151.561, 88.292, 71.104, 64.636) | 0.015 |
| 900  | (167.643, 98.367, 80.179, 73.772) | 0.015 |
Table 4: Optimal designs for Example 4

| $\rho$ | $n_{opt}$                  | $N$     |
|-------|---------------------------|--------|
| 0.05  | (94.711, 58.748, 46.726, 36.904) | 236.945 |
| 0.15  | (86.419, 56.434, 47.679, 39.419) | 229.951 |
| 0.25  | (84.762, 55.968, 47.846, 39.941) | 228.517 |
| 0.35  | (85.928, 56.084, 47.613, 39.766) | 229.391 |
| 0.45  | (90.748, 55.829, 46.027, 39.878) | 232.482 |
| 0.55  | (91.174, 55.365, 45.537, 40.371) | 232.447 |
| 0.65  | (89.245, 53.795, 44.863, 42.144) | 230.047 |
| 0.75  | (87.895, 53.445, 44.964, 42.581) | 228.885 |
| 0.85  | (86.617, 53.129, 45.067, 42.981) | 227.794 |
| 0.95  | (54.050, 44.199, 47.604, 53.685) | 199.538 |