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Statistical methods for continuous outcomes in partially clustered designs

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ABSTRACT
We address statistical issues involved in the partially clustered design where clusters are only employed in the intervention arm, but not in the control arm. We develop a cluster adjusted t-test to compare group treatment effects with individual treatment effects for continuous outcomes in which the individual level data are used as the unit of the analysis in both arms, we develop an approach for determining sample sizes using this cluster adjusted t-test, and use simulation to demonstrate the consistent accuracy of the proposed cluster adjusted t-test and power estimation procedures. Two real examples illustrate how to use the proposed methods.

1. Introduction
Development and use of interventions aimed at effecting behavior change, i.e., behavioral interventions, has dramatically increased. Behavioral interventions offer health professionals and their patients viable, and sometimes more effective, alternatives to medicinal and device-focused treatment strategies. Behavioral interventions are often delivered to individuals within specific groups or clusters, which is the cluster design. For example, if the aim is to test a lifestyle intervention that is delivered by way of facilitated support groups, then each distinct support group represents a cluster.

There are two common types of cluster designs in behavioral clinical trials. The first one is the group randomized trial (GRT) in which entire groups are randomly assigned to study conditions and interventions are delivered in groups which exist prior to randomization, and the second one is the individual randomized group treatment (IRGT) trial in which individuals are randomly assigned to study conditions but interventions are delivered in groups which are established after randomization. For cluster trials (either GRT or IRGT), the intraclass correlation may develop over time as a result of the intervention among participants (e.g., mutual interaction) or other common factors (e.g., a shared group leader). In the literature, analysis techniques for cluster trials where clusters are employed in both arms are well established and sample size formulae can be found in a number of books (e.g., Murray, 1998; Donner and Klar, 2000).
In this paper, we are interested in a study design, which is a modification of the GRT and IRGT. In this design, clusters are employed in only one arm that delivers the intervention. We refer to this as a partially clustered design (as used in the paper by Baldwin, 2011). Several recently completed NIH-funded behavioral clinical trials have employed this partially clustered design: (1) The Heart Failure Adherence and Retention Trial (HART) was a single-center, multisite, behavioral trial (Powell et al., 2010). Participants with heart failure were randomly assigned to either a behavioral intervention arm in which participants received group-based self-management training and counseling, or an attention control arm in which participants received educational materials through the mail and tailored interactions by phone. The primary objective was to compare the behavioral intervention to the control with respect to death and rehospitalization. In HART, each facilitated group in the intervention arm represents a cluster. (2) The Mexican-American Trial of Community Health Workers (MATCH) was a multicenter behavioral trial that recently completed follow-up (Rothschild et al., 2012). Participants diagnosed with Type 2 diabetes were randomized to receive either self-management and lifestyle training from an assigned and trained Community Health Worker (CHW) or culturally appropriate diabetes education materials through the mail. The primary objective was to compare the behavioral intervention to the control on change in hemoglobin A1c (a measure of diabetes severity) over the duration of follow-up. In MATCH, each CHW and the participants this CHW facilitated form a cluster. The common feature of these two behavioral trials is that there are no clusters in the control arm in terms of delivering treatment, i.e., the treatment was delivered to each individual instead of groups in the control arm.

This type of study design complicates the determination of the required sample sizes and statistical analysis since the cluster effects only affect one arm and the variance structure is different between arms. Ignoring the cluster effects, which is equivalent to assuming that the sampling design is a simple random sample from the total population, leads to an underestimate of the variance of the intervention group means and an underestimate of the variance of the intervention effects (Murray et al., 2008; Pals et al., 2008) and results in an inflated type I error rate. In order to evaluate intervention effects for studies with a partially clustered design, we need to compare group treatment effects with individual treatment effects. However, very little methodology exists for doing this.

The general scenario we often encounter in designing partially clustered behavioral clinical trials includes the following characteristics: (1) There are a fair amount of studies whose total sample sizes are relatively small; (2) cluster sizes vary because it is not unusual the cluster sizes are slightly different at pre-test. One reason could be that it is common for patients to be lost to follow-up before reaching the assessment time for the primary endpoint. For example, in HART, we have a total number of 42 clusters with cluster sizes varying from 2 to 14; (3) The sample size estimation is based on the primary hypothesis. For example, we hypothesize that the mean change in hemoglobin A1c, from baseline to month 12, among those in the intervention arm will be at least 0.7% lower than the mean change among those in the control arm; (4) The intraclass correlation coefficient is not equal to 0 in the treatment arm with clusters which leads to different variance structures in different arms. Although the partially clustered design is a modified design of GRT and IRGT, existing methods, which treat subjects as being clustered in both arms, do not have immediate extensions to situations where clusters are only employed in one arm. Assuming that all subjects are observed in clusters implies that the intraclass correlation coefficient $\rho$ is the same in both treatment arms and a single value of $\rho$ is estimated in the analysis.
Several researchers have addressed sample size and power issues for the partially clustered design. However, the scenarios described in their papers are somewhat different than the general scenario described above. For example, Roberts and Roberts (2005) presented a general formula which maximized power for a given sample size by finding the optimal allocation ratio between treatment assignments. Moerbeek and Wong (2008) considered the design and analysis for studies with the partially clustered design in which they described a method to estimate the sample size as a function of cost and provided the best choices for the number of clusters and the total number of participants in the control arm under a given cost structure.

There are two papers which discussed statistical issues for studies with the partially clustered design under the general scenario described above. Hoover (2002) discussed a statistical test and power estimation to compare continuous outcomes with heterogeneous subgroup effects (in both treatment arms) using cluster level data as the unit of the analysis. In addition, he discussed how to obtain a cluster adjusted t-test and its degrees of freedom (\( r' \) in his paper) when there was no heterogeneity in terms of delivering treatment in the control arm. Esserman et al. (2013) discussed statistical testing and sample size estimation to compare a continuous outcome at both a single time point and longitudinally over time for clinical studies with subgroup heterogeneity in only one arm. Their approach for a single time point (\( t_{\text{mod}} \) and \( r \) in the paper) was equivalent to one option in Hoover’s paper (the modified Equation (1) and \( r' \)). Both methods by Hoover (2002) and Esserman et al. (2013) used the cluster level data as the unit of the analysis for the treatment arm with clusters but the individual level data as the unit of the analysis for the treatment arm without clusters. In their approach the cluster adjusted t statistic and its degrees of freedom were functions of mean and variance of the outcome at the cluster level and the individual level for the intervention arm and for the control arm, respectively. However, as discussed in Roberts and Roberts (2005), Hoover and Esserman’s method (for simplicity, labeled the HE method) would underestimate the power when used to compare group versus individual treatments in a study with the partially clustered design. Hence, we develop a cluster adjusted t-test to overcome the problem in the HE method and to take into account unequal variances in both arms, unequal cluster sizes in the treatment arm with clusters, and different effects of different treatment strategies (group treatments vs. individual treatments) simultaneously. Our approach is developed in particular for comparing group treatment effects with individual treatment effects and uses the individual level data as the unit of the analysis in both treatment arms. With this cluster adjusted t-test, the natural next step is to estimate the sample size based on this test which is a more general approach and suitable for studies with either large samples or small samples.

The goal of this paper is to develop an approach to compare two independent sample means or mean differences for studies with a partially clustered design. Specifically, we develop a cluster adjusted t-test in which individual level data are used as the unit of the analysis in both arms, and estimate the required sample size using this test. In terms of organization, in Section 2 we describe the basic notation and assumptions. In Section 3, we discuss the development of the cluster adjusted t-test where clusters are only employed in the intervention arm. In Section 4, we present how to plan a study with the partially clustered design when comparing group treatment effects with individual treatment effects. In Section 5, we use simulated data to illustrate the impact of the intraclass correlation on Type I error rate and the consistent accuracy of the cluster adjusted t-test and power estimation by comparing with the unadjusted t-test and the HE method. In Section 6, we illustrate use of the proposed methods for the HART and the MATCH studies. Finally, we conclude with some discussion in Section 7.
2. Notation and assumptions

Consider a study design with two treatment arms: intervention, denoted by \( I \), and control, denoted by \( C \). We assume that there are \( n_k \) participants in cluster \( k \), a total number of \( K \) clusters in the intervention arm, and no clusters in the control arm. \( N_I \) which is the total number of participants in the intervention arm, is defined as \( N_I = \sum_{k=1}^K n_k \) and \( N_C \), which is the total number of participants in the control arm, is defined as \( N_C = m \ast N_I \) where \( m \) is the allocation ratio of treatment assignments. For the intervention arm, \( Y_{ik}^I \) represents the outcome measure for participant \( i \) in cluster \( k \), where \( i = 1, 2, \ldots, n_k \) and \( k = 1, 2, \ldots, K \), \( \bar{Y}^I \) represents the overall sample mean, and \( \bar{Y}^I_k \) represents the sample mean for participants in cluster \( k \). For the control arm, \( Y_{j}^C \) represents the outcome measure for participant \( j \), where \( j = 1, 2, \ldots N_C \), and \( \bar{Y}^C \) represents the overall sample mean.

For participants in the intervention arm, we define

\[
Y_{ik}^I = \mu_I + u_k + \epsilon_{ik}, \text{ for } i = 1, 2, \ldots, n_k, k = 1, 2, \ldots, K
\]

then we have

\[
\bar{Y}^I_k = \mu_I + u_k + \bar{\epsilon}_k, \text{ for } k = 1, 2, \ldots, K
\]

\[
\bar{Y}^I = \mu_I + \bar{u} + \bar{\epsilon}_e
\]

where \( \mu_I \) denotes the overall mean of the outcome measure, \( u_k \) denotes the random effect of the \( k \)th cluster which is assumed to be distributed as i.i.d. \( N(0, \sigma^2_u) \), and \( \epsilon_{ik} \) denotes the random error of the \( i \)th participant in the \( k \)th cluster which is assumed to be distributed as i.i.d. \( N(0, \sigma^2_\epsilon) \), then we have

\[
\bar{\epsilon}_k \sim N\left(0, \frac{\sigma^2_\epsilon}{n_k}\right), \text{ for } k = 1, 2, \ldots, K
\]

\[
\bar{\epsilon}_e \sim N\left(0, \frac{\sigma^2_\epsilon}{N_I}\right)
\]

\[
\bar{u} = \frac{1}{N_I} \sum_{k=1}^K n_k u_k
\]

where \( \sigma^2_\epsilon \) is the within cluster variance and \( \sigma^2_u \) is the between cluster variance. The total sample variance in the intervention arm is

\[
S_I^2 = \frac{\sum_{k=1}^K \sum_{i=1}^{n_k} (Y_{ik}^I - \bar{Y}^I)^2}{N_I - 1}
\]

For participants in the control arm, we define

\[
Y_{j}^C = \mu_C + \epsilon_j, \text{ for } j = 1, 2, \ldots, N_C
\]

where \( \mu_C \) denotes the overall mean of the outcome measure and \( \epsilon_j \sim N(0, \sigma^2_\epsilon) \). The total sample variance in the control arm is

\[
S_C^2 = \frac{\sum_{j=1}^{N_C} (Y_{j}^C - \bar{Y}^C)^2}{N_C - 1}
\]

Due to the multilevel structure in the intervention arm, there are three different variances: within cluster variance \( \sigma^2_\epsilon \), between cluster variance \( \sigma^2_u \), and total variance \( \sigma^2_I \) where \( \sigma^2_I = \sigma^2_\epsilon + \sigma^2_u \). The relationship between the variances associated with the two levels of data structure is characterized by the intraclass correlation coefficient \( \rho \) which is a measure of the
clustering effect and defined as $\rho = \frac{\sigma_u^2}{\sigma_I^2}$. In addition, we make the following assumptions: (1) The value $\rho$ is unknown but the same across all clusters in the intervention arm; and (2) cluster sizes are prespecified.

3. **Cluster adjusted $t$-Test**

The objective in this section is to derive a test statistic to compare two independent sample means or mean differences where clusters are employed only in the intervention arm and the individual level data are used as an unit of the analysis for both treatment arms.

3.1. **Hypothesis testing**

In this section, we derive the cluster adjusted $t$-test to test the following null ($H_0$) and alternative ($H_1$) hypotheses:

$$H_0 : \mu_I - \mu_C = 0$$

$$H_1 : \mu_I - \mu_C = \mu_d$$  \hspace{1cm} (3.1)

where $\mu_d \neq 0$. For clinical studies without clustered designs, when we compare two independent sample means, for example $\bar{X}_1$ and $\bar{X}_2$, Student $t$-test is used. If we cannot assume equal variances between the two groups (with sample size $n'_1$ in one group and $n'_2$ in the other group), the $t$-test is calculated as

$$T = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{s_1^2}{n_1'} + \frac{s_2^2}{n_2'}}}$$  \hspace{1cm} (3.2)

Under $H_0$, the cluster adjusted test statistic $t$ is defined as

$$t = \frac{\bar{Y}_I - \bar{Y}_C}{\sqrt{Q * S_I^2 + \frac{s_C^2}{N_C}}}$$  \hspace{1cm} (3.3)

where

$$Q = \frac{\rho * \sum n_i^2}{N_I^2} + \frac{1 - \rho}{N_I}$$

$$1 - \rho + \frac{(N_I^2 - \sum n_i^2) * \rho}{N_I * (N_I - 1)}$$

The detailed derivations of $t$ and $Q$ are given in Appendix A.

3.2. **Sampling distribution of the statistic $t$**

In this section we discuss the distribution and degrees of freedom of the test statistic $t$ defined in Equation (3.3). Dividing by $\sigma$ in both denominator and numerator in Equation (3.3), we obtain

$$t = \frac{\bar{Y}_I - \bar{Y}_C}{\frac{\sigma}{\sqrt{Q * S_I^2 + \frac{s_C^2}{N_C}}}}$$  \hspace{1cm} (3.4)
where

\[ \sigma^2 = \text{Var}(\bar{Y}_i - \bar{Y}_C) \]

\[ = \left( \frac{\sum n_k^2 \rho}{N_j^2} + \frac{1 - \rho}{N_i} \right) \sigma_i^2 + \frac{\sigma_C^2}{N_C} \]

\( \sigma_i^2 \) and \( \sigma_C^2 \) can be estimated as

\[ \hat{\sigma}_i^2 = \frac{S_i^2}{1 - \rho + \frac{(N_j^2 - \sum n_k^2 \rho)}{N_j} \frac{N_i}{N_j}} \]

\[ \hat{\sigma}_C^2 = S_C^2 \]

Then \( \sigma^2 \) can be estimated by \( S^2 \) where

\[ S^2 = \frac{\rho \sum n_k^2}{N_j^2} + \frac{1 - \rho}{N_i} \left( \frac{N_j^2 - \sum n_k^2 \rho}{N_j} \frac{N_i}{N_j} \right) \sigma_i^2 + \frac{S_C^2}{N_C} \]

\[ = Q \cdot S_i^2 + \frac{S_C^2}{N_C} \]

The detailed derivations of all variances are given in Appendix A. Under \( H_0 \), the numerator in Equation (3.4) follows a standard normal distribution. In the following we discuss the distribution and approximate degrees of freedom \( \nu \) for the denominator in Equation (3.4).

According to Theorem 3.1 in the paper by Box (1954), \( \frac{h S_i^2}{E S_i} \) is distributed approximately as a \( \chi^2 \) with degrees of freedom \( h \) which can be calculated as

\[ h = \frac{((1 - \rho)N_i(N_i - 1) + (N_j^2 - \sum n_k^2 \rho) \rho^2)(K - 1)}{N_i^2(K - 1)(N_i - K)(1 - \rho) + (1 - \rho)N_i(K - 1) + (N_j^2 - \sum n_k^2 \rho) \rho^2} \]

The detailed derivation is given in Appendix B. As we already knew that \( \frac{(N_C - 1)S_C^2}{\sigma_C^2} \) is distributed as a \( \chi^2 \) with degrees of freedom \( N_C - 1 \), hence, the denominator in Equation (3.4) follows a \( \chi^2 \) distribution with approximate degrees of freedom \( \nu \), where \( \nu \) is approximated by the Satterthwaite equation as

\[ \nu = \frac{\sigma^4}{Q^2 \cdot \frac{\sigma_i^4}{h} + \frac{\sigma_C^4}{(N_C - 1)N_C^2}} \]

The detailed derivation of the approximation of \( \nu \) is given in Appendix A. Hence, the cluster adjusted test statistic \( t \) defined in Equation (3.3) follows a \( t \) distribution with approximate degrees of freedom \( \nu \). In order to estimate the \( t \) statistic defined in Equation (3.3), we first need to estimate \( \bar{Y}_i \), \( S_i^2 \), and \( \rho \) using data from the intervention arm and estimate \( \bar{Y}_C \) and \( S_C^2 \) using data from the control arm.

When \( n_1 = n_2 = \cdots = n_K = n \), we have

\[ Q = \frac{\frac{\rho}{K} + \frac{1 - \rho}{N_i}}{1 - \rho + \frac{\rho \sum (N_i - n)}{N_i - 1}} \]

\[ h = \frac{((1 - \rho)(N_i - 1) + (N_i - n) \rho^2)}{(N_i - K)(1 - \rho) + (K - 1)(1 - \rho + n \rho)^2} \]
If the intraclass correlation coefficient $\rho$ in the intervention arm is equal to zero, we have

$$Q = \frac{1}{N_I}, \quad h = N_I - 1, \quad \sigma^2 = \frac{\sigma_I^2}{N_I} + \frac{\sigma_C^2}{N_C}$$

and

$$\nu = \frac{\sigma^4}{(N_I-1)N_I^2} + \frac{\sigma_C^4}{(N_C-1)N_C^2},$$

then Equation (3.3) becomes Equation (3.2).

To test the hypothesis (3.1), if $t > t_{(1-\alpha/2),\nu}$ or $t < -t_{(1-\alpha/2),\nu}$ then we reject $H_0$.

4. Sample size estimation

The objective in this section is to discuss how to plan a study with the partially clustered design. In the following, we describe the approach of how to estimate the required sample size to test hypothesis (3.1) using the cluster adjusted $t$ statistic defined in Equation (3.3), and discuss the input parameters we need and how to make assumptions for the input parameters.

Given Type II error $\beta$, the power function for the cluster adjusted $t$-test is defined as

$$1 - \beta = 1 - F_{\nu}(t_{v,(1-\alpha/2)}|\lambda) + F_{\nu}(-t_{v,(1-\alpha/2)}|\lambda)$$

(4.1)

where the non-centrality $\lambda$ is calculated as $\lambda = \frac{\nu d^2}{\sigma^4}$ and $F_{\nu}$ is a cumulative non-central $t$ distribution function with degrees of freedom $\nu$ and a non-centrality parameter $\lambda$.

In general, when we plan a study with a clustered design, we prespecify the average cluster size $n$ and estimate the total number of clusters $K$. The following are input parameters: Type I error $\alpha$, Type II error $\beta$, intraclass correlation coefficient $\rho$ and the average cluster size $n$ in the intervention arm, variance in the intervention arm $\sigma_I^2$, variance in the control arm $\sigma_C^2$, and treatment assignment allocation ratio $m$. We directly estimate the number of clusters $K$ from the cumulative non-central $t$ distribution using Equation (4.1). Alternatively, we could prespecify the total number of clusters $K$ and estimate the cluster size $n$ using Equation (4.1).

Then the sample size needed in the intervention arm is estimated as $N_I = n \times K$, the sample size in the control arm is estimated as $N_C = m \times N_I$, and the total sample size is $N = N_I + N_C$.

Among those parameters, the prespecified value for $\rho$, $\sigma_I^2$, and $\sigma_C^2$ often comes from literature, previous studies, or experts’ opinions.

5. Simulation

In this section, we first apply the unadjusted $t$-test, the HE method, and the proposed cluster adjusted $t$-test on the simulated data to illustrate the impact of the intraclass correlation on Type I error rate and verify the accuracy of the proposed cluster adjusted $t$ test, and then we verify the accuracy of the power estimation. The possible ranges for $n$, $K$, $m$, and $\rho$ used in the simulation study are based on the scenarios we often encounter for our study design. In addition, we consider a few extreme scenarios. The assumptions of the distribution parameters for $Y$ and $\epsilon$ are based on one of our studies.

5.1. Impact of intraclass correlation on Type I error rate

Before we apply the proposed cluster adjusted $t$-test on real data, we first need to verify the accuracy of the proposed method. The purpose of the simulation studies in this section is to illustrate the impact of the intraclass correlation on Type I error rate when we use the three
Table 1. Selected empirical significance levels of unadjusted $t$ and cluster adjusted $t$ tests with equal allocation of treatment assignments.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Unadjusted $t$-test</th>
<th>Proposed method</th>
<th>HE method</th>
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different $t$-tests. We simulated a group of data sets by gradually increasing the intraclass correlation coefficient $\rho$, applied the three different $t$-tests on each of the simulated data sets with a known intraclass correlation coefficient, and estimated the empirical Type I error rates to examine which test could provide an accurate test result. Data were simulated under the following specifications: the number of clusters varied from $K = 2$ to $K = 30$, the cluster size, which is the total number of participants in each cluster, varied from $n = 5$ to $n = 100$, the treatment assignment ratio $m$ varied from $m = 0.3$ to $m = 2$, the intraclass correlation coefficient $\rho$ in the intervention arm varied from $\rho = 0.005$ to $\rho = 0.3$, $\epsilon_{ik} \sim N(0, 1)$ for $i = 1, 2, \ldots, n_k$ and $k = 1, 2, \ldots, K$, $u_k \sim N(0, \frac{\rho}{1-\rho})$ for $k = 1, 2, \ldots, K$, and $\epsilon_j \sim N(0, 1)$ for $j = 1, 2, \ldots, N_C$. For each combination of $n$, $K$, $m$, and $\rho$, a total number of 10,000 replications were generated with Type I error $\alpha = 0.05$ and 0.1.

The Type I error rates are jointly affected by $n$, $K$, $\rho$, and $m$. Table 1 presents the selected results of empirical significance levels for the unadjusted $t$-test (Equation (3.2), the second column), the proposed cluster adjusted $t$-test (Equation (3.3), the third column), and the HE method (the last column) when $m$ is equal to 1. The results show that the unadjusted $t$-test provides poor control of Type I errors with actual empirical rejection rates much higher than the assumed significance levels. For instance, when $m = 1$, $n = 100$, $K = 2$, and $\rho = 0.1$, the empirical significance level is 0.428, which is 856% of the assumed significance level of 0.05, and the empirical significance level is 0.508, which is 508% of the assumed significance level of 0.1. As the intraclass correlation coefficient $\rho$ increases for the same $K$ and $n$, the empirical significance levels are further away from the assumed significance levels. These results not only prove that the unadjusted $t$-test provides poor control of Type I error but also present the magnitude of the impact. Hence, it is very important to correct for cluster effects. The HE method did not provide good control of Type I errors for some scenarios.
Table 2. Selected empirical significance levels of unadjusted $t$ and cluster adjusted $t$ tests with unequal allocation of treatment assignments.

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<th>HE method</th>
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For example, when $K = 2$, $n = 5$, 100, and $K = 3$, $n = 10$ the empirical significance levels are constantly larger than the assumed significance levels for all choices of $\rho$s. In addition, the empirical significance levels are further away from the assumed significance levels as the intraclass correlation coefficient $\rho$ increases for the above-mentioned scenarios. However, the proposed cluster adjusted $t$-test has actual empirical significance levels that are indistinguishable from the assumed significance levels. That is, the significance levels of the cluster adjusted $t$-test proposed in this paper are quite accurate for all different scenarios including the extreme cases (e.g., $K = 2$, $n = 5$ or 100). For illustration purpose, we only present the results for $K = 2$, $n = 5$, 100, $K = 3$, $n = 10$, $K = 10$, $n = 20$, $K = 30$, $n = 5$, 20, and $\rho = 0.005$, 0.05, 0.1, 0.3. We have similar results for all other scenarios.

Table 2 presents the selected results of empirical significance levels for the unadjusted $t$-test (Equation (3.2), the second column), the proposed cluster adjusted $t$-test (Equation (3.3), the third column), and the HE method (the last column) when $m$ is not equal to 1. Again, the results show that the cluster adjusted $t$-test proposed in this paper has actual empirical significance levels that are indistinguishable from the assumed significance levels for all scenarios including extreme cases. The HE method provides poor control of Type I errors for some scenarios. For example, when $K = 2$, $n = 100$ the empirical significance levels are constantly larger than the assumed significance levels for all choices of $\rho$s and $ms$ and when $\rho$ increases the empirical significance levels tend to be further away from the assumed significance levels. The unadjusted $t$-test provides poor control of Type I errors. As the intraclass correlation coefficient $\rho$ increases, the empirical significance levels are further away from the assumed significance levels. For the same $\rho$, $n$, and $K$, when $m$ increases, the empirical significance levels increase and are even further away from the assumed significance levels. For
the same \(m, n, \) and \(K,\) when \(\rho\) increases, the empirical significance levels increase and are even further away from the assumed significance levels. For the same \(n, \rho, \) and \(m,\) when \(K\) increases, Type I error rates are similar, which indicates that the number of clusters does not have big impact on the Type I error rate. However, for the same \(K, m, \) and \(\rho,\) when \(n\) increases, the empirical significance levels increase and are even further away from the assumed significance levels, which indicates that the cluster size has a significant impact on the Type I error rate. For illustration purpose, we only present the results for \(K = 2, n = 100, K = 10, n = 10,\) and \(\rho = 0.005, 0.05, 0.1, 0.3.\) We have similar results for all other scenarios.

### 5.2. Sample size estimation and power comparison

In this section, we illustrate how to estimate the sample size using the approach described in Section 4 and use simulation studies to verify the accuracy of the power estimation.

Table 3 presents the selected results of sample size estimation with various combinations of parameters \(n, K, m,\) and \(\rho.\) The top part of Table 3 presents the sample size estimation results when we fix cluster size \(n\) and all other parameters except \(K.\) We assumed \(\alpha = 0.05,\) at least 80% power, \(n = 5\) to 100, \(m = 0.3\) to 2, \(\rho = 0.005\) to 0.3, \(Y_{ik} \sim \mathcal{N}(1.5, 3)\) for \(i = 1, 2, \ldots, n_k\) and \(k = 1, 2, \ldots, K,\) and \(Y_{jC} \sim \mathcal{N}(1, 1.5)\) for \(j = 1, 2, \ldots, N_C.\) Using Equation (4.1), we estimated the total number of clusters \(K.\) The bottom part of Table 3 presents the sample size estimation results when we fix the total number of clusters \(K\) and

<table>
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<th>(\rho)</th>
<th>(n)</th>
<th>Actual power</th>
<th>(m)</th>
<th>(K)</th>
<th>(N_{ij})</th>
<th>Proposed method Empirical power</th>
<th>HE method Empirical power</th>
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<th>(\rho)</th>
<th>(K)</th>
<th>Actual power</th>
<th>(m)</th>
<th>(n)</th>
<th>(N_{ij})</th>
<th>Proposed method Empirical power</th>
<th>HE method Empirical power</th>
</tr>
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<td>0.81</td>
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</table>
all other parameters except \( n \). We assumed \( K = 15–30 \) and the assumptions for other parameters were the same as above. Using Equation (4.1), we estimated the cluster size \( n \). The results in Table 3 show that when all other parameters are kept the same, the larger the intraclass correlation coefficient \( \rho \), the larger the estimated sample size.

In order to verify the accuracy of the power estimation using the cluster adjusted \( t \)-test, we again conducted simulation studies using the same assumptions for the input parameters used in the sample size estimation. We simulated 10,000 replicates with the sample size \( N \) estimated using Equation (4.1) for each of the parameter combinations and calculated the empirical powers. Table 3 presents the selected results of power comparisons. The “Actual Power” column is the actual power used to estimate the sample size using Equation (4.1). The simulation results show that the empirical powers estimated using our proposed cluster adjusted method are indistinguishable from the actual powers used to estimate the sample size for all scenarios of the input parameters. However, the estimated empirical powers using the HE method are constantly lower than the actual powers used in the sample size estimation. In addition, the empirical powers are much lower than the actual powers for some scenarios, for example, when \( \rho = 0.01, m = 2, n = 30 \), the empirical power = 65%, \( \rho = 0.01, n = 60, m = 2 \), the empirical power = 50%, \( \rho = 0.01, n = 60, m = 1 \), the empirical power = 70%, \( \rho = 0.01, n = 30, m = 1 \), the empirical power = 73%, and \( \rho = 0.1, n = 30, m = 2 \), the empirical power = 73%. For illustration purpose, we only present the results for \( \alpha = 0.05, \rho = 0.01, 0.1, m = 0.5, 1, 2, K = 15, 20, 30, \) and \( n = 10, 30, 60 \). We have similar results for all other scenarios.

6. Example

In this section, we present two examples to illustrate how to use the proposed methods estimating the sample size and comparing mean differences between group treatment effects and individual treatment effects.

6.1. Example 1: Sample size estimation

The MATCH study was developed to test the hypothesis that the use of indigenous CHWs, trained to provide culturally appropriate diabetes education, could promote pro-active self-management among inner-city dwelling Mexican-Americans with Type 2 diabetes mellitus. The primary hypothesis was that a CHW intervention, compared to an attention control, would result in an improvement in short-term physiologic outcomes and result in increased frequency of self-management behaviors. Participants were randomized to either the CHW intervention arm or the control arm. The CHW intervention emphasized knowledge and skills in diabetes self-management with repeated opportunities to practice goal-setting and self-management. The CHW intervention was delivered through 36 individual home visits over two years. Participants randomized to the control arm received 36 bilingual newsletters called DiabetesAction, which were mailed to participants on the same schedule as the participants in the CHW arm received their intervention.

Based on the above description, participants are clustered within CHWs in the intervention arm but not in the control arm. If we redesign the study by considering the partially clustered design, the sample size estimation is based on detecting a difference in mean hemoglobin A1c between the two arms of 1.0 with a standard deviation of 1.775 for both arms, Type I error 0.05, and at least 80% of power. We assumed that the cluster size \( n \) varied from 6 to 20, the intraclass correlation coefficient \( \rho \) was equal to 0.01, 0.05, and 0.15, and the treatment
Table 4. Sample size estimation for redesigning MATCH.

<table>
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<tr>
<th>$m$</th>
<th>$n$</th>
<th>$\rho$</th>
<th>$K$</th>
<th>$N_i$</th>
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</tr>
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<td>0.05</td>
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<tr>
<td></td>
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<td>4</td>
<td>80</td>
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</table>

Assignment allocation ratio $m$ was equal to 1. Using Equation (4.1), we estimated the number of clusters $K$. Table 4 shows the sample size estimation results for the primary hypothesis with various intraclass correlation coefficients and the cluster sizes.

6.2. Example 2: Cluster adjusted $t$-test

The HART is another cluster behavioral clinical trial with the partially clustered design. In this study there was a total of 902 participants, with 451 participants assigned to the intervention arm. In the intervention arm, there were 42 clusters where the cluster sizes varied from 2 to 14 (median = 8). Our interest in this example was the secondary endpoint which examined the effect of self-management interventions on the health-related quality of life (qol).

We first tested the significance of the intraclass correlation coefficient $\rho$ in the intervention arm in order to decide whether or not we need to use the cluster adjusted $t$-test. If $\rho$ is not significantly different from zero in the intervention arm which indicates that there is no cluster effects, we can simply apply the $t$-test without adjusting for cluster effects; otherwise, we need the cluster adjusted $t$-test. This testing can be done using the SAS proc mixed (Singer (1998) presented the similar approach). For this example, we found that $\rho$ was significantly different for the following three continuous variables: the difference of qol health and functioning score between baseline and visit 3 (qolhscore13), qol psychologic and spiritual score at visit 4 (qolpschore4), and qol health and functioning score at visit 4 (qolhscore4). Second, when the test showed the intraclass correlation coefficient $\rho$ was significantly different from zero, we then estimated the intraclass correlation coefficient $\rho$ for each outcome using the data from the intervention arm. As we presented in Section 2, the intraclass correlation coefficient is defined as $\rho = \frac{\sigma^2_u}{\sigma^2_I}$ where $\sigma^2_u$ and $\sigma^2_I$ can be estimated by $ES_{IB}^2$ and $ES_{I}^2$, respectively. The estimates of $ES_{IB}^2$ and $ES_{I}^2$ can be found in Appendix A. Again we can use the SAS proc mixed to estimate the value of $\rho$ (Singer, 1998). Last, we compared the mean differences of the above-mentioned three variables between two treatment arms using Equation (3.3) with the value $\rho$ estimated from the second step. Table 5 presents the $p$-values using the unadjusted two-sample $t$-test and the proposed cluster adjusted $t$-test.
Table 5. Mean/mean difference comparisons using unadjusted $t$-test and cluster adjusted $t$-test for HART secondary endpoints.

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<th>Control</th>
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7. Discussion

In this paper, we have described methods for planning and analyzing data from studies with the partially clustered design in which clusters are only employed in the intervention arm. We developed a cluster adjusted two-independent-sample $t$-test to compare group treatment effects with individual treatment effects allowing unequal cluster sizes in the intervention arm. We also discussed an approach to estimate the required sample sizes for continuous outcomes allowing unequal allocation of treatment assignments between two treatment groups. The simulation results presented in Tables 1–3 show that the proposed approach consistently produces accurate and reliable results as compared to using an unadjusted $t$-test and the HE method.

The novel aspect of the proposed method is that individual level data are used as the unit of the analysis for both treatment arms, instead of using cluster level data as the unit of the analysis in the treatment arm with clusters. There are several advantages of the proposed method: (1) It provides consistently accurate results of the statistical test and power estimation for various scenarios including extreme cases, (2) it has better performance than other existing methods which indicates that analyzing data at the individual level would be more appropriate for this particular design, and (3) it not only adjusts for cluster effects and unequal cluster sizes, but also adjusts for individual treatment effects due to group intervention by using individual level data as the unit of the analysis.

The proposed method is suitable and works well if we have a large sample or the outcome variable follows an asymptotic normal distribution. Here, we considered one level of clustering in the intervention arm, but it is relatively straightforward to extend the proposed method to more than one level of clustering.

In estimating the sample size, we assumed that the cluster sizes are equal across different clusters. In reality, the cluster sizes could be different. Some research has shown that the effect of unequal cluster sizes on the design effect was small (Kerry and Bland, 2001; van Breukelen et al., 2007) and a method to adjust the estimated sample size when the cluster sizes are unequal was given in the paper by van Breukelen et al. (2007). We have allowed for unequal allocation between the different treatment arms in estimating the required sample sizes. This could be necessary in some situations, e.g., for reducing cost or if there is a higher dropout rate in the intervention arm. van Breukelen et al. (2007) showed that there is not much loss in efficiency for estimating the treatment effect when there is unequal allocation. In addition, for a fixed sample size, we could use Equation (4.1) to maximize the power by allowing different allocations of treatment assignments. Although there is no closed-form solution of $m$ from Equation (4.1), we could evaluate different values of $m$, for example, $m = 0.5, 1, 2$, etc., to identify the optimal solution of $m$ which maximizes the power.

The program codes will be available upon a request.
References


Appendix A: Derivation of variance and degrees of freedom

Derivation of $ES_I^2$

The total sample variance in the intervention arm, denoted by $S_T^2$, includes within cluster sample variance, denoted by $S^2_{IW}$, and between cluster sample variance, denoted by $S^2_{IB}$. Let us define

$$SST = \sum_{k=1}^{K} \sum_{i=1}^{n_k} (Y_{ik}^I - \bar{Y}^I)^2$$

$$= \sum_{k=1}^{K} \sum_{i=1}^{n_k} (Y_{ik}^I - \bar{Y}^I_{ik})^2 + \sum_{k=1}^{K} \sum_{i=1}^{n_k} (\bar{Y}^I_{ik} - \bar{Y}^I)^2$$

$$= SSE + SSA$$
where the expected within cluster sample variance is

\[ E S^2_{IW} = \frac{\sum_{k=1}^{K} \sum_{i=1}^{n_k} E(Y_{ik}^l - \bar{Y}_{k}^l)^2}{N_l - K} \]

and the expected between cluster sample variance is

\[ E S^2_{IB} = \frac{\sum_{k=1}^{K} \sum_{i=1}^{n_k} E(\bar{Y}_{k}^l - \bar{Y}^l)^2}{K - 1} \]

In the following we derive the above two expectations. Since we have

\[ Y_{ik}^l = \mu_l + u_k + \epsilon_{ik} \]
\[ \bar{Y}_{k}^l = \mu_l + u_k + \bar{\epsilon}_k \]
\[ \bar{Y}^l = \mu_l + \bar{u} + \bar{\epsilon} \]

where

\[ \epsilon_{ik} \sim N(0, \sigma^2_{\epsilon}) \]
\[ \bar{\epsilon}_k \sim N\left(0, \frac{\sigma^2_{\epsilon}}{n_k}\right) \]
\[ \bar{\epsilon}_.. \sim N\left(0, \frac{\sigma^2_{\epsilon}}{N_l}\right) \]
\[ u_k \sim N(0, \sigma^2_u) \]
\[ \bar{u} = \frac{1}{N_l} \sum_{k=1}^{K} n_k u_k \]

Then we have

\[ E(S^2_{IW}) = \frac{\sum_{k=1}^{K} \sum_{i=1}^{n_k} E(Y_{ik}^l - \bar{Y}_{k}^l)^2}{N_l - K} \]
\[ = \frac{\sum_{k=1}^{K} \sum_{i=1}^{n_k} E(\mu_l + u_k + \epsilon_{ik} - \mu_l - u_k - \bar{\epsilon}_k)^2}{N_l - K} \]
\[ = \frac{(\sum_{k=1}^{K} n_k - K)\sigma^2_{\epsilon}}{N_l - K} \]
\[ = \sigma^2_{\epsilon} \]

\[ E(S^2_{IB}) = \frac{\sum_{k=1}^{K} \sum_{i=1}^{n_k} E(\bar{Y}_{k}^l - \bar{Y}^l)^2}{K - 1} \]
\[ = \frac{\sum_{k=1}^{K} \sum_{i=1}^{n_k} (E(u_k - \bar{u})^2 + E(\bar{\epsilon}_k - \bar{\epsilon}_..)^2)}{K - 1} \]

where

\[ \frac{\sum_{k=1}^{K} \sum_{i=1}^{n_k} E(u_k - \bar{u})^2}{K - 1} = \sum_{k=1}^{K} n_k E(u_k^2 + \bar{u}^2 - 2u_k\bar{u}) \]
\[
\left( N_l - \frac{\sum_{k=1}^{K} n_k^2}{N_l} \right) \sigma_u^2 \over K - 1
\]

and
\[
\frac{\sum_{k=1}^{K} \sum_{i=1}^{n_k} E(\hat{e}_{ik} - \bar{e}_..)^2}{K - 1} = \frac{\sum_{k=1}^{K} n_k (E\hat{e}_{ik}^2 + E\hat{e}_{..}^2 - 2E\hat{e}_{ik}\hat{e}_{..})}{K - 1}
= \frac{\sum_{k=1}^{K} n_k \left( \frac{\sigma^2}{n_k} + \frac{\sigma^2}{N_l} - 2 \frac{n_k \sigma^2}{N_l n_k} \right)}{K - 1}
= \sigma^2_{\epsilon}
\]

Hence, we have
\[
ES_{IB}^2 = \sigma^2_{\epsilon} + \left( N_l - \frac{\sum_{k=1}^{K} n_k^2}{N_l} \right) \frac{\sigma^2_u}{K - 1}
\]

Then
\[
ES_l^2 = \frac{E(SST)}{N_l - 1}
= \sigma^2_{\epsilon} + \frac{(N_l^2 - \sum_{k=1}^{K} n_k^2)}{N_l(N_l - 1)} \sigma^2_u
\]

When the cluster sizes are equal, i.e., \( n_1 = n_2 = \cdots = n_K = n \), then we have
\[
E(S_{IW}^2) = \sigma^2_{\epsilon}
\]
\[
E(S_{IB}^2) = \sigma^2_{\epsilon} + \frac{(N_l - n)}{K - 1} \sigma^2_u
\]
\[
ES_l^2 = \sigma^2_{\epsilon} + \frac{N_l - n}{N_l - 1} \sigma^2_u
\]

Since
\[
\sigma^2_u = \sigma^2_l \rho
\]
\[
\sigma^2_{\epsilon} = \sigma^2_l (1 - \rho)
\]

Then we rewrite \( ES_l^2 \) as
\[
ES_l^2 = \left[ (1 - \rho) + \frac{N_l^2 - \sum_{k=1}^{K} n_k^2}{N_l(N_l - 1)} \rho \right] \sigma^2_l
\]

when \( n_1 = n_2 = \cdots = n_K = n \) we have
\[
ES_l^2 = \left[ (1 - \rho) + \frac{N_l - n}{N_l - 1} \rho \right] \sigma^2_l
\]

**Derivation of Variance of \( \bar{Y}_i - \bar{Y}_C \)**

\[
Var(\bar{Y}_i - \bar{Y}_C) = Var(\bar{Y}_i) + Var(\bar{Y}_C)
= \left( \frac{\rho \sum n_k^2}{N_l^2} + \frac{1 - \rho}{N_l} \right) \sigma^2_l + \frac{\sigma^2_{\epsilon}}{N_C}
\]
When \( n_1 = n_2 = \cdots = n_K \) we have

\[
\text{Var}(\bar{Y}_\cdot - \bar{Y}_C) = \frac{\rho \sigma_i^2}{K} + \frac{(1 - \rho)\sigma_j^2}{N_i} + \frac{\sigma_C^2}{N_C}
\]

**Derivation of Degrees of Freedom \( \nu \)**

Since

\[
ES_i^2 = \left( 1 - \rho + \frac{N_i^2 - \sum n_k^2}{N_i(N_i - 1)} \rho \right) \sigma_i^2
\]

then \( \sigma_i^2 \) can be estimated as

\[
\hat{\sigma}_i^2 = \frac{S_i^2}{1 - \rho + \frac{(N_i^2 - \sum n_k^2) \rho}{N_i(N_i - 1)}}
\]

Since

\[
\sigma^2 = \text{Var}(\bar{Y}_\cdot - \bar{Y}_C)
\]

\[
= \left( \frac{\sum n_k^2 \rho}{N_i^2} + \frac{1 - \rho}{N_i} \right) \sigma_i^2 + \frac{\sigma_C^2}{N_C}
\]

Then \( \sigma^2 \) can be estimated by \( S^2 \) where

\[
S^2 = \frac{\rho \sum n_i^2}{N_i^2} + \frac{1 - \rho}{N_i} \frac{S_i^2}{1 - \rho + \frac{(N_i^2 - \sum n_k^2) \rho}{N_i(N_i - 1)}} + \frac{S_C^2}{N_C}
\]

(A.1)

where

\[
Q = \frac{\frac{\rho \sum n_i^2}{N_i^2} + \frac{1 - \rho}{N_i}}{1 - \rho + \frac{(N_i^2 - \sum n_k^2) \rho}{N_i(N_i - 1)}}
\]

From Equation (A.1) we have

\[
\text{Var}S^2 = \left( \frac{\rho \sum n_i^2}{N_i^2} + \frac{1 - \rho}{N_i} \right) \text{Var}S_i^2 + \frac{\text{Var}S_C^2}{N_C}
\]

As we already knew

\[
\text{Var}S_C^2 = \frac{2\sigma_C^4}{N_C - 1}
\]

Similarly

\[
\text{Var}S_i^2 = \frac{2\sigma_i^4}{h}
\]

For \( t \) defined in Equation (3.3) in the main paper to be a \( t \)-distribution for some value of \( \nu \), \( \frac{vS^2}{\sigma^2} \) has \( \chi^2 \) distribution with degrees of freedom \( \nu \). Since

\[
\text{Var} \frac{vS^2}{\sigma^2} = 2\nu
\]

\[
\frac{v^2}{\sigma^4} \text{Var}S^2 = 2\nu
\]
\[
\frac{\text{Var}S^2}{\sigma^4} = \frac{2}{\nu}
\]

then we have

\[
\nu = \frac{2\sigma^4}{\text{Var}S^2} = \frac{\sigma^4}{Q^2 \frac{\sigma_i^2}{h} + \frac{\sigma_i^2}{(N_c-1)N_c^2}}
\]

**Appendix B: Derivation of degrees of freedom \( h \)**

According to Theorem 3.1 in the paper by Box (1954), \( S_i^2 \) is distributed approximately as a constant \( g \) times \( \chi^2 \) distribution with degrees of freedom \( h \), where

\[
g = \frac{\text{Var}(S_i^2)}{2E(S_i^2)}
\]

\[
h = \frac{2(E(S_i^2))^2}{\text{Var}(S_i^2)}
\]

Hence, we have

\[
\frac{hS_i^2}{ES_i^2} \sim \chi^2_h
\]

Define

\[
\text{MSE} = \frac{\text{SSE}}{N_I - K}
\]

\[
\text{MSA} = \frac{\text{SSA}}{K - 1}
\]

According to Searle et al. (1992),

\[
\text{Var}(\text{MSE}) = \frac{2\sigma^4_e}{N_I - K}
\] \hspace{1cm} (B.1)

and

\[
\text{Var}(\text{MSA}) = \frac{2\left[(1 - \rho) + \frac{N_I^2 - \sum_{k=1}^{K} n_k^2}{N_I(K-1)} \rho \right]^2 \sigma_i^4}{K - 1}
\] \hspace{1cm} (B.2)

Since

\[
S_i^2 = \frac{\text{SSE} + \text{SSA}}{N_I - 1} = \frac{N - K}{N_I - 1} \text{MSE} + \frac{K - 1}{N_I - 1} \text{MSA}
\]

\[
\text{Var}(S_i^2) = \left( \frac{N_I - K}{N_I - 1} \right)^2 \text{Var}(\text{MSE}) + \left( \frac{K - 1}{N_I - 1} \right)^2 \text{Var}(\text{MSA})
\] \hspace{1cm} (B.3)

Substituting \( \text{Var}(\text{MSE}) \) and \( \text{Var}(\text{MSA}) \) by Equations (B.1) and (B.2) into Equation (B.3), we have
\[ h = \frac{2(ES^2)}{Var(S^2)} \]

\[ = \frac{((1 - \rho)N_i(N_i - 1) + (N_i^2 - \sum n_i^2)\rho)^2 \ast (K - 1)}{N_i^2(K - 1)(N_i - K)(1 - \rho)^2 + ((1 - \rho)N_i(K - 1) + (N_i^2 - \sum n_i^2)\rho)^2} \]

When all cluster sizes are equal, we have

\[ h = \frac{[(1 - \rho)(N_i - 1) + (N_i - n)\rho]^2}{(N_i - K)(1 - \rho)^2 + (K - 1)(1 - \rho + n\rho)^2} \]