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Technical and measurement report

Sample size estimation for cluster randomized controlled trials

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ABSTRACT

Cluster randomized controlled trials (cRCTs) are commonly used by clinical researchers. The advantages of cRCTs include preventing treatment contamination, enhancing administrative efficiency, convenience, external validity, ethical considerations, and likelihood of increased compliance by participants. However, when designing a cRCT, clinical researchers are faced with challenges, such as cluster units that may not have an equal number of participants within each. In this Technical Note, we discuss approaches for estimating the sample size, while taking into account unequal cluster sizes, and strategies for optimizing the design of cluster trials.

Introduction

Randomized controlled trials (RCTs) are the gold standard design for experimental studies, as they can reduce many of the risks of bias that threaten clinical trials (Campbell and Walters, 2014; Rutterford et al., 2015). However, there remain other risks of bias that random allocation alone does not address (Torgerson, 2001). Treatment contamination is one example, and can occur when treatment providers or participants learn what the 'other' group have been doing, and begin to blend that into their allocated intervention, thus 'contaminating' it. This corrupts the internal validity of the study, weakens its ability to detect between-groups differences, resulting in falsely concluding the trial treatment does not have a significant effect, when in truth it does (Type II error). When treatment contamination is a risk, a cluster RCT (cRCT) is recommended (Campbell and Walters, 2014; Donner and Klar, 2004; Rutterford et al., 2015; Torgerson, 2001).

In cRCT, randomization is done at the level of the study sites, centres, clinics or clinicians (Rutterford et al., 2015). All participants attending that site or clinician are automatically in that "cluster", and receive the intervention allocated to the cluster (Campbell and Walters, 2014). This reduces the likelihood of contact with the clinicians or participants of the 'other' group. Other advantages of a cRCT include enhanced administrative efficiency, convenience, increased external validity, ethical considerations, and likelihood of increased compliance by participants (Campbell and Walters, 2014; Donner and Klar, 2004; Rutterford et al., 2015). On the other hand, cRCT design reduces the statistical efficiency of the trial (Eldridge et al., 2004, 2006; Rotondi and Donner, 2011), adds complexity to the statistical approach for estimating the sample size and analysing the main findings (Campbell and Walters, 2014; Rutterford et al., 2015). Obtaining a robust estimate of the required sample size is crucial for conducting a trial that is statistically sound and financially feasible (Rutterford et al., 2015; van Breukelen and Candel, 2012).

This technical note aims to discuss factors that affect sample size estimation of a cRCT, and present different approaches to estimate the sample size when designing a two-arm, cRCT with a continuous outcome measure. Numerous factors need to be taken into account when designing and estimating the sample size of a cRCT (Table 1). Below, we present an overview of each of these factors, and the effect of these on planning and estimating sample size of a cRCT.

The design effect

Cluster RCTs are statistically less efficient than normal RCTs, due to the problem of variance inflation, caused by the fact that participants within a cluster unit are dependent, which increases sampling error in this type of trial (Cornfield, 1978; van Breukelen and Candel, 2012). To account for the statistical inefficiency of cRCTs, a larger sample size is usually required, when compared to a standard RCT.

There are different methods for estimating sample size of cRCT (Campbell and Walters, 2014; van Breukelen and Candel, 2012). A common and simple approach to estimate sample size for a cluster trial is to multiply the estimated sample size of a standard RCT by a factor, referred to as the "design effect" (DE) (Equation (1)). Inflating the sample size of a standard trial by DE increases the statistical power of the cRCT (Donner et al., 1981).

$$DE = 1 + (n - 1) \times \rho \quad (1)$$

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Table 1
Effect of different factors on the design and sample size of cluster randomized controlled trials.

Factor	Effect on required sample size
Design effect	Cluster RCTs add sampling error compared with standard RCTs, therefore are statistically less efficient and require a larger sample size
Number of clusters	The greater the number of clusters, the smaller the required sample size
Size of clusters	The fewer participants per cluster, the smaller the required sample size
Intracluster correlation coefficient (ICC)	The smaller the ICC, the smaller the required sample size
Allocation ratio	Equal allocation ratio requires smaller sample size
Attrition	Researchers may consider accounting for individual or cluster drop-outs
Baseline measurements	Including covariates into the analysis increases statistical power, reducing the required sample size
Outcome measure	The type of outcome measure (i.e., binary, continuous, count, ordinal, time-to-event and rate) dictates the formula used to estimate the sample size of the trial.

where:

DE = design effect;
n = cluster size (i.e. number of participants per cluster);
ρ = intracluster correlation coefficient;

The DE is a function of cluster size and the intracluster correlation coefficient (ICC). The ICC measures the degree of similarity of clustered data (Rutterford et al., 2015), and takes into account how much the variance differs within and between-clusters (Killip et al., 2004). Therefore, the larger the ICC or the cluster size, the larger the DE. The impact of cluster size and ICC on the DE is illustrated in Fig. 1.

The total number of participants (considering a two-arm trial, with equal allocation) for a cRCT is defined by Equation (2):

$$SS_{cluster\ RCT} = SS_{standard\ RCT} \times DE \quad (2)$$

where:

$SS_{cluster\ RCT}$ = total sample size in a cluster RCT;
$SS_{standard\ RCT}$ = total sample size in a standard RCT;
DE = design effect, from (1).

The number of participants required per group in a standard RCT can be readily calculated using trusted online resources (e.g. Sample Size Calculator) (Kohn et al., 2016), and is defined by Equation (3):

$$n_{standard\ RCT} = \frac{2\sigma^2(Z_{1-\alpha/2} - Z_{1-\beta})^2}{\Delta^2} \quad (3)$$

where:

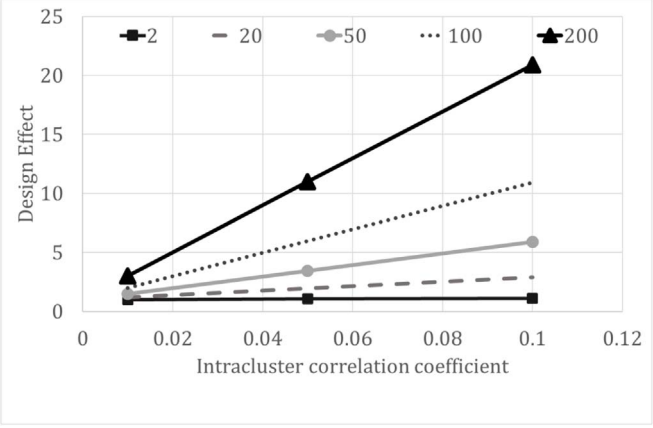

Fig. 1. Relationship between intracluster correlation coefficient (x axis), the Design Effect (y axis) and the cluster size. Black line with square = cluster size of 2 participants per cluster; Grey dashed line = cluster size of 20 participants per cluster; Grey line with circle = cluster size of 50 participants per cluster; Dotted black line = cluster size of 100 participants per cluster; black line with triangle = cluster size of 200 participants per cluster.

Z = the x'th percentage point of the standard normal distribution;
Δ = clinically important difference between groups for the primary outcome measure;
σ^2 = variance of primary outcome measure;
α = significance level;
β = power;
$n_{individual\ RCT}$ = sample size per group.

While the approach described above is simple to implement, it assumes clusters with similar size. Recruitment for clinical trials is usually a challenge, and so most cluster trials tend to end up with unequal cluster sizes (Eldridge et al., 2004). This reduces the statistical power of the trial (Eldridge et al., 2006). Therefore, it is recommended that researchers adopt Equation (2) for estimating, *a priori*, the sample size of a cRCT with equal cluster sizes, so that the trial will not be underpowered. Guidance on how to estimate the sample size requirement in a cRCT with unequal cluster sizes is provided below – but first, some considerations with regard to the number and size of clusters, and variability of the outcome between clusters.

Number of clusters

When estimating the sample size, researchers need to determine the number of clusters and the number of participants per cluster (van Breukelen and Candel, 2012). Trials should avoid having too few clusters. Using a small number of clusters increases the required sample size (Table 1), because of variance inflation. The greater the number of clusters, the closer to a normal distribution data will be (Rutterford et al., 2015). Adding an extra cluster is an effective way to increase the power of a trial (Donner and Klar, 2004). However, adding an extra cluster to a trial will likely increase costs and logistical challenges, as it will involve recruiting a relatively large number of participants in order to match the size of the other clusters in the trial (Campbell and Walters, 2014).

There are cases where the number of clusters is fixed due to geographical or logistic issues (Campbell and Walters, 2014; Hemming et al., 2011). In these cases, assuming that the size of clusters is equal, the number of clusters (defined *a priori*) will be appropriate as long as it is larger than the product of the number of required participants and the estimated ICC (Hemming et al., 2011).

Size of clusters

The size of each cluster impacts on the statistical power of a trial, as it impacts on the variability of the outcome measure (van Breukelen and Candel, 2012). The fewer participants per cluster, the smaller the required sample size (Table 1, Fig. 1), however a greater number of clusters then becomes necessary. That occurs because the larger the cluster size, the larger the DE (Equation (1)).

In trials with unequal cluster sizes, the larger the size difference between clusters, the larger the sample required to achieve the same statistical power for a certain alpha (Fig. 1). That happens because the

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