

Introduction to Cluster Randomized Trials

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As healthcare professionals, we frequently read studies evaluating new interventions. Traditionally, most of these studies are individually randomized controlled trials, in which individual patients are randomly assigned to a new treatment. However, we may also encounter a different methodological design: the cluster-randomized controlled trial (cRCT).

To critically appraise these studies, we need to understand what a cRCT is, why it is used, and whether the appropriate methodology was applied. The purpose of this article is to provide the tools to assess the quality and validity of these trials.

What is a cluster?

Clustered data is a hierarchical or multilevel structure in which participants are grouped according to their environment. The data can be structured at two levels

(e.g., patients by treating physicians) or at three levels (e.g., patients by treating physicians and treating physicians by hospitals). Individuals within the same cluster share unmeasured characteristics of that cluster (such as care protocols) or population characteristics (such as the average severity of the condition treated at a high-complexity center).¹

Observations of individuals within the same cluster tend to be correlated; that is, they are not independent.² Even after adjusting for measured characteristics, the results for two patients treated at the same endoscopy center, for example, will tend to be more similar to each other than the results for two patients treated at different centers. This may be attributable to unmeasured characteristics, such as the expertise of the center's endoscopists, sedation protocols, or the socioeconomic characteristics of the patient population attending the centers.¹

The intraclass correlation coefficient (ICC) measures the proportion of total outcome variance that can be attributed to differences between clusters. Its values range from 0 (no similarity or group effect) to 1 (all individuals in the cluster have the same outcome). Reporting the ICC allows for quantifying the effect of clustering.¹

Why a cRCT instead of an individual clinical trial?

If individual trials are the gold standard, why would a researcher decide to randomize entire clusters rather than individual patients?

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Several reasons that justify this approach include:³

1. Preventing treatment contamination: this occurs when participants in the control group are also exposed to the intervention under study. Let's consider a study is designed to evaluate a new dietary counseling protocol for patients with irritable bowel syndrome. If patients are randomized individually, within the same clinic, treating physicians would have to apply the new protocol to patients in the intervention group and standard care to those in the control group. In practice, it would be difficult for the physicians at this clinic not to be influenced by the new educational approach, and they would likely apply elements of the new counseling protocol to patients in the control group. In contrast, randomizing entire clinics (clusters) to implement either the new protocol or usual care avoids this risk of contamination.

2. Nature of the intervention: cluster randomization is the only feasible method in certain settings.² Many interventions operate at the group level, modifying the physical or social environment, and therefore cannot be delivered to individuals in isolation. For example, implementing a new electronic health record system for colorectal cancer screening alerts will affect the entire hospital equally.

3. Logistical feasibility: In some cases, it may be more cost-effective and convenient to implement a cluster-based intervention, such as when expensive equipment requiring extensive training is used.

What are the consequences of ignoring the existence of clusters?

Analyzing a cRCT by comparing all treated individuals with all controls as if they were not grouped is an error. Ignoring the effect of the intra-cluster correlation underestimates the variance and overestimates the significance of the differences. It is worth noting that even small ICC values are sufficient to yield spuriously narrow confidence intervals and artificially low *P*-values. For example, a simulation study using previously published data showed that an ICC of 0.02 increased the probability of committing a Type I error to 9% (rather than the 5% assumed by the authors).^{1,4} Thus, an investigator might conclude that an intervention is statistically significant and clinically relevant, when in fact the result was due to chance and the use of an

inappropriate statistical method that did not account for clustering.

What should be considered when calculating the sample size for a cRCT?

Because observations within the same cluster are not independent, a cRCT is statistically less efficient than a conventional clinical trial. This means that to achieve the same statistical power, a larger number of participants must be recruited. If *m* is the cluster size (assuming an equal number of individuals in each cluster) and *p* (rho) is the ICC, the inflation factor or design effect associated with cluster randomization is $1 + (m-1)p$. When assessing sample size, it is important to note that adding more participants within a single cluster has a limit to its usefulness. Therefore, to improve the study's statistical power it is always more efficient to increase the number of clusters than to increase the number of individuals per cluster.³⁻⁵

What is the unit of randomization in a cRCT?

To serve as valid units of randomization, clusters must have identifiable characteristics and boundaries, whether structural, jurisdictional, or geographic.⁴

How should a cRCT be analyzed?

There are statistical procedures that account for clustering and prevent erroneous results. When reviewing the methods section of an article, we should determine which approach was used. There are two main approaches: cluster-level analysis and individual-level analysis.⁶

1. Cluster-level analysis: this is a straightforward technique that is often preferable when the total number of clusters in the trial is very small (e.g., fewer than 15 per arm). It involves first summarizing individual-level data by calculating means or proportions for each cluster (e.g., the *H. pylori* eradication rate observed at each center) and, second, comparing these aggregated effect measures using conventional statistical tests (such as Student *t* test for independent samples). Its advantage is that the ICC does not need to be modeled; its disadvantage is the loss of analytical flexibility because adjustment for covariates (such as age or comorbidities) is difficult.³

2. Individual-level analysis: due to its flexibility, the most common approach is to use all patient data applying regression models that account for the hierarchical structure of the data. There are two main families of models for this purpose:

Generalized estimating equation models (GEE, or marginal models): These estimate regression coefficients by treating the variation between clusters as a nuisance parameter that must be corrected for. The result of a GEE model is interpreted as a marginal effect or population average. In other words, it tells us the average effect of the intervention across the entire study population. One of its limitations is that it can handle only a single level of clustering (e.g., clustering by hospital, but not by physician within the hospital simultaneously). In addition, they may underestimate the standard error if the number of clusters is small.¹

Multilevel regression models (hierarchical models, mixed-effects models, or random-effects models): These models begin with a conventional regression and then include cluster-specific random effects, which account for the homogeneity of the results within each group. Unlike GEE models, multilevel models estimate the conditional or cluster-specific effect. This means that the estimated effect represents the expected change in the outcome when comparing two individuals belonging to the same cluster. Furthermore, these models allow us to decompose the total variance by calculating what percentage of the variation is attributable to differences between clusters versus variation among individuals. Another advantage is that they allow for the handling of multiple levels of clustering (for example, patients by treating physicians, who are in turn grouped by hospital). However, these models are more complex and require assumptions about the distribution of cluster-specific random effects.

3. Covariance analysis (ANCOVA) models: These can be used at both the cluster and individual level. They allow the final outcome to be adjusted for a covariate, in this case, the baseline or pre-randomization values of the outcome variable (provided that this variable is continuous).

Using ANCOVA at the individual-level is a re-

commended strategy when there are limitations in statistical power, as it allows for a reduction in the required sample size.

Another consideration is the analytical strategy. It must be defined in advance what to do when participants or entire clusters do not adhere to the assigned treatment. In superiority trials, it is recommended to perform an intention-to-treat analysis: this means analyzing all participants based on the treatment assigned during randomization, regardless of whether they actually adhered to it. The intention-to-treat analysis tends to reduce the Type I error compared to the per-protocol analysis.

How should one report or evaluate the publication of a cluster-randomized controlled trial (cRCT)?

Several literature reviews have identified critical deficiencies in the publication of cRCTs. For this reason, an extension of the 2010 CONSORT statement for cluster trials was developed and published in 2012. It included a checklist of elements that must be present in the reporting of these studies. Additional information must be included that is not required for individual clinical trials, such as analysis methods that account for clustering, the number of clusters, their size, and, above all, the estimate of the ICC along with its degree of uncertainty.⁵

In conclusion, the validity of the results of a cluster-randomized controlled trial depends on the use of the appropriate methodology. By answering the questions outlined above, we are able to critically appraise this type of study.

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