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Concept, characteristics and implications of cluster randomization

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"Cluster randomized trials will not yield reliable evidence about the effectiveness of health interventions and policies unless their methodological conduct and reporting are sound."

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The concept of cluster randomization

The vast majority of randomized controlled trials in health research are structured around the individual patient: the patient is recruited and allocated independently to either intervention or control arm, administered the allocated intervention and observed prospectively. This design is optimal in the sense that the number of independent allocation units is the same as the number of observations to be analyzed. On the other hand, the defining feature of a cluster randomized trial is that natural groups ('clusters') of individuals are allocated as a unit and, thus, the number of independent units allocated is smaller than the number of observations. Cluster randomized trials are not new; there are now four texts addressing their design and analysis, including references [1–3]. Researchers considering this design should bear in mind that cluster randomized trials are more difficult to design and analyze correctly, are more susceptible to biases [4,5] and raise distinct ethical challenges that may require more thought and time at the protocol development and research ethics application stages [6,7]. The decision to adopt cluster rather than individual randomization should therefore not be made lightly.

Characteristics of cluster randomized trials

A unique characteristic of cluster randomized trials is that they may have distinct units of allocation, intervention and observation. Interventions are often complex and may be targeted at the cluster level (e.g., healthcare organisations, or communities), professionals associated with each cluster and/or the individual cluster members themselves. Interventions may be administered separately to individuals or as one package to the entire cluster. Outcomes may be observed on individual cluster members or professionals, or collected from routine health administrative sources. A descriptive survey of a random sample of 300 main reports of cluster randomized trials in health research illustrates some of their complexities [8]. Units of allocation were diverse including primary care practices, schools, residential areas, hospitals, nursing homes, worksites and sports teams. The median number of clusters randomized was 21 (interquartile range 12–52); the median cluster size was 34 (interquartile range 13–89). A third had interventions targeted at the health system or cluster organization, half had interventions targeted at professionals, and half had interventions targeted at the individual cluster members themselves. (A trial could have more than one type of intervention). Approximately a third had complex interventions targeted at multiple levels. Only 17% evaluated patient medical interventions (e.g., drugs or vaccines) and it was possible for individuals to opt out of the interventions in only 28% of studies. Approximately half included outcomes

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routinely collected in health administrative sources and a fifth observed outcomes on professionals; 22% were conducted without any recruitment of, or contact with, individual cluster members.

Decision to adopt cluster randomization

The decision to adopt cluster rather than individual randomization has major implications for trial design, implementation and analysis that must be carefully considered. Sometimes the unit of randomization is dictated by the nature of the intervention: changes in health services delivery, community-wide health promotion messages or training of health professionals to improve quality of care naturally require cluster randomization. However, for individual-level interventions, researchers should weigh the pros and cons of this design. A common reason for adopting cluster randomization is to prevent contamination due to sharing of information between intervention and control participants, but there may be circumstances where a modest risk of contamination is preferable to dealing with the additional complexities of cluster randomization [9]. Other common reasons for adopting cluster randomization are that it may help recruitment when all cluster members are offered the same intervention, simplify trial organization or administration, save costs as only half of centers need to be supplied with an intervention, and enhance compliance due to interaction among cluster members [1,3,4].

Implications of cluster randomization

A major implication of cluster randomization is that the design is statistically less efficient than an individually randomized design with the same total number of observations. This is a result of positive correlation among observations from the same cluster. To compensate, the sample size relative to an individually randomized trial must be increased by a factor of: $1+(m-1)\rho$, where m is the average cluster size and ρ is an advance estimate of the intracluster correlation coefficient (ICC). The ICC is a measure of average correlation among multiple observations from the same cluster. For most clinical outcomes it is safe to assume an ICC <0.05, while for process variables, larger estimates of up to 0.15 are possible [10]. For example, consider a trial requiring 50 patients per arm when implemented as an individually randomized design. To yield the same power when implemented as a cluster randomized design with an average of 25 patients per cluster and assuming an ICC of 0.05, this sample size must be increased by a factor of 2.2. Thus, a minimum of 110 patients or five clusters per arm (always rounding up to a multiple of cluster size) is required. However, this may not be a sufficient number of randomization units to balance important prognostic characteristics between the arms; it also restricts the options available for analysis and may limit the perceived generalizability of the results. A design with a larger number of clusters is preferable. Trials with fewer than five clusters per arm should be avoided. If substantial variability in cluster sizes is anticipated, a further increase of the sample size may be required [11].

Sometimes either the number of clusters or the cluster size is limited by availability or feasibility. If the number of clusters is limited, a cluster randomized trial may not be viable, as increasing the cluster size offers diminishing returns and beyond a certain point has virtually no effect on power. To determine if a design is feasible, the number of available clusters must be greater than the product of the number of individuals required under individual randomization and the ICC [12].

Pre-intervention measures of the outcome can be used to improve the efficiency of the design. In a cluster randomized trial, pre- and post-intervention measures can be observed either on the same individuals (referred to as a cohort design), or on independent samples of individuals (cross-sectional design). There are advantages and disadvantages to each [13].

Data from cluster randomized trials must be analyzed using statistical methods that account for the ICC. Standard methods, such as t-tests, chi-squared tests, and linear or logistic regression analyses, treat observations as independent and will yield p-values that are too low and confidence intervals that are too narrow. Regression analyses that attempt to account for clustering by including cluster indicators as fixed effects are invalid. Generally, trials with a large numbers of clusters offer more flexibility with respect to analysis [14]. One commonly used class of procedures is mixed-effects linear or logistic regression analysis in which a random intercept representing each cluster is added to the model specification to account for the ICC. For dichotomous outcomes, provided there are at least 40 clusters, the method of generalized estimating equations may be preferred over mixed-effects logistic regression as regression coefficients then have the usual interpretation as population-averaged effects. Analysis options for trials with a small number of clusters are limited and include parametric or nonparametric analyses of cluster-level summary scores (e.g., cluster means or cluster proportions) [4]. These procedures are robust but may not provide optimal power. The advice of a statistician is required to ensure that appropriate statistical procedures are adopted and that all assumptions are met.

There are other implications of cluster randomized designs. As they often randomize a small number of

clusters, the risk of baseline imbalances is greater than in individually randomized trials and design features such as stratification or minimization may be especially important [15]. They are more prone to selection biases. Although it is generally preferable to identify and recruit individuals prior to cluster randomization to avoid such biases, this is not always possible. If patients must be identified and/or recruited after cluster allocation, this should ideally be done by someone blinded to allocation status of clusters, and not by the patients' health professionals [5,6].

Informed consent procedures may be different in cluster randomized trials. It can be difficult to determine exactly who ought to be considered the research subjects and whose consent is required [16]. Consent may need to be sought after cluster allocation and separately for different aspects of the trial: intervention, data collection, or both [17]. The Ottawa Statement presents the first set of research ethics guidelines specific to cluster randomized trials [18].

Finally, cluster randomized trials have special reporting requirements [15]. The design should be clearly identified as 'cluster randomized' in the title or abstract. Researchers should explain the rationale for adopting cluster rather than individual randomization. The sample size calculation and analysis sections should clearly indicate how the ICC was accounted for. It should be clearly stated from whom, when and for what informed consent was sought [19].

Checklist for researchers

Cluster randomized trials will not yield reliable evidence about the effectiveness of health interventions and policies unless their methodological conduct and reporting are sound. Several reviews have shown less than adequate quality, with no noticeable improvement in recent years [9,20]. In our review of 300 cluster randomized trials, only 55% reported a sample size calculation and of these, only 61% accounted for the ICC in the calculation [9]. Furthermore, only 56% used stratification or some other design feature to balance baseline characteristics, and only 70% accounted for the ICC in the analysis. Failure to implement these basic methodological requirements has profound implications for interpretation of results from cluster randomized trials.

We conclude with a checklist of items for researchers to consider:

- Is there a clear rationale for choosing cluster randomization? If not, individual randomization is preferred;
- Consult with a statistician to ensure that sample size calculation and analysis plan are appropriate, ensure that the number of clusters is sufficient to allow valid analysis and interpretation of results;
- Consider the risks of baseline imbalances and, if necessary, account for them in the design; implement recruitment procedures that minimize the risk of bias;
- Adhere to the Ottawa recommendations for the ethical design and conduct of cluster randomized trials;
- Adhere to the reporting guidelines set out in the Consort extension to cluster randomized trials.

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