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Appropriate statistical methods were infrequently used in cluster-randomized crossover trials

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Abstract

Objective: To assess the design and statistical methods used in cluster-randomized crossover (CRXO) trials.

Study Design and Setting: We undertook a systematic review of CRXO trials. Searches of MEDLINE, EMBASE, and CINAHL Plus; and citation searches of CRXO methodological articles were conducted to December 2014. We extracted data on design characteristics and statistical methods for sample size, data analysis, and handling of missing data.

Results: Ninety-one trials including 139 end point analyses met the inclusion criteria. Trials had a median of nine clusters [interquartile range (IQR), 4−21] and median cluster-period size of 30 individuals (IQR, 14−77); 58 (69%) trials had two periods, and 27 trials (30%) included the same individuals in all periods. A rationale for the design was reported in only 25 trials (27%). A sample size justification was provided in 53 (58%) trials. Only nine (10%) trials accounted appropriately for the design in their sample size calculation. Ten of the 12 cluster-level analyses used a method that accounted for the clustering and multiple-period aspects of the design. In contrast, only 4 of the 127 individual-level analyses used a potentially appropriate method.

Conclusions: There is a need for improved application of appropriate analysis and sample size methods, and reporting, in CRXO trials.

Keywords: Cluster-randomized crossover trial; Crossover; Cluster; Sample size; Design; Statistical analysis

1. Introduction

The cluster-randomized crossover (CRXO) design is gaining popularity in settings where cluster randomization is required, but the parallel group cluster-randomized design is not feasible because the required number of clusters is prohibitively large [2,3]. In the CRXO design, hospitals, schools, or other groups of people (‘‘clusters’’) are randomly assigned to a sequence of interventions. Each cluster receives each intervention at least once in a separate period of time, leading to the formation of ‘‘cluster-periods’’ [4,5]. Within each cluster, each cluster-period may contain a repeated cross-section of different individuals, a cohort of the same individuals who are followed over time, or a mixture of the same and different individuals [6].

This design differs from the parallel group cluster-randomized design and the individually randomized crossover design. In the parallel group cluster-randomized design [7], each cluster is assigned only a single intervention, rather than a sequence of interventions. Each cluster therefore contains a single cross-section of different individuals. In the individually randomized crossover design [8], a cohort of individuals, rather than a series of clusters of individuals, are randomly assigned to a sequence of interventions. We refer the reader to Hooper and Bourke [9] for examples of other cluster designs conducted over multiple periods.

In both the individually randomized crossover design and CRXO design, randomization of the intervention

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What is new?

Key findings

- Reporting of the rationale for using cluster-randomized crossover (CRXO) trials was uncommon, despite this being a recommended reporting item for cluster-randomized trials [1]. Sample size calculations were commonly not reported, and only a minority of CRXO trials used sample size methods that appropriately accounted for the design.
- Only rarely did the used statistical methods account for the design, that is, adjust for the clustering and multiple period aspects.

What this adds to what was known?

- This is the first systematic review of CRXO trials. The results of this review provide a comprehensive assessment of the design characteristics, statistical methods for sample size, data analysis, and handling of missing data in CRXO trials.

What is the implication and what should change now?

- Trialists need to account for both the cluster randomization and multiple period aspects of the design in sample size calculations and statistical analyses. Methods and assumptions need to be clearly reported and justified.
- The development of reporting guidelines for CRXO trials is needed to facilitate clearer and complete reporting.

sequence serves to control for period effects (i.e., changes that occur over time that are unrelated to the intervention); and a key requirement of the two period design is that the effect of an intervention given in one period does not carry over into the next period [5,8]. In CRXO designs where cluster-periods contain different individuals, the potential for carryover is limited because any carryover can only take place at the cluster level. However, in CRXO designs where the same individuals are followed over time, carryover can also take place at individual subject level, and therefore, its potential is similar to that in individually randomized crossover designs.

The efficiency of a CRXO trial relative to an individually randomized trial or a parallel group cluster-randomized trial depends on the relationship between the outcomes from individuals within and between each cluster-period [6]. Individuals within a cluster tend to have more similar outcomes than individuals across clusters [7]. For example, because of differences in case-mix between patients presenting to different hospitals, patients in the same hospital may have more similar outcomes than patients in other hospitals. Likewise, individuals within a cluster-period tend to have more similar outcomes than individuals in different clusters. This similarity is typically measured by the within-cluster within-period intracluster correlation (ICC) [3−6,10]. This tendency for similar outcomes increases the uncertainty in the estimation of the effect of each intervention compared with outcomes that are independent.

If the environment of the cluster remains similar over time, then the outcomes of individuals within each cluster across different cluster-periods tend to be similar also. This tendency is typically measured by the within-cluster between-period ICC [3,5,6,10]. By comparing the interventions within cluster, the cluster-specific variation is removed from the comparison, and the uncertainty of the difference between interventions is decreased when there is a positive within-cluster between-period ICC [5]. Therefore, the crossover element of the design can offset the loss of precision arising from cluster randomization.

In the analysis of data from a parallel group cluster-randomized trial, it is recognized that the analysis must account for the correlation within clusters to correctly estimate the uncertainty in the intervention effect, for example, by including the cluster unit of randomization as a random effect in a generalized linear model (GLM) (e.g., Eldridge 2012). However, it is unclear whether trialists recognize that both the within-cluster within-period and the within-cluster between-period ICCs must be appropriately incorporated into sample size calculations and analyses to yield appropriate sample sizes and intervention effects with the correct standard errors in CRXO trials.

There have only been limited reviews examining the application and use of analytical methods for CRXO trials. These reviews have taken place in the introductory sections of methodological articles with the purpose of illustrating the design and highlighting the need for appropriate methods of analysis [4,5,10,11]. Therefore, we used systematic review methodology to examine the settings, design characteristics, justifications for using the design, quality of reporting, and sample size and analysis methods of trials that have used the CRXO design [12]. In this article, we focus on the design characteristics; statistical methods for sample size and data analysis, and the appropriateness of those methods; and the completeness of reporting of the statistical methods.

We begin with a brief review of recommended sample size and analysis methods for CRXO trials in Section 2. In Section 3, we outline the systematic review methods. Results are presented in Section 4 and discussed in Section 5.

2. Brief review of sample size and analysis methods for CRXO trials

Only limited methodological research has been published to guide trialists in performing sample size