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BACKGROUND ARTICLE

Cluster randomized controlled trials in primary care: An introduction

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Abstract

Background: Cluster randomized trials occur when groups or clusters of individuals, rather than the individuals themselves, are randomized to intervention and control groups and outcomes are measured on individuals within those clusters. Within primary care, between 1997 and 2000, there has been a virtual doubling in the number of published cluster randomized trials. A recent systematic review, specifically within primary care, found study quality to be both generally lower than that reported elsewhere and not to have shown any recent quality improvement. **Objective:** To discuss the design, conduct and analysis of cluster randomized trials within primary care in terms of the appropriate expertise required, potential bias, ethical considerations and expense. **Discussion:** Compared with trials that involve the randomization of individual participants, cluster randomized trials are more complex to design and analyse and, for a given sample size, have decreased power and a broadening of confidence intervals. Cluster randomized trials are specifically prone to potential bias at two levels—the cluster and individual. Regarding the former, it is recommended that cluster allocation be undertaken by a party independent to the research team and careful consideration be given to ensure minimal cluster attrition. Bias at the individual level can be overcome by identifying trial participants before randomization and at this time obtaining consent for intervention, data collection or both. A unique ethical aspect to cluster randomized trials is that cluster leaders may consent to the trial on behalf of potential cluster members. Additional costs of cluster randomized trials include the increased number of patients required, the complexity in their design and conduct and, usually, the need to recruit clusters *de novo*.

Conclusion: Cluster randomized trials are a powerful and increasingly popular research tool. They are uniquely placed for the conduct of research within primary-care clusters where intracluster contamination can occur. Associated methodological issues are straightforward and surmountable and just need careful consideration and management.

Key words: Cluster randomized controlled trials, research methodology, primary care

Introduction

Cluster randomized trials occur when groups or clusters of individuals, rather than the individuals themselves, are randomized to intervention and control groups and outcomes are measured on individuals within those clusters (1). This approach overcomes the obvious difficulties of contamination between intervention and control groups when randomization occurs within the same organizational unit or general practice (2). Torgerson (3), however, has suggested that the potential likelihood and impact of such contamination can be overstated. He calculates that around 30% contamination can be sus-

tained before the sample size has to be doubled to take into account the reduced effect size from such contamination. It appears reasonable to suggest, however, that most practitioners would find it difficult to provide two differing types of care, independently allocated, to patients within their own practices.

A growing appreciation of their popularity within primary care is confirmed by a virtual doubling, between 1997 and 2000, in the number of published cluster randomized trials specifically in primary care (4). Their utility is wide ranging, as highlighted by examples such as the prevention of dog bites (5), management of diabetes (6) and an analysis of the

impact of unflued gas heaters on respiratory health (7). The Medical Research Council has published a practical and influential discussion of the methodological and ethical considerations pertaining to cluster randomized trials (1). The CONSORT statement has also been recently extended to cluster randomized trials (8). General reviews of the quality of cluster randomized trials have highlighted concerns regarding design and conduct quality (9,10). A recent systematic review, specifically within primary care, found study quality to be both generally lower than that reported elsewhere and not showing any recent quality improvement (4).

Donner (11) has suggested that communicating appropriate methodology to researchers involved in designing and analysing cluster randomized trials is a greater challenge than further methodological developments. We therefore consider it opportune to discuss the design, conduct and analysis of cluster randomized trials within primary care in terms of biostatistical considerations, potential bias, ethical considerations and expense. This paper is intended as an introduction to cluster randomized controlled trials—more detailed information is available in both the references and two seminal texts (12,13).

Biostatistical considerations

Compared with trials that involve the randomization of individual participants, cluster randomized trials are more complex to design and analyse (8). In particular, for a given sample size, they have decreased power and a broadening of confidence intervals in comparison to randomization by individual. The design effect (deff) is the amount by which sample size for a cluster randomized trial has to be increased to allow for clustering as compared to an equivalent study randomized by individual. This is calculated to be:

$$\text{deff} = [1 + (m - 1)\rho]$$

where m is the average number of patients selected per cluster (practice) and ρ is the intraclass correlation coefficient, which is the proportion of the total variance of the outcome that can be explained by the variation between clusters.

From this equation, it is clear that any increase in cluster size and/or intraclass correlation coefficient causes a multiplicative increase in the number of patients required for a cluster randomized trial to achieve usually accepted levels of power and significance. For example, a study with 30 patients per cluster and an intraclass correlation coefficient of 0.05 will have a deff of 2.45, that is, we would need to more than double the sample size required for a non-clustered design. This also suggests, other

resource issues being equal, that a study with many practices, each with only a small number of patients, is more efficient than one with only a few practices, each with many patients. Estimates of intraclass correlations in primary care are available. For example, Campbell et al. (14) suggest 0.05 to 0.15 for process outcomes, and less than 0.05 for outcome variables. Kerry and Bland (15) indicate that the intraclass correlation coefficient is likely to be smaller for trials where the intervention is on the patient compared with when the intervention is on the doctor's behaviour. For example, they quote a coefficient of 0.0036 for a study involving patient intervention to prevent thrombosis, and 0.019 for a trial of guidelines to improve the appropriateness of general practitioners' referrals for X-ray examinations. Finally, Murray et al. (16) point out that a cluster randomized trial is unlikely to have sufficient power with fewer than 8 to 10 practices per intervention arm. Unfortunately, in a recent systematic review within primary care (4), only 20% of the trials reporting sample size calculation made allowance for clustering.

Analysis of cluster randomized trials is also more complex than individually randomized trials. The unit of inference in cluster randomized trials may be either at the level of the cluster or individual. Recent papers recommend conditional models such as mixed-model regression when the focus is on change within individuals, and marginal models such as generalized estimating equations (GEE) when the focus is on group comparisons (16). This crucial area is comprehensively discussed in the two seminal texts (12,13) and will always require specialist input. It is therefore vital that the skills of a biostatistician be available at the early stages of a cluster trial design and during analysis. Due to the limited availability of such skills (17), this can be problematic—the establishment of organizations such as the Special Interest Group in Epidemiology at the Society of Academic Primary Care in the United Kingdom is welcome. An equivalent Australian group is the Primary Care Alliance for Clinical Trials (PACT) (18).

Potential bias

General concerns of randomized trials in relation to selection and measurement bias, as well as confounding, apply equally to cluster randomized trials. Cluster randomized trials are specifically prone to potential bias at two levels—the cluster and individual (19). Even with the best of intentions to use a random process, bias is possible at the former level if certain clusters are allocated to a particular arm for specific reasons. Puffer (19) has recommended that

cluster allocation be undertaken by a party independent to the research team to ensure the allocation of clusters is performed randomly. Whilst this may appear somewhat extreme, it does ensure complete transparency and, as clusters are usually all recruited first and then allocated, the associated workload is minimal. As in individually randomized trials, attrition bias must be considered. The loss of entire clusters, as opposed to individuals, will clearly have profound implications.

Once the clusters have been allocated, selection and recruitment of participants, especially if done in an unblinded manner, can introduce bias. The potential for selection bias within clusters is particularly high (8). The participants can also, once allocation has occurred, introduce bias by differential consent rates. Bias at the individual level can be overcome by identifying trial participants before randomization and at this time obtaining consent for intervention, data collection or both. *Identification and recruitment of patients should ideally be undertaken by someone blinded to the group allocation. Objective measures of eligibility and routine and frequent checking for differences between arms in the number of invitees, recruits and refusals is also important (1).*

These concerns are not merely theoretical. Puffer (19), in a recent review of 36 cluster randomized trials published in three leading general journals, found potential bias at the cluster level for 58% and at the individual level for 39% of the trials.

Ethical considerations

Unique to cluster randomized trials is that cluster leaders may consent to the trial on behalf of potential cluster members (20). Edwards (21) reviewed the unique ethical considerations of cluster randomized trials for “guardians. . . who have the power to deliver that cluster”. Such guardians in practice are often general practitioners who must act, as an advocate, in the best interests of the cluster. Edwards highlighted the potential conflicts of interest for guardians, especially if financial incentives are available. A distinction is made between cluster-cluster and individual-cluster trials, although overlap does occur (1). In the former, the guardian consents to both the trial entry and the intervention (when the whole cluster receives it, e.g. fluoridation of the water supply). In the latter, when individuals within clusters receive specific treatments (e.g. a complex practice intervention to improve secondary cardiac care), their individual consent can be sought. For both, ethical committees in guiding the guardian in the decision of whether to enrol a cluster, or not, play a crucial, but obviously not definitive, role. A cluster representation mechanism (e.g. a plebiscite

for cluster-cluster and a general practitioner acting in good faith for individual-cluster trials) may be considered (1).

The general ethical concerns of randomized trials—determination of clinical equipoise (22), conducting of confirmatory trials, and perceived tension between informed consent and the doctor-patient relationship (23,24)—are also common to cluster randomized trials. We believe that, with the increasing popularity of cluster randomized trials within general practice, the latter deserves some consideration. General practice rightly prides itself on the special place which the, often long-term, doctor-patient relationship holds in the discipline. Hellman portrays a scenario where a patient “anxious to please their physician. . . may have difficulty refusing to participate in the trial the physicians describe. The patients may perceive their refusal as damaging to the relationship, whether or not it is so” (23).

It would be most regrettable if, in attempting to strengthen the evidence base in general practice, the strength of the doctor-patient relationship was usurped. The potential of this occurring could be decreased by consent being sought by a researcher external to the practice, but this may pose significant feasibility problems and breach privacy considerations of the practice to its patients (25,26). The increased numbers of patients required to answer clinical questions within cluster randomized trials emphasize that these general ethical concerns need to be clearly reconciled in advance of trial commencement.

Expense

Randomized trials in general are expensive. Additional costs of cluster randomized trials include the increased number of patients required, the complexity in their design and conduct and, usually, the need to recruit clusters de novo. *The latter can be overcome through the development of a network of research clusters similar to that of the Medical Research Council in the United Kingdom. PACT (18) and its equivalent may have a role to play in the development of such networks in other countries. Funding for primary-care research is limited. The balance between conducting expensive “high level” cluster trials and simpler and cheaper studies needs to be considered (27).*

Conclusions

Cluster randomized trials are a powerful and increasingly popular research tool. They are uniquely placed to contribute to primary-care research where intracluster contamination can occur. They share the

same strengths and potential biases as trials which are randomized by individual. Additional issues to be considered in their design and conduct are sample size calculations, analysis by cluster and the individual, potential biases at cluster and individual level, consent by cluster leaders, and expense. The MRC cluster randomized trial pamphlet (1) is a very practical source of advice for those intending to conduct such trials. These issues are surmountable and just need careful consideration and management to ensure that cluster trials contribute optimally to the growing high-quality evidence base of primary care.

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