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Pseudo cluster randomization: balancing the (dis)advantages of cluster and individual randomization

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Abstract

While designing a trial to evaluate a complex intervention one may be confronted with the dilemma that randomization at the level of the individual patient risks contamination, whereas cluster randomization risks incomparability of study arms and recruitment problems.

Literature provides only few solutions to this dilemma and these are not always feasible. As an alternative solution for this dilemma we developed a new randomization method called pseudo cluster randomization. In pseudo cluster randomization clusters (e.g. health care professionals, classes, wards) are randomized in two groups. Depending on this randomization, the participants are randomized in majority to one study arm.

This has important advantages. Compared with cluster randomization the occurrence of selection bias and poor recruitment is prevented, because treatment allocation remains concealed. Limiting the exposure of clusters to the innovative intervention lowers risk of contamination. With contamination present, pseudo cluster randomization can be more efficient than individual or cluster randomization.

Randomized clinical trials; Cluster randomization; Selection bias;
Contamination; Recruitment

Introduction

Sometimes trying to avoid one pitfall may lead to unwillingly running into another. While designing a health services evaluation trial (Dutch EASYcare Study) we faced such a dilemma (Melis et al., 2005; Melis et al., 2008c; Melis et al., 2008a). Randomization at the level of the individual patient risked a cross-over in services received such that the control group patients received services that were intended only for the intervention group (Reuben, 2006). This is called contamination. However, cluster randomization (Donner et al., 1981; Campbell et al., 2004), which is an accepted solution to avoid such contamination, risked incomparability of study arms and recruitment problems (Torgerson, 2001; Puffer et al., 2003). Although several authors have hinted at the existence of this dilemma, still many health services researchers are unaware of it, and literature provides only few options to deal with it. We solved the problem by combining cluster and individual randomization in a new randomization method called pseudo cluster randomization. We explain the dilemma of individual versus cluster randomization, and present the alternative of pseudo cluster randomization using the Dutch EASYcare study as an example.

Methods

Dilemma

In the Dutch EASYcare Study we wanted to evaluate the effects of a nurse led home visiting program compared to usual care in improving health related quality of life of older people with common geriatric problems (e.g. falls, dementia) (Melis et al., 2005). It was impossible to blind the patients from the intervention they received: in the intervention arm patients were visited by a specialist geriatric nurse, in the control arm they were not. The primary care physicians participated in the intervention model: nurse and primary care physicians had frequent consultations to guide the

management of individual cases. The primary care physicians' exposure to the intervention resulting from their participation could lead to contamination of control patients and thus introduce contamination bias, when patients had been randomized individually.

In general, the consequence of contamination bias is reduction of the intervention effect (Torgerson, 2001). To retain sufficient power the study size has to be increased. It may also lead to important problems in interpreting (especially negative) study results: was there no effect, or was the effect lost due to contamination?

Had we used cluster randomization – an often used alternative in case of contamination – in the EASYcare trial, all patients of one primary care physician would have received the same treatment: either the nurse led care program or usual care (Donner et al., 1981; Campbell et al., 2004). Cluster randomization would have effectively prevented the occurrence of contamination bias. Unfortunately, it would also have introduced two serious threats to validity. Our intervention required that patients had to be enrolled one by one at the moment they experienced certain problems. Had cluster randomization been used, the referring primary care physician would have known the randomization outcome after the inclusion of the first patient. This would most likely have reduced the rate of recruitment in the control group, because primary care physicians would probably be less interested in the trial when they could not administer the innovative treatment as well (Puffer et al., 2003). This is important, because recruitment of subjects is always a challenging issue (Ferrucci et al., 2004; Medical Research Council, 2000). Even more importantly, prior knowledge of the randomization outcome would probably have influenced the selection of patients. Even with tight eligibility criteria the eligibility of an individual patient is prone

to interpretation, and knowledge on the allocation outcome influences this. Different selection of patients in the therapy arms would have led to selection bias and incomparable treatment arms.

The methodological dilemma becomes clear: randomization at the level of the individual patient is predicted to cause contamination bias, whereas cluster randomization probably introduces selection bias and recruitment problems.

Solutions from literature

Several authors describe this methodological dilemma, but literature provides only a few options to deal with it (Puffer et al., 2003; Campbell et al., 2004; Jordhoy et al., 2002; Hahn et al., 2005; Torgerson, 2001).

Selection bias resulting from cluster randomization can sometimes be prevented using an early patient recruitment procedure: the recruitment of the patients is completed before randomization of the clusters (Moore et al., 2001). In the EASYcare trial this was impossible: it is impractical and unethical to postpone an individual intervention until recruitment of all patients in the trial is completed. Another disadvantage of pre-randomization recruitment is that it can jeopardize the generalizability as well as the validity of the trial results due to selective drop out of subjects before and after randomization (Moore et al., 2001; Campbell et al., 2004).

If complete enrollment prior to randomization is not an option, it may be helpful to have an independent recruiter to recruit the patients (Hahn et al., 2005). However useful this may be in some situations: it is an expensive and often impractical solution, because the identification of eligible patients during routine care is no longer possible.

Another way to deal with selection bias (not to prevent it!) in a cluster randomized design is statistical correction, but adjustment by statistical methods is

often imperfect and can only be made for known confounders, making this solution less desirable.

Sometimes may individual randomization be the most appropriate approach, even if contamination is present (Torgerson, 2001). We already mentioned that dilution of the effect by contamination in a fully randomized trial requires an increase in sample size. However, a larger sample size is also necessary in a cluster randomized design, because the sample size has to take into account clustering of data that occurs in cluster randomization (so called “design effect”). The result may be that the sample size needed for a cluster randomized design does not differ substantially from the sample size needed for an individually randomized trial.

Neither of the solutions proposed previously was suitable in the Dutch EASYcare Study. In this trial, we solved the problem by combining cluster and individual randomization in a new randomization method called pseudo cluster randomization.

Pseudo cluster randomization

In pseudo cluster randomization the clusters first are randomized into two types: H (high) and L (low) (figure 1) (Borm et al., 2005). In a second step, randomization at the patient level is carried out within these clusters. The majority of the subjects in the H clusters receive the intervention, while the smaller rest receive control care. The randomization ratio in the L clusters is reversed.

In the EASYcare trial 80 percent of the patients in the H clusters received the intervention, while the rest received usual care, and of the L clusters 20 percent received the intervention and 80 percent usual care.

Results

Aspects of pseudo cluster randomization

The pseudo cluster randomization approach has important advantages, directed towards selection bias and contamination. The researchers do not know in which type of cluster they are, nor do they know in advance what treatment a patient will be on. This reduces the chance of selection bias. In the EASYcare study a large majority of primary care physicians (67%) thought that a 1:1 randomization ratio was used and those primary care physicians who estimated more uneven randomization ratios tended to be less certain of their estimation. Patients in the intervention and control arm of the Dutch EASYcare Study were very comparable, meaning that it is unlikely that selection bias occurred (Melis et al., 2008b).

No longer are half of the clusters randomized to control care for all patients. This is an advantage because doctors may be less willing to recruit when patients have no chance of receiving the innovative treatment with expected benefit over regular care. Indications for this were also present among the physicians who participated in the EASYcare trial. They had a strong preference for their patients to be randomized to the intervention (Visual Analogue Scale 14.5 (SD 15.6); 0-100: 0 indicates strongly favoring the intervention arm), and more than half (58%) would have recruited less patients if all their patients had been on regular care (Melis et al., 2008b).

The rationale behind pseudo cluster randomization with respect to contamination reduction is that the contamination of the control group can be limited by restricting the number of patients on the experimental treatment in a cluster. This limits contamination under the condition that the dissemination of elements of the experimental treatment to the control group is a gradual process that depends on the number of experimental treatments in each cluster (Borm et al., 2005; Teerenstra et al., 2006). In L-clusters most of the patients receive control care and only few

patients are on the intervention program. In the EASYcare study, this meant that the contamination due to the intervention treatment was smaller compared to individual randomization, because there were only very limited possibilities for the participating primary care physicians to gain proficiency in the new treatment. The contamination of control patients in H-clusters may have been substantial, as the majority of the patients in such clusters were on the intervention program, but their numbers were small (as the controls were in the minority in H).

Finally, when contamination is present and the clusters have a moderate size (6-20 participants), pseudo cluster randomization generally is more efficient than randomization on a patient or cluster level (Teerenstra et al., 2006). In the EASYcare trial, pseudo cluster randomization indeed required a smaller sample size than individual or cluster randomization.

Discussion

The benefits of multidisciplinary, tailored care programs may be intuitively clear; it remains a challenge to show the benefits convincingly (Medical Research Council, 2000; Campbell et al., 2000). This may be due to insufficient research methodology, which means that improvements of the methodology need to be made (Reuben, 2006). We have proposed a new research design that addresses three major issues frequently encountered when studying complex interventions: recruitment, contamination, and comparability of study arms (Medical Research Council, 2000). However, in every situation the advantages of the available methods have to be carefully weighed against their limitations. The first issue is the assumption underlying pseudo cluster randomization that contamination is limited when the cross exposure to the other intervention is limited. In general, this is

depends on the nature of the intervention under study. We believe this assumption was justified in the EASYcare study because the intervention was a complex collaboration of nurse, primary care physician, and geriatrician that cannot be easily copied. However, this assumption is more debatable if an intervention is very simple to execute. If this condition is not satisfied and already one single patient on the experimental treatment will lead to complete contamination of all other patients, then it is necessary to prevent cross exposure in every way, and cluster randomization is the only solution.

The predictability is another issue. In pseudo cluster randomization it is higher than in individual randomization, but it will always be less than in cluster randomization. At the end of the trial the large majority of primary care physicians believed a 1:1 randomization ratio was used in the EASYcare trial. During the trial this majority probably was even larger, because primary care physicians were blinded for the exact randomization proportions as well as the groups they were in. Thus, predictability probably is not substantially higher than in an individually randomized trial.

We would like to underline the plea from those authors who have argued that it is necessary to account for possible contamination bias when designing a randomized trial. Bearing this in mind, our main message is to keep an eye for comparability of study groups as well. Pseudo cluster randomization may be a useful solution, when individual randomization is expected to lead to contamination, and cluster randomization may result in selection bias or poor recruitment. Which method is best has to be considered on a trial-by-trial basis.

Along with the compelling need for effective health care, comes the increasing need for effective methods for their study (Ferrucci et al., 2004). "We will need to

improve the science of studying health services [...] before we can prove what our eyes, ears, and hearts tell us is true“(Reuben, 2006). With pseudo cluster randomization a statistically efficient method is added that can be used to minimize contamination without introducing serious selection bias or recruitment problems.

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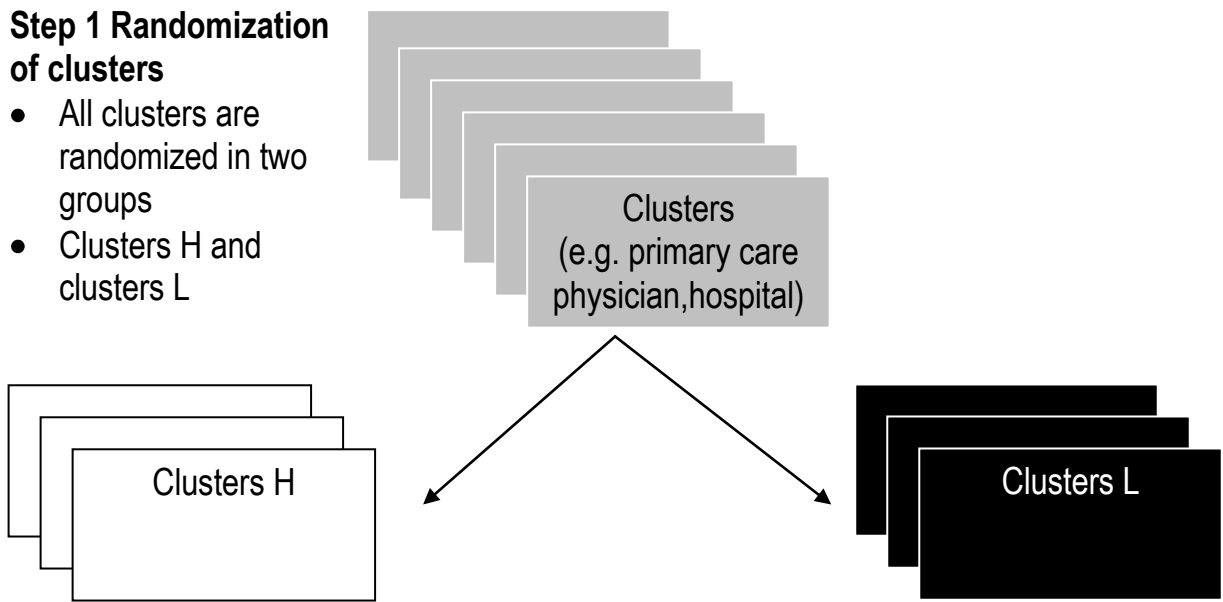
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Figure 1. Pseudo cluster randomization

Step 1 Randomization of clusters

- All clusters are randomized in two groups
- Clusters H and clusters L



Step 2 Randomization of patients within a cluster

- Clusters H: most patients randomized to intervention arm
- Clusters L: most patients randomized to control arm

