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Bias in identifying and recruiting participants in cluster randomised trials: what can be done?

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Summary

Cluster randomised trials are widely used to evaluate certain types of interventions, where groups of participants rather than individuals are randomised. Allocation concealment is regarded as crucial for individually randomised trials so that bias in the patients recruited can be avoided. However recruiting subjects blind to their allocation status presents particular challenges for cluster trials. Many trial reports suggest that investigators are not aware of any difficulties that lack of blinding may cause. For investigators who are aware, it is often difficult to see how lack of blinding can be avoided. This paper describes some strategies that can be used to reduce bias in identifying and recruiting participants: (i) not recruiting individual participants, (ii) recruiting participants before randomisation, (iii) recruiting in settings outside the clusters, (iv) masking recruiters. Authors of trial reports should ensure that they report how participants were identified and at what stage this was done, as well as reporting the potential eligible population in each cluster where possible. If these steps are taken then bias in future trials will be reduced and greater transparency of reporting will increase confidence in trial results.

Background

Allocation concealment is regarded as crucial for an individually randomised controlled trial. This is the process, prior to randomization which conceals the allocation from those selecting participants for randomization thus avoiding selective recruitment. In cluster randomised trials, groups, or clusters, of participants, rather than individual participants, are randomised yet data are collected on individual participants. Selective recruitment of individual participants can occur in these trials if those recruiting participants know participants' allocation status, even when allocation has been adequately concealed at randomisation.

Two recent reviews found that up to 40% of cluster trials published in major medical journals may be biased [1,2] yet articles and books [3,4] on cluster randomised trials have tended to focus on statistical issues rather than the need to ensure unbiased sampling of individuals within the cluster.

Cluster randomised trials have a long history in education [5], where the problem of evaluating a novel curriculum is relatively straightforward [6]. Most commonly, children are identified from school or class registers with little or no problem of selection bias being introduced after randomisation, and no consent is required from the children themselves or their parents. Many health care trials can be designed along similar lines, with potential participants being all those who belong to a cluster. The Kumasi stroke prevention trial, (Box 1) evaluating an educational intervention to reduce salt intake in Ghanaian villages, identified and recruited participants before randomisation of the villages [7].

In this paper we describe how bias may occur when individual participants are identified or recruited in cluster randomised trials. and discuss how it can be avoided.

Trials in which individual participants are not recruited

When an intervention takes place at the cluster level outcomes are collected from routine data with adequate regard to confidentiality and data protection, and there is no change in the care arrangements of participants, it may be ethically acceptable not to recruit individual patients, even in today's increasingly restrictive research environment. One example of this is the IRIS trial (Box 2), which is evaluating an intervention to increase the identification and referral of women who are victims of domestic violence. (http://www.controlled-trials.com/ISRCTN74012786/74012786).

In trials without individual patient recruitment, bias can still occur if individual participants are *identified* by those aware of allocation status. In a trial randomising general practices, [8] patients consulting for ischaemic heart disease were identified by the GPs and data collected by individuals that were aware of the cluster allocation status, even though there was no patient recruitment.

Some would consider that individual recruitment with consent into trials is mandatory [9] and failure to do so contravenes ethical principles. Eldridge and colleagues [10] discuss the balance between scientific considerations and the need for consent in cluster randomised trials. Given the wide variety of interventions and designs each study needs to be considered on a case by case basis. Further discussion of this issue is beyond the scope of this paper.

Trials in which individual participants can be identified and recruited before randomisation

For trials of chronic disease management, it may be possible to identify and consent patients before clusters are randomised. This is often not done, however, even when possible. Kannus and colleagues [11], identified and randomised 22 clusters where older people are supported to live in the community. After randomisation, participants were asked if they would be prepared to take part in a study evaluating the use of hip protectors. In the control group 91% agreed to participate and allow the researchers to collect data on hip fractures; in contrast, only 69% of the intervention group participated, possibility because they did not want to wear the hip protectors. Studies using this approach tend to show a benefit of hip protectors whilst individually randomised trials do not; this difference might be due to selection bias from the trial design [12].

The key to preventing this sort of problem is trial design [6]. Although some have proposed statistical methods, such as propensity scores, to correct for observed group imbalances [13], analytical solutions to try to address the problem are unsatisfactory in that we can never be sure that we can fully correct for unobserved covariate imbalances.

Even for acute conditions, recruitment before randomisation is possible if risk factors for the condition are well established. For example, women with a previous episode of a urinary tract infection have an elevated risk of developing another acute episode [14]. Investigators wishing

to conduct a cluster randomised trial of a treatment for women with a urinary tract infection could recruit a cohort of women who have had a urinary tract infection in the past and then randomise clusters. The drawback of this approach is the recruitment of more people than needed and, depending upon the latent time to symptom development, the trial may need to be relatively long, both of which will increase trial costs.

More generally, one drawback of identifying and recruiting participants before randomisation is the possibility of a long delay between recruitment and intervention implementation which is generally seen as undesirable. To avoid this, clusters can be randomised immediately all their patients have been recruited. Alternatively, after a block of clusters have completed recruitment, these clusters could be randomised. The advantage of this latter approach is that balance in the number of clusters in each intervention group can be assured while keeping allocation status concealed from the last cluster to enter the trial. In the Kumasi trial (Box 1), blocks of two were used, but larger blocks could be substituted.[7] In a trial of patient-held records for adults with learning difficulties, the number of patients per cluster was small and blocks of ten practices were randomised simultaneously[15].

Trials in which individual participants have to be identified or recruited after randomisation

If it is not possible to identify and recruit before cluster randomisation, then masked recruiters may be used, ideally recruiting outside the cluster setting to avoid unmasking by contact with cluster staff aware of cluster allocation. In the ELECTRA trial, (Box 3) patients with an acute

episode of asthma were recruited from a clinic in an accident and emergency department by researchers blind to allocation status. Following recruitment, all patients were then referred to the liaison nurse, who told them which intervention group they were in [16]. In this example all eligible patients were attending a secondary care setting. In some trials, this method might bias the sample towards more serious cases or result in recruitment of patients not belonging to study clusters.

If participants are recruited within cluster settings, masked recruitment may still be possible when potential participants can be identified and recruited by masked recruiters outside the clinical consultation. An example of this is a trial evaluating training of health professionals where potential participants were mothers bringing children under five for health care (Box 4) [17]

When masked recruitment is not an option, some effort can be made to standardise recruitment across intervention groups. King and colleagues [18] evaluated an educational intervention to manage patients with incident depression. The trialists trained reception staff to recruit the participants. Because the control and intervention recruitment staff had the same training the possibility of recruitment bias was reduced. Nevertheless, reception staff may still introduce selective recruitment, and using non-clinical recruiters may result in some ineligible participants being recruited. In this instance we should include them in the analysis (i.e., intention to treat) as the dilution effects are not as serious a threat as selection bias.

It has been proposed to try and mask allocation status from treating and recruiting clinicians by using a partial split plot design [19]. Clinicians are masked to the allocation of their clusters, and to maintain clinician blinding a small proportion of patients in the control clusters are randomised to the intervention group and a small proportion of intervention patients to the control group. A study undertaken in Holland suggests that this design can be used successfully to mask recruiting clinicians using a 4:1 randomisation ratio with cluster sizes of up to 10 participants [18]. However, the design cannot be used in trials evaluating interventions aimed at cluster staff and the masking is only likely to be maintained if cluster sizes are small; when cluster sizes are large it is likely that health professionals in clusters will be able to guess which group they are in. In addition, the presence of those receiving the intervention within the control clusters could contaminate the rest of the cluster. This will dilute effect size estimates. Some of the dilution effects may be offset, however, by using latent variable analytical methods, such as complier average causal effect (CACE) analysis – although these approaches tend to increase the width of the confidence intervals [20].

When recruiting incident cases, bias may occur if clusters allocated to an undesired treatment group withdraw between randomisation and recruitment of first patient. To avoid this, clusters may be randomised once an 'index case' has been recruited [13]. The POST trial [21] used this method; participants were patients being discharged from hospital following a coronary event. Implementing the intervention as and when a patient presents is likely to present practical difficulties for interventions aimed at cluster staff, but more importantly does not necessarily prevent future selective recruitment beyond the index case. However it may be useful where the number of eligible patients per cluster is likely to be small.

In the BEAM trial pilot study, physicians who had been trained to actively manage back pain recruited twice as many incident cases, with lower severity, as physicians in the control group [22]. One solution might have been to try to mask researchers to the intervention status of the practice to identify patients from the practice computer and gain their consent to participate. An alternative could have been to recruit chronic back pain sufferers from practice lists before randomisation of the clusters and use them in the evaluation. But in the event, investigators abandoned a clustered design for this part of their study.

Patient information

Whatever the timing of recruitment, both intervention and control groups should be given similar information about the trial prior to consent, which is information about the trial rather than necessarily information as part of the intervention. However, fully informing the controls of the intervention could dilute the intervention effect, causing bias. In the Kumasi trial, the information sheet did not mention salt but referred to changing diet and all subjects were asked to attend health education sessions on a variety of subjects with the addition of salt reduction in the intervention clusters. How much information control patients should receive in these circumstances has been the subject of debate [23]. This dilemma is not restricted to cluster randomised trials [24] but in a cluster trial there may be a temptation to have very different information sheets for the intervention and control groups. This should be avoided.

Participants may also receive information from cluster staff, who may know the aim of the intervention but be unaware of the importance of masked recruitment and possibility of

contamination. There is a need to ensure all staff are adequately trained and that information about the trial aims and the cluster allocation is on a "need to know" basis.

Measuring possible selection bias

When there is no design solution to masking recruitment, wherever possible authors should report sufficient information to enable readers to judge for themselves whether or not differential recruitment has taken place. Firstly authors should report the size of the potential eligible population as well as numbers recruited. Where eligible patients can be identified from practice computers prior to consent this is fairly straightforward. Where participants are recruited as a result of a consultation or event, it may be possible to check for eligible patients who were not recruited retrospectively. A trial in pregnant women to reduce baby walker use (Box 5), reported the number of participants as a percentage of live births in each intervention group [25]. Where it is not possible to obtain an unbiased estimate of the total eligible population, total cluster size could be used instead, such as in the UK BEAM study [20].

However even if there are no differences in recruitment rate, there may be differences in the make up of the groups. This could be examined, although it is possible that differences may occur in unmeasured covariates. Statistical testing for baseline imbalances could be carried out and has been recommended to detect possible selection bias due to subversion [26], although we would strongly caution against this as significant differences may occur by chance.

Conclusion

We have articulated some options for avoiding selection bias in cluster trials. Researchers should be aware of the situations in which bias can occur and carefully consider some of the options set out in this paper when designing their trials: not recruiting individual participants, recruiting participants before randomisation, recruiting outside the cluster setting, masking recruiters. Analytic solutions to this problem [13] are much less satisfactory because we can never be sure that we can fully correct for unobserved covariate imbalances.

Cluster trials should be reported clearly including how clusters are recruited. Two areas that are not currently adequately covered by the relevant CONSORT reporting standards [27] for cluster trials: first, investigators should report how participants were identified and at what stage this was done; second, the total potential population within each intervention arm should be reported, where possible. The adoption of these minor suggestions will facilitate the assessment of the likely internal validity of a cluster trial.

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Key points

- Recent reviews of cluster trials have found that a significant proportion are at risk of selection bias through poor design.
- A key problem is participant recruitment unless this occurs before randomisation selection bias can be introduced.
- Ideally cluster trials should be designed so that patients are identified before the cluster is randomised.
- When this is not possible recruitment by someone masked to the cluster allocation should be attempted.
- Cluster trials need to report cluster sizes to enable the reader to ascertain whether there is differences in recruitment between treatment groups.

Box 1

Trial in which individual participants can be identified and recruited before randomisation

Kumasi Stroke Prevention Trial

Clusters: 12 villages in Ghana

Eligible participants: All residents aged 40 to 75

Methods of selecting participants: 1896 selected from village census using random sampling, stratified for age and sex

Recruitment method: on 3 mornings selected participants invited to attend temporary field station for health screening in their village; those suffering serious illness and pregnant or lactating women were excluded 1013 (53%) consented

Intervention: community education to reduce dietary salt

Outcome: reduction in blood pressure after 6 months

Comment: After 2 villages had completed recruitment these were randomized, one to intervention and one to control. As villages varied in the age and sex of their populations stratified sampling ensured balance between intervention groups.

Box 2

Trial in which individual participants are not recruited

IRIS Identification and referral intervention to improve safety

Clusters 48 General Practices in east London and Bristol

Eligible participants: All registered women over 16

Intervention: Educational package to practices, enhanced referral systems, feedback to practices

Outcome: Referral rates per 100 women

Comment : Outcome data was obtained from practice notes by researchers and no patient identifiable data taken outside practices. Additional screening of women for domestic violence in consultations was not anticipated to affect usual care in a negative way

Box 3

Trial in which individual participants are recruited outside the cluster setting

ELECTRA: T**he east London randomised controlled trial for high risk asthma**.

Clusters: 44 general practices in east London

Eligible participants: All registered patients attending or admitted to the Royal London Hospital or GP out of hours service for acute asthma attack

Methods of selecting participants: Researcher, blind to allocation status of patients, recruited patient in accident and emergence department

Allocation to intervention: all patients saw the liason nurse who informed them which group they were in

Intervention: Patient review in a nurse led clinic and liaison with general practitioners and practice nurses comprising educational outreach, promotion of guidelines for high risk asthma, and ongoing clinical support.

Outcome: Percentage of participants receiving unscheduled care for acute asthma over one year and time to first unscheduled attendance

Comments: Although control patients saw the nurse briefly the effect was minor contamination and thought to be better than risking bias in recruitment.

Box 4

Trial in which patients are recruited within cluster setting by masked recruiters

Impact of counseling on careseeking behaviour in families with sick children: cluster randomized trial in rural India

Clusters: 12 primary health care centres in rural India

Eligible participants: Children under 5 presenting for curative care and their mothers

Methods of selecting participants: Field workers masked to allocation status enrolled at centres when mothers and children attended the centres

Intervention: Doctors underwent 5 day training covering counseling, communication and clinical skills. They were also given cards to assist them and copies of these cards could be given to mothers.

Outcome: Careseeking behaviour of mothers

Comments: The precise objectives of the study were not disclosed to the field workers who recruited. They were told that the study aimed to assess children's illness load and how families respond to illness. Field workers provided similar information to the families when seeking their consent.

Box 5

Trial in which patients are recruited within cluster setting with data on recruitment rates

Baby walker trial

Clusters: 64 general practices in Nottinghamshire

Eligible participants: All pregnant women of at least 28 weeks gestation

Methods of selecting participants: Midwives recruited in practices. Midwives had been trained to standardise recruitment.

Intervention: Educational package aimed at discouraging owning and using a baby walker, delivered by midwives and health visitors.

Outcome: Percentage of women possessing and using a baby walker from postal questionnaire when baby was 9 months old.

Number of women recruited as a percentage of live births was 21.4% in the intervention group and 22.9 % in the control group. Percentage of women intending to get a baby walker at baseline was 24.9% in the intervention practices and 36.7% in the control practices.

Comments: Women in the intervention group may have been exposed to the intervention prior to recruitment.

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