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Have Cluster Randomised Trials a Role in Health Care Research?

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**Review article**

**ABSTRACT**

Cluster Randomised trials, where groups of individuals are randomised to different treatments and outcomes measured on individuals, have many limitations inherent in the trial design. Selection bias can be introduced into cluster randomised trials at the individual level due to participant recruitment procedures. The sample size of a cluster randomised trial needs to be much larger than that for an individually randomised trial as the clustering effect means that the study has a decreased statistical power and broader confidence interval than a similar study randomised by the individual. Bias can be an issue in cluster trials so in order to reduce bias as much as possible some factors should be considered at the design, sampling and analysis stages which can keep the level of bias to a minimum. Despite the limitations, however, cluster randomised trials have many uses in health care research when individually randomised trials are not feasible or practical or the level of contamination is estimated to be quite high. Cost is not a reason to conduct a cluster randomised trials as the required increase in sample size would negates other cost savings.

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INTRODUCTION

Cluster randomisation is where groups of individuals are randomised to different treatments and the outcomes are measured on individuals within those clusters. Therefore randomisation is at group level, but the analysis is at individual level. This can lead to difficulties in analysis as independence cannot be assumed. However, cluster randomised trials are still used in healthcare and therefore, their uses and limitations should be considered. This paper acknowledges the limitations of cluster randomised trials in health care, but also highlights areas where they are still the most appropriate method to use. The limitations of cluster randomisation should be taken into account at the design phase of a clinical trial.

LIMITATIONS OF CLUSTER RANDOMISED TRIALS

The inherent design of a cluster randomised trial leads to certain limitations as different sorts of participants may be selected into the various arms of the trial defeating the objective of randomisation. In a review of 36 cluster trials, some evidence of susceptibility to risk of bias at the individual level existed in 39% of the studies. [1] Members of the clusters cannot be treated as independent [2] therefore an increased sample size is required which may increase the cost, length and complexity of the trial.

The sample size of a cluster randomised trial needs to be much larger than that for an individually randomised trial as the clustering effect means that the study has a decreased statistical power and broader confidence interval than a similar study randomised by the individual. Between cluster variation is termed intracluster correlation (ICC). It takes into consideration the variety of observations taken from individuals in the same cluster and the variance of the true cluster means. The larger the ICC the greater the sample size required. [3]

There is much variation in reporting in Cluster Randomised Trials despite guidelines published by CONSORT. [4] It is important to allow for clustering in the sample size calculation, however in systematic reviews in both occupational therapy [5] and stroke research [6] only 50% and 66% respectively reported the ICC used in sample size generation. This lack of information limits the ability of the reader to assess the appropriateness or otherwise of the sample size.

There is a trade-off between the cluster level for randomisation and the statistical power of the study. The design effect equation, described by Murphy et al., [8] suggests that a study with many clusters, each with a small number of participants, is more effective than one with a few clusters, each with many participants. Therefore randomising at hospital level rather than consultant level would further reduce contamination, but also decrease the statistical power of the study as it reduces the number of clusters.

Selection bias can be introduced into cluster randomised trials at the individual level due to participant recruitment procedures. Often participants has to be recruited prospectively after the groups have been randomised. Should the researcher or clinician have foreknowledge of the allocation group, which is generally the case in cluster randomised trials, different sorts of participants may be selected into the various arms of the trial defeating the objective of randomisation. Allocation concealment has been shown to strongly impact on treatment effect sizes. Individually randomised trials that used inadequate allocation concealment, compared with those that used adequate methods, were associated with an increased estimate on treatment benefit. [7] Therefore, for cluster randomised trials, it would be better if the participants were recruited prior to randomisation or if this isn’t possible identification and selection of participants would be undertaken by someone blinded to the allocation.

Due to the design nature of a cluster trial, cluster leaders can consent to the trial on behalf of potential cluster members. [8] However the participants consent must be obtained for data analysis which generally leads to consent being obtained post randomisation. A certain number of participants will be lost to the study which will impact on data analysis as cluster size imbalances can induce a loss of power, particularly if the number of clusters is small. [9] This can be addressed by identifying participants and obtaining consent prior to randomisation.
Bias can be an issue in cluster trials so in order to reduce bias as much as possible some factors should be considered at the design, sampling and analysis stages which can keep the level of bias to a minimum. An appropriate sample size should be used and ICC should be used in the calculation of sample size. The number of clusters should be increased as much as possible. Identifying the participants prior to randomisation or else having the person who selects the participants blinded to the allocation groups would help reduce selection bias. It is also important at the analysis stages that appropriate statistical evaluations are used which take clustering into consideration.

USES OF CLUSTER RANDOMISED TRIALS

Despite the limitations cluster randomised trials have many uses in health care research when individually randomised trials are not feasible or practical or the level of contamination is estimated to be quite high.

**Intervention affecting groups**

When an intervention will affect groups rather than individuals cluster trials may be suitable. This is particularly relevant in research related to public health. In instances where there is a modification of the environment or behavioural factors of participants, individually randomised trials are not logical. An example of such a trial was conducted by Williamson et al. where modification of the environment and mortification factors were tested to see if they could prevent inappropriate weight gain in children from rural parishes. This study attempted to provide health behaviour modification through classroom instruction and modification of the child’s environment. It would not be practical to provide separate instruction to some students in the class or modify the environment for some students without affecting the other students therefore this study was a cluster design involving 17 schools where the school was the cluster.

Another such study in public health was published by Starkey et al. in 2005 which looked at methods to prevent adolescent smoking. This study was taking advantage of the influence of peers on smoking habits of adolescents therefore one could not individually randomise the participants and assume that those in the control group would not be influenced by their peers. This study tested whether peer supporters in year 8 could be recruited and trained to effect a reduction in smoking uptake among their fellow students. Therefore, this trial was designed as a cluster randomised controlled trial where school was the unit of randomisation of which there were 59 schools.

**Where it is inappropriate to deny access to some patients**

In certain instances the use of an individually randomised trial could lead to ethical dilemmas due to inequality of care within a hospital which would not arise in a cluster trial. For example, if a medical emergency team were established in a hospital it would be difficult or impossible to randomise patients where the medical emergency team would be used for some patients and not others. Therefore a trial which looked at the implications of the introduction of a medical emergency team on the documentation of vital signs required a cluster randomization technique where the cluster was the hospital.

**To avoid contamination**

Contamination in clinical trials occurs where members of the control group inadvertently also receive the intervention. In a review of cluster randomised trials in occupational therapy the most commonly cited reason for selection of a cluster randomised controlled trial design was to prevent contamination. However, it is very difficult to calculate the likely levels of contamination. Torgerson suggested that looking at the mean proportion of patients who crossed from one arm to another in an individually randomised trial using Zelan’s method would be a measure of contamination. This would give an indication of the level of contamination for this particular trial, but the level of contamination would differ depending on the type of trial and often there aren’t prior relevant individually randomised trials using Zelan's methods available to assist in the estimation of the likely contamination. When looking at the number of participants required in a cluster trial to detect a difference
between two groups where the true effect size is 25% it was found that approximately 30% contamination could be sustained in an individually randomised trial to take account of the reduced effect size of such contamination while the use of cluster randomisation rapidly leads to doubling of the sample size.\textsuperscript{12} Again estimating the amount by which the sample size for the individually randomised trial needs to be inflated by to allow for contamination is difficult. In certain trials where contamination is considered to be quiet high cluster randomisation may be the optimal trial design.

Continuing professional development (CPD) has become fundamental for healthcare professionals. A real assessment of the effectiveness of CPD strategies would be to investigate the effect the strategy has on patient care. If one is to assess the effect of professional education on patient care it would be impossible to individually randomise patients in a prospective study as the health professional could not be asked to use their knowledge gained with some patients but not with others. The risk of contamination would be very high. A before after study or a cluster randomisation method would be the more feasible options. A before-after individually randomised study would have limitations as time trends may mean that other factors rather than that being investigated may affect the outcome. Also the study would have to take place over a longer time period. Furthermore, if the intention is to evaluate the usefulness or otherwise of an intervention but the intervention has already taken place, a before after study may not be possible.

With certain studies where the health professional gains knowledge through their involvement in the study, cluster randomisation may again be more appropriate. An example would be in studying the use of patient related outcomes in improving doctor patient communication.\textsuperscript{13} If a doctor is trained to use patient related outcomes with some of their patients they would not completely forget about the value of assessing patient’s quality of life when they are treating patients who have been randomised to the group that does not provide the patient related outcomes data. Although the control group does not complete questionnaires the doctor will be conscious of health related quality of life issues and may discuss patient related outcomes with these patients. This new training of the doctors is likely to affect the way they deal with all future patients. Therefore due to the high risk of contamination a cluster randomised trial should be considered.

**Cost**

Cluster randomisation therefore has specific uses in healthcare research as outlined previously. However, some researchers would use cluster trials for cost reasons. This should be considered with caution. Should the trial require the purchase of expensive equipment a cluster design may be considered so that the new resource is fully utilised in order to be cost-effective. However the cost issue should be evaluated in advance to ensure there is a real saving once one takes into consideration the increased sample size and the more complex statistical analysis required. It may turn out than in individually randomised trial could still be less expensive, although the equipment might not be used for all patients.

There are limitations with the use of cluster trials and because of this they have received some bad press in recent times as prior to 1993 many cluster trials did not take clustering into account in the analysis and therefore were statistically inaccurate. However, reports are beginning to show an awareness of the need to allow for clustering in analysis leading to more accurate statistics in cluster trials.\textsuperscript{14} There are still a lot of improvements possible in the methodology and design of cluster trials. If possible individuals should be identified before random allocation to clusters but if this isn’t possible an independent recruiter should be used to recruit participants.\textsuperscript{15} It is important for investigators who use cluster trials that they make available the ICC estimates from their studies as it can be difficult for investigators to find estimates of ICC’s to use at the planning stages for sample size estimation.

In a review of cluster trials it was found that only one fifth of studies reported the ICC used for sample size estimation.\textsuperscript{16} If it wasn’t used in sample size estimation this would be a weakness in the study. The level of randomisation of the cluster should be considered and the numbers of clusters increased as much as possible.
CONCLUSION

There are many uses for cluster trials in health care where there is a high likelihood of contamination, where the intervention affects groups of individuals, where it is inappropriate to deny access to some patients to the intervention or possibly for cost reasons. Its role in reducing costs may not be a valid reason, however due to the increased sample size requirements. When appropriate measures are taken to reduce the risk of bias in cluster trials at the design, sampling and analysis stages cluster trials can potentially have a valuable role in health care research.

Summary

- In cluster randomised trials members of the cluster cannot be treated as independent so the sample size needs to be increased.
- ICC should be used in calculating sample size.
- Selection bias can be reduced by identifying participants prior to randomisation or by the recruiter being blinded to the group allocation.
- Clustering should be allowed for in data analysis
- Well conducted cluster trials where bias is reduced as much as possible have a valuable place in health care research.
- Cluster trials are particularly useful in health care research when there is a high risk of contamination, where the intervention affects groups or where it is inappropriate to deny access to the intervention for some patients.

DECLARATION OF CONFLICTING INTEREST

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