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Cluster randomised trials:

Methodological and ethical considerations



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1. Introduction and scope

Cluster randomised trials (CRTs) are becoming increasingly important in health technology assessment. CRT designs are used not only to evaluate group interventions but also individual interventions where group level effects are relevant. However, CRTs raise methodological, reporting, and ethical issues that are generally not encompassed by standard clinical trials guidance. Consequently, Council identified the need to complement its **MRC guidelines for good clinical practice in clinical trials** (ref 1) with additional advice on CRTs.

The foundation for this guidance was laid by a workshop held in 2001 and co-chaired by Professor David Jones (Department of Epidemiology and Public Health, University of Leicester) and Professor Andy Haines (London School of Hygiene and Tropical Medicine). The workshop built on a 1999 NHS Health Technology Assessment report: **Methods for evaluating area-wide and organisation-based interventions in health and healthcare: a systematic review** (ref 2).

Many of the speakers and participants at the workshop have helped with the preparation of the guidance, and to them we extend our thanks (see *footnote*)*. We especially thank Dr Richard Ashcroft (Department of Primary Health Care and General Practice, Imperial College School of Medicine), Dr Sarah Edwards (Centre for Ethics in Medicine, University of Bristol), and Dr Jane Hutton (Department of Statistics, University

of Warwick) for their help in preparing the ethics section.

Whilst this advice is primarily for researchers supported by the MRC, we hope that other researchers, and those involved in reviewing research, will find it helpful. The guidance is deliberately brief; the references and further reading suggestions provide more details for those who seek in-depth information on specific topics.

As with other MRC guidance, this report is available on the MRC's website at www.mrc.ac.uk; changes will be highlighted there as the need arises.

2. What are CRTs?

In CRTs clusters of people, or intact social units, rather than individuals are randomised to intervention and control groups and outcomes are measured on individuals within those clusters. CRTs are also known as group randomised trials or community randomised trials.

3. When to consider CRTs

There are several key reasons for considering cluster randomisation:

- The intervention to be studied is itself delivered to and affects groups of people rather than individuals. Examples include changes in general practice organisation and use of local radio for health promotion.
- The intervention is targeted at health professionals with the aim of studying its impact on patient outcomes. An example would be education about guidelines for a

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particular medical condition; it would be difficult for professionals receiving such education not to let this affect the management of all of their patients.

- The intervention is given to individuals but might affect others within that cluster - ie contamination. For example, recipients of a behavioural intervention to promote weight loss or reduce smoking might share their information with others attending the same clinic.
- If the intervention involves supplying equipment or staff to an administrative unit, then by randomising these units rather than individuals only a subset of the units would receive the equipment or staff. This may be cheaper or administratively more convenient.

CRTs may be especially valuable in developing country settings, where in rural areas in particular the sense of community is strong, and community-level consent and cooperation are essential. Additionally, many trials in developing countries are of interventions against infectious diseases; here CRTs can measure the overall effect of an intervention at the population level, encompassing both the direct effect of an intervention on an individual's susceptibility to infection and the indirect effect due to changes in risk of transmission to other individuals or herd immunity. A good example is the Mwanza trial of sexually transmitted disease (STD) treatment to reduce HIV transmission. Prompt treatment of STDs was expected to reduce the infectiousness of HIV-positive individuals and the susceptibility of HIV-negative individuals, as well as reducing the overall incidence of STDs in the population (ref 3). Another area in which cluster designs may be needed is in the evaluation of complex interventions. These are interventions in which several components may act interdependently to affect key processes and outcomes. Thus, components may affect several levels of an organisation such as a stroke unit, and it will

often be appropriate to randomise at the highest level of the intervention such as the team rather than to randomise practitioners or patients. The MRC has published separate guidance on complex interventions (ref 4). That guidance draws attention to the importance of measuring the outcomes of complex interventions across domains such as biomedical, psychosocial, and economic. These different outcome domains need to be considered separately in the power calculations for CRTs since intraclass correlation coefficients as well as expected effect sizes (see below) may vary.

4. Challenges of CRTs

The main consequence of a cluster design is that, unlike individually randomised trials, the outcome for each participant cannot be assumed to be independent of that for any other participant since those within a cluster are more likely to have similar outcomes. This lack of independence influences the design and analysis of CRTs: standard approaches to sample size estimation and analysis no longer apply. There are also challenges in the conduct of the trials because there are two levels of participant involvement - individual and cluster - and ethical considerations.

Post-randomisation recruitment bias deserves special mention. Thus for many CRTs, after clusters have been recruited and randomised, individuals within clusters still have to be recruited. For example, general practices might be recruited to a CRT of a new computer-based educational anti-smoking intervention versus an information leaflet (control), both to be administered by community midwives to pregnant women. Smokers will need to be identified and recruited in both intervention and control clusters so that interventions can be given and follow-up questionnaires sent out to determine how many women quit smoking. Although the easiest option would

undoubtedly be to use the midwives to identify the smokers, it may well be that midwives in the intervention arm identify and recruit more smokers simply because they have a "new and exciting" intervention to offer. The result may be recruitment of a different cohort of smokers in intervention and control clusters and a biased outcome. Possible solutions to this problem include objective measures of eligibility, recruitment by someone who is blind to the arm the patient is in, and routine and frequent checking for differences between arms in numbers of invitees, recruits, and refusals.

Related issues associated with CRTs include:

- The unit of inference may be intended at individual level whereas randomisation is at cluster level.
- There may only be small numbers of clusters (units of intervention) available, which could result in low power and a relatively high probability of chance imbalance between treatment arms.
- Reporting of CRTs needs special consideration.

Because of these problems, CRTs should be avoided unless individually randomised trials are scientifically inferior or practically impossible. Investigators should justify why they cannot use an individually randomised design and explain clearly why a CRT is preferable (ref 5).

5. Design

There are two main approaches to randomisation in CRTs:

Unrestricted allocation

Completely randomised: clusters from a single pool, with no pre-stratification or matching according to baseline characteristics, are allocated to treatment groups.

Restricted allocation

Clusters are first divided into strata according to prognostic (baseline) characteristics (eg socioeconomic status, geographical location) and then allocated to groups within the designated strata.

Stratified: when there are more than two clusters in a stratum, within each stratum clusters are allocated to treatment groups by simple or block randomisation.

Matched pair: a special example of a stratified design in which one of the two clusters in each stratum is randomly assigned to each intervention.

The decision to adopt a completely randomised, matched pair, or stratified design depends on:

- Number of clusters available to be randomised (since CRTs tend to have relatively small numbers it can be more efficient to match or stratify).
- Degree of heterogeneity between clusters.
- Ability to achieve a good match on variables that are strongly correlated with outcome.

A **completely randomised** design is most suited to trials in which large numbers of clusters are available for randomisation; if this approach is used for few clusters, the treatment groups are likely to be unbalanced with respect to baseline characteristics. However, stratification (in the design and/or analysis) may still be valuable with large numbers of clusters to reduce the level of between-cluster variation and hence improve precision. *An example of a completely randomised design is the ACEH trial of impact of vitamin A supplementation on symptoms of respiratory and enteric infections among Indonesian children aged one to five years (ref 6). In this trial villages were the unit of randomisation, with 229 in the experimental group and 221 in the control group.*

The aim of **restricted allocation** (stratification or minimisation) is to provide groups that are more evenly balanced with respect to baseline characteristics. Statistical power will also be increased provided the baseline characteristics selected as stratifying factors are strong predictors of outcome. These baseline variables may be related to the characteristics of the individuals within clusters or to the characteristics of clusters. Another consideration, particularly when cluster sizes are uneven, is stratification by cluster size to ensure balanced-sized intervention groups.

A **matched-pair** design can provide very tight and explicit balancing of potentially important prognostic factors at baseline. However, this approach should be used cautiously because of several important limitations. Thus:

- (i) it may be difficult to find matching variables to create distinct pairs;
- (ii) although matching may reduce the variance of the intervention effect, the resulting increase in power may be reduced or even cancelled out by a loss of information on between-cluster variability (ie loss of degrees of freedom), especially with small numbers of matched pairs;
- (iii) it is difficult to estimate the intra-cluster correlation coefficient (ICC, see section six) from data arising from a matched-pair design without making special assumptions (however, there are methods of analysis that do not require such estimates, ref 7); and
- (iv) if a particular cluster drops out of the study the entire stratum will be eliminated in the analysis, so power is reduced. *An example of a matched-pair design is the Community Intervention Trial for Smoking Cessation (COMMIT), whose primary outcome variable was the five-year smoking cessation rate among heavy smokers (ref 8). 11 pairs of communities were matched for community size,*

population density, demographic profile, community structure, and geographical proximity.

By comparison with matched-pair designs, in **stratified designs** there is replication of clusters within each intervention/stratum combination. Consequently, the between-cluster variation can be estimated directly since the cluster effect can be separated from both the intervention effect and the stratum effect - a separation that cannot readily be made in the matched-pair design (ref 2). *An example of a stratified design is the Child and Adolescent Trial for Cardiovascular Health (CATCH) (ref 9), a large community health trial for the prevention of cardiovascular disease. The strata were four US cities, with 24 schools randomly assigned to the experimental or control group within each city.*

6. Within and between cluster variation, and sample size

CRTs, like conventional RCTs, must be large enough to ensure adequate power and/or precision. However, in CRTs, because of the correlation of individual-level responses within clusters, there are two components of variation:

- (i) within cluster; and
- (ii) between cluster.

These sources of variation should be estimated separately and both must be taken into account when calculating sample size for CRTs; standard statistical methods do not do this. The two components may be estimated either via the notion of intra-cluster correlation (ICC) or, a similar concept, the coefficient of variation between clusters (CV) (ref 10). The ICC represents the correlation between responses of individuals in the same cluster, which is equivalent to the proportion of the total variation explained by variation between clusters (ref 2).

Since participants within any one cluster are more likely to have similar outcomes, the outcomes are not completely independent. Thus, the statistical power of a CRT may be substantially less than that of a similar-sized individually randomised trial. Special sample-size formulae are now available for CRTs (refs 2, 10, 11), however expert statistical guidance should be sought. In general, CRTs with fewer than five clusters per arm are inadvisable, since parametric tests may be unreliable with such small numbers and nonparametric tests require at least four to six clusters per arm to achieve statistical significance. Power curves can be plotted and used to help decide on the trade-off between number of participants per cluster and number of clusters. A useful rule of thumb is that increasing the number of clusters offers more increase in power than increasing the number of individuals per cluster, although logistical and economic implications may need to be borne in mind alongside the statistical considerations (ref 12).

7. Analysis

Choice of analytical technique should be an integral part of CRT planning, for which expert statistical advice is essential. The most appropriate approach will depend on the study design, the number of clusters, and the number of individuals per cluster.

Statistical analysis of CRTs must take into account the clustering effect, otherwise values are likely to be too small and confidence intervals too narrow (ie the chances of spuriously significant findings are increased). Consequently, standard statistical techniques as applied to individual-level data are not appropriate (ref 2). However, methods of analysis are available based on analysis of aggregated data from each cluster by use of the t-test or permutation test (ref 11). Adjustment for cluster level covariates is straightforward, while adjustment for individual level covariates may be done

within a two-stage approach (ref 7). The permutation test (ref 11) offers an alternative non-parametric approach, which has been adapted so that adjustment can be made for group-level and individual-level covariates, including variables involved in restricted randomisation (refs 13,14).

Alternatively, the individual-level data can be analysed by means of multilevel/hierarchical regression modelling techniques that allow for the clustering and permit both individual-level and group characteristics to be taken into account (ref 15). Hierarchical modelling also allows exploration of sources of variation and modelling of complex variance structures (ref 15).

Classical hierarchical models have limitations. The confidence interval obtained for the intervention effect is too narrow since this is based on estimated variance components, and there is no allowance for uncertainty (ref 15). It is not straightforward to obtain confidence intervals for relevant functions of parameters in models with complex variance structures, for example differences between cluster-level variances. Also, an assumption of normality is required for the random cluster effects, and the validity of this may be difficult to assess. Bayesian hierarchical modelling (refs 16, 17) enables appropriate interval estimates to be obtained for the intervention effect and for functions of model parameters, and provides an approach to investigating robustness of the parametric assumption for the cluster effects. Bayesian estimation also allows incorporation of prior information (ie informative priors) to represent the knowledge about ICCs derived from sources external to the current trial. If a Bayesian approach is adopted, it is essential to state in advance the source and structure of the prior distributions that are proposed for the principal analysis (refs 16, 17).

8. Reporting CRTs

As for RCTs, CRTs must not only be designed and analysed appropriately but also reported in such a way that readers can understand how the conclusions were reached. New guidelines for the reporting of CRTs have been suggested (ref 18).

9. Ethical issues in selection, design, and implementation of cluster randomised trials

The fundamental principles underpinning research on human beings have been elaborated and refined in various national and international guidelines (refs 19-24):

- Participants' interests must prevail over those of science and society, where there is a conflict.
- The research must have potential to generate scientific understanding that may be a basis for improvements in human health and wellbeing.
- There must be a favourable balance of risk and benefit for participants.
- Participants must give their voluntary informed consent (special safeguards apply when this is not possible).
- An independent research ethics committee must review the research proposal.

Similarly, norms for the conduct of clinical trials are widely agreed (refs 22, 25, 26):

- Approval will always be necessary from the research sponsor (in a UK NHS setting, ref 25).
- A data and safety monitoring committee should be established (where appropriate) to review interim data and to advise, on a regular basis and in the light of agreed stopping guidelines, whether it is necessary for the trial to cease recruitment.
- Attention should be paid to ensuring that recruitment is fair and equitable with

regard to the interests of individuals and communities taking part.

- The issue of post-trial access to effective interventions for the participating individuals or communities should be discussed in advance with the appropriate authorities - and an in-principle decision reached - before the trial starts.
- Participants should be informed about the decision during the process of obtaining informed consent; this information is also essential for research ethics committee review. In addition, the issue of provision of a successful intervention to the wider community should likewise be discussed with relevant authorities before the research is undertaken.
- Since it is generally agreed that research which is of poor scientific quality will be unethical, research proposals must be thoroughly peer reviewed. Such review should include statistical review by an expert in the design proposed. It will normally be a principle of good management for the trial team to include appropriate expertise in the medical and statistical aspects of the protocol.
- As well as consent to interventions, consent is required for any physical investigation or other intrusion or inconvenience carried out purely for the purposes of research.

These ethical principles and norms, which were devised for individually randomised trials, apply equally in spirit and mostly in substance to CRTs, although some specific adjustments are required in their application. For example:

- The issue of the degree of evidence that is sufficient to justify early stopping might be complicated by different accrual rates in different clusters, as well as the timing of follow-up relative to the periods of recruitment and intervention across the clusters. Within and between cluster information has to be evaluated. Disadvantages associated with early

stopping of an RCT, such as lack of credibility, imprecision, and bias, will be accentuated for CRTs (refs 27, 28).

- The roles of the guardians of the patients interests during the trial, the gatekeepers of access to patient groups, and sponsors of the research are even more important in CRTs where individuals may not have the opportunity to give informed consent to participation.
- Particular attention must be paid to ensuring that the interests of individual participants in a CRT are monitored, since their ability to consent to participation in the trial, or to leave the trial, may be absent or weaker than is usual in a standard individually randomised trial.
- Where individual decisions exist, so consent can in principle be obtained from individuals, this should be done. However, the rationale for using a cluster design may preclude this.

Types of intervention

In applying these ethical principles to CRTs, it is useful to recognise that some interventions that researchers may wish to evaluate by means of a CRT fall clearly into one of the following categories:

- A:** Interventions that are received (or not) by a whole cluster together - there is only one decision to be made for each cluster and individual choice does not exist. Examples would be fluoridation of the water supply, or the showing of information videos in a GP practice waiting room.
- B:** Interventions that individuals can decide individually, without reference to others, to receive (or not).

Many interventions fall somewhere between A and B. For example, individual choice may be theoretically possible but only at considerable expense or trouble. Or some part of the intervention package may be subject to individual choice whereas other

parts are not. Nevertheless, since the application of the ethical principles to the two categories is very different, clarity about these makes consideration of intermediate interventions easier.

Type A interventions

Type A interventions do not allow individual choice, so the concept of individual consent is not helpful (individual consent could be sought, but if refused the intervention might still be chosen *for the cluster*, and hence received by the refusing individual). There is thus a need to consider consent for whole clusters together. Similarly, benefit and harm needs to be considered at cluster level. Thus, for such interventions, application of the fundamental principles listed above needs to be at cluster level - ie substitute the word "cluster" for the word "participant". Practical questions then arise - ie how best to define and obtain "cluster consent", and similarly how to assess the interests of a cluster (when individuals within the cluster may have opposing interests).

Type B interventions

These do allow individual choice, so it would in fact be possible, though perhaps not scientifically or economically desirable, to evaluate them in an individually randomised trial. That being the case, putting participants' interests first demands that no member of a cluster should be individually disadvantaged, in prospect, by the cluster's participation in the CRT (this is the standard applied to individually randomised trials). This is an extremely strong requirement, and only trials of a specific design - namely those that offer *an additional option* to members of some ("active" arm) clusters, are likely to meet it. Even here, concern may arise about the artificial withholding of options from some clusters - for instance when an initially novel option becomes widely available.

Participation of a cluster in a cluster trial, even when the intervention is type B, is a cluster-level decision, with attendant practical problems as to who represents the cluster. But for type B interventions the criterion required for consent to be given (and not be withdrawn) is clear - it must be to the advantage (or at least not to the disadvantage) of *every single person in the cluster* for the cluster to be entered, or to continue, in the trial.

Cluster representation mechanism

Agreement to participation in the trial will normally be necessary from one or a series of gatekeepers (for example, where the CRT involves randomisation by primary care practice, this will normally be the general practitioners involved). However, neither research ethics committee approval nor gatekeeper agreement is truly equivalent to consent. An individual, body, or mechanism that can represent the interests of the cluster is required - for convenience this will be labelled the "cluster representation mechanism" (CRM). The appropriate nature of the CRM will vary depending on the circumstances - both the nature of the cluster and the nature of the intervention. Thus, agreement to fluoridate the water supply might be obtained by plebiscite, while GPs might agree to the distribution of an information leaflet to people in their waiting rooms. The ethical principle here is that the CRM must act in good faith, and in this regard only in the interests of the cluster represented (refs 27,29). CRMs, or gatekeepers, may be appropriate advocates for patients who wish to withdraw from the cluster by seeking assignment to another health care team. CRMs should be independent of the research team, and careful to avoid conflicts of interest. Where these cannot be avoided, they must be declared to the sponsor of the research, the research ethics committee, and, where possible, to the cluster community.

The role of CRM is analogous, in respect of decisions about clusters, to that of individuals for individual decisions. The same safeguards and formalities should thus apply:

- For each cluster researchers must identify a CRM to take on the role of acting in the interests of the cluster/individuals in the cluster (as appropriate, see above).
- The CRM must produce a formal document for the cluster that certifies and sets out its ability to do this (sufficient knowledge of the circumstances, beliefs, and values of members of the cluster; any delegated authority from/for the cluster; lack of conflicts of interest). The document should state specifically that the CRM considers the cluster's participation in the trial to be in the interests of the cluster as a whole/in the interests of each member of the cluster (as appropriate, see above).
- The CRM must be kept suitably informed and active, and continue to act only in the interests of the cluster/individuals.
- The CRM has essentially the same rights as a patient in an individually randomised trial - including the absolute right to withdraw the cluster, without adverse impact on the cluster, if it decided that the study was not now in the interests of the community.
- Approval from a research ethics committee would be contingent on the CRM confirming that the trial was in the interests of the cluster, and not withdrawing that opinion.

Individual consent

It is important to seek individual consent where possible. The fact that individual choice does not exist for a type A intervention (or for cluster randomisation) does not, for instance, prevent individual consent being sought for giving a complementary type B intervention which is part of the intervention package, or for taking samples, recording information, or

extracting data from records. The provisions of the MRC's **Personal information in medical research** (ref 30) guidelines would apply to the use of records in research. Individuals could, for instance, withdraw from the study although not from the type A intervention.

Information

Even though individual choice may be absent or compromised, it will usually be possible to inform cluster members of the trial alternatives and design. This should be the default position, and is an important element in allowing individual cluster members to make their opinions known via the CRM, or indeed in giving individuals the opportunity of avoiding the intervention (eg in the case of fluoridation, by buying bottled water).

Contamination

Researchers may wish to use a CRT design to reduce the risk of "contamination"; in such cases they will not wish to fully inform members of clusters as to the exact nature of all the arms in the trial. Concern about contamination has perhaps been overemphasised, and carefully designed individually randomised trials might be more widely used in such circumstances (ref 5). If there are cogent reasons for using a CRT to minimise contamination, the same principles as set out above must apply. When the intervention is of minimal or no impact on the individuals concerned, the sponsor, the ethics committee, and CRM may agree that it is not necessary to fully inform the cluster as to the nature of the trial, and that it is still in the interests of the cluster to participate. A model here is the obtaining of data from patient records, subject to the Data Protection Act (1998), under which fair processing implies that patients are informed in general terms about the uses to which their records are put. Cluster members could thus be informed about the nature of the research, and the kinds of uses for which their data could be used, as well as the

protective measures in place to prevent misuse of their data.

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