11.3: Randomization schemes for community or group-based interventions

As discussed in Chapter 4, trial designs have been increasingly employed in recent years, in which the unit of allocation of the intervention is a community or group, rather than an individual. These cluster randomized trials may involve the randomization of communities that can be quite large; consequently, the number of communities that can be included in a trial is often relatively small and may be of the order of 20 communities or fewer. If a method of simple unrestricted randomization is used to allocate interventions to communities, there is a reasonably high chance that there may be differences between the two groups of communities, unrelated to the interventions, that may bias the measurement of the effects of the intervention. It is common therefore to employ some method of restricted randomization in the allocation of interventions to communities (see also Chapter 4, Section 4.2).

3.1 Matched-pairs design

A matched-pairs design is a special case of stratified randomization, in which the strata are each of size two. Communities are matched into pairs, the pairs being chosen so that the two communities in a pair are as similar as possible with respect to potential confounding variables; in the absence of any intervention, the two communities would be expected to have similar incidence rates of the disease or other outcome under study. One member of each pair is assigned at random to one intervention group and one to the other. Similar matching procedures can be employed when there are more than two intervention groups. For example, with three groups, matched triplets would be employed.

Recent research on the design of cluster randomized trials has indicated that, although matched-pairs randomization remains a valid study design, other methods of randomization, such as stratified randomization or constrained (restricted) randomization, discussed in Sections 3.2 and 3.3, may generally be more appropriate design strategies (Hayes and Moulton, 2009). The major reason for this is because, if a trial is designed as a matched-pairs study, then it must be analysed as such. In technical terms, pairing reduces the number of ‘degrees of freedom’ that are available in
the statistical comparison of the outcome measures in the intervention and comparison communities, compared to an unmatched design. This has little consequence if the number of communities is large, but, if the number is small, as is typically the case, then matching reduces the statistical power of a trial to detect an intervention effect of a given size (unless the matching factors are very closely correlated with the outcome).

### 3.2 Stratified design

For the reasons outlined, unrestricted randomization in a cluster randomized trial may lead to imbalance with respect to potential confounding factors between the different comparison arms of the trial, unless the number of clusters is very large. Pair matching of communities is one way of attempting to overcome this problem to ensure better balance between the arms of the trial, but this strategy may be associated with a substantial loss of statistical power. An intermediate alternative is to adopt a **stratified**, rather than a matched-pairs, design. A stratified design involves the grouping of communities into a number of strata, based on the expected rate of disease in the absence of the intervention. For example, in a study on malaria, communities with high transmission intensity would be put into the same stratum, and those with low transmission intensity would be put into a different stratum. The communities within each stratum are then randomly allocated between the different intervention arms of the trial.

In practice, it is often challenging to decide which communities should go into the same stratum. If there are baseline rates available for the disease under study from surveillance or from a previous study, then these may provide a reasonable guide as to the expected rates in the different communities in the absence of the interventions. However, the rates of some diseases may vary substantially from year to year, and what happened in the past may not be a very good guide for what will happen in the future. Quite commonly, such rates are not available, and the investigator has the alternative of conducting a pre-trial study to estimate disease rates in each community or, based on ecological and epidemiological considerations, of making some estimate of what the rates might be. The first of these options adds to the cost of the study, whereas there may be considerable uncertainties regarding the utility and accuracy of the second approach. A fuller discussion of these issues is given in (Hayes, R. J. and Moulton, L. H. 2009. *Cluster randomized trials*. Boca Raton, Fla.; London: Chapman & Hall/CRC.)

A stratified design is associated with less loss of statistical power than a matched-pairs design and will assist in making the communities in the different arms of the trial more comparable with respect to potential confounding factors. There may still remain some imbalance with respect to these factors, but it is possible to adjust for this in the analysis of the trial, provided, of course, the relevant confounding factors have been measured. Methods for the analysis of cluster randomized trials and the adjustment for confounding factors are beyond the scope of this book and will generally require the input of a specialist statistician.

(Hayes and Moulton 2009) suggest that, in practical situations, it is likely that the use of three or four strata will provide most of the advantages provided by pair matching, such that communities can be very accurately paired with respect to expected disease rates during the trial. With respect to the choice of the number of strata, these authors suggest that there should be no more than two strata if there are six or fewer clusters per arm, and no more than three strata if there are 7–10 clusters per arm.
3.3 Constrained randomization design

A further method of controlling for confounding is to adopt a method known as constrained or restricted randomization. Consider a trial to be conducted in 12 communities, six of which will be allocated to the intervention under test, the remaining six serving as control communities. Using a simple unrestricted randomization design, six communities would be selected at random to receive the intervention, and the other six would serve as controls. By chance, it might happen that the six intervention communities all turn out to be close to a major highway, and the six control communities are all more distant from the highway. If the disease we are studying might be related to proximity to the highway (for example, HIV infection rates show this characteristic in some situations), then we may be rather unhappy with this particular selection of intervention communities, as there would be a priori reasons for believing there would be differences in disease rates, irrespective of the effect of the intervention we wanted to test. In these circumstances, we might reject the initial random selection of communities and select another set of random numbers to determine which our intervention communities are. While this strategy may not seem unreasonable, it is clearly dangerous to allow an investigator to override a randomization procedure if he or she does not like the result!

Constrained randomization designs aim to exclude from consideration random allocations that result in unsatisfactory imbalance between communities in the intervention and control arms. In the study already outlined, involving 12 communities, there are 924 possible different allocations of which communities comprise the six in which the intervention will be applied. Conceptually, we could imagine examining each of these possible allocations and deciding which of them we would be happy with and which would cause us concern. Suppose there were, for example, 400 for which there seemed to be a reasonable balance of confounding factors between the putative intervention and control communities. We could restrict our consideration of possible allocations to these 400, and choose one of these at random to be the one that was actually used in the trial. This is the basic principle of the constrained or restricted randomization design.

Examining all 924 possible allocations would be a considerable undertaking and would be even more difficult if the total number of communities was more than 12. It is therefore necessary to seek some more automated method of deciding which randomizations are acceptable. In practice, what is done is to define some key variables for which we wish to achieve reasonable balance across the intervention and control arms. These key variables are then compared in each of the possible randomizations, and a rule is set up to exclude a randomization if the difference between the key variables in putative intervention and control arms is more than some specified amount. Thus, the selection of 'acceptable' randomizations can be programmed into a computer, so that the selection is done automatically once the acceptability criteria for balance between the intervention and control communities have been defined.

The procedure described as a modification of simple unrestricted randomization can also be incorporated into a stratified design, so that there is a selection of acceptable possible randomizations within each stratum.

Both stratification and restricted randomization can be used to achieve good balance (avoid confounding), but stratification also aims to reduce between-cluster (within-stratum) variation, and hence to increase power and precision.

Box 11.1 Use of restricted randomization in a community randomized trial of an adolescent sexual health intervention in Tanzania

In this trial, carried out to evaluate the impact of a multi-component sexual health intervention on HIV and other adverse
outcomes among adolescents in Tanzania, the 20 rural study communities were grouped into three strata, based on their expected risk of HIV infection (Hayes et al., 2005). There were six communities in the low-risk stratum, eight in the medium-risk stratum, and six in the high-risk stratum.

There is a total of 28 000 ways of assigning half the communities in each stratum to the intervention arm and half to the control arm. Because the total number of communities is quite small, not all of these 28 000 allocations would provide a good balance of key characteristics across treatment arms. Restricted randomization was therefore used to achieve an acceptable balance by applying the following criteria:

- mean HIV prevalence in each treatment arm within 0.075% of overall mean
- mean prevalence of *Chlamydia trachomatis* (CT) infection in each treatment arm within 0.1% of overall mean
- two of the 20 communities were close to gold mines, and one of these was to be allocated to each treatment arm
- even distribution of intervention communities across the four administrative districts in which the trial was carried out.

HIV and CT prevalence were based on an initial survey of young people carried out in each study community. Prevalences of HIV and CT (also an STI) were assumed to be correlated with sexual behaviour in the study communities and therefore to be predictors of the risk of acquiring HIV infection during the trial. HIV prevalence is often increased in mining communities, and it was important to ensure that one mining community was allocated to each treatment arm. Finally, ensuring an even distribution of intervention communities across districts helped to ensure that the trial was acceptable to local leaders.

A computer program was used to check each of the 28 000 possible allocations against the balance criteria, and 953 allocations satisfied the criteria and were listed. One of these was chosen randomly at a public randomization ceremony.

Source: data from Hayes, R. J., et al., The MEMA kwa Vijana project: design of a community randomised trial of an innovative adolescent sexual health intervention in rural Tanzania, *Contemporary Clinical Trials*, Volume 26, Issue 4, pp. 430–42, Copyright © 2005 Elsevier Inc. All rights reserved.