4.6: Trial population

6.1 Criteria for selection of trial population

The criteria for selection of the population to be included in the trial depends primarily upon what condition the intervention is directed against and upon the purpose of the trial. In general, the population will be chosen from an area in which there is high incidence of the condition of interest, because the higher the incidence of the primary trial outcome, the smaller the study population for the trial has to be. Exceptions are when the purpose of the trial is to determine the efficacy under special epidemiological circumstances or in special population groups such as in pregnant women.

Good community and governmental co-operation and participation are also key factors in the successful conduct of a trial. The trial area should be accessible at the times surveys are to be conducted (for example, during the rainy season). Well-qualified and experienced field teams should be available or be able to be recruited. In addition, access to high-quality clinical and laboratory facilities may be necessary for the trial. If required, entomological, behavioural science, economic, and other appropriate disciplinary expertise should be available. Planning the trial will be much simplified if baseline data are already available in the trial area.

If the trial design involves the repeated follow-up of members of the study population over several years, as will be the case for many intervention trials, it is important to select a location for the trial in which substantial migration into, or especially from, the area is unlikely to occur. Migration rates in excess of 10% per year are not uncommon in many rural areas and may be considerably higher in urban or peri-urban settings. Unless the trial is conducted within a demographic surveillance population, migration rates may well not be known in advance, so a rapid survey of a sample of the proposed trial population may be useful to determine if a reasonable proportion of the population have been resident in the area for several years.
The choice of trial population may affect the external validity of the trial results. For example, many micronutrient trials are carried out in areas with high prevalence of the specific deficiency. The health impact from supplementation in such areas is likely greater than what would be expected in areas where micronutrient deficits are less frequent, which may represent the majority of areas where supplements will be used in the future.

6.2 Inclusion and exclusion criteria

In general, the trial population should be chosen to represent the group that would be the target for the intervention in a potential future public health programme, if the intervention is found to be effective within the trial. Care should be taken to define the target population. To the extent feasible, those included should be the persons for whom benefit is likely to be the greatest, and those excluded should be the persons for whom benefit is likely to be minimal or indeed who may be harmed. Specific inclusion and exclusion criteria should be developed for the trial. For example, because the major morbidity and mortality associated with malaria in a holoendemic area are seen in infants and young children, these groups are likely to be the focus of a major field trial of a malaria vaccine in such an area, though older children and adults might be used in preliminary studies to test the safety of the vaccine in those who already have some immunity or may be the focus of a vaccine trial where malaria transmission is much less intense.

In early trials of an explanatory nature, special groups at high risk may form the trial population, either to maximize the potential effect, to ensure good compliance, or to facilitate the logistics. Valuable information concerning the potential of the intervention can result, but the extent to which the results can be extrapolated to the general population may be limited.

Exclusion criteria need to be carefully considered so as to eliminate subjects who may be put at greater risk by the intervention or who have underlying conditions that may interfere with the assessment. Exclusion criteria should be stated explicitly and unambiguously, before the trial begins. It is usual to exclude from trials those who are seriously ill, those who are very old, those who are very young, and pregnant women, unless any of these are the specific target group for the intervention. These groups are excluded either because it is considered that they are unlikely to derive benefit from the intervention, or if they are thought to be more likely to be susceptible to possible adverse effects of the intervention, or they are likely to suffer adverse events (AEs) which might incorrectly be associated with the intervention if they are included. Ascertainment of pregnancy is difficult, especially in its early stages, without specific testing, and, in some trials, this may not be feasible. Sometimes all women of childbearing age are excluded from trials, if it is thought that damage may be caused by the intervention to the fetus. Against this must be balanced the potential benefit that the excluded groups may receive from the intervention. Also, if pregnant women or children, for example, have been excluded from a trial that shows the intervention to be effective, resulting public health programmes may consider it is inappropriate for them to receive the intervention, in case there are unforeseen risks to them or because the safe and optimal dosage of any drugs involved are not known. As a result, it may be appropriate to include them in later ‘bridging’ trials, with careful monitoring of pregnancy outcomes.

6.3 The size of the trial population

Attention needs to be given to the required size of the trial, in terms of the precision of the effect estimates and of the power to detect important differences. These aspects are discussed in detail in Chapter 5. It is important to allow for the
loss of power that results from group randomization if such a design is adopted (see Chapter 5, Section 6).

For interventions that are likely to be given to large numbers of individuals, if they are subsequently introduced into disease control programmes, there are strong arguments in favour of designing trials of the interventions to also be large not only to pick up any rare side effects, but also to obtain a relatively precise measure of their expected impact.

### 6.4 Compliance

Conclusions from a trial will be based on a comparison of the outcome measures adopted for the trial in those allocated to the alternative intervention arms of the trial. Only a certain proportion of those allocated to a particular intervention will receive that intervention effectively. Effective delivery of an intervention requires both that the provider carries out the intervention procedure correctly and that the trial participants co-operate in the desired fashion. In field trials, the provision of the intervention will usually be under the control of the investigator, but a successful trial also requires the compliance of the participants, who are not under the control of the investigator, and will depend on the understanding and co-operation of the community involved. Hence, the strong emphasis in this manual on the importance of communication and feedback between the investigating team and the participating communities has a pragmatic, as well as an ethical, basis.

In most trials, however, some participants will not fully comply, and the intervention procedure either will not be carried out or it will not be done in an effective manner. For trials to determine the public health value of an intervention (pragmatic trials), some degree of non-compliance may give a more realistic measure of effectiveness than a tightly controlled trial in which every effort is made to ensure that the intervention is effectively delivered, but for explanatory studies, in which an important objective may be to determine the maximum effect possible, every effort should be made to keep compliance high. Wherever possible, the degree of compliance should be continually monitored, at least on a sample basis. This might be done, for example, by doing urine or blood analyses to check that the expected drug or nutritional supplement has actually been ingested. For intervention measures that are administered sequentially over time or on a continuing ongoing basis, repeated specimens should be taken. In a trial to measure the impact of introducing improved water supplies, for example, it will be important to measure the proportion of the target population who actually access the improved water source. This is particularly relevant in trials in which a health effect is mediated through a change in behaviour, as is the case in a breastfeeding promotion trial with morbidity or mortality as endpoints. Documenting compliance with counselling—assessed through changes in feeding practices—is essential.

A further aspect of compliance that is sometimes overlooked is that those in the ‘control’ arm of a trial, who are allocated to routine care or placebo, may adopt the test treatment under study. For example, if health centres in some villages are allocated to receive an intervention, such as offering voluntary medical male circumcision or improved STD treatment, while those in other villages serve as controls, people in the control villages may go to the health centres in the intervention villages to obtain the intervention. Monitoring for the possible occurrence of this latter form of non-compliance (sometimes called ‘contamination’) is important. Care should also be taken in the construction of the different treatment groups to minimize the opportunity for such contamination. In the circumcision example, ensuring there is clear geographical separation of villages in the different arms of this trial by leaving a ‘buffer zone’ would be one means of minimizing contamination.