4.2: Definition of trial objectives

Once an idea for a trial has been formulated, it will be necessary to detail the specific objectives of the trial. To do this, the researcher will need to find out what has already been done regarding the evaluation of the intervention or interventions of a similar kind. This may involve meeting or corresponding with those undertaking similar studies, and it will almost invariably involve conducting a systematic literature review to find out what has been published that is relevant (see Chapter 3).

With this background information, the objectives of the trial can be formulated. These should include the overall aim or purpose of the trial, such as ‘to evaluate the efficacy of a specific microbicide gel for the prevention of HIV infection in women’ or ‘to measure the impact of a breastfeeding promotion strategy on the incidence of diarrhoeal diseases in infants’. The specific objectives give more detailed statements of the particular questions that the trial is designed to answer, or the hypotheses that it will test. Finally, a list of subsidiary objectives may be given which relate to issues which are not central to the overall objectives but about which information will also be gathered while the trial is in progress.

2.1 The idea for a trial

One of the most creative phases of the planning of a trial is the selection of the subject area of the research and the formulation of the specific questions that will be addressed. A major motivation for most successful researchers is that they are doing something that they really enjoy and are researching questions about which they feel passionate. Their motivation may come from scientific curiosity about the causes or treatment or control of a particular disease, or about the effects of a specific intervention, or their concern may be to explore different ways that health or social systems can improve the public health. The field researcher may be motivated by working directly with people in their communities and be stimulated by the challenges posed by working in remote or difficult situations, outside of the hierarchy that may exist, for example, in a hospital environment.
The development or refinement of an idea for a field trial should take place in interaction with others at local, national, and possibly international levels. The research activity must not only be acceptable to the population in which it will be undertaken, but also to those who will authorize it nationally and to those who will fund it. Most good ideas for field research on the control of a disease that is of public health importance are likely to attract support.

Field research likely to receive the highest priority, both nationally and internationally, is that directed at control of diseases of greatest public health importance. An important preliminary to the development of a research proposal on a specific disease or condition may be a survey in the local community to determine the importance of the disease of interest. Such local data might be presented side by side with estimates of the global burden of disease attributable to the condition being studied.

The progress of science (and of public health) is not only dependent on groundbreaking first trials that show that a new intervention can be effective in one context. Progress also requires the replication of such trials in different settings to determine whether the findings from the original trial may be generally applicable. Replications of trials of bacille Calmette–Guérin (BCG) vaccination against TB and leprosy and of rotavirus vaccines, for example, have shown substantial variations in the efficacy of the vaccines in different parts of the world. This is even more important for effectiveness trials of interventions that are delivered through routine services where results may show important variations from one location to another, due to contextual differences. Although sometimes disparagingly called ‘me too!’ trials, such confirmatory (or otherwise!) trials are very important for the assessment of the public health usefulness of an intervention in a specific context.

A trial may either test for superiority or for equivalence. The choice will depend on the nature and effectiveness of the comparison intervention and has important implications for the choice of trial size (see Chapter 5). For example, if the aim is to test whether a new drug for the treatment of visceral leishmaniasis is more effective than the standard drug treatment, this will require what is called a ‘superiority’ trial. However, it could be that the new drug is much cheaper or is thought to have fewer side effects. If this was confirmed in a field trial, it would be likely to be adopted even if it was no more effective than the standard drug, so a trial that is designed to test for ‘non-inferiority’ or ‘equivalence’ would be appropriate.

### 2.2 Trial purpose

The statement of the purpose of a trial (termed ‘goal’ by some agencies) should convey to the reader the type of intervention, or package of interventions, to be evaluated (without details of how it will be applied, dose, and so on) and the endpoints against which the impact will be measured, without necessarily specifying the magnitude or precise nature of the impact expected or which the trial will be designed to detect. It may also include a description of the ways in which the results of the trial may influence public health policy and contribute to scientific knowledge. For example, in a trial of the use of the drug ivermectin against onchocerciasis, the statement of the purpose might be ‘to assess the impact of mass treatment with ivermectin on the transmission of onchocerciasis and to measure any side effects in those treated with the drug’. For a trial of a new vaccine against the blood stages of the malaria parasite, the purpose may be ‘to measure whether a *Plasmodium falciparum* asexual blood stage vaccine reduces episodes of clinical malaria’. For a trial to test the effect of cash payments conditional on girls either staying in, or returning to, secondary school on their risk of HIV infection, the purpose might be ‘to assess whether educational conditional cash transfers reduce acquisition of HIV infection in girls’. Finally, for the example of the equivalence trial of a new drug for visceral leishmaniasis treatment, the
purpose might be ‘to test whether the new drug is at least as effective as the standard treatment for treatment of visceral leishmaniasis’.

### 2.3 Specific objectives of the trial

In the specific objectives (called specific aims by some agencies), a quantitative statement should be made regarding the size of the effect of an intervention that a trial is designed to detect and the precision with which the effect will be measured. Such specifications are necessary in order to calculate how large a trial should be, using the methods described in Chapter 5. The nature of the intervention should be given in more detail than in the statement of purpose (for example, dose and frequency of administration), and the endpoints of the trial clearly stated. They should also include a specification of the size of the trial and detail the population in which the intervention will be applied. For the example of the trial of ivermectin against onchocerciasis, the specific objectives would include a statement of the size of the impact on transmission which the trial would have a reasonable chance of detecting and the frequency with which adverse reactions of different kinds would have to occur to be detected in the trial, while, for a malaria vaccine, a more detailed description of the formulation of the vaccine would be required and statements included on the magnitude of the true effects on the incidence of malaria that the trial would be very likely to detect as being statistically significant.

Finally, for the conditional cash transfer trial (see Section 2.2), the specific objectives should state the size of payment, to whom it will be given (for example, to the girl herself, her parents, or some combination of the two), the age range of the girls in the trial, and the size of effect on HIV incidence that the trial would have a reasonable chance of detecting.

The proper specification of the specific objectives is crucial to a successful trial. They should include a concise, but detailed, description of the intervention to be evaluated, the outcome(s) of interest, and the population in which the trial will be conducted. The more specific and detailed the objectives are, the clearer it will be how to design a study to meet them. It is crucial to set appropriate objectives, and it is worth spending time to get these both correct and unambiguous.

### 2.4 Subsidiary objectives of the trial

In the context of many trials, there will be secondary endpoints which will be measured in the trial but which are not the prime purpose for which the trial is conducted. Also substudies may be included, having subsidiary objectives, such as the comparison of various serological tests or the analysis of genetic markers and their correlation with disease. It may be decided to add other objectives on to an intervention trial which do not relate to the main objectives. In the trial of ivermectin against onchocerciasis, for example, the impact on some other parasitic diseases might be assessed.

To increase the plausibility of trial findings, it is important to document changes in intermediate outcomes, which are directly related to the outcomes of principal interest, whenever this is possible. This requires laying out an ‘impact model’ (see also Chapter 15), describing how the intervention is expected to lead to the major outcome being studied. For stand-alone biological interventions, these models tend to be quite simple. For example, a trial of the effect of periodic vitamin A supplementation on child mortality should document that the vitamin A status improved in children receiving the supplement, but not in the comparison group. Impact models for non-biological interventions are often more complex. For example, in the conditional cash transfer trial, the impact on retention in secondary school and school achievement grades or the impact on reported sexual risk behaviours or on the incidence of other STDs or of pregnancy could also be studied, as well as the primary endpoint of HIV incidence. Impact models are essential for deciding which
intermediate indicators must be measured.

The introduction of an intervention may also provide a special opportunity for determining particular key factors in the pathogenesis of disease. For example, trials of ivermectin, a microfilaricide, against *Wuchereria bancrofti* may provide evidence for the role of microfilaria, as compared to that of adult worms, in the pathogenesis of lymphatic filariasis disease. Decisions to add on studies of this kind should not be taken lightly, as they will invariably need additional commitment of resources and may involve the trial population in additional inconvenience. They may thus have a negative impact on the primary objectives, perhaps by overstretched the trial team's technical or managerial resources, and the final 'cost' to the trial may be much greater than it appeared to be in purely monetary terms.

Once a large field trial is successfully under way, it is not unusual for the trial organizers to be approached by other investigators who wish to graft on additional procedures to answer questions of interest to them. There may be considerable value in utilizing the same trial for multiple purposes, but full consideration should be given to the extra work that this will entail, especially for key members of the research team, and to other possible harmful effects such as upsetting the rapport between the trial team and the trial population.