4.1: Introduction to trial design

Trials should be designed to produce unambiguous estimates of the effects of interventions, which are precise enough for public health planning. A common goal of all intervention studies, including trials, is to evaluate the effect of a specific intervention (or a specific package of interventions) applied in a specific manner to a well-defined population. In the trial design, the major issues will be: (1) the nature of the intervention, the strategy for its implementation, and the natural size of the unit at which the intervention is applied (for example, individual, household, school, village, district); (2) the likely effects, including possible adverse effects, and how they should be measured; and (3) the comparisons that need to be made with other interventions.

In most LMICs, disease control is the responsibility of the Ministry of Health (MOH). Therefore, wherever possible, the Ministry should be involved in the planning and monitoring of trials, and the results must be made available in such a way that they are of direct relevance to national disease control activities (see Chapter 23). As the Ministry is often the implementing agency for interventions in public health programmes, it is generally desirable that independent investigators actually conduct the trials of interventions.

This chapter gives an overview of the main factors to consider in the development and implementation of health intervention trials in LMICs.

1.1 Planning a trial

The trial planning process is a major exercise which starts, and which should be largely completed, before any field activities have taken place, other than initial feasibility studies and small-scale pilot investigations (see Chapter 13). The planning process should encompass all aspects of the trial, from formulation of detailed objectives, based on the initial idea, through preparation for all field activities, collection of data, and analysis of results, to their publication, dissemination, and potential use in disease control. The plan should also try to anticipate the form of any studies that will
follow, depending on the possible different outcomes of the trial.

Detailed planning is necessary for several purposes. First, information on the trial will be required by local and national administrations for them to review as part of the trial approval process. A similar description will be required by any agency that is going to review the proposal for funding. The detail required in such grant applications varies greatly from agency to agency. Some require a comprehensive document with full details of all trial procedures, while others put quite a small upper limit on the size of any application they are prepared to review. It is usually more time-consuming to prepare the former kind of application, but the latter kind may present a more formidable challenge, because, in relatively few words, the investigators have to present convincing evidence that they have considered and worked out all issues that would have been included in the longer type of application. Advice on the preparation of grant applications is given in Chapter 8.

A second reason for detailed planning at the start of an investigation is that possible problems must be anticipated in advance and solutions thought through, in order to reduce the likelihood of the trial falling behind schedule or having to be radically changed or abandoned, due to problems that could have been foreseen and avoided. Commonly, funding agencies require a section on potential risks to the trial, in which the investigators are asked to specify what could go wrong and the consequences this would have for the trial. It is rare to be able to predict all potential problems, but the more that have been considered in advance, the smaller the chance of catastrophe.

Realistic estimates must be made of the resources needed (for example, for transport, staff salaries, allowances, items of equipment) and the likely trial duration, including the time to analyse and report the trial, in order to be able to calculate the required budget for the trial. Underestimating the support needed may jeopardize some of the objectives, which may have to be revised or abandoned in the middle of the trial, whereas overestimating the cost may prejudice the funding agency against agreeing to support the trial. It is tempting to underestimate costs in the hope of increasing the chance of funding, but this may be self-defeating and, in any case, will often be picked up by the experienced investigators asked to review the trial proposal by the funding agency. The time it will take to conduct and analyse a trial is also often underestimated, particularly for trials where implementation of the intervention, or package of interventions, is not directly under the control of the evaluators but depends instead on the MOH or other partners. Advice on the preparation of budgets is given in Chapter 18.

In the present chapter, the steps to be included in the trial plan are discussed in the approximate order that they would arise, from the formulation of objectives through to the eventual publication, dissemination, and use of the findings. In the remaining chapters, specific issues relevant to the planning process are reviewed in greater detail, and cross-references are given in this chapter, where appropriate.

### 1.2 Ethical considerations in designing a trial

Ethical considerations impinge on many aspects of the design and conduct of trials and are discussed fully in Chapter 6. Briefly, any research investigation that involves human subjects should be submitted for ethics committee review. Intervention trials in some communities in LMICs may pose specific ethical dilemmas. The dogma that an investigator ‘should treat everyone in the trial as though they were a member of his or her own family’ is both difficult to apply and often inappropriate in situations of extreme poverty, in which some trials in LMICs will take place. Related issues concern the responsibility that an investigator has to those who live in the same community as the trial subjects but who,
for whatever reason, are not included in the trial, and what happens regarding the public health use of an intervention after a trial has shown an intervention to be efficacious. Very commonly, an investigator must walk a tightrope, balancing his or her responsibilities to the individuals in the trial with those related to the potential of the interventions being evaluated to improve public health. The MOH knows these problems well, as they are implicit in any allocation of the health budget between the various potential preventive and curative services, but, commonly, the officials allocating the routine health budget are several steps removed from the individuals and communities that their decisions will affect. The field trial researcher usually has to face these issues directly. There are no simple solutions to these problems. It is important that each research study is subject to strict ethical review, with due attention to the specific conditions in and under which it will be conducted.

1.3 Trial governance

Since the first edition of this book was published, there has been a much greater emphasis on trial governance and quality control (QC) in trials. There are now extensive international guidelines on the governance of clinical trials, in which the roles of bodies, such as the trial ‘sponsor’, the principal investigator (PI), the trial Steering Committee, and the Data and Safety Monitoring Committee (DSMC), are discussed and defined. These aspects are considered in more detail in Chapter 7.