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1
Types of intervention and their development

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1 INTRODUCTION

The variety of new interventions and new strategies that are being developed against the major diseases common in developing countries is wide and includes drugs, vaccines, vector control measures, new approaches to health education, and new uses of established products. Research workers from a wide range of disciplines are needed to develop, assess, and deploy these interventions, ranging from molecular biologists to social scientists. Field trials are required to determine how interventions, both old and new, may best be applied in populations and to determine what impact they have in improving the health of the population.

In this chapter the characteristics of the different kinds of intervention that may be used in control programmes against tropical diseases are reviewed. The general strategies of use for each are outlined and the implications of these strategies for the design, conduct and interpretation of field trials are indicated.

2 DIFFERENT KINDS OF INTERVENTION TO BE EVALUATED

Interventions may be divided into two broad categories, those that are used to treat a disease process already underway and those that are used to prevent the initiation of the disease process. Some interventions fall into both categories. The primary effect of preventive strategies is to reduce the incidence of new cases of disease whereas that of treatment strategies is to interfere with the natural history of the disease process by curing or alleviating the disease or preventing the development of more severe disease or death.

The basic unit to which an intervention is applied will depend upon the nature of the intervention and the strategy for its use. The unit may be the individual, the family or household, or the community.

2.1 Drugs for treatment of disease

The way in which a drug is to be used for disease control will influence the design of field trials to evaluate its impact. Most drugs employed in tropical disease control programmes are used to kill or inhibit the pathogen in the host. Strategies for disease control that use such agents involve case detection (which requires an appropriate case definition and diagnostic method) followed by treatment designed to reduce morbidity and mortality. Often the success of this approach depends critically upon case finding, and for diseases such as tuberculosis and leprosy it depends also on case holding, i.e. being able to follow and treat each patient at regular intervals over a long period of time. Case finding and treatment may also reduce transmission of an agent if cases are the main reservoirs of infection, if case detection methods locate a high proportion of prevalent cases, and if the treatment is sufficiently effective.

2.2 Treatments for prevention of infection or disease

Drugs or other interventions may also be used for prevention of infection or disease. Generally, the use of drugs for prophylaxis does not require individual diagnosis, but community or group diagnosis is needed to identify groups that should receive the prophylaxis. Whether requiring specific diagnosis or not, therapeutic or preventative agents are usually taken on an individual basis, though sometimes interventions to be applied on a mass basis can be distributed to a community through the water supply (for example, fluoride against dental caries) or in food (for example, diethylcarbamazine for filariasis and chloroquine for malaria in medicated salt, and vitamins in fortified bread).

Prophylaxis is usually aimed at preventing or limiting infection, particularly in those at high risk for a limited period of time (for example, antimalarials taken by those visiting malarious areas). The value of such an approach is limited by the duration of action of the intervention, by adverse reactions to the prophylactic agent, and possibly by the role of the intervention in stimulating the development of drug resistant organisms. For some purposes prophylaxis may be used by those who are permanent residents of tropical disease endemic areas (for example, antimalarials in pregnancy, and vitamin A supplementation in areas of deficiency).

Drugs also may be used prophylactically for treatment of preclinical infection (for example, during the incubation period before onset of symptoms, as for *gambiense* type of trypanosomiasis), or for treatment of subclinical infection (for example, ivermectin against onchocerciasis, and praziquantel against schistosomiasis).

Strategies for the use of such interventions include the mass treatment of entire populations or the targeted treatment of identifiable subgroups (such as school-age children) in areas where the infection is sufficiently prevalent. In some cases the objective of such treatment is to reduce the transmission of the agent in the community; in others it is applied only for the benefit of the individual treated. Treating all those in a defined group may be more cost-effective than screening the whole group and only treating those found to be infected.

2.3 Vaccines for prevention

Vaccines protect individuals at risk of acquiring infection by inducing a variety of immune mechanisms. These immunological reactions may lead to protection from infection, reduction of parasitic proliferation within the host after invasion (and hence curtailment of disease) and/or reduction of transmission from the host. Vaccines may be administered to protect individuals at risk of acquiring

infection, to prevent disease in those already infected, or to reduce transmission of the disease agent.

2.4 Vector control

Vector control measures are preventive interventions often directed at the environment. Measures requiring evaluation may include new formulations and novel ways of applying insecticides, new and improved selective biological agents against disease vectors, engineering techniques for reducing vector habitats, community involvement in eliminating vector breeding sites and in deploying traps, housing and screening improvement for reducing human–vector contact, and new strategies involving combinations of methods particularly with the objective of reducing insecticide resistance. For most of these methods intermediate process indicators, such as reduction in vector density, are the principal means for assessment, but ultimately it is also necessary to determine the impact of the measures on the health status of the population.

2.5 Diagnostic tests

The evaluation of diagnostic tests *per se* is not considered to be within the scope of intervention trials as addressed in this manual. However, the specificity, sensitivity, and the positive and negative predictive values of any diagnostic tests utilized in an intervention trial must be taken into account in the design of a trial. Diagnostic tests may need to be evaluated for the proper interpretation of a trial or for its successful conduct.

Diagnostic tests have been developed, or are being developed, for all the major tropical diseases. In some cases diagnostic tools are being developed to replace the current ones because they may be simpler, cheaper, more robust for use in the field, and/or provide improved sensitivity or specificity. In other cases tools are being developed that measure some new characteristic, such as the presence of malarial sporozoite antigens and antibodies. For the former group of tests the major type of study required is that for validation to demonstrate sensitivity, specificity, and predictive values. For the latter group, however, after validation studies, descriptive studies of the newly measured characteristics must be

carried out to determine their epidemiological features, their variation over time, their prognostic significance, and to evaluate their usefulness for disease control programmes.

2.6 Educational interventions

Some interventions directed at disease control are based solely upon changing human behaviour through educational or promotional techniques (for example, anti-smoking campaigns or campaigns to promote breast feeding). Nearly all health interventions must have an associated educational component for effective disease control, but the extent of educational effort required ranges from provision of simple information (for example, when and where a clinic will be held) to efforts at increasing understanding (for example, the importance of immunization) and even to attempts to change lifestyles (for example, diet, sexual habits). Education to increase knowledge and impart new skills may be necessary but is rarely sufficient to induce behavioural change. Individuals must also have the capacity and will to act on the knowledge and to use the skills. The nature of an educational intervention may need to be researched through careful investigations in the community using the kinds of methods discussed in Chapters 5 and 10.

Examples of educational components of disease control programmes include developing effective community participation in programmes that need broad coverage for effective immunization or drug distribution, that require people to recognize disease symptoms for early treatment, that necessitate active co-operation in home improvements or insecticiding programmes, that involve direct action and responsibility in deploying vector, or intermediate host, traps, or that need community efforts for environmental improvements such as developing and maintaining improved water supplies or better disposal methods for faeces.

2.7 Environmental alteration

Many of the most effective methods for controlling tropical diseases involve alterations to the environment. Nearly all such alterations are directed at reducing transmission of the agent causing

disease. Classic vector control measures include drainage of swamps, elimination of casual water (for control of the *Aedes* mosquito), clearing of bush (for tsetse fly control), control of water levels in irrigation schemes, and urban water drainage systems. Means to reduce human faecal and urine contamination have included latrine construction, provision of sewage systems, clean water supplies, and protected food storage. Nearly all require substantial educational efforts and some lifestyle changes.

3 BIOMEDICAL–BEHAVIOURAL CONTINUUM OF INTERVENTIONS

As noted in Section 2, field trials of interventions against tropical diseases will usually involve aspects of human behaviour and this may have important implications for the trial design. Interventions can be classified along a biomedical–behavioural continuum. At one extreme is the purely biomedical intervention which requires no behavioural change, for example, insecticide spraying of river rapids against *Simulium damnosum* larvae. At the other extreme are behavioural interventions which have a biomedical rationale but no biomedical element or agent, for example, boiling of drinking water. Trials of interventions that have a large behavioural component typically require a greater emphasis on social research than do purely biomedical interventions, but there are few interventions for which some kind of social research is not appropriate.

The intervention to be evaluated in a trial must be defined precisely, not only in terms of the biological and chemical composition of the agent, but also in terms of any health education or promotion that is a component part of the intervention strategy. Both may influence the measured impact on disease, sometimes independently, and it will be important to take this into account when designing the appropriate 'control' intervention. For example, if it is important to assess the impact of the biomedical intervention, independent of a health education component, it may be necessary to include the health education component for those in the 'control' group also.

The co-operation required from the study subjects to ensure effective application of an intervention ranges from passive

acquiescence to active change of behavioural patterns. Change may involve innovative behaviour or alteration of existing habits. If an intervention involves behavioural alterations, prior social research into the reasons for existing behaviour is likely to be required. Such enquiries may indicate the intensity and levels of educational effort (community or individual) required to ensure co-operation.

4 EVOLUTION OF NEW INTERVENTIONS AND DISEASE CONTROL STRATEGIES

Many intervention products, and especially drugs and vaccines, are likely to originate from basic research in laboratories. Such products must go through a long series of tests before they can be considered for use in the kinds of field trials which are the focus of this manual. Before any human use, a new product will be tested in the laboratory for its activity and toxicity in various *in vitro* and animal test systems. If it successfully passes through these stages, studies of safety, toxicity, and activity may be conducted in a small number of human volunteers with careful clinical monitoring. A series of further studies, each including increasing numbers of subjects, must be carried out before a new product can be introduced for widespread use. Careful monitoring, often in a clinical setting for possible adverse reactions, is characteristic of early studies. The optimal dose and frequency of application must be worked out. Early investigations will include some measures of effects which often are intermediate to the outcome of principal interest. For example, with a vaccine, the induction of an immune response may be assessed, which it is hoped will correlate with protection or activity against the disease of interest. To determine efficacy, trials are always required that include a comparison intervention (which may be a placebo if there is no effective equivalent intervention against the disease under study), in which the interventions are allocated between subjects or groups of subjects on a random basis. Legal registration procedures are mandated in most countries before a drug or vaccine can be put into general use, and these procedures normally require documentation of safety and efficacy of the intervention based on randomized controlled trials involving many hundreds of subjects. Registration issues are not

specifically addressed in this manual. Many field trials will involve products already registered, but those responsible for the registration of interventions that must undergo field trials may find the manual useful.

The purposes of field trials may change as experience with an intervention accumulates. Sometimes, particularly in early trials of a new intervention, the purpose of the study is analytic, to demonstrate an effect or to establish a matter of principle with little consideration as to whether the intervention is practicable at the population level for disease control. An example might be the use of a malaria vaccine that must be administered monthly to be effective. Such studies are sometimes called 'explanatory' (Schwartz and Lellouch 1967). Once an effect against the disease under study has been demonstrated there might then be greater impetus to develop new formulations of the intervention or different schedules that would be more practicable for application in a disease control programme. Subsequent, and generally larger, trials are conducted in which the purpose is to establish the benefit of an intervention applied under the circumstances of general use. These studies, on which this manual will be largely focused, are often called 'pragmatic' studies (Schwartz and Lellouch 1967).

Although laboratory development of new products may serve as the impetus for field trials, some interventions, or intervention strategies, are developed directly as a result of field studies and experience, such as the vaccine strategy for smallpox eradication and the use of tsetse fly traps for the control of trypanosomiasis transmission. Thus, trials may be needed not only of the product itself, but also of the way that product is used or delivered. Trials like these would involve intervention 'packages' which might include, for example, the same drug or vaccine, but provided with different education approaches or delivery methods. Sometimes an intervention that has been shown to be effective must be added into an ongoing disease control programme that involves other kinds of interventions. For example, it is expected that when malaria vaccines become available they will be added to other malaria control methods based on a combination of vector control and case finding and treatment strategies. Further studies of how best to integrate these interventions into an overall strategy will have to be worked out. In addition, policy and planning decisions about disease control will have to be guided by appropriate cost-

effectiveness analyses. Although these further studies are beyond the scope of this manual, it may be helpful to keep such issues in mind in planning field trials in concert with those responsible for disease control programmes.

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2
Study design

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1 INTRODUCTION

Intervention studies should be designed to produce unambiguous evaluations of the effects of interventions which are precise enough for the purpose of public health planning. A common goal of an intervention study is to evaluate the effect of a specific intervention applied in a specific manner to a well-defined population. In the design the major issues will be; first, the nature of the intervention, the strategy for its use and the natural size of the unit at which intervention operates (for example, individual, household, village, geographical area); second, the effects and how they should be measured; and third, the comparisons that need to be made with other interventions.

In most developing countries disease control is the direct responsibility of the Ministry of Health. Therefore, wherever possible, the Ministry should be involved in, if not directly responsible for, the planning and conduct of trials, and the results must be made available in such a way that they are of direct relevance to national disease control activities.

1.1 The study plan

This chapter gives an overview of the factors to consider in the planning of field trials of interventions against tropical diseases. The planning process is a major exercise which starts, and which should be largely completed, before any substantial field activities have taken place, other than initial feasibility studies and small-

scale pilot investigations. The study plan encompasses all aspects of an investigation, from formulation of detailed objectives based on the initial idea, through preparation for all field activities, through collection of data and analysis of results, to their publication, dissemination, and use in disease control. The plan should also take account of the form of any studies that will follow, depending on the possible different outcomes of the study in hand.

Detailed planning is necessary for several purposes. First, details of the plan of investigation will be required by local and national administrations to review for approval. A similar description will be required by the agency that is going to review the proposal for funding or support. The detail required in such grant applications varies greatly from agency to agency. Some require a thick document with full details of all study procedures, while others put quite a small upper limit on the size of any application they are prepared to review (for example, six pages). 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 to be included in the longer application.

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 study falling behind schedule, or having to be abandoned, due to unexpected problems. It is rare to be able to predict all potential problems, but the more that have been considered in advance then the smaller the chance of catastrophe.

A good estimate of the resources needed (for example, for transport, staff, allowances, items of equipment) must be made in order to be able to calculate the level of funding to be requested in any grant application. Underestimating the support needed may jeopardize some of the objectives, which may have to be revised or abandoned in the middle of the study, whereas overestimating the cost may prejudice the funding agency against agreeing to support the study. Sufficient time must also be allocated for the various stages of a trial.

In this chapter the steps to be encompassed in the study 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

Ethical considerations impinge on many aspects of the design and conduct of intervention studies. Any research investigation on human subjects should be submitted for ethics committee review. The submission must make clear that the ethical implications of all aspects of a study have been given full consideration by the investigator. Intervention trials against tropical diseases in communities whose residents are often poor and deprived in many ways may pose difficult ethical dilemmas for an investigator and for the bodies that must review the research proposals. The dogma that an investigator should treat everyone in an investigation as though they were a member of his or her own family is both difficult to apply and probably inappropriate in the situations of extreme poverty in which many tropical diseases flourish. A related issue concerns the responsibility that an investigator has to those who live in the same community as the study subjects but who, for whatever reason, are not included in the study. Very commonly an investigator must walk a tightrope, balancing his or her responsibilities to the individual with those related to the improvement of the public health. The Ministry of Health knows these problems well as they are implicit in any allocation of the health budget between preventive and curative care, but, commonly, allocation of the routine health budget is regarded as one step removed from that encountered by the public health research worker in the community, who may have to face these issues directly in the context of a specific research investigation. 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. A discussion of the issues involved is given in Chapter 4.

2 DEFINITION OF STUDY OBJECTIVES

Once an idea for a study has been formulated, it will be necessary

to detail the objectives of the study. 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 certainly involve conducting a literature review to find out what has been published that is relevant.

With this background information the objectives of the study can be formulated. These will include the purpose, which is a general statement regarding the role that the intervention to be evaluated might have for the control of disease. The specific objectives give more detailed statements of the magnitude and nature of any effects of the intervention on disease that the study has been designed to detect. Finally, a list of subsidiary objectives will be given which relate to issues which may not be central to the overall objectives but on which information will also be gathered while the study is in progress.

2.1 The idea for a study

The most creative phase of the planning of a research study 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 doing. Their motivation may come from scientific curiosity about the causes and control of a particular disease, or about the effects of a specific intervention, or their concern may be less specific and relate to an interest in exploring different ways of improving 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 a field research idea will 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. Good ideas for field research on the control of a disease which is of public health importance are likely to attract support. It may be

important for investigators to make early contact with the agencies that might be sources of support for a study. These agencies may have their own agenda and have listed their priorities for the support of research. Clearly, proposed investigations that fit in with such priorities are likely to be viewed sympathetically if support is requested.

Many funding agencies encourage investigators to contact them early in the planning process when only the outline of a study has been formulated, so that the agency can advise how a proposal might be developed to fit in with their own priorities. An investigator is not obliged to follow such advice, but much work can be saved if the advice is at least considered before detailed planning of a study is undertaken. Funding agencies may publish a list of their priorities for research. For example, each of the committees that review research proposals for the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) has drawn up a research plan for their target disease which details the investigations they are anxious to support with high priority. Outline protocols may have been developed for some of these studies, which particular investigators would have to tailor for use in the situation in which they will work.

Field research that is likely to be given the highest priority, both nationally and internationally, is that directed at the control of diseases which are of greatest public health importance. Thus, an important preliminary to the development of a research proposal on a specific disease or condition may be a more general survey in the local community to determine the relative importance of the disease of interest as one of the major health problems, both medically and as perceived by the local population.

A good justification for some studies may be that they attempt to replicate observations that have been made in other geographical locations. The progress of science (and of public health) is dependent upon the replication of experiments (trials) in different settings to determine whether the findings from a study may have arisen through some kind of bias, or may apply only in special circumstances, or may be generally applicable. Replication of trials of BCG vaccination against tuberculosis and leprosy, for example, have shown substantial variations in the efficacy of that vaccine against both diseases in different parts of the world.

'Confirmatory' (or otherwise!) studies are very important for the assessment of the public health usefulness of an intervention.

2.2 Purpose

The statement of the purpose of a research project should describe the main questions to be addressed by the research without going into detail (which will be done in the specific objectives). It should give a reader a clear idea of the nature of the research that will be undertaken. The purpose of a leprosy vaccine trial might be 'to assess the protective efficacy against leprosy induced by a mixture of BCG and armadillo-derived killed *Mycobacterium leprae* bacilli among the contacts of leprosy patients in Venezuela'. For a study of the use of the drug ivermectin against onchocerciasis 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 the effect of a *Plasmodium falciparum* asexual blood-stage vaccine in reducing morbidity and mortality due to malaria'.

The purpose should convey to the reader the type of intervention which is to be evaluated (without details of how it will be applied, dose, and so on) and the end-points against which the impact will be measured, without necessarily specifying the magnitude nor precise nature of the impact expected, or which the study will be designed to detect. It might also include a description of the ways in which the results of the trial may influence public health policy and contribute to scientific knowledge.

2.3 Specific objectives

In the specific objectives a quantitative statement should be made regarding the size of the effect of an intervention that a study 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 study should be, using the methods described in Chapter 3. The nature of the intervention should be given in more detail than in the statement of purpose (for example, dose, frequency of administration) and the endpoints of the study clearly

stated. They should also include a specification of the size of the study and detail the population in which, or to which, the intervention will be applied. Thus, for a trial of a leprosy vaccine, the specific objectives might include 'to conduct a randomized trial among contacts (aged 6 to 64 years) of leprosy patients comparing the incidence of leprosy among those given BCG alone with that among those given a mixture of BCG plus armadillo-derived killed *M.leprae* bacilli (6×10^8 bacilli/dose). The trial will have 90 per cent power to detect a protective effect of 70 per cent (of BCG and *M.leprae* versus BCG) at the 5 per cent level of statistical significance in the five years following vaccination'.

For the example on the trial of ivermectin against onchocerciasis the specific objectives would include a statement of the size of the impact of 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 study.

For the malaria vaccine, a more detailed description of the formulation of the vaccine would be required and statements included on the magnitude of the effects on disease that the trial would be expected to ascertain.

The proper specification of the specific objectives is a key to the conduct of a successful study. 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 study 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 the appropriate objectives and it is worth spending time to get these right.

2.4 Subsidiary objectives

In the context of many trials sub-studies will 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 onto an intervention trial which do not relate to the main objectives. In a trial of ivermectin against onchocerciasis, for example, the impact on some other parasitic diseases might be assessed, or in a trial of a vaccine against leprosy, the effect on tuberculosis

could also be studied. The introduction of an intervention may provide a special opportunity for determining particular key factors in the pathogenesis of disease, for example, trials of ivermectin, a microfiliaricide, 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 study population in additional inconvenience. They may thus have a negative impact on the primary objectives and the final 'cost' for the study may be much greater than it appeared initially in monetary terms.

Once a large field study is underway successfully it is not unusual for the study 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 study 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 study team and the population.

3 SELECTION OF INTERVENTIONS

3.1 Characteristics required

The choice of an intervention to be subject to large-scale field evaluation will be influenced by the following criteria. The intervention should be such that it could be introduced into a national or regional disease control programme (though this criterion might not apply for 'explanatory' trials—see Chapter 1, Section 4). The dose (when applicable) should be optimal. Evidence would usually be required from short-term studies that the intervention is relatively safe and produces a convincing intermediate response. When an action has to be repeated several times (for example, vitamin supplements), there should be corresponding evidence that the interval between each action gives an effective schedule. For some interventions the concept of dose is meaningless, such as the application of a diagnostic or screening test. Corresponding

relevant evidence would then be required that the test is adequate (for example, previous studies indicating sensitivity, specificity and predictive values). For continuous or repeated treatments, similar considerations apply to the duration of treatment. For example, with vitamin supplementation the duration required will depend on whether the outcome of interest is the acute effect of severe deficiency or the chronic effect of more moderate deficiency. In addition to being safe and giving promise of being efficacious, it must be acceptable to those to whom it is directed, relatively easy to deliver and, at least eventually, be of sufficiently low cost that it can be incorporated into the national disease control strategy.

3.2 Number of interventions compared

The choice of the number of different interventions to compare in a field trial is likely to be determined not only by the number of competing alternatives but also by the implications the choice has on the size of the study, which in turn is dependent on the frequency with which the outcome of interest occurs. 'Rare' outcomes require large studies (as discussed in Chapter 3). For example, in a trial of leprosy vaccines in South India it was planned that each 'arm' (one of the alternative intervention assignments) included in the study would include around 65 000 subjects in order that the study had the desired statistical power to detect effects. Clearly in this situation a decision to add another arm would have had enormous cost and logistic consequences (M. Gupte, personal communication).

If the outcome is common, however, studies to compare more than two interventions may be undertaken more readily. For example, if seroconversion following vaccination is the outcome of interest, it may be straightforward to compare multiple vaccines or vaccination strategies in a single study.

It is important to note, however, that many researchers try to build too many comparisons into a study. There is often a tendency to divide groups after the sample size has been calculated or to plan comparisons within groups, without going through the appropriate computations (as given in Chapter 3).

Comparisons within a study can always be made with much greater confidence than those between studies. Thus if drug A is found to be 50 per cent 'better' than a placebo in one trial and drug

B is found to be 50 per cent better than a placebo in another trial, it will not necessarily be possible to conclude that A and B are equally effective, as the circumstances in which the two trials were conducted will not have been identical. A further trial may be necessary for a direct comparison of A and B. If the need for this trial could have been anticipated in advance it would have been more efficient to conduct one trial involving both drugs A and B and a placebo. A trial like this may be more complex to organize and would probably have to be substantially larger than either of the '2-arm' studies.

3.3 Combined interventions

For some diseases there are several possible interventions that may reduce the disease impact on a population. For example, interventions against malaria include destruction of mosquito breeding sites, spraying of residual insecticide, personal protection measures (for example, use of bed-nets and repellents), drug prophylaxis, and drug treatment, and studies might be designed to evaluate each of these interventions individually. A malaria control programme may choose to use more than one intervention at the same time and may wish to evaluate the impact of the 'strategy' rather than the individual components of it. In such a case, the intervention trial might compare an integrated strategy incorporating several different measures applied simultaneously with a control group in which only the routine measures normally available would be applied.

In developed countries, several studies of this kind have been conducted for the prevention of heart disease. Those in the intervention group were advised to smoke less, take more exercise, eat less fat, and so on, and their subsequent cardiovascular disease rates were compared with those in a group who were not so advised. The advantage of this kind of study is that if no effect is seen then it may be reasonable to conclude that no one of the components of the intervention was effective (at least, as applied in the trial), but the disadvantage is that if an effect is demonstrated it is not possible to be sure what fraction of the overall result each of the various components of the intervention was responsible for. It is also possible when no effect is seen that a beneficial effect of one component of the intervention has been counter-balanced by a deleterious effect of another component.

3.4 Choice of comparison intervention

The best way to evaluate an intervention is to compare its effect with that of another intervention in the same population at the same time. The allocation of individuals or groups of individuals to the different interventions should be 'at random' (see Section 4.1 and Chapter 7). In general, the intervention that is the current 'best' should be used as the comparison, but the choice of the 'control' intervention is not always straightforward and may involve difficult ethical issues (Chapter 4). When no effective intervention is known the comparison must be with a group in which 'no intervention' is made; in general a placebo should be administered in order to preserve 'blinding' (Section 4.1). For example, before the development of ivermectin no effective and safe treatment for onchocerciasis existed. Thus, placebo-controlled trials of the drug were ethically acceptable, at least until the beneficial effects of ivermectin had been established. For most tropical diseases, however, some kinds of intervention exist and may already be deployed by the health services or by a control programme in the area where a trial is planned. Only in rare circumstances would it be ethical to withdraw these existing interventions for the purposes of a trial. A more difficult issue is with respect to the extent to which they should be introduced in the context of a trial. If it is known that regular prophylaxis with anti-malarial drugs reduces mortality from malaria, for example, would it be necessary to give this intervention to all those in the 'control' arm of a malaria vaccine trial, even though in normal circumstances few of them would be on prophylaxis? Indeed, would it even be ethical to withhold prophylaxis from those who would be receiving a malaria vaccine whose efficacy against mortality was unknown? The optimistic reader will seek a definitive answer to these questions in Chapter 4! Unfortunately, the search will be in vain as there are no general definitive solutions to problems such as this; each situation has to be considered on its own merits, taking full account of the circumstances in which a particular investigation is planned.

In a leprosy vaccine trial in Venezuela, the new leprosy vaccine

consisted of a mixture of BCG and killed *M.leprae* bacilli. When the trial was designed a choice was made between using BCG for the control arm (the efficacy of BCG alone against leprosy in Venezuela was unknown) or using a placebo. BCG was chosen even though doing this might reduce the chance of showing a protective effect (as BCG alone may be protective). The inclusion of a placebo arm would have allowed the protective effect of BCG alone to be evaluated but the incidence of leprosy was too small for a third arm in the study. The major purpose of the trial was to evaluate whether a leprosy-specific vaccine (i.e. one which included *M.leprae* bacilli) would be more effective than a non-specific vaccine (for example, BCG). If the comparison had been with a placebo instead of BCG, any effect due to BCG could not have been distinguished from that due to the addition of *M.leprae* bacilli to the vaccine.

The use of a placebo may be very important to derive an unbiased measure of effect (see Section 4.1 and Chapter 7, Section 3), but it requires careful ethical justification. In a placebo-controlled trial of vitamin A supplementation in Ghana, the objective was to determine if a reduction of child mortality was produced by supplementation. As eye signs of vitamin A deficiency are effectively treated by vitamin A supplements, all in the trial were monitored for such signs and withdrawn from the placebo group immediately such signs were detected, even though this was likely to reduce the power of the study to detect an impact of vitamin A supplementation on mortality.

4 ALLOCATION OF INTERVENTIONS

4.1 Randomization and 'blindness'

Once a potential intervention has been shown to be safe and acceptable for use in humans and the dose schedule established, studies should be conducted to evaluate quantitatively the benefit attributable specifically to the intervention under trial compared to some other intervention, having excluded the confounding effect of other variables. The only general way rigorously to exclude the biasing effects of other factors is to base allocation decisions as to which intervention is applied to a particular individual or group on a random mechanism. Incorporation of randomization into the study is a most important design issue (see Chapter 7).

The randomized intervention trial is as close to a rigorously scientific experimental study involving human beings as it is possible to achieve ethically. The main study design features of a randomized trial include the following:

1. To avoid bias in assignment to the alternative interventions all eligible patients are assigned at random to the alternative treatment groups. This involves two steps; the first is selecting participants on the basis of the criteria for eligibility that have been established, and the second is the randomization procedures to ensure that each selected participant has an equal opportunity to receive a particular intervention procedure.
2. To avoid bias in the assessment of the endpoints the person(s) assessing the outcome measures should not know to which intervention group the participant is assigned (i.e. the assessor should be 'blind' to the intervention group).
3. To avoid bias in behaviour of the participant the participant should also be 'blind' (i.e. the intervention group assignment should not be known by the participant).

If neither the assessor nor the participant is aware of the intervention allocations, the study is said to be 'double-blind'. If only the assessors (or, more rarely, only the participants) are aware of the allocations, the study is called 'single-blind'. For situations in which there is no presently useful treatment or preventive method, a placebo of some sort must be used if double-blinding is to be assured. The 'double-blind' approach is the key to the elimination of bias in the assessment of the impact of an intervention and, wherever possible, a 'double-blind' design should be used. Sometimes it is not possible because of the nature of the intervention procedure, but even if the providers of the intervention must know the assignments an independent assessor may be kept 'blinded'. The more clearly defined and objective the outcome to be measured, the less critical it becomes to ensure blinding of the assessor. Similarly, the less likely a patient is to be influenced by knowledge of which treatment is being given, the less important is the blinding.

4.2 Unit of application

The unit to which an intervention is applied may be the individual, the family (household), or the community (environment). The unit for randomization will usually vary in parallel with this. The choice of the unit for application of the intervention depends upon the nature of the intervention, the administrative method for its application, and the purpose for which the intervention is being applied. In statistical terms the most efficient design, in most circumstances, is to use the individual as the unit of application and this should be the design of choice unless there is good reason for household or community (group) application and randomization. There are four general reasons for applying an intervention to a group rather than by individual.

First, group allocation is appropriate when, by its nature, the intervention must be applied on a geographical area or community-wide basis, such as most environmental alterations, many vector control measures, and commonly used approaches to educational interventions.

Second, it may be logistically easier to administer the interventions to individuals in groups rather than on an individual basis. Often it is simpler administratively and/or more acceptable to the people to randomize by household or village rather than by individual. Furthermore, with individual randomization there may be risk of sharing medications within households or villages.

Third, if the purpose of applying the intervention is to reduce transmission of infection, the appropriate unit of application would be the 'transmission zone', i.e., the area in which humans, vectors, and intermediate hosts may be interacting and sharing a common pool of parasites. Factors of importance in defining such zones include the flight range of vectors and the movements of people, vectors, and intermediate hosts. To reduce interchange ('contamination') among transmission zones it may be useful to have intervening buffer zones that are not involved in the study. For many diseases the size of the transmission zones may be difficult to determine and may vary over time.

Some interventions may be applied to individuals but with the expectation that there may be an effect on transmission through applying them to a high proportion of individuals in the community. The extent of coverage required to produce such effects

depends upon the epidemiological circumstances, the presence of other control measures, and the type of intervention procedure being introduced. For example, the use of a malaria vaccine to reduce the transmission of malaria in parts of Africa where the disease is 'holoendemic' may require so near to complete coverage that such a purpose would not be seriously considered. In some areas of south-east Asia, however, where control measures have greatly reduced transmission, the addition of vaccines may be sufficient to eliminate transmission.

For some types of intervention procedures, when the procedure itself provides individual benefit, such as ivermectin in the treatment of onchocerciasis, a further important issue is whether reduction of transmission provides a benefit in addition to the individual reductions of morbidity/mortality. Study designs to demonstrate this additional benefit are likely to be complex.

A fourth reason for applying interventions to a group or community as a unit would be for trials involving an intervention of already proven efficacy in individuals but for which the delivery may be more effectively carried out on a group or community basis. The trial might consist of a comparison of different delivery systems. Generally, the end-result desired in this type of study is based upon cost-effectiveness criteria. The issue under evaluation might be whether it is possible to achieve a greater amount of disease reduction for a given expenditure (or alternatively, a given amount of disease reduction for less expenditure) by use of a community-based distribution system than by the usual methods. Many types of community-based distribution systems require community participation studies. The principles involved in cost-effectiveness studies and community participation studies are beyond the scope of this manual.

When group randomization is adopted, the efficiency of the design can be improved by ensuring that the groups allocated to the different intervention arms are comparable. When there are large numbers of units to be allocated, randomization itself will ensure comparability, but usually when communities or other groups are the units to be randomized, the number of units is quite limited and randomization may leave considerable differences between the groups in the different arms. Attempts can be made in the analysis to allow for these differences, but the persuasiveness of the results may be reduced if the conclusions depend upon

extensive statistical manipulation of the study results. A more efficient approach to increase the comparability of the groups in the different arms is to stratify the groups into 'blocks' having similar underlying, pre-intervention, risks of the disease outcome in question and then to randomize within each block. Stratification should be in terms of variables which are either strongly related to the risk of the outcome under study, or in terms of this risk itself. For example, in studies of malaria in which villages are to be randomized, the villages might be stratified according to their pre-study malaria prevalence or incidence rates, if such information is available, and the randomization done within strata. For studies comparing two interventions villages with similar malaria rates might be paired and one village in each pair randomly allocated to each intervention.

Often, good information on the distribution of the outcome measures will not be available in the study population. In such circumstances baseline studies to obtain the required information should be considered. Sometimes, as an alternative, surrogate measures must be used (i.e. measures which are thought to correlate closely with the outcome measures of principal interest). In the absence of detailed data on the population, geographical proximity and socio-economic level may be used as stratification characteristics. Thus, if a small geographic area is chosen as the randomization unit, the total study area would be divided into regions containing a small number of relatively homogeneous units and, within each region, an equal number of units allocated to each treatment arm. The regions may be limited in size so that the number of units within a region is simply the number of treatment arms (i.e. one unit per treatment arm in each region).

4.3 'Stepped-wedge' design

The issue of the ethics of randomization is presented in acute form in situations where previous studies, perhaps using short-term endpoints or a more intensive intervention than is feasible on a population basis, indicate that the intervention is likely to be beneficial. Withholding the intervention from those in one of the treatment arms for the duration of the trial may then be argued to be unacceptable. An approach that can be adopted in this situation is the phased introduction of the intervention on a group by group

basis, until the entire target population is covered. The order in which the groups are given the intervention is randomized. This approach has been used in The Gambia to evaluate the long-term effects of vaccination against the hepatitis B virus (HBV). The study design is illustrated in Fig. 2.1. This type of design has been called a 'stepped wedge' design (The Gambia Hepatitis Study Group 1987). The power of this approach, compared to a simple allocation of groups to one or other treatment arms, is of the order of 75–80 per cent, depending on the number of groups. The same considerations apply to stratification and blocking as in the static allocation designs.

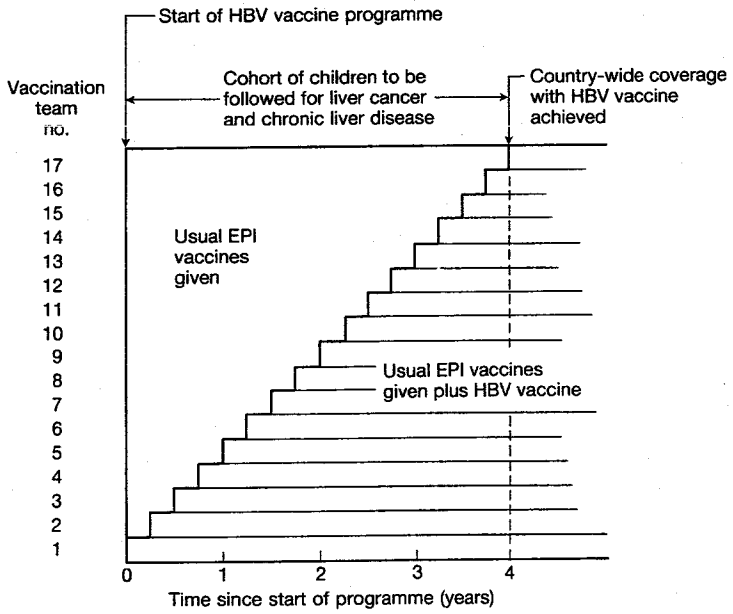

Fig. 2.1 The 'stepped wedge' study design used to evaluate the impact of hepatitis B vaccination on liver cancer rates in The Gambia (The Gambia Hepatitis Study Group 1987). Hepatitis B vaccine was introduced into the routine child vaccination programme over a period of 4 years. The order in which the different vaccination teams (there were 17 at the time of the trial was planned) began to use the vaccine was random. At the end of 4 years there was a cohort of children who had received the vaccine and a cohort who had not. These cohorts will be followed to compare the incidence rates of liver cancer and chronic liver disease.

4.4 Other approaches to allocation

The allocation of interventions to individuals based on a random mechanism is the only general approach to rigorously exclude the potential biasing effects of other factors. Reports are not uncommon in which the allocation of alternative interventions in a trial has not been randomized. A common approach is to compare the incidence or prevalence of the disease under study before and after the intervention has been applied and to attribute any difference to the effect of the intervention. This approach has little to commend it as it may be very misleading to assume that in the absence of the intervention the disease rate would have remained the same. Many diseases, and especially those of parasitic or infectious origin, vary greatly in incidence and severity from year to year and place to place, for reasons that are incompletely understood. Certainly variations in climate (for example, temperature and rainfall) can have profound effects. Some diseases show marked declines over time in some communities (for example, tuberculosis) which cannot be related to any obvious specific factor. 'Before and after' evaluations of interventions in such situations may be very misleading.

Another commonly employed approach is to apply an intervention in one community and not in another and to attribute any difference in disease rates between the two communities as being due to the intervention. This also may be very misleading for reasons similar to those outlined above.

The main reason often advanced for using a non-random allocation between intervention groups is for simplicity of design and administrative ease. Approaches like these also seem easier to explain to officials and to gain public acceptance. The rationale for randomization is difficult to communicate, even to other scientists, but the arguments in favour of randomization, as outlined above, are extremely strong, and failure to accept this approach has frequently led to studies from which erroneous conclusions have been drawn.

There are, however, situations in which allocation cannot be made on a randomized basis. There are occasions when the benefits of an intervention appear so clear that a properly randomized trial cannot be contemplated. The value of the intervention then has to be assessed by comparison of the situation

before and after its introduction, or by the use of case-control studies after the intervention has been introduced (Smith 1987). Temporal comparison is clearly confounded with whatever trends in disease rates that are occurring in the population independently of the specific intervention, and with changes in the pattern of ascertainment of the outcome, a likely concomitant of the intervention introduction. Conclusions can be sharpened by comparison with time trends in disease rates in neighbouring regions where intervention has not occurred, and also by consideration of the sharpness with which changes in disease rates take place and related to the speed with which the intervention is introduced over the entire population. Knowing and recording possible confounding variables in the areas being compared may also be useful. For example, in a study in which an objective is to reduce transmission of lymphatic filariasis by treating the human population with antifilarial drugs, monitoring the vector population for changes in density and infectivity may be useful.

While acknowledging these exceptions to use of randomization as the basis of allocation, such studies cannot achieve the rigour of a randomized design and any conclusions drawn from such studies must be viewed with some caution.

5 CHOICE OF OUTCOME MEASURES

For many interventions there will be a range of outcomes that could be affected and which might be of interest to study. Nutritional supplements, for example, might effect any or all of the following:

(1) biochemical measures;
(2) short term acute consequences of deficiency;
(3) the consequences of chronic deficiency;
(4) mortality ascribed to the conditions which the intervention is intended to rectify; and
(5) total mortality.

In determining which outcome is of the greatest importance for the study, consideration must be given to:

(1) whether the outcome is of public health significance;

(2) whether the probable effect on that outcome is large enough to be of interest; and

(3) whether it can be accurately recorded.

Total mortality and age-specific mortality rates are of basic public health importance, and systems can usually be set up to ensure that they are well recorded (sometimes requiring considerable input), but they are unlikely to be sufficiently affected by many interventions to enable effects to be detected with studies of manageable size. Mortality from specific causes should be more greatly affected, but may be much more difficult to ascertain accurately. Using total mortality clearly dilutes the effect that might be seen if specific causes were examined, since the random variation in rates arising from the unaffected causes is included. The choice may have to be made between setting up special mechanisms to improve the quality of the information on cause of death, or to allow for a dilution of the observed effect by increasing the size of the study. It should be stressed that for conditions that are life threatening, mortality is a most important outcome to evaluate.

Short-term outcomes are clearly attractive in that if used as the outcome on which the design is based, then the study size will be smaller and the duration shorter than if mortality were to be used. The danger is that the short-term measure may in itself be of no consequence to health and the effect of the intervention on that outcome may not correlate well with the effect on more serious conditions. There is, for example, little point in measuring an antibody response to infection if it bears no relation to the risk of disease. Conversely, however, if it is known that a short-term outcome is highly correlated with an outcome of greater public health consequence (and is effectively a surrogate measure of the more important outcome) it is generally highly efficient to focus most studies on the former outcome.

In most circumstances, the appropriate outcome for determining the duration and size of the trial would be the most serious consequence of the specific condition at which the intervention is aimed. For measles vaccination in technically advanced countries, the onset of the disease would be the natural end-point, rather than death from the disease, and certainly not total mortality. In contrast, for countries where mortality from measles is high, death

from measles might well be the outcome of choice. If mechanisms for establishing accurate diagnosis were inadequate, total mortality might even be considered (especially as measles vaccine may reduce the risk of death attributable to diseases other than measles).

With this perspective, short-term 'intermediate' outcomes should not be discarded but included as valuable monitoring mechanisms. They provide information as to whether the programme is on target to meet its more basic goals, and if it is not on target, should help to identify what remedial action is required. When short-term outcomes are used in this way, any assumptions about the natural history of the disease should be clearly stated.

Definition of the main outcome will have consequences for the duration of the trial. Prior information should be available on the time needed for the intervention to affect the outcome. In some situations, such as the prevention of liver cancer in adult life by hepatitis B vaccination in the first year of life, the final outcome measure may not be observed for several decades. The role of intermediate outcomes then becomes important.

A final and important point to stress in this section is that it is essential that attention is given to monitoring the severity and frequency of adverse effects of an intervention. In their desire to assess the effectiveness of an intervention, investigators often do not pay sufficient attention to finding and documenting adverse effects, which may require additional effort and resources. In most situations, the future applicability of the conclusions drawn from a study will involve an assessment of the balance between positive and negative effects.

6 STUDY POPULATION

6.1 Criteria for selection of trial population

The criteria for selection of the population to be included in the trial depend 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 endemicity for the condition of interest. The higher the incidence of the disease of interest, in general, the smaller the study population for the trial has to be. Sometimes, however, the purpose of

the trial is to determine the efficacy under special epidemiological circumstances or in special population groups, such as pregnant women. Good community and governmental co-operation and participation are also key factors in the successful conduct of a trial. The study 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, and other appropriate disciplinary expertise should be available. Planning the trial will be much simplified if baseline data are already available in an area.

If the study 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 study in which substantial migration into, or especially from, the area is unlikely to occur. Migration rates in excess of ten per cent a year are not uncommon in many rural areas and may be considerably higher in some areas and in urban or peri-urban settings. It is often not easy to ascertain migration rates during the planning of a study. A rapid survey of a sample of the proposed study population may be useful to determine if a reasonable proportion of the population have been resident in the area for several years.

6.2 Inclusion and exclusion criteria

In general, the trial population should be chosen to represent the group that will be the target for the intervention in a public health programme. 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 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 a trial. For example, because the major morbidity and mortality associated with malaria in a holoendemic area is 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 adults and older children 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 or volunteers may form the study 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 may 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 study 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 they are unlikely to derive benefit from the intervention or because they might be considered more likely to be susceptible to possible adverse effects of the intervention. Ascertaining pregnancy is difficult, without specific testing, and in some trials it may not be feasible to detect women in the early stages of pregnancy. 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 women may receive from the intervention and it may be appropriate to include them in later trials with careful monitoring of pregnancy outcomes.

6.3 Size

Strict attention needs to be given to the required size of the study, 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 3. It is important to allow for the loss of power that results from group randomization if such a design is adopted (see Chapter 3, Section 6).

For interventions that are likely to be given to large numbers of individuals if they are introduced into disease control programmes, there are strong arguments in favour of designing trials of the interventions to be large also, 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 an intervention study will be based on the comparison of the outcome measures adopted for the trial between those allocated to the alternative intervention arms of the study. 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 appropriate 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 study, 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 and, where 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 for chemoprophylaxis agents and nutritional supplements. For intervention measures that are given sequentially over time, or on a continuing ongoing basis, repeated spot samples should be taken.

A further aspect of compliance which is sometimes overlooked is that those in the 'control' arm of a trial, who are allocated to routine care may adopt the active treatment under study. For example, if those in some villages are allocated to receive an intervention and those in other villages serve as controls, those in

the latter villages may go to the former villages to obtain the intervention. Monitoring for the possible occurrence of this latter form of non-compliance (sometimes called 'contamination') is of importance. Care should also be taken in the construction of the different treatment groups to minimize the opportunity for such contamination. For example, if the intervention consists of a vaccine, given by peripatetic vaccination teams, clear geographical separation of those in the different arms of this study would be one means to help prevent crossing-over.

7 IMPLEMENTATION

7.1 Community acceptance

Critical to the conduct of a successful intervention study is that the study population co-operates well during the conduct of the trial and accepts the intervention offered. They must feel a part of the trial and perceive it to be for their benefit. To ensure these aspects will require careful planning and investigation before the trial starts, including appropriate discussion with, and explanation to, community leaders and the potential participants themselves. Feedback and interaction should be continued throughout the course of the study. These aspects are discussed in several chapters and form the foci of Chapter 4 (on ethical considerations), Chapter 5 (on community involvement), and part of Chapter 10 (on social research methods).

7.2 Staff recruitment and training

The dedication and commitment of the staff employed to conduct a field research project is essential. This will involve their careful selection, training, and encouragement. They must understand the importance of their role in the study and how it relates to that of others. The importance of high-quality work must be emphasized and this must be monitored throughout the study (see Section 9 and Chapters 11 and 12).

7.3 Field organization

All aspects of field procedures should be planned in advance and

potential problems and solutions anticipated (for example, actions in case of staff sickness, vehicle or computer failure). The study design must reflect not only what should be done, but also what can be done given the constraints under which the study must be conducted. These aspects are considered in detail in Chapter 11 and Chapter 12. Issues relating to mapping and conducting a census of the study area are covered in Chapter 6.

8 DATA HANDLING

8.1 Data collection

A necessary part of any trial will be the collection of certain items of basic data on all participants. These will include identification information, such as name, age, sex, place of residence, and information on other factors that may influence the risk of occurrence of the outcome measures under study in the trial. Further data will be collected during the course of the trial to monitor the application of the interventions and to record information on the outcomes of interest. The conduct of a population census is described in Chapter 6 and methods to obtain information by questionnaire at the start of a trial or during its course are described in Chapter 9. Methods for obtaining data through anthropological and sociological survey methods are outlined in Chapter 10. Of crucial importance in any trial is the proper measurement of the incidence of endpoints against which the intervention is designed to protect and these aspects are discussed in Chapter 8.

8.2 Data processing

Methods of coding and computer processing of data collected in a trial are described in Chapters 9 and 13.

9 QUALITY CONTROL

In most intervention studies members of the population are invited to participate, the intervention is applied, perhaps repeatedly, and the population is kept under surveillance until the final outcomes are recorded. The quality of each step in this process must be

carefully monitored. The two major reasons, which hardly need stating, are first to ensure that each operation is being performed to an acceptable standard, and second to identify areas where attention is required. A third reason is to be able to ascertain, at the end of a study which failed to show anticipated effects, the possible reasons for failure. The damage done by a misleading negative result can be serious and widespread. The following are major aspects of quality control that need attention.

9.1 The intervention

Regular monitoring of the delivery of the intervention should be an integral part of the design to ensure that there is no slippage in the quality as a trial goes on. For example, in a vaccination trial continual review would be needed of the quality of the vaccination techniques being used by field workers. The quality of the agents used in the intervention needs checking. For example, the potency of each batch of vaccine used should be assayed, together with monitoring of the maintenance of the cold chain.

Short-term endpoints may be used as monitoring assays at this stage in a trial. At the individual level, repeated surveys of physiological measures of response to the intervention will provide an overall assessment of whether an effective intervention agent has been effectively delivered. Examples would be antibody levels against a vaccine, or levels of a micronutrient in serum. Such evaluations may have to be done or be evaluated by an independent monitor for the trial, to ensure that those who will assess the main endpoints in the trial are kept blind to the identity of those in intervention and control groups.

9.2 Follow-up

For many intervention studies, the endpoints of interest may not emerge for a lengthy period after the start of the intervention. It may not be necessary to keep the entire study population under active observation, and this is often not feasible (for example, cases might be detected as they report to clinics rather than by conducting periodic surveys of the study population), but it is essential that the study is designed in such a way that losses to the study population (for example, cases who do not go to clinics) will

not distort the conclusions. The follow-up rate should be monitored closely in order to identify potential problems at an early stage (for example, disgruntlement in a particular village, a field-worker whose work quality is declining). If possible the reasons that individuals are lost to follow-up should be ascertained and this information should be analysed to assess any effect that the losses might have on the interpretation of the results of the study.

9.3 Assessment of study outcomes

Mechanisms have to be established to ensure that the quality of information on the outcomes is acceptable. This requirement may well affect the choice of outcome to be used in the main evaluation. Ongoing monitoring is required to establish that the data on outcomes are maintaining acceptable quality and that no biases are present in the way outcomes are recorded in different treatment arms. Attention needs to be paid to inter-observer variation in the assessment of the outcomes, and changes that may occur in this variation as the study progresses.

9.4 Other field and laboratory procedures

Quality control should pervade all field activities and the question as to how high quality is to be achieved and maintained should be addressed specifically for all activities. This is discussed in most of the chapters that follow.

Laboratory procedures must be subject to constant scrutiny and 'blind' coded duplicate samples should be introduced into the workload regularly to monitor performance.

In interview surveys a proportion of respondents should be re-interviewed by a second interviewer, blind to the results of the first interviewer, to check on the repeatability of the responses.

It is important that all involved in the study accept and understand the need for constant checking and re-checking. Errors are bound to occur and their detection should not result in a reprimand unless there is evidence of dishonesty or continual carelessness. Incentives or rewards to encourage high-quality work may be worthwhile.

All members of the field team are, and must be made to feel, important contributors to the research project. Feedback of results

and progress should be continuous so that they can appreciate where their contribution fits into the overall project. Neglect is a great stimulus to poor quality work.

10 ANALYSIS AND REPORTING

10.1 Planning the main analyses

The main analyses that are expected to result from the trial should be developed in some detail with the use of dummy tables. Such an exercise is a great help in clarifying exactly what data are actually needed and provides a useful guide for planning the study. All specific objectives should be tied to the analyses.

10.2 Ongoing analyses

Analysing the results of a trial as data accumulate is an important way of monitoring the satisfactory progress of a study. Administrative analyses of the numbers of participants recruited each day or week and of the data collected by different field workers are important for quality control. A running tally should be kept of the numbers of subjects experiencing the different endpoints of interest to verify that the estimates of incidence rates used to plan the size of the trial were appropriate. Ideally, the investigators will be blind with respect to which interventions have been allocated to which participants, but differences in these respects between the different interventions might be analysed by a data monitoring committee (as discussed in the next section). Other aspects of ongoing analyses are reviewed in Chapter 13.

Interim reports based on ongoing analyses during the course of a trial may be required by national authorities and by the funding agency supporting the conduct of the study. These may be required to check that the original proposal is being adhered to.

10.3 Data monitoring committee

For large trials it is advisable for the investigators to set up an independent data monitoring committee. Such a committee may serve several functions.

The most important function might be to hold the randomization code for the study and to monitor the results of the trial as they accumulate. If there is evidence of a substantial risk of adverse reactions associated with any of the interventions under study, the committee would have the power to stop further recruitment. Similarly, if evidence accumulates that one intervention is substantially better than the others (or one is substantially worse), the committee would recommend that the study be ended. The advantage of these functions being undertaken by an independent committee is that it means that the investigators are kept blind to the randomization codes, which is an important way of ensuring unbiased assessment of the study endpoints. The circumstances in which a study will be prematurely ended should be carefully considered when the study is being designed and the data monitoring committee should be party to such discussions. It will not be possible to predict all possible situations that may cause a decision to be taken to end a study, but this should be done to the extent possible. In particular, there should be consideration as to how large a difference may be apparent between the interventions with respect to their impact on specific endpoints, before it is decided to end the study. In some circumstances it may be important to go on beyond the point where statistical significance is reached. These issues are discussed in Chapter 3, and there are also ethical considerations which are discussed in Chapter 4.

The committee might also set up independent quality control checks on study procedures and, for example, may arrange to review the diagnoses of all cases of the diseases of interest arising in the study (which should be done, of course, 'blind' to knowledge of the randomization codes).

In some trials the data monitoring committee may consist of one person, sometimes called the 'clinical monitor'.

10.4 Analysis methods

The analysis of a large field trial may be a complex undertaking and may well require the services of a professional statistician. It is not feasible in a manual of this kind to detail all of the analysis methods that it might be appropriate to employ in different trials. In Chapter 14 an outline is given of the main methods of analysis that are likely to be employed. It is included as it summarizes

relevant methods that are not covered as comprehensively in most basic epidemiological texts or books on medical statistics.

10.5 Reporting results

Once a field trial has been completed and the results analysed it is essential that the results, and their implications, are made available to the scientific community, to those who participated in the study and to those responsible for designing and implementing regional and national disease control strategies. Some remarks on these aspects are made in Chapter 15.

REFERENCES

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