6.3: Special issues in field trials in low- and middle-income countries

Trials of an intervention should be undertaken only when there is uncertainty about the balance of potential benefit and potential harm, with respect to the intervention. The assessment of the extent of such uncertainty will be a critical factor in deciding whether or not it is justifiable to conduct a trial. If one trial provides good evidence of a beneficial effect, further trials of the same agent or procedure, even under very different epidemiological circumstances, will be more difficult to justify than if the first trial had not been conducted. Only if there are good reasons to believe that the results might be different under these different circumstances would further trials be indicated, and indeed a case could be made that it would be unethical not to conduct a further trial in such circumstances.

In communities which are poor and deprived and whose inhabitants may be at substantial risk of premature death and serious disease from many causes, the balance between the potential benefits of an intervention and the risk of harm may be different from that which might apply in a more privileged community. For example, a higher level of vaccine-related adverse effects might be acceptable in a trial of a vaccine against a disease that was responsible for many deaths and considerable disability in a community than would be acceptable in a study in a community in which the disease was rarely fatal and rarely caused severe disability.

In general, it is easier to persuade those who are sick than those who are well to participate in a medical research investigation. Field trials of preventive measures often involve those in the latter category and, unlike most clinical trials, take place in the community, rather than in a clinic or hospital. The task of obtaining consent for the conduct of a study in such a setting involves some special issues discussed in Section 3.1.

3.1 Obtaining communal and individual consent

In communities in many LMICs, decisions about participation in a particular project may be taken initially at a communal level. The permission of community leaders needs to be sought for a research investigation to take place in their
community. Only once such approval has been granted is it appropriate to seek approval at a household, and then an individual, level. Thus, permission to conduct a research project may be obtained first through trusted and respected community leaders, rather than through individual community members or through the heads of households. Although such procedures may seem strange and be unnecessary in many HICs and might even be regarded as challenging the right of an individual to make autonomous decisions, they are part of the cultural norm in many other societies.

In a clinical trial conducted in a hospital or clinic setting, the investigator may be able to take considerable time to explain the nature of the trial to each participant, as usually the total number of subjects in a study is relatively small. Field trials of some interventions (for example, vaccines) may be large, sometimes involving thousands, or even tens of thousands of participants, and it is more challenging to explain the trial in detail to all participants. Some of the potential methods for informing potential participants about the study have been outlined in Section 2.4. It is important to note that obtaining ‘communal consent’ does not dispense with the need to also seek and gain individual informed consent. However, those from whom communal consent is sought should be able to represent properly the participants and to protect their interests. In reality, judgements about whether or not to participate in a research investigation depend greatly on the level of trust that investigators enjoy in a community. If a participant trusts an investigator to protect their interests, then they are more likely to agree to take part in the research. Participants will generally expect community leaders to protect their interests also and thus the importance of communal consent, as well as individual consent.

Before a community is approached regarding the possible participation of members of the community in a trial, it will usually be necessary to seek permission from the relevant local health authority, including those responsible for the medical care of the population. Subsequently, the initial approach to a community is likely to be best made to those recognized as leaders in the community. Generally, field trials are likely to be carried out by, or in direct co-operation with, the Ministry of Health and local health authorities. In such circumstances, it will usually be appropriate for discussions with community leaders to be initiated by such authorities, or at least to include their active participation. The extent of such discussions, and precisely who within a community should be involved, depends on the nature of the intervention that is to be studied. Most communities are heterogeneous, and sometimes there are factions within a community that have their own leaders whose co-operation must be sought. The people may not recognize those who are considered as the ‘official’ leaders, and others must be brought into discussions. Public notices and public meetings may also be useful.

It must be re-emphasized that obtaining communal consent for a study does not relieve investigators of their responsibility to explain the study procedures and the potential risks and benefits to those individuals who are being invited to participate, and those individuals must also be informed and be aware that they are free to refuse to participate or to withdraw from the investigation at any time without penalty of any kind.

It is also important to stress that consent to participate in a research investigation is not a one-off event in which the ethical requirements are satisfied, for example, once a signature is appended to the informed consent document. Consent to participate in a trial requires an ongoing dialogue between investigators and participants from the start of a trial through to its end. Investigators must take pains to keep participants informed of the progress of a trial, unexpected developments, and other findings, possibly from parallel studies that may impact on the trial.
3.2 Potential benefit and the risk of harm

The simple Hippocratic caveat ‘do no harm’ is not a sufficient guide to ethical decisions concerning trials of interventions. The introduction of a new intervention requires the demonstration of benefit. Furthermore, since almost any intervention procedure involves some risk of harm, albeit usually small, it is necessary to assess in intervention trials the balance of benefits against risks. In general, ethical review committees are disinclined to approve studies in which healthy persons will be exposed to more than very small risks in the context of a research investigation. Thus, it may be unacceptable to carry out a trial using a vaccine associated with serious side effects, even if it offers protection against a disease that is more serious than the side effects. For example, if one person dies as a result of vaccination for every ten persons who are saved from dying, it is unlikely that such a product would be used, even though the ‘public health’ balance appears to be in favour of the vaccine. More weight is given to harm that results from a deliberate medical intervention than is given to the harm done by the ‘natural’ disease against which the intervention protects. Furthermore, legal concerns of litigation may sometimes be given greater weight than would seem appropriate from a strictly public health viewpoint.

A proposed research investigation should be viewed within the context of the overall problems facing the community in which it is to be conducted. The community should have a reasonable expectation of benefiting from the research in both the short and long term. The effects of the conduct of a field trial in a community may be immediate and evident or may be quite subtle. Even the mere presence of the research workers in a community may have side effects (for example, increased cash flow, availability of transport to other centres), and the impact of such effects should be considered in planning the research.

The possibility of long-term harm must be considered, even if there are short-term benefits.

3.3 Incentives

In some circumstances, it may be reasonable to provide direct incentives as an encouragement to participation in a research project. If this is done, it must be recognized that there may be a fine line between compensating individuals for time and income lost as a result of participation in the study and ‘bribing’ subjects to take part. It may be considered reasonable to give a small snack after a blood sample has been taken, or to repay bus or taxi fares to participants who travel to a research centre, or to give simple medications for minor ailments, but monetary payments to encourage individuals to participate in a trial that are greater than the wages they forego or the expenses they incurred will usually be viewed as a form of undue inducement. It is difficult to lay down any absolute rules as to what is acceptable, and it is necessary to review each situation on its merits in the local context. The level of compensation to be offered will generally be considered carefully by the local ERC, whose concern will be that the level proposed does not constitute undue inducement for individuals to participate in the research.

3.4 Standard of care

There are two aspects of standard of care that have been much debated in the context of trials in LMICs. The first is with respect to the choice of the control intervention against which the effects of some new intervention is to be compared. This is discussed in Section 3.5. The second is the standard of medical and other care offered to all the participants in a
trial. When a trial is conducted in a poor community, the resources available for the trial (including additional medical personnel) may enable the standard of medical care to trial participants to be greatly improved over what would be available in the absence of the trial. Some such improvements may be essential for the scientific purposes of the trial such as improving the diagnostic facilities for detection of the disease that is the primary focus of the trial. However, the extent to which the general medical care provided to trial participants should be enhanced will need to be carefully considered in the context of each specific trial. Introducing improvements that cannot be sustained beyond the duration of the trial may, in the long run, be damaging to local communities or provoke unrealistic expectations of the local medical services. To the extent possible, improvements implemented during a trial should be designed so that they can be maintained with the resources available to the local medical service after the trial. This may involve specific training of local staff, introducing improvements in the routine medical records system, rather than setting up a parallel system, or ensuring a regular supply of drugs and other treatments that could be maintained by the local medical service after the trial. Inevitably, however, there will be some enhancements that are introduced that may be difficult to maintain after the trial. The aim should be that these are not disproportionate. In general, the provision of health care for a community is the responsibility of the national or local health services, and the research should neither usurp nor undermine existing services. It is essential therefore that the organizers of a field trial develop and maintain close links with those responsible for the normal provision of health care. Discussion of these aspects is an essential component of the submission for permission to conduct the trial to the local ethics committee.

3.5 Choice of ‘control’ interventions

The Declaration of Helsinki states that ‘the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention’. Using this principle, comparison with a placebo is acceptable only if there is no convincing evidence that any intervention is effective. This principle of comparing a new intervention with the best current proven intervention seems reasonable at first sight, but it has given rise to much controversy. The controversy has centred on global ‘best’ interventions that are neither currently available nor likely to become available to the population in which the trial is being conducted, either because of their cost or because of the feasibility of implementing the intervention (for example, radiotherapy for conditions in countries in which there is little or no provision for such treatment). The ‘purists’ hold that, if the global ‘best’ intervention is not included as the control arm, then the trial is unethical and should not be conducted. The pragmatists, who often have experience of conducting trials in LMICs, hold that this position is itself ‘unethical’, as it prevents research investigations that may lead to important public health benefits in deprived populations. There is no space to expand on these arguments in detail here, but the issue is discussed at some length in other publications (for example, Council for International Organizations of Medical Sciences, 2009; Nuffield Council on Bioethics, 2002; Rid et al., 2014). The view of the pragmatists, including ourselves, is that, if an effective intervention is known, but its cost is beyond that which would make it feasible to introduce it into the local health care system (and there is little prospect that the cost can be reduced by means such as shifting production of pharmaceuticals to generic manufacturers), then it may well be acceptable to exclude it from consideration as a possible comparison intervention in a trial. In some circumstances, it may be acceptable to try to test a new intervention that might be, at best, equivalent to an existing intervention or may even be inferior to it if, for example, it is cheaper or simpler to apply, or more stable, or associated with fewer adverse reactions, or is more acceptable to the community than the existing intervention. In such circumstances, the purpose of the trial might be to show that the efficacy of the intervention was ‘equally good or not much worse than’ the existing intervention.
3.6 Choosing the primary endpoint

The choice of the primary endpoint for a trial, which will usually determine the necessary minimum size and duration of the trial, will generally depend on scientific, rather than ethical, considerations. Generally, the most important endpoints, in terms of assessing the impact of an intervention, will be in the reduction of severe disease or death. However, in a trial with either of these as the primary endpoint, there may be less severe outcomes, which occur with greater frequency than the severe forms of disease. The benefits of the intervention against these, often chosen as secondary, endpoints may become apparent, before sufficient cases of the more severe primary trial outcome have accumulated to reliably assess the impact of the intervention on the primary outcome. For example, in a trial of a vaccine to measure the impact of the vaccine on the incidence of severe malaria (primary trial outcome), the impact on milder malaria (secondary trial outcome) may be apparent much sooner than the impact on severe disease. Having demonstrated impact on the secondary trial outcome, some may argue that it is unethical to continue the trial, because there is no longer ‘equipoise’ between the effects of the control and the new intervention. There is no simple answer to such debates, but it is very important that careful consideration is given to such possibilities at the time the trial is designed, so that a clear decision can be taken at that stage, rather than being taken ‘on the hoof ’ when the situation emerges. Sometimes, this may result in some secondary outcomes not being measured so as to avoid the potential problem! Alternatively, the decision may be taken not to break the allocation code for secondary trial outcomes until the end of the trial, or the interim results may be made available only to the DSMC, and not to the trial investigators. Alternatively, the prior decision may be taken to continue the trial until the numbers necessary to satisfy the primary trial outcome have been achieved, because of the public health importance of knowing the impact on severe disease or death. These aspects should be clearly presented to the relevant ethics committees when they consider the trial. Also relevant is what feedback will be given to trial participants of results that become available during the conduct of the trial, so that they can assess whether or not they wish to withdraw from the trial.

3.7 Duration and size of a trial

In field trials, it may be necessary to establish the efficacy of the intervention not only in the population as a whole, but also in special subgroups. This may involve the measurement of efficacy in persons of certain ages or for persons with underlying or associated conditions such as malnutrition. It will also be necessary to determine the duration of efficacy and to have a reasonably precise estimate of the degree of efficacy.

It may be argued therefore that the appropriate point at which to stop a trial should be when sufficient evidence has been collected to support, or reject, the introduction of the intervention by the health services generally, rather than at the point when the difference in response in intervention and control groups is first established beyond reasonable doubt. For many interventions, it is important to establish both the degree and the duration of protection. Thus, a trial might be continued beyond the point at which protection is first established to determine if there is long-lasting protection. For example, it may be established in the first 6 months of a malaria vaccine trial that the vaccine is protective, but, to be of public health value, it may be necessary to demonstrate that long-lasting protection is achieved. This may necessitate continuing the trial for at least 2 or 3 years with the maintenance for this period of an unvaccinated group or of a group whose members had received an inferior vaccine. In some circumstances, this will be considered acceptable, but, in others, it will not. Again, each situation must be considered on its own merits, and much will depend on how far the investigators extend their horizon of responsibility, with respect to the public health use of the...
Often, the most important outcome in a trial may not be observed until a considerable time after the intervention has been applied, but there may be intermediate outcomes against which the intervention is also assessed. For example, a vaccine may produce a good antibody response long before any protection against disease is shown. Demonstration of efficacy against the intermediate outcome (antibody response) might be considered grounds for ending a trial if it is reasonable to assume that the effect observed on the intermediate outcome would necessarily carry over to the more distant trial outcome (protection against disease), even though efficacy against that outcome had not been formally demonstrated. What is ‘reasonable to assume’ is often a matter of considerable debate, and the ethics of continuing a trial, once protection against intermediate endpoints has been established, must be argued in the particular circumstances surrounding a trial. Immunological measures which are thought to correlate with protection against clinical disease may not do so. For example, in one trial in which this aspect was examined, the protection that BCG conferred against TB did not correlate well with the induction by the vaccine of sensitivity to a tuberculin skin test (D’Arcy Hart et al., 1967), even though it was possible to put forward plausible immunological arguments for believing that such a correlation should exist.

An example of the ethical difficulties that may arise is provided by trials of malaria vaccines. Early treatment with appropriate anti-malarials is normally curative for falciparum malaria, and, in a trial, it would be unethical to withhold such treatment from those with clinical malaria. Yet the main purpose of such a vaccine is the prevention of death from malaria, not of infection, nor even the prevention of minor malaria illness. Indeed, it is conceivable that there may not be a good correlation between the protection of a vaccine against the last two outcomes and the protection against death as the outcome. The dilemma is that, in most of Africa where malaria continues to kill hundreds of thousands of children annually, medical services are not adequate to provide the level of curative care that would be provided in a trial, nor are they likely to be so in the near future. Because malaria is a treatable disease and effective treatment should be made available to all those who are diagnosed with malaria during a trial, it is likely that mortality from malaria in a trial would be at a very low level—too low to allow this to be a primary outcome in a reasonably sized trial—and therefore the primary outcome may have to be either clinical malaria or severe disease (which may also be at a lower level, because of the treatment and care provided in the context of the trial). The assumption would have to be made that any efficacy demonstrated against clinical malaria and/or against severe disease would be likely to carry over into the prevention of malaria mortality. It may not be possible to address the impact on mortality until the vaccine is in public health use, and assessment might be made through specially set-up surveillance or Phase IV studies (see Chapter 22). Such studies may be set up to be very large, such that it would only be realistic to leave the treatment of cases of malaria to the existing system of medical care.

There are very strong reasons for conducting early trials of a new intervention to assess the impact of the intervention against the outcomes which are of greatest public health importance, rather than starting with trials against intermediate outcomes, if, by studying intermediate outcomes, further trials against more important outcomes may be compromised. Sometimes, knowledge from other studies may be sufficient to be confident that, if effects are demonstrated against intermediate outcomes, then impacts on more important outcomes will necessarily follow, but all too often, such an assumption is not warranted.

There are strong reasons for conducting very large trials of interventions that are likely to be used on large numbers of people in the future if the interventions are effective, much larger than would initially seem necessary to achieve only a statistically significant difference in outcome. The results of very large trials, if the trials have been adequately managed,
can be much more convincing and are more likely to lead to the implementation of the intervention in disease control programmes than are the results of small trials.

Again, part of the dilemma relates to where the investigator places the horizon of responsibility. If the view is taken that the investigator, by taking on the responsibility of a field study, also takes on responsibility to provide full medical care of the subjects under study, then a study of a malaria vaccine with prevention of death as the endpoint could not be undertaken. If the view is taken that the horizon of responsibility extends to all those who are at risk of dying from malaria, including those who would not be included in the trial but who may benefit eventually from the vaccine, then a trial might be conducted with death as an endpoint, but the design of such a trial would be challenging!

### 3.8 Monitoring safety during a trial

All clinical studies require safety monitoring throughout the duration of the trial and, in some cases, for a defined period after the completion of the study. Investigators are responsible for the detection and reporting of adverse events or serious adverse events and to the sponsor, the ethics committee, and regulatory authorities, according to the time period and procedures specified in the protocol (see Chapters 7 and 12).

The ethics committee should review a study when serious and unexpected adverse events related to the conduct of a study or study product are reported, as the events may affect the benefit/risk balance of the study. Refer to the *International conference on harmonisation guideline for clinical safety data management: definitions and stand- ards for expedited reporting* for more detail (<www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf>).

### 3.9 Special ethical issues in cluster randomized trials

In addition to ethical issues common to all randomized trials, additional ethical con- cerns can arise in cluster or group randomized trials (Edwards et al., 1999).

Most ethical issues specific to cluster trials are related to: (1) the legitimacy of in- formed consent when sought at group level, (2) the potential conflicts between indi- vidual autonomy vs group consent, and (3) the differential benefit that one cluster may have over another in some trials.

Most of the issues concerning informed consent in cluster randomized trials are discussed in Section 3.1. These include the identification of different levels at which consent can, or should be, sought and who has the legitimacy to determine whether researchers may approach groups or communities.

A potential issue in cluster randomized trials is when the request for individual con- sent is obtained after randomization and allocation of the cluster to the intervention or control arm of the trial. This should not cause an ethical concern per se, but it could lead to bias in the nature of the consent in the different intervention groups and thus be of scientific concern.
3.10 Reporting and feedback of results

At the completion of an investigation, there is a responsibility to inform the community in which a trial has been conducted of the results of the study in such a way that its members can understand the implications of the findings. Indeed, such feedback should be ongoing, as the research progresses. Not only is it important ethically that participants should be kept informed of the progress of the research, but, if this is done, it is also likely to encourage their continued participation. The procedures to ensure this feedback takes place should be planned from the start of an investigation.

There is also a responsibility to feed back the results of the research to the relevant local or national health services and disease control programmes, so that these groups can assess the implications of the findings for their own activities.

These issues are discussed in greater detail in Chapter 23.

The anonymity of participants in a trial should always be respected, and there should be no danger that any of them will be identified through any publication of the results of a trial. The same rights of confidentiality should be considered for communities, as well as for individuals. It will sometimes be appropriate to keep the identity of the community anonymous, particularly if sensitive issues are discussed, such as hygiene practices or sexual or other practices that are sometimes condemned by other cultures (such as female genital cutting, infanticide, or anal sex). Sometimes, it is not possible to disguise a particular location, and, in some circumstances, it may be important that the community be identified to aid interpretation of the study results. Indeed, communities are sometimes proud to be associated with a particular research programme, and the name of the community or place may be used as the title of the project (for example, the Garki malaria project (Molineaux and Gramiccia, 1980)).

3.11 What happens after the trial?

The closure of a trial presents special challenges, especially when the intervention group receives significant improvements in the quality of care, while the control group receives usual care, which, in many LMICs, will be suboptimal care or even no care. The challenges are even greater when the intervention has been shown to be successful. Should the benefits of the intervention be sustained in the study group and, if so, how and with whose resources? Should the intervention be extended to the control group (at the minimum), and possibly to the whole community in which the trial was conducted? If yes, how and with whose resources? These are often difficult questions and should be addressed from the inception of the trial, and the implications included in any discussions with the trial funder and trial sponsor. How they are tackled will depend on the setting, the nature of the intervention, the strength of the health system, and the availability of other partners working the study area. If the intervention can be mainstreamed into the health or other services of the community, this should be explored with the relevant decision makers. If, for example, the intervention concerns children and there is a United Nations Children's Fund (UNICEF) programme in the area that can help to extend it to the communities, these alliances should be established. If there is an opportunity for the local health administration to apply for a local, regional, or international grant to help extend the intervention, the trial team should help with preparing this grant. If the trial team plans to take responsibility for extending the intervention, appropriate funding and timelines should be reflected in the project plan and budget.
3.12 Special ethical issues in Phase IV (post-licensure) studies

Phase IV studies with drugs and vaccines are needed to evaluate effectiveness, long-term safety, and potential drug interactions. For safety surveillance, or pharmacovigilance, a system should be in place for collecting, monitoring, and evaluating information from health care providers and patients on AEs that may be associated with medications and biological products. These issues are discussed in greater detail in Chapter 22.

Ethical concerns, as well as quality of data, should be carefully examined in relation to the physician’s relationship with the sponsors, marketing of products, incentives, and biased observations. Special informed consent is not always needed when the intervention under study is already part of the routine public health system. However, if participants are asked for more detailed follow-up than would usually be required, to answer specific questionnaires or to perform additional examinations, special informed consent for research may be needed and ethical review of the Phase IV study protocol required.

Post-licensing studies are also used to explore new routes, formulations, and new or modified indications or drug associations of a registered product. In the case of evaluation for a new indication for a known product (label extension studies), the development protocols and ethics review should follow the same path as for a new product.