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Chapter 6 Ethical considerations

1. Introduction to ethical considerations

For any research investigation involving human subjects, there must be careful consideration of ethical issues that may arise in the planning, conduct, and reporting of the study. With very few exceptions, such research is not permitted unless the study has been approved by at least one formal ethics review committee (ERC). All research funding agencies require approval of the research by the appropriate ERC(s) before they will confirm an award for an intervention study. Often ethical review will be required from more than one such committee, for example, by both an institutional and a national ethics review committee, and/or in each of the countries involved in a trial. The ethics committee(s) will not only review the study protocol but usually will require full details of the study plan and procedures and will usually have specific application forms that must be completed. They may require payment of an administration fee for considering an application, irrespective of the outcome of the application. The committee will pay particular attention to informed consent documents and how consent to take part in the research will be obtained from potential study participants. Any significant changes in the study plan, either before it starts or during the conduct of the study, such as adding new objectives, extending the trial catchment area, or adding/removing inclusion or exclusion criteria, require approval by the ERC.

It is important that the ethical aspects of a research study are considered from its inception; for that reason, this chapter is placed early in the book. An underlying philosophy in this chapter is that it is difficult, and often inappropriate, to lay down ethical rules that apply to all studies in all places; each study should be judged in the context of the circumstances in which it will be conducted. A study judged unethical in one place might be considered ethical in another, and both of these might be ‘correct’ judgements.

Most ethical issues arise from conflicts between competing sets of values. For example, the medical practitioner is dedicated to the provision of the best medical care for an individual who is his or her patient. However, this dedication may be in direct conflict with that of the public health professional whose goal is to achieve maximum health benefits in a community with the limited resources available, which may entail restricting resources available to any one patient. Consuming large amounts of resources on one patient may deprive others of benefit. The appropriate balance between benefit for the individual and benefit for the community depends very much on the particular situation. The conflict is most obvious in situations of poverty and deprivation—just those conditions in which most field trials are conducted in LMICs. Those conducting field trials of interventions against diseases associated with poverty are likely therefore to be faced with especially difficult ethical dilemmas. Resolution of such dilemmas often depends upon where the investigators place their horizon of responsibility. If they consider their responsibility is confined to the participants in a trial, then some studies to resolve important public health issues might be viewed as unethical. But to assess the likely public health impact of an intervention in the wider community, it may be important to continue a trial beyond the point when it is established that one intervention is superior to another, in order to obtain a better estimate of the magnitude of the beneficial effect. Knowledge of the extent of benefit is needed, in order to make an informed decision about whether the benefit is sufficient to introduce the intervention on a widespread basis, especially if it is more expensive than the intervention that is currently available. If the investigators consider their responsibility is extended to the entire population, then they may regard it as unethical to stop a trial before a reasonable estimate of that benefit is obtained.

It is important to recognize that the primary purpose of an intervention trial is not to benefit the specific participants in the trial, but rather to obtain information about the effects of the intervention that will inform decisions about whether the intervention should be introduced on a widespread basis. Although trial participants may derive benefit, for example, they might receive better medical care in the trial than they would with the normal medical services, this is incidental to the main purposes of the trial.

Although intervention trials are not conducted with the prime aim of benefiting those in the trial, investigators have a specific responsibility for participants in a trial and must ensure that they are not harmed as a consequence of taking part in the trial and might derive some benefit. In so far as is possible, at a minimum, participants in a trial should be placed in no worse a situation than would have been the case had they not participated in the trial. It is, of course, not

always possible to guarantee this, as sometimes there may be unexpected adverse events associated with an intervention, but it is important to minimize the possibility of harm to trial participants.

There is sometimes a conflict between what is best for the 'future population' and what is best for those participating in a trial. Such conflicts may pose serious ethical dilemmas, for which there are few 'cookbook' solutions. Each situation has to be considered individually and preferably during the planning of the trial, so that potential ethical issues can be thought through in advance and, where necessary, guidance can be sought from properly constituted ethics committees. This issue is discussed further in Section 2.

It is not the purpose of this chapter to provide comprehensive guidance on all of the ethical considerations that must be considered in designing and conducting a field trial. Substantial sets of ethical guidelines have been published by a number of international bodies, and we give reference to these in the chapter, especially in Section 2.8. Rather we highlight some of the basic ethical principles related to randomized trials in Section 2 and then focus on some of the particularly difficult, and sometimes controversial, issues that arise in field trials in LMICs.

2. Widely accepted ethical principles concerning research on human subjects

The ethical principles related to medical research involving human subjects were summarized in the Declaration of Helsinki. This declaration was first formulated in 1964 and has subsequently been debated and revised a number of times, most recently in 2008 (World Medical Association, 2008). While some parts of the declaration remain hotly debated, the basic principles are generally accepted. They were reproduced and further elaborated with special reference to LMICs by the Council for International Organizations of Medical Sciences (CIOMS) (Council for International Organizations of Medical Sciences, 2009). The main principles are the following.

2.1. Scientific merit

To be ethical, research must have scientific merit, preferably in the judgement of an independent scientific committee, rather than only by the researchers themselves. This assessment will generally be made in the peer review process employed by funding agencies. The methods of the research should be appropriate to the aims of the research, and results from any relevant previous or ongoing research should be taken into account in its design. Over the last decade or so, there has been much greater insistence by research funding bodies and ethics committees, as well as research journal editors, that some kind of systematic review of prior research on a topic is conducted before further research on the topic is planned. This is to avoid unnecessary duplication of research where a new study needlessly addresses research questions that have been effectively answered previously. An outline of how to conduct systematic reviews is given in Chapter 3. Anyone proposing a trial should also review the clinical trial registers (see Chapter 7, Section 5), so that they are aware of trials that are already under way which might be addressing similar issues.

The investigator is also obliged to design and conduct the research in such a way that the results from the study are likely to provide answers to the questions being addressed. This includes attention to the appropriate size and duration of the study, as well as to other aspects of its design. For example, a study that is too small to address properly the principal research question may be deemed to be unethical. Furthermore, for research concerning interventions, achievement of the trial objectives must be linked, directly or indirectly, to some kind of action that is expected to lead to improved health for the population, or future population, of which the trial participants are in some way representative. Not all research findings will have immediate health consequences for the population, but the research should be on the pathway that is expected to lead ultimately to such benefit.

2.2. Equitable selection of subjects

The potential benefits of research and the risks and burdens associated with the research should be distributed equitably among communities and among individuals within communities. The economically and socially deprived are often at the highest risk of disease. There is, on the one hand, an imperative to ensure that the appropriate research is conducted in such groups and, on the other hand, an imperative to ensure that they are not exploited in research that will mainly benefit the more wealthy and privileged. For example, it would generally be deemed unacceptable to conduct a trial of an expensive treatment in a deprived group, unless it was expected that the cost of the treatment was likely to be reduced in the immediate future to a level that could be afforded by the community or that, even if there was no reduction in cost, the treatment would at least be made accessible to those in the community in which the trial was conducted, should it be found to be efficacious. Such treatment should not be restricted solely to those who had participated in the trial but should also be provided to those in similar circumstances in the community. Whether the

'community' is the local population in the trial area or a much larger, possibly national, group will often be an important aspect to consider before a trial is started.

2.3. Voluntariness

Voluntariness implies that individuals and communities enrol, continue, or withdraw from the study of their own free will, with full knowledge of the consequences of their participation or withdrawal. They should not be forced or coerced by investigators, officials, family, or friends, enticed by financial or other rewards. Nor should their decisions be constrained by socio-economic or political conditions. The principle of voluntariness is a key component of the informed consent process. Voluntariness, however, applies only as far as community leaders, adult individuals, or legal guardians of children are at liberty to make free choices. In some LMICs, researchers must take extra efforts to understand, for example, the influence that unequal gender relations might have on voluntariness and design information and procedures to minimize this influence. Illiteracy is another factor that may influence voluntariness when the information channels for the study favour those who can read over those who cannot. Any monetary compensation for participants' time or transport fares should be of a level that does not interfere with their freedom of choice, i.e. it should be sufficient to cover the actual costs, but not be an undue inducement to participate in the study (see Section 3.3). Particular attention should be paid to thanking potential participants who want to participate in a trial but are excluded because they are found not to meet the inclusion criteria.

2.4. Informed consent

It is now an established principle that 'informed consent' must be obtained from all participants in a medical or social research investigation on human subjects. Where the participant is not able to give informed consent for themselves, it is usually acceptable to request this from their parent or legal guardian.

Each potential participant should be given a comprehensive explanation as to why the research is being conducted, why they are being invited to participate, what possible benefits, risks, and burdens may arise for them personally as a result of participating in the research, and what benefits are expected to accrue to them and to the community as a result of the research. Translating these goals into a set of procedures that will be used to convey this information in a specific study is often challenging. Special problems arise with respect to field trials in LMICs, commonly involving large numbers of subjects, in obtaining assurance that all individuals are properly informed about these aspects.

Often, a research funding body or ERC will require the use of a consent form that participants must sign in the presence of a witness. The form must give full details of the study, with respect to the aspects outlined in Sections 2.1 to 2.3. It is becoming more widely recognized, however, that, in some societies, the insistence on obtaining a witnessed signature, or thumbprint, on such a form may not guarantee that the consent was fully informed, especially in communities where many are not literate. Moreover, in some societies, the requirement to sign a consent form may actually cause undue fear and anxiety, as when people in the local culture would typically sign or mark documents only in connection with legal transactions such as transferring property or if they were to be arrested. The ethical review process may include an option to request a waiver of signed consent, provided that certain other protective conditions are met. With or without the collection of a signature, what is most important is the *consent process,* through which study personnel have a conversation with prospective participants to make sure that they understand all the key points of information, have an opportunity to ask questions, and understand that they are free to say 'no'. It is *always* the investigator's responsibility to ensure that subjects are properly informed of the potential risks and benefits of participation in a study. It is common practice, in some trials, to include a short 'test' to check that the potential study participant has understood the key information before they are asked to sign the consent form, with the opportunity to receive further explanation of points that they do not fully understand.

Lema et al. (2009) conducted a systematic review on consent procedures in clinical trials in Africa and reported that consent often was not truly voluntary; consent procedures are difficult to implement, due to cultural factors and low literacy, and local ethical review committees may be weak or ill-equipped. These findings are reinforced by a study of informed consent for HIV testing in South Africa that found that, although all women had given informed consent for the testing, they were coerced in direct and indirect ways into providing consent, and many felt they did not, in fact, have a choice (Groves et al., 2010). It is therefore very important that investigators endeavour to ensure that consent is truly informed and non-coercive.

Special provisions must be made for potential participants who are not competent to provide informed consent such as children or patients who are comatose. Such persons require an advocate who is legally and morally responsible for

decisions taken on their behalf. Even when the advocate provides consent, the subject should have the right to refuse, if he or she is able to, but, in practice, it may be difficult, for example, for a young child to exercise that right. In general, research procedures should not be conducted on children, unless they have already been demonstrated to be safe in adults and, if appropriate, efficacious in adults also.

The information provided to potential participants to obtain consent for taking part in a trial would be expected to include that listed in Box 6.1.

The checklist in Box 6.1 was drawn up in the context of trials in HICs, but the same principles apply for trials in LMICs. In the latter, however, it may be necessary to go to some lengths to give the required explanations and in ways that will be comprehensible in the context of the local attitudes and beliefs in the communities in which the trial will be undertaken. Often investigators will first meet with community leaders to explain the trial and to seek permission to conduct the investigation. This might be followed by community meetings at which the trial investigators explain the trial and the procedures to be followed and then answer any questions. After that, potential participants might be given further information, often in written form, that they can take home and discuss with neighbours, friends, and others advisors in the community, before they are asked to provide informed consent. Although key steps of the informed consent process should usually be done face-to-face, it is sometimes effective to get a prospective participant to watch a video or listen to an audio message that explains aspects the study. And sometimes photographs or diagrams can be very useful to supplement a verbal explanation.

2.5. Confidentiality

The confidentiality of all information collected in a research investigation must be maintained and only released to others with the explicit consent of all those concerned. The proportion of individuals who agree to participate in a study, especially one in which sensitive information is being collected (for example, whether or not an individual is infected with HIV), may be increased if careful explanations are given as to how confidentiality will be maintained and who within the study team will have access to such information. In many studies, it will be appropriate to identify individuals on record forms by a code number only, with the list linking names to the codes being kept separately in a secure place, with access limited to only those who must be able to link trial data back to specific individuals.

2.6. Coercion

In general, there are fewer legal and institutional safeguards to protect the rights of individuals in LMICs than there are in most HICs. When research workers are employed by, or identified with, the state authorities or with those who provide medical care, there is a danger that they might be tempted to exploit this position, with greater or lesser degrees of subtlety, to coerce subjects to participate in a study. Coercion and deception, even when rationalized as being for the ‘greater good’, are unacceptable. Full and open explanations of all study procedures, with the explicit understanding that participation is voluntary and those who decline will not be penalized, may be time-consuming, but this is the only acceptable approach.

2.7. Review and approval by ethics committees

Most research investigations must go through several levels of scientific and ethical review to assess their acceptability. The number of levels will depend on the nature of the research, national regulations, and from which agencies support for the research is being sought.

All ethical review bodies will require that each individual participant in a study is provided with sufficient information on potential risks and benefits to enable them to make an informed decision on whether or not to participate. Illiteracy and differing cultural concepts of health and disease do not alter the basic requirements for informed consent. If permission to approach and recruit individual members of the population has been obtained by virtue of a communal decision, individual informed consent is still necessary, and the research worker and the ethics committee must assure themselves that there is no coercion on individuals to participate. The principles that consent must be given by each individual, rather than assumed, and that all prospective participants have the right of refusal must be regarded as the minimal safeguards.

As well as being acceptable to individual participants, a trial may be reviewed at a community level through either a formal or an informal review committee. In addition, there may be local and national ethical and scientific review bodies to satisfy. If funding for a study is sought from an international agency, there may be a further level of ethical review. For example, research proposals submitted to the WHO are reviewed by the WHO Research Ethics Review

Committee (WHO ERC). The committee will only review proposals that have first been approved by national and, if appropriate, local ethics committees. Given all these potential steps, it is very important that investigators allow sufficient time for research and ethics approval. Although many are much faster, it is not uncommon for some ethics committees to take as long as 6 months to review a proposal.

In the case of multicountry studies, it is common that the ethics committees review a master protocol and then subsequently individual or country-specific protocols. The latter are needed to describe how the master protocol was adapted to local reality and resources. The review of protocols for additional study sites is usually more straightforward, given that the main ethical and methodological issues of the study have already been reviewed. In some cases, a centralized ethics committee has been used to review multicentre studies, but generally ERCs are reluctant to delegate responsibility for review to a committee outside of their own country.

Ethics committees should be properly constituted and operating under defined standard operating procedures (SOPs) (see first reference in Section 2.8). Their main role is to ensure that ethical principles, as established by universal guidelines, are applied in the research and the rights, safety, well-being, and confidentiality of participants are protected. The committee review should focus on ethical and quality assurance aspects of the protocol, addressing its relevance, risks (physical, psychological, social, economic), and potential benefits. In some cases, the trial does not bring immediate benefit to the participants, but the knowledge generated will be for the benefit of broader society. In local committees, the inclusion of members representing the group of patients or communities under study enables a better understanding of the social and cultural aspects involved. Ideally, the members of ethics committees comprise a multidisciplinary group with experience in research and should include lay persons who can bring a non-medical perspective to the review. As the focus of review is on fairness and ethical issues, in most cases, there is no need for all members to be knowledgeable about the medical or scientific aspects. However, it is also helpful that a medical or scientific member be available to explain in more detail the rationale or concept for the procedures to be carried out and products to be administered.

The protocol should include copies of case report forms, examples of questionnaires to be used, as well as a model of informed consent in the committee's working language and in the local language, as it is going to be applied. Social sciences methodologies, such as focus group discussions, or in-depth interviews, also require proper description and a list of the topics that will be covered in the protocol.

It is common that, before approval, the ethics committee requests additional information or description of procedures not fully detailed in the protocol, so investigators should endeavour to be comprehensive in their initial application. The queries or deliberations of the ethics committee are transmitted by the secretary to the PIs or sponsor, who should submit a revised version of the protocol with amendments and clarification, following the instructions of the committee. The more complete and detailed the protocol is, the less time will be required for reviewing. However, very often, a resubmission is needed, and the investigator should allow for time for clearance.

Some ethics committees require reports during a trial to ensure compliance with procedures and to evaluate any protocol deviations or to follow up AEs. Serious adverse reactions occurring during a trial that are considered related to the intervention should be reported to the ethics committee, and the balance between risks and benefits should be continually reassessed by the investigators (or by the Data and Safety Monitoring Board, (DSMB) on behalf of the investigators; see Chapter 7, Section 4). Frequency and procedures for reports and review of trial operations and data are laid down by the committee on a case-by-case basis.

Ethics committees pay special attention to studies involving vulnerable individuals, and the protocol should ensure that there is no undue inducement to participate. Vulnerable individuals, according to Good Clinical Practice (GCP) guidelines (International Conference on Harmonisation, 1996), are individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Other vulnerable subjects include children (commonly defined as all those below 18 years of age, but this varies between countries), patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, prisoners, and those incapable of giving consent. In some countries, there are special regulations regarding research involving indigenous populations.

Before initiating a trial, the investigator should have written approval of the protocol, written informed consent documents, subject recruitment procedures, and any other written information to be given to participants. The

investigator is responsible for complying with the study protocol that was approved by the ethics committee and agreed by the sponsor and regulatory authority (if appropriate).

A clinical trial legal and financial liability insurance, which is compulsory in some countries, provides the participants and sponsor financial protection against specific contingencies such as death, disability, or other health-related complications that may occur from the participation in a trial. In most cases, liability is product-related, and lawsuits against pharmaceutical companies have increased over the years, as more careful pharmaco-epidemiological studies have been able to identify adverse effects of new products when used in a large number of people or over a long period of time. Some ethics committees will not review a protocol without having a copy of the clinical trial insurance certificate.

2.8. Useful guidance documents

Research involving human subjects is conducted in countries with widely varying socio-economic, health, and research ethics infrastructure. However, irrespective of where the research is conducted, for the ethics infrastructure to be effective, it must have officially recognized regulations or guidelines, a system for oversight and monitoring, and well-functioning research ethics committees. Many LMICs lack laws or regulations governing ethics in research and face the challenge of deciding which international guidelines to use. These guidelines are increasing in number, are not harmonized, and require interpretation or adaptation to local circumstances. Many ethics committees also face the challenge of ensuring adequate ethical review of research protocols.

The following is a selection of the most important guidance documents.

2.8.1. Operational guidelines for ethics committees that review biomedical research

These were produced by the WHO Tropical Diseases Research Programme in 2000. They set out operational guidelines for ethics committees, in order to facilitate, support, and ensure quality of the ethical review of biomedical research in all countries of the world. Targeted for use by national and local bodies, these guidelines define the role and constituents of an ethics committee and detail the requirements for submitting an application for review. The review procedure and details of the decision-making process are provided, together with necessary follow-up and documentation procedures. They can be downloaded from <http://www.who.int/tdr>.

2.8.2. International conference on harmonisation/WHO good clinical practice standards

This document (International conference on harmonisation, 1996) provides a unified standard for the European Union, Japan, the USA, Australia, Canada, the Nordic countries, and the WHO. Thus, any country that adopts this guideline technically follows this same standard.

2.8.3. The Declaration of Helsinki—ethical principles for medical research involving human subjects

The Declaration of Helsinki is a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. It was adopted in 1964 and has since undergone several amendments, including one in 2008 (available at <http://www.wma.net/en/30publications/10policies/b3/17c.pdf>.

2.8.4. International Ethical Guidelines for Epidemiological Studies

In 2009, the CIOMS published its revised guidelines (Council for International Organizations of Medical Sciences, 2009). The book contains ethical guidance on how epidemiologists—as well as those who sponsor, review, or participate in the studies they conduct—should identify and respond to the ethical issues that are raised by the research process. The book can be ordered from WHO through e-mail: cioms@who.int.

2.8.5. The ethics of research related to health care in developing countries

This book was produced in 2002 (Nuffield Council on Bioethics, 2002) and updated in 2005 (Nuffield Council on Bioethics, 2005). It defines the ethical standards for health care research in LMICs (<http://www.nuffieldbioethics.org/research-developing-countries>).

2.8.6. Consolidated Standards of Reporting Trials (CONSORT)

CONSORT 2010 provides a checklist of information to include when reporting a randomized trial. It includes a flow diagram of the process through the phases of a randomized trial. Diligent adherence to these guidelines facilitates clarity, comprehensiveness, and transparency of reporting (Schulz et al., 2010).

2.8.7. Extending the CONSORT statement to randomized trials of non-pharmacologic treatments

The CONSORT statement has been extended to address specific issues that apply to trials of non-pharmacologic treatments and behavioural intervention (Boutron et al., 2008).

2.8.8. Other useful background documents

- *The Belmont report: ethical principles and guidelines for the protection of human subjects of research* (<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>)
- *The common rule, title 45 (public welfare), code of federal regulations, part 46 (protection of human subjects)*, subparts A–D; *The international ethical guidelines for biomedical research involving human subjects. (CIOMS)* (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>)
- Canada: *Tri-council policy statement: ethical conduct for research involving humans* (<http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf>)
- Indian Council of Medical Research: *Ethical guidelines for biomedical research on human participants* (<http://icmr.nic.in/ethical_guidelines.pdf>)
- Finally, see the very useful international compilation of human subjects protections maintained by the US Office for Human Research Protections (OHRP) (<http://www.hhs.gov/ohrp/international/index.html>).

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 intervention they are evaluating.

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 so do. 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 standards*

for expedited reporting for more detail (<http://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 concerns 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 informed consent when sought at group level, (2) the potential conflicts between individual 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 consent 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.

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Boxes

Box 6.1 Information that should be provided to potential participants to seek consent for taking part in a trial

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. An explanation of why the subject has been asked to participate in the trial.
3. A description of any reasonably foreseeable risks or discomforts to the subject.
4. A description of any benefits to the subject or to others which may reasonably be expected from the research.
5. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
6. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
7. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
8. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject.
9. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional elements of informed consent

When appropriate, one or more of the following elements of information shall also be provided to each subject.

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research.
4. A statement that significant new findings that arise during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
5. The approximate number of subjects involved in the study.

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