6.2: 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 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.

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.

Adapted from U.S. Food and Drug Administration, Code of Federal Regulations, Title 21, Section 50.25, 2013, available from <http://www.fda.gov>. This box is not covered by the Creative Commons licence terms of this publication.
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 justifiable 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](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 <www.wma.net/en/30publications...ies/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


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 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(<www.pre.ethics.gc.ca/pdf/eng/..._FINAL_Web.pdf>)

• Indian Council of Medical Research: Ethical guidelines for biomedical research on human participants (<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>).