

1991 INTERNATIONAL GUIDELINES FOR ETHICAL REVIEW OF EPIDEMIOLOGICAL STUDIES

INTRODUCTION

These Guidelines are intended for investigators, health policy-makers, members of ethical review committees, and others who have to deal with ethical issues that arise in epidemiology. They may also assist in the establishment of standards for ethical review of epidemiological studies.

The Guidelines are an expression of concern to ensure that epidemiological studies observe ethical standards. These standards apply to all who undertake any of the types of activity covered by the Guidelines. Investigators must always be held responsible for the ethical integrity of their studies.

Epidemiology is defined as the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems.

Epidemiology has greatly improved the human condition in the present century. It has clarified our understanding of many physical, biological and behavioural dangers to health. Some of the knowledge obtained has been applied to the control of environmental and biological threats to health, such as diseases due to drinking polluted water. Other epidemiological knowledge has become part of popular culture, leading to changed values and behaviour, and thus has led to improved health: examples include attitudes towards personal hygiene, tobacco smoking, diet and exercise in relation to heart disease, and the use of seat-belts to reduce the risk of traffic injury and death.

Epidemiological practice and research are based mostly on observation, and require no intervention more invasive than asking questions and carrying out routine medical examinations. Practice and research may overlap, as, for example, when both routine surveillance of cancer and original research on cancer are conducted by professional staff of a population-based cancer registry.

Epidemiological research is of two main types: observational and experimental:

Three types of observational epidemiological research are distinguished: *cross-sectional studies* (also known as surveys), *case-control studies*, and *cohort studies*. These types of study carry minimal risk to study subjects. They involve no intervention other than asking questions, carrying out medical examinations and, sometimes, laboratory tests or xray examinations. The informed consent of subjects is normally required, although there are some exceptions - for example, very large cohort studies conducted exclusively by examining medical records.

A *cross-sectional* study (survey) is commonly done on a random sample of a population. Study subjects are asked questions, medically examined, or asked to submit to laboratory

tests. Its aim is to assess aspects of the health of a population, or to test hypotheses about possible causes of disease or suspected risk factors.

A *case-control* study compares the past history of exposure to risk among patients who have a specified condition (cases) with the past history of exposure to this risk among persons who resemble the cases in such respects as age and sex, but do not have the specified condition (controls). Differing frequency of past exposure among cases and controls can be statistically analysed to test hypotheses about causes or risk factors. Case-control studies are the method of choice for testing hypotheses about rare conditions, because they can be done with small numbers of cases. They generally do not involve invasion of privacy or violation of confidentiality. If a case-control study requires direct contact between research workers and study subjects, informed consent to participation in the study is required; if it entails only a review of medical records, informed consent may not be required and indeed may not be feasible.

In a *cohort study*, also known as a longitudinal or prospective study, individuals with differing exposure levels to suspected risk factors are identified and observed over a period, commonly years, and the rates of occurrence of the condition of interest are measured and compared in relation to exposure levels. This is a more robust research method than a cross-sectional or case-control study, but it requires study of large numbers for a long time and is costly. Usually it requires only asking questions and routine medical examinations; sometimes it requires laboratory tests. Informed consent is normally required, but an exception to this requirement is a retrospective cohort study that uses linked medical records. In a retrospective cohort study, the initial or base-line observations may relate to exposure many years earlier to a potentially harmful agent, such as x-rays, a prescribed drug or an occupational hazard, about which details are known; the final or endpoint observations are often obtained from death certificates. Numbers of subjects may be very large, perhaps millions, so it would be impracticable to obtain their informed consent. It is essential to identify precisely every individual studied; this is achieved by methods of matching that are built into record linkage systems. After identities have been established to compile the statistical tables, all personal identifying information is obliterated, and therefore privacy and confidentiality are safeguarded.

An experiment is a study in which the investigator intentionally alters one or more factors under controlled conditions to study the effects of doing so. The usual form of epidemiological experiment is the *randomized controlled trial*, which is done to test a preventive or therapeutic regimen or diagnostic procedure. Such experiments involving human subjects should be regarded as unethical unless there is genuine uncertainty about the regimen or procedure and this uncertainty can be clarified by research.

Usually in this form of experiment, subjects are allocated at random to groups, one group to receive, the other group not to receive, the experimental regimen or procedure. The experiment compares the outcomes in the two groups. Random allocation removes the effects of bias, which would destroy the validity of comparisons between the groups. Since it is always possible that harm may be caused to at least some of the subjects, their informed consent is essential.

Epidemiology is facing new challenges and opportunities. The application of information technology to large data-files has expanded the role and capacity of epidemiological studies. The acquired immunodeficiency syndrome (AIDS) epidemic and its management have given

epidemiological studies new urgency; public health authorities are using population-screening studies to establish prevalence levels of human immunodeficiency virus (HIV) infection for purposes of monitoring and restricting the spread of infection. Ahead lie entirely new challenges, such as those arising from the conjunction of molecular and population genetics.

PREAMBLE

The general conduct of biomedical studies is guided by statements of internationally recognized principles of human rights, including the Nuremberg Code and the World Medical Association's Declaration of Helsinki, as revised (Helsinki IV). These principles also underlie the Proposed International Guidelines for Biomedical Research Involving Human Subjects, issued by the Council for International Organizations of Medical Sciences in 1982. These and similar national codes are based on the model of clinical medicine, and often address interests of "patients" or individual "subjects". Epidemiological research concerns groups of people, and the above codes do not adequately cover its special features. Proposals for epidemiological studies should be reviewed independently on ethical grounds.

Ethical issues often arise as a result of conflict among competing sets of values, such as, in the field of public health, the conflict between the rights of individuals and the needs of communities. Adherence to these guidelines will not avoid all ethical problems in epidemiological studies. Many situations require careful discussion and informed judgement on the part of investigators, ethical review committees, administrators, health-care practitioners, policy-makers, and community representatives. Externally sponsored epidemiological studies in developing countries merit special attention. A framework for the application of these guidelines is set by the laws and practices in each jurisdiction in which it is proposed to undertake studies.

The purpose of ethical review is to consider the features of a proposed study in the light of ethical principles, so as to ensure that investigators have anticipated and satisfactorily resolved possible ethical objections, and to assess their responses to ethical issues raised by the study. Not all ethical principles weigh equally. A study may be assessed as ethical even if a usual ethical expectation, such as confidentiality of data, has not been comprehensively met, provided the potential benefits clearly outweigh the risks and the investigators give assurances of minimizing risks. It may even be unethical to reject such a study, if its rejection would deny a community the benefits it offers. The challenge of ethical review is to make assessments that take into account potential risks and benefits, and to reach decisions on which members of ethical review committees may reasonably differ.

Different conclusions may result from different ethical reviews of the same issue or proposal, and each conclusion may be ethically reached, given varying circumstances of place and time; a conclusion is ethical not merely because of what has been decided but also owing to the process of conscientious reflection and assessment by which it has been reached.

GENERAL ETHICAL PRINCIPLES

All research involving human subjects should be conducted in accordance with four basic ethical principles, namely *respect for persons*, *beneficence*, *non-maleficence*, and *justice*. It is usually assumed that these principles guide the conscientious preparation of proposals for scientific studies. In varying circumstances, they may be expressed differently and given different weight, and their application, in all good faith, may have different effects and lead to different decisions or courses of action. These principles have been much discussed and clarified in recent decades, and it is the aim of these Guidelines that they be applied to epidemiology.

Respect for persons incorporates at least two other fundamental ethical principles, namely: a) *autonomy*, which requires that those who are capable of deliberation about their personal goals should be treated with respect for their capacity for self-determination; and b) *protection of persons* with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse.

Beneficence is the ethical obligation to maximize possible benefits and to minimize possible harms and wrongs. This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to assure the well-being of the research subjects.

Non-maleficence ("Do no harm") holds a central position in the tradition of medical ethics, and guards against avoidable harm to research subjects.

Justice requires that cases considered to be alike be treated alike, and that cases considered to be different be treated in ways that acknowledge the difference. When the principle of justice is applied to dependent or vulnerable subjects, its main concern is with the rules of *distributive justice*. Studies should be designed to obtain knowledge that benefits the class of persons of which the subjects are representative: the class of persons bearing the burden should receive an appropriate benefit, and the class primarily intended to benefit should bear a fair proportion of the risks and burdens of the study.

The rules of distributive justice are applicable within and among communities. Weaker members of communities should not bear disproportionate burdens of studies from which all members of the community are intended to benefit, and more dependent communities and countries should not bear disproportionate burdens of studies from which all communities or countries are intended to benefit.

General ethical principles may be applied at individual and community levels. At the level of the individual (*microethics*), ethics governs how one person should relate to another and the moral claims of each member of a community. At the level of the community, ethics applies to how one community relates to another, and to how a community treats each of its members (including prospective members) and members of other groups with different cultural values (*macroethics*). Procedures that are unethical at one level cannot be justified merely because they are considered ethically acceptable at the other.

ETHICAL PRINCIPLES APPLIED TO EPIDEMIOLOGY

Informed Consent

Individual consent

1. When individuals are to be subjects of epidemiological studies, their informed consent will usually be sought. For epidemiological studies that use personally identifiable private data, the rules for informed consent vary, as discussed further below. Consent is informed when it is given by a person who understands the purpose and nature of the study, what participation in the study requires the person to do and to risk, and what benefits are intended to result from the study.

2. An investigator who proposes not to seek informed consent has the obligation to explain to an ethical review committee how the study would be ethical in its absence: it may be impractical to locate subjects whose records are to be examined, or the purpose of some studies would be frustrated - for example, prospective subjects on being informed would change the behaviour that it is proposed to study, or might feel needlessly anxious about why they were subjects or study. The investigator will provide assurances that strict safeguards will be maintained to protect confidentiality and that the study is aimed at protecting or advancing health. Another justification for not seeking informed consent may be that subjects are made aware through public announcements that it is customary to make personal data available for epidemiological studies.

3. An ethical issue may arise when occupational records, medical records, tissue samples, etc. are used for a purpose for which consent was not given, although the study threatens no harm. Individuals or their public representatives should normally be told that their data might be used in epidemiological studies, and what means of protecting confidentiality are provided. Consent is not required for use of publicly available information, although countries and communities differ with regard to the definition of what information about citizens is regarded as public. However, when such information is to be used, it is understood that investigators will minimize disclosure of personally sensitive information.

4. Some organizations and government agencies employ epidemiologists who may be permitted by legislation or employees' contracts to have access to data without subjects' consent. These epidemiologists must then consider whether it is ethical for them, in a given case, to use this power of access to personal data. Ethically, they may still be expected either to seek the consent of the individuals concerned, or to justify their access without such consent. Access may be ethical on such grounds as minimal risk of harm to individuals, public benefit, and investigators' protection of the confidentiality of the individuals whose data they study.

Community agreement

5. When it is not possible to request informed consent from every individual to be studied, the agreement of a representative of a community or group may be sought, but the representative should be chosen according to the nature, traditions and political philosophy of the community or group. Approval given by a community representative should be consistent with general ethical principles. When investigators work with communities, they will consider communal rights and protection as they would individual rights and protection. For communities in which collective decision-making is customary, communal leaders can

express the collective will. However, the refusal of individuals to participate in a study has to be respected: a leader may express agreement on behalf of a community, but an individual's refusal of personal participation is binding.

6. When people are appointed by agencies outside a group, such as a department of government, to speak for members of the group, investigators and ethical review committees should consider how authentically these people speak for the group, and if necessary seek also the agreement of other representatives. Representatives of a community or group may sometimes be in a position to participate in designing the study and in its ethical assessment.

7. The definition of a community or group for purposes of epidemiological study may be a matter of ethical concern. When members of a community are naturally conscious of its activities as a community and feel common interests with other members, the community exists, irrespective of the study proposal. Investigators will be sensitive to how a community is constituted or defines itself, and will respect the rights of underprivileged groups.

8. For purposes of epidemiological study, investigators may define groups that are composed of statistically, geographically or otherwise associated individuals who do not normally interact socially. When such groups are artificially created for scientific study, group members may not readily be identifiable as leaders or representatives, and individuals may not be expected to risk disadvantage for the benefit of others. Accordingly, it will be more difficult to ensure group representation, and all the more important to obtain subjects' free and informed consent to participate.

Selective disclosure of information

9. In epidemiology, an acceptable study technique involves selective disclosure of information, which seems to conflict with the principle of informed consent. For certain epidemiological studies non-disclosure is permissible, even essential, so as to not influence the spontaneous conduct under investigation, and to avoid obtaining responses that the respondent might give in order to please the questioner. Selective disclosure may be benign and ethically permissible, provided that it does not induce subjects to do what they would not otherwise consent to do. An ethical review committee may permit disclosure of only selected information when this course is justified.

Undue influence

10. Prospective subjects may not feel free to refuse requests from those who have power or influence over them. Therefore the identity of the investigator or other person assigned to invite prospective subjects to participate must be made known to them. Investigators are expected to explain to the ethical review committee how they propose to neutralize such apparent influence. It is ethically questionable whether subjects should be recruited from among groups that are unduly influenced by persons in authority over them or by community leaders, if the study can be done with subjects who are not in this category.

Inducement to participate

11. Individuals or communities should not be pressured to participate in a study. However, it can be hard to draw the line between exerting pressure or offering inappropriate inducements and creating legitimate motivation. The benefits of a study, such as increased or new knowledge, are proper inducements. However, when people or communities lack basic health services or money, the prospect of being rewarded by goods, services or cash payments can

induce participation. To determine the ethical propriety of such inducements, they must be assessed in the light of the traditions of the culture.

12. Risks involved in participation should be acceptable to subjects even in the absence of inducement. It is acceptable to repay incurred expenses, such as for travel. Similarly, promises of compensation and care for damage, injury or loss of income should not be considered inducements.

Maximizing Benefit

Communication of study results

13. Part of the benefit that communities, groups and individuals may reasonably expect from participating in studies is that they will be told of findings that pertain to their health. Where findings could be applied in public health measures to improve community health, they should be communicated to the health authorities. In informing individuals of the findings and their pertinence to health, their level of literacy and comprehension must be considered. Research protocols should include provision for communicating such information to communities and individuals.

Research findings and advice to communities should be publicized by whatever suitable means are available. When HIV-prevalence studies are conducted by unlinked anonymous screening, there should be, where feasible, provision for voluntary HIV-antibody testing under conditions of informed consent, with pre- and post-test counselling, and assurance of confidentiality.

Impossibility of communicating study results

14. Subjects of epidemiological studies should be advised that it may not be possible to inform them about findings that pertain to their health, but that they should not take this to mean that they are free of the disease or condition under study. Often it may not be possible to extract from pooled findings information pertaining to individuals and their families, but when findings indicate a need of health care, those concerned should be advised of means of obtaining personal diagnosis and advice.

When epidemiological data are unlinked, a disadvantage to subjects is that individuals at risk cannot be informed of useful findings pertinent to their health. When subjects cannot be advised individually to seek medical attention, the ethical duty to do good can be served by making pertinent health-care advice available to their communities.

Release of study results

15. Investigators may be unable to compel release of data held by governmental or commercial agencies, but as health professionals they have an ethical obligation to advocate the release of information that is in the public interest.

Sponsors of studies may press investigators to present their findings in ways that advance special interests, such as to show that a product or procedure is or is not harmful to health. Sponsors must not present interpretations or inferences, or theories and hypotheses, as if they were proven truths.

Health care for the community under study

16. The undertaking of an epidemiological project in a developing country may create the expectation in the community concerned that it will be provided with health care, at least while the research workers are present. Such an expectation should not be frustrated, and,

where people need health care, arrangements should be made to have them treated or they should be referred to a local health service that can provide the needed care.

Training local health personnel

17. While studies are in progress, particularly in developing countries, the opportunity should be taken to train local health workers in skills and techniques that can be used to improve health services. For instance, by training them in the operation of measuring devices and calculating machines, when a study team departs it leaves something of value, such as the ability to monitor disease or mortality rates.

Minimizing Harm

Causing harm and doing wrong

18. Investigators planning studies will recognize the risk of causing harm, in the sense of bringing disadvantage, and of doing wrong, in the sense of transgressing values. Harm may occur, for instance, when scarce health personnel are diverted from their routine duties to serve the needs of a study, or when, unknown to a community, its health-care priorities are changed. It is wrong to regard members of communities as only impersonal material for study, even if they are not harmed.

19. Ethical review must always assess the risk of subjects or groups suffering stigmatization, prejudice, loss of prestige or self-esteem, or economic loss as a result of taking part in a study. Investigators will inform ethical review committees and prospective subjects of perceived risks, and of proposals to prevent or mitigate them. Investigators must be able to demonstrate that the benefits outweigh the risks for both individuals and groups. There should be a thorough analysis to determine who would be at risk and who would benefit from the study. It is unethical to expose persons to avoidable risks disproportionate to the expected benefits, or to permit a known risk to remain if it can be avoided or at least minimized.

20. When a healthy person is a member of a population or sub-group at raised risk and engages in high-risk activities, it is unethical not to propose measures for protecting the population or sub-group.

Preventing harm to groups

21. Epidemiological studies may inadvertently expose groups as well as individuals to harm, such as economic loss, stigmatization, blame, or withdrawal of services. Investigators who find sensitive information that may put a group at risk of adverse criticism or treatment should be discreet in communicating and explaining their findings. When the location or circumstances of a study are important to understanding the results, the investigators will explain by what means they propose to protect the group from harm or disadvantage; such means include provisions for confidentiality and the use of language that does not imply moral criticism of subjects' behaviour.

Harmful publicity

22. Conflict may appear between, on the one hand, doing no harm and, on the other, telling the truth and openly disclosing scientific findings. Harm may be mitigated by interpreting data in a way that protects the interests of those at risk, and is at the same time consistent with scientific integrity. Investigators should, where possible, anticipate and avoid misinterpretation that might cause harm.

Respect for social mores

23. Disruption of social mores is usually regarded as harmful. Although cultural values and social mores must be respected, it may be a specific aim of an epidemiological study to stimulate change in certain customs or conventional behaviour to lead through change to healthful behaviour - for instance, with regard to diet or a hazardous occupation.

24. Although members of communities have a right not to have others impose an uninvited "good" on them, studies expected to result in health benefits are usually considered ethically acceptable and not harmful. Ethical review committees should consider a study's potential for beneficial change. However, investigators should not overstate such benefits, in case a community's agreement to participate is unduly influenced by its expectation of better health services.

Sensitivity to different cultures

25. Epidemiologists often investigate cultural groups other than their own, inside or outside their own countries, and undertake studies initiated from outside the culture, community or country in which the study is to be conducted. Sponsoring and host countries may differ in the ways in which, in their cultures, ethical values are understood and applied - for instance, with regard to autonomy of individuals.

Investigators must respect the ethical standards of their own countries and the cultural expectations of the societies in which epidemiological studies are undertaken, unless this implies a violation of a transcending moral rule. Investigators risk harming their reputation by pursuing work that host countries find acceptable but their own countries consider offensive. Similarly, they may transgress the cultural values of the host countries by uncritically conforming to the expectations of their own.

Confidentiality

26. Research may involve collecting and storing data relating to individuals and groups, and such data, if disclosed to third parties, may cause harm or distress. Consequently, investigators should make arrangements for protecting the confidentiality of such data by, for example, omitting information that might lead to the identification of individual subjects, or limiting access to the data, or by other means. It is customary in epidemiology to aggregate numbers so that individual identities are obscured. Where group confidentiality cannot be maintained or is violated, the investigators should take steps to maintain or restore a group's good name and status. Information obtained about subjects is generally divisible into:

Unlinked information, which cannot be linked, associated or connected with the person to whom it refers; as this person is not known to the investigator, confidentiality is not at stake and the question of consent does not arise.

Linked information, which may be:

- anonymous, when the information cannot be linked to the person to whom it refers except by a code or other means known only to that person, and the investigator cannot know the identity of the person;
- non-nominal, when the information can be linked to the person by a code (not including personal identification) known to the person and the investigator; or
- nominal or nominative, when the information is linked to the person by means of personal identification, usually the name.

Epidemiologists discard personal identifying information when consolidating data for purposes of statistical analysis. Identifiable personal data will not be used when a study can be done without personal identification - for instance, in testing unlinked anonymous blood samples for HIV infection. When personal identifiers remain on records used for a study, investigators should explain to review committees why this is necessary and how confidentiality will be protected. If, with the consent of individual subjects, investigators link different sets of data regarding individuals, they normally preserve confidentiality by aggregating individual data into tables or diagrams. In government service the obligation to protect confidentiality is frequently reinforced by the practice of swearing employees to secrecy.

Conflict of interest

Identification of conflict of interest

27. It is an ethical rule that investigators should have no undisclosed conflict of interest with their study collaborators, sponsors or subjects. Investigators should disclose to the ethical review committee any potential conflict of interest. Conflict can arise when a commercial or other sponsor may wish to use study results to promote a product or service, or when it may not be politically convenient to disclose findings.

28. Epidemiological studies may be initiated, or financially or otherwise supported, by governmental or other agencies that employ investigators. In the occupational and environmental health fields, several well-defined special-interest groups may be in conflict: shareholders, management, labour, government regulatory agencies, public interest advocacy groups, and others. Epidemiological investigators may be employed by any of these groups. It can be difficult to avoid pressures resulting from such conflict of interest, and consequent distorted interpretations of study findings. Similar conflict may arise in studies of the effects of drugs and in testing medical devices.

29. Investigators and ethical review committees will be sensitive to the risk of conflict, and committees will not normally approve proposals in which conflict of interest is inherent. If, exceptionally, such a proposal is approved, the conflict of interest should be disclosed to prospective subjects and their communities.

30. There may appear to be conflict when subjects do not want to change their behaviour and investigators believe that they ought to do so for the sake of their health. However, this may not be a true conflict of interest, as the investigators are motivated by the subjects' health interests.

Scientific objectivity and advocacy

31. Honesty and impartiality are essential in designing and conducting studies, and presenting and interpreting findings. Data will not be withheld, misrepresented or manipulated. Investigators may discover health hazards that demand correction, and become advocates of means to protect and restore health. In this event, their advocacy must be seen to rely on objective, scientific data.

ETHICAL REVIEW PROCEDURES

Requirement of ethical review

32. The provisions for ethical review in a society are influenced by economic and political considerations, the organization of health care and research, and the degree of independence of investigators. Whatever the circumstances, there is a responsibility to ensure that the Declaration of Helsinki and the CIOMS International Guidelines for Biomedical Research Involving Human Subjects are taken into account in epidemiological studies.

33. The requirement that proposals for epidemiological studies be submitted to independent ethical review applies irrespective of the source of the proposals - academic, governmental, health-care, commercial, or other. Sponsors should recognize the necessity of ethical review and facilitate the establishment of ethical review committees. Sponsors and investigators are expected to submit their proposals to ethical review, and this should not be overlooked even when sponsors have legal power to permit investigators access to data. An exception is justified when epidemiologists must investigate outbreaks of acute communicable diseases. Then they must proceed without delay to identify and control health risks. They cannot be expected to await the formal approval of an ethical review committee. Nevertheless, in such circumstances the investigator will, as far as possible, respect the rights of individuals, namely freedom, privacy, and confidentiality.

Ethical review committees

34. Ethical review committees may be created under the aegis of national or local health administrations, national medical research councils, or other nationally representative health-care bodies. The authority of committees operating on a local basis may be confined to one institution or extend to all biomedical studies undertaken in a defined political jurisdiction. However committees are created, and however their jurisdiction is defined, they should establish working rules - regarding, for instance, frequency of meetings, a quorum of members, decision-making procedures, and review of decisions, and they should issue such rules to prospective investigators.

35. In a highly centralized administration, a national review committee may be constituted to review study protocols from both scientific and ethical standpoints. In countries with a decentralized administration, protocols are more effectively and conveniently reviewed at a local or regional level. Local ethical review committees have two responsibilities: - to verify that all proposed interventions have been assessed for safety by a competent expert body, and - to ensure that all other ethical issues are satisfactorily resolved.

36. Local review committees act as a panel of investigators' peers, and their composition should be such as can ensure adequate review of the study proposals referred to them. Their membership should include epidemiologists, other health practitioners, and lay persons qualified to represent a range of community, cultural and moral values. Committees should have diverse composition and include representatives of any populations specially targeted for study. The members should change periodically to prevent individuals from becoming unduly influential, and to widen the network involved in ethical review. Independence from the investigators is maintained by precluding any member with a direct interest in a proposal from participating in its assessment.

Ethical conduct of members of review committees

37. Ethical review committee members must carefully guard against any tendencies to

unethical conduct on their own part. In particular, they should protect the confidentiality of review-committee documents and discussions. Also, they should not compel investigators to submit to unnecessary repetition of review.

Representation of the community

38. The community to be studied should be represented in the ethical review process. This is consistent with respect for the culture, the dignity and self-reliance of the community, and the aim of achieving community members' full understanding of the study. It should not be considered that lack of formal education disqualifies community members from joining in constructive discussion on issues relating to the study and the application of its findings.

Balancing personal and social perspectives

39. In performing reviews, committees will consider both personal and social perspectives. While, at the personal level, it is essential to ensure individual informed and free consent, such consent alone may not be sufficient to render a study ethical if the individual's community finds the study objectionable. Social values may raise broad issues that affect future populations and the physical environment. For example, in proposals for the widespread application of measures to control intermediate hosts of disease organisms, investigators will anticipate the effects of those measures on communities and the environment, and review committees will ensure that there is adequate provision for the investigators to monitor the application of the measures so as to prevent unwanted effects.

Assuring scientific soundness

40. The primary functions of ethical review are to protect human subjects against risks of harm or wrong, and to facilitate beneficial studies. Scientific review and ethical review cannot be considered separately: a study that is scientifically unsound is unethical in exposing subjects to risk or inconvenience and achieving no benefit in knowledge. Normally, therefore, ethical review committees consider both scientific and ethical aspects. An ethical review committee may refer technical aspects of scientific review to a scientifically qualified person or committee, but will reach its own decision, based on such qualified advice, on scientific soundness. If a review committee is satisfied that a proposal is scientifically sound, it will then consider whether any risk to the subject is justified by the expected benefit, and whether the proposal is satisfactory with regard to informed consent and other ethical requirements.

Assessment of safety and quality

41. All drugs and devices under investigation must meet adequate standards of safety. In this respect, many countries lack resources to undertake independent assessment of technical data. A governmental multidisciplinary committee with authority to co-opt experts is the most suitable body for assessing the safety and quality of medicines, devices and procedures. Such a committee should include clinicians, pharmacologists, statisticians and epidemiologists, among others; for epidemiological studies, epidemiologists occupy a position of obvious significance. Ethical review procedures should provide for consultation with such a committee.

Equity in the selection of subjects

42. Epidemiological studies are intended to benefit populations, but individual subjects are expected to accept any risks associated with studies. When research is intended to benefit mostly the better off or healthier members of a population, it is particularly important in selecting subjects to avoid inequity on the basis of age, socioeconomic status, disability or other variables. Potential benefits and harm should be distributed equitably within and among

communities that differ on grounds of age, gender, race, or culture, or other variables.

Vulnerable and dependent groups

43. Ethical review committees should be particularly vigilant in the case of proposals involving populations primarily of children, pregnant and nursing women, persons with mental illness or handicap, members of communities unfamiliar with medical concepts, and persons with restricted freedom to make truly independent choices, such as prisoners and medical students. Similar vigilance is called for in the case of proposals for invasive research with no direct benefit to its subjects.

Control groups

44. Epidemiological studies that require control (comparison) or placebo-treated (i.e., non-treated) groups are governed by the same ethical standards as those that apply to clinical trials. Important principles are that:

- (i) the control group in a study of a condition that can cause death, disability or serious distress should receive the most appropriate currently established therapy; and
- (ii) if a procedure being tested against controls is demonstrated to be superior, it should be offered promptly to members of the control group.

A study will be terminated prematurely if the outcome in one group is clearly superior to that in the other, and all subjects will be offered the better treatment. Research protocols should include "stopping rules", i.e., procedures to monitor for, and act upon, such an event.

Investigators must continually bear in mind the potential benefits of the study to the control group, and the prospect of improved health care from applying the findings to the control group.

Randomization

45. Trials in which the choice of regimen or procedure is determined by random allocation should be conducted only when there is genuine uncertainty about differences in outcome of two or more regimens or procedures. Where randomization is to be used, all subjects will be informed of the uncertainty about optimum regimens or procedures, and that the reason for the trial is to determine which of two or more is in the subjects' best interests. Informing subjects about such uncertainty can in itself arouse anxiety among patients, who may already be anxious for other reasons; therefore, tact and delicacy are required in communicating the information. Ethical review committees should ascertain whether investigators refer explicitly to informing subjects about this uncertainty, and should enquire what will be done to allay subjects' anxiety about it.

Random allocation also can cause anxiety: persons chosen for, or excluded from, the experimental regimen or procedure may become anxious or concerned about the reasons for their being chosen or excluded. Investigators may have to communicate to members of the study population some basic concepts about application of the laws of chance, and reassure them that the process of random allocation is not discriminatory.

Provision for multi-centre studies

46. When participation in a multi-centre study is proposed according to a common protocol, a committee will respect different opinions of other committees, while not compromising on the application of the ethical standards that it expects investigators to observe; and it will attempt to reconcile differences so as to preserve the benefits that only a multi-centre study can achieve. One way of doing so could be to include in the common protocol the necessary

procedures. Another would be for the several committees to delegate their review functions to a joint committee of the centres collaborating in the study.

Compensation for accidental injury

47. Some epidemiological studies may inadvertently cause harm. Monetary losses should be promptly repaid. Compensation is difficult when it is not appropriate to make monetary payments. Breach of confidentiality or insensitive publication of study findings, leading to loss of group prestige, or to indignity, may be difficult to remedy. When harm results from a study, the body that has sponsored or endorsed the study should be prepared to make good the injury, by public apology or reparation.

Externally sponsored studies

48. Externally sponsored studies are studies undertaken in a host country but initiated, financed, and sometimes wholly or partly carried out by an external international or national agency, with the collaboration or agreement of the authorities or the host country.

Such a study implies two ethical obligations:

The initiating agency should submit the study protocol to ethical review, in which the ethical standards should be no less exacting than they would be for a study carried out in the initiating country.

The ethical review committee in the host country should satisfy itself that the proposed study meets its own ethical requirements.

49. It is in the interest of the host country to require that proposals initiated and financed externally be submitted for ethical approval in the initiating country, and for endorsement by a responsible authority of the same country, such as a health administration, a research council, or an academy of medicine or science.

50. A secondary objective of externally sponsored studies should be the training of health personnel of the host country to carry out similar study projects independently.

51. Investigators must comply with the ethical rules of the funding country and the host country. Therefore, they must be prepared to submit study proposals to ethical review committees in each country. Alternatively, there may be agreement to the decision of a single or joint ethical review committee. Moreover, if an international agency sponsors a study, its own ethical review requirements may have to be satisfied.

Distinguishing between research and programme evaluation

52. It may at times be difficult to decide whether a particular proposal is for an epidemiological study or for evaluation of a programme on the part of a health-care institution or department. The defining attribute of research is that it is designed to produce new, generalizable knowledge, as distinct from knowledge pertaining only to a particular individual or programme.

For instance, a governmental or hospital department may want to examine patients' records to determine the safety and efficacy of a facility, unit or procedure. If the examination is for research purposes, the proposal should be submitted to the committee that considers the ethical features of research proposals. However, if it is for the purpose of programme evaluation, conducted perhaps by staff of the institution to evaluate a therapeutic programme

for its effects, the proposal may not need to be submitted to ethical review; on the contrary, it could be considered poor practice and unethical not to undertake this type of quality assurance. The prospect of benefit or avoidance of harm to patients may constitute an ethical value that outweighs the risk of breaching the confidentiality of former patients whose medical records are liable to be inspected without their consent.

If it is not clear whether a proposal involves epidemiological study or routine practice, it should be submitted to the ethical review committee responsible for epidemiological protocols, for its opinion on whether the proposal falls within its mandate.

Information to be provided by investigators

53. Whatever the pattern of the procedure of ethical review, the investigator must submit a detailed protocol comprising:

- a clear statement of the objectives, having regard to the present state of knowledge, and a justification for undertaking the investigation in human subjects;
- a precise description of all proposed procedures and interventions, including intended dosages of drugs and planned duration of treatment;
- a statistical plan indicating the number of subjects to be involved;
- the criteria for terminating the study; and
- the criteria determining admission and withdrawal of individual subjects, including full details of the procedure for obtaining informed consent.

Also, the protocol should:

- include information to establish the safety of each proposed procedure and intervention, and of any drug, vaccine or device to be tested, including the results of relevant laboratory and animal research;
- specify the presumed benefits to subjects, and the possible risks of proposed procedures
- indicate the means and documents proposed to be used for eliciting informed consent, or, when such consent cannot be requested, state what approved alternative means of obtaining agreement will be used, and how it is proposed to protect the rights and assure the welfare of subjects;
- provide evidence that the investigator is properly qualified and experienced, or, when necessary, works under a competent supervisor, and that the investigator has access to adequate facilities for the safe and efficient conduct of the research;
- describe the proposed means of protecting confidentiality during the processing and publication of study results; and
- refer to any other ethical considerations that may be involved, and indicate that the provisions of the Declaration of Helsinki will be respected.