# International Ethical Guidelines for Epidemiological Studies

Prepared by the
Council for International Organizations of Medical Sciences (CIOMS)
in collaboration with the World Health Organization (WHO)

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The updating process, which began in 2003, was initiated by the CIOMS Secretariat by requesting a number of experts and institutions involved in the formulation of the 1991 CIOMS *International Guidelines for Ethical Review of Epidemiological Studies* to list new and additional topics to be covered in the updated version. Subsequently, drafting was carried out initially by an established Core Group of experts listed in Appendix 4, supported by Professor Juhana E. Idänpään-Heikkilä, then CIOMS Secretary-General, and Mr. Sev Fluss, Senior Adviser of CIOMS and chaired by Professor Michel Vallotton, Swiss Academy of Medical Sciences and President of CIOMS. The task of finalizing the various drafts was led by Professor Alexander Capron, Professor of Law and Medicine, University of Southern California, Los Angeles, California, USA as Principal Rapporteur, assisted by Professor Rodolfo Saracci, Director of Research in Epidemiology, National Research Council, Pisa, Italy and Professor Idänpään-Heikkilä and the CIOMS Secretariat. A consultation was held on the draft Guidelines in June 2007; the participants are listed in Appendix 5. The interest and comments of the many organizations and individuals who responded to the drafts of the Guidelines posted until now on the CIOMS website or otherwise made available are gratefully acknowledged (Appendix 5). A further meeting of the Core Group was held in November 2007 to incorporate the suggestions of the consultants and other comments on the pre-final draft to be posted again in February 2008 on the CIOMS website.

## BACKGROUND

The Council for International Organizations of Medical Sciences (CIOMS) is an international non-governmental organization in official relations with the World Health Organization (WHO). It was founded under the auspices of WHO and the United Nations Educational, Scientific and Cultural and Organization (UNESCO) in 1949; among its mandates is to maintain collaborative relations between national and international medical and scientific groups and the United Nations and its specialized agencies, particularly UNESCO and WHO.

In the late 1970s, CIOMS began working in collaboration with WHO on ethics in relation to research. The initial objective was to prepare guidelines to indicate how the ethical principles that should govern the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki (first issued by the World Medical Association in 1964 and amended in 1975), could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements. The first product of this CIOMS/WHO undertaking was the publication in 1982 of *Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects*.

The period that followed saw rapid advances in medicine and biotechnology, the growth of multinational clinical trials and of research involving children and other vulnerable groups, a shift in attitudes towards regarding human subjects research as largely beneficial rather than threatening, and the outbreak of the HIV/AIDS pandemic. These developments raised new ethical issues not considered in the preparation of *Proposed Guidelines*. Moreover, the Declaration of Helsinki was again twice revised (in 1983 and 1989). It therefore was timely to revise and update the 1982 guidelines, and CIOMS, with the cooperation of WHO and its Global Programme on AIDS, in 1993 issued *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.

During this period, CIOMS and its collaborators also recognized that ethical guidance was also needed for public health research. Therefore, even before the revision of the biomedical research guidelines was completed, *International Guidelines for Ethical Review of Epidemiological Studies* were published in 1991.

In the years that followed, it became apparent that the biomedical guidelines would need to be revised again to address additional issues, especially those arising in controlled clinical trials carried out in low-resource countries by sponsors from richer countries. The updating, which was also necessitated by a major revision in the Declaration of Helsinki in 2000, resulted in the publication by CIOMS and WHO of revised *International Ethical Guidelines for Biomedical Research Involving Human Subjects* in 2002. Like the 1982 and 1993 versions, the new document was designed to be of use, particularly to low-resource countries, in defining national policies on the ethics of biomedical research (and particularly clinical trials of pharmaceuticals), applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving human subjects.

The process of revising the research guidelines that began in the late 1990s made clear that developments in the ethical analysis of all types of research using human subjects had potential implications for the 1991 Guidelines for epidemiological studies. Furthermore, the growing recognition of the importance of epidemiological research to improving the health of the public highlighted the importance of bringing the 1991 guidelines into line with current thinking on ethics and human rights. Therefore, in 2003 CIOMS constituted a core group to consider how the existing ethical guidance for epidemiological studies should be updated. The group initially attempted to make changes in the 1991 document, but then put aside that draft because of the response from persons involved in ethical review committees that they found it difficult to relate the epidemiological guidelines to CIOMS 2002 *International Ethical Guidelines for Biomedical Research.* The group recognized how widely the latter document has been disseminated, so that it is now the basic conceptual and practical guide when research undergoes ethical review in institutions around the world, particularly in developing countries. Intending to ensure that ethical principles are consistently applied to all types of research, the core group decided to prepare a Supplement to the 2002 document that would address the special features of epidemiological studies. The group thereby meant to connect the ethics of epidemiological research with the standards and analysis that have been developed for other types of research involving human subjects and to ease the process of review because many of those using the proposed supplement–especially members of, and

administrators for, ethical review committees–would have experience with using the 2002 *Guidelines* in the context of biomedical research projects.

In February 2006, a draft of the supplement was posted on the CIOMS website and opened to comment from interested parties. The response from groups and individuals involved in biomedical research was largely positive, but the same was not true among epidemiologists. Some accepted the drafters' insistence that the manner of presentation did not signify that the field of epidemiology should be regarded as derivative from or secondary to clinical research. (Quite the contrary, as the drafters noted: the field of epidemiology predates many of the methods now used in clinical research.) But many objected that epidemiologists were not necessarily conversant with the 2002 *Guidelines* and would therefore find it burdensome to have to switch back and forth between the epidemiology supplement and the biomedical research document. They were also concerned that the supplement would not provoke ethical review committees that principally review biomedical research to sufficiently adjust their expectations–and also their membership–to take account of important differences raised by epidemiological studies. At the same time, the critics also stated that ethical review committees that mostly review public health research and other epidemiological studies would find it simpler to have a stand-alone set of guidelines.

A second issue, concerning the scope of the new guidance document for epidemiological research, also emerged from the comments on the 2006 draft. In conducting some studies, epidemiologists alter the physical, chemical, social or psychological conditions to which members of a population are exposed. Such population trials resemble the clinical trials of new drugs and devices that are the principal focus of the 2002 CIOMS *International Ethical Guidelines* except that sometimes the unit of study is not an individual person but a community or other group. It would therefore be possible for those interventional or experimental epidemiological studies to be designed and reviewed under the 2002 document, and to restrict the current guidelines to the unique features of observational epidemiological studies. But such an approach would have several disadvantages.

First, while the CIOMS 2002 guidelines are familiar to many ethical review committees, some committees that only review epidemiological studies may not be familiar with them. These committees would be better served by a single booklet that

addresses both observational and interventional epidemiology. Likewise, epidemiologists, who may move from conducting an observational study to an interventional study, should not have to shift back and forth between one document and the other. Therefore, it is the intention of the core group that this guidance document encompass all types of epidemiological studies.

In the case of interventional studies, the present Guidelines are generally the same as those in the 2002 document,[1] but whenever appropriate the commentary has been focused on issues that arise in epidemiological rather than biomedical research. For example, in biomedical research the focus of protection is typically on avoiding physical or psychological harm; in the context of international studies, attention has often been directed towards the responsibilities of commercial sponsors of research from high-resource countries when they test their products in low-resource countries. In epidemiological research, the sponsors are more likely to be public agencies than commercial companies and the risks are more likely to involve socioeconomic harm (such as through dissemination of private information) rather than physical injury. Of course, some epidemiological research does utilize biomedical interventions (such as vaccines) in one or more population groups, where the risk can be physical as well as social. And even observational studies can involve physical risks, if the failure to change conditions means that some of the subjects of a study are exposed to avoidable risks of harm. Indeed, one of the most infamous cases of unethical research in the Twentieth Century, the so-called Tuskegee Syphilis Study, involved the observation of untreated disease in a group of poor African-Americans in rural Alabama over a forty-year period; the fact that the subjects were unaware of their diagnosis and of the purpose for the public health officials' interest in them and were not offered treatment when antibiotics became generally available caused a scandal that propelled the development of formal rules for research with human beings in the United States.

The present Guidelines address observational studies by noting, in the commentary, the ways in which it may be appropriate to treat such research differently than interventional studies (for example, regarding informed consent).

[1] Small changes have been made in the wording of Guidelines where this was necessary in light of differences between biomedical and epidemiological research, and three Guidelines (22-24) have been added in the present document; they are not, however, narrowly concerned with epidemiological research and are considered appropriate for inclusion in CIOMS's next edition of the *International Ethical Guidelines for Biomedical Research Involving Human Subjects.*

# INTRODUCTION

"Epidemiology is 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." (John Last, *Dictionary of Epidemiology*, 4th edition) This volume sets forth ethical guidance regarding the first part of this definition, namely, 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 process of producing this information.

Epidemiology has made essential contributions to the improvement in human health achieved over the past century. It can be reasonably expected that the field will continue to do so by using ever more powerful and sophisticated scientific tools to increase the understanding of the distribution of health and illness and of their many physical, chemical, biological, behavioural, social and environmental determinants. Indeed, further improving the health of the public depends on making greater use of the tools of epidemiology. At the same time, it is essential that this new knowledge, and the changes for the good that it prompts, be derived from studies conducted according to recognized ethical standards. By focusing on the distinctive aspects of epidemiological research, this document aims to provide the field with just such a set of ethical standards.

Epidemiological research today encompasses a wide spectrum of research ranging from the investigation of disease causation using the tools of molecular biology in populations to the evaluation of health services and from analysis of the social factors conditioning health and disease to large-scale studies of new public health interventions to prevent disease. All aspects of health when studied at the level of the population are the proper domain of epidemiology, which also provides essential inputs for clinicians, policymakers and social analysts, for example on disease frequency or on the effects of different interventions to control a disease.

In epidemiology, the term "studies" encompasses both routine applications of epidemiological methods–for example, in public health surveillance or hospital quality evaluation–and investigations designed to produce new scientific knowledge and theories; the latter are addressed in the present Guidelines and commentaries. The text adopts the usage common in biomedical research, in which the term "study" is

used–along with "investigation" or "trial"–to designate research activities; thus in what follows, references to "epidemiological studies" denote epidemiological research rather than practice.

*Research and practice.* In order to avoid imposing on the ordinary practice of medicine all the rules and procedures created over the past six decades to protect research subjects, it is conventional to define "research" as involving activities that are designed to develop or contribute to generalizable knowledge. Generalizable knowledge consists of theories, principles or relationships, or the accumulation of information on which they are based, that can be corroborated by accepted scientific methods of observation and inference. In contrast, when a physician or psychologist varies conventional treatment in an attempt to produce a better result for a patient, one might say that he or she was "experimenting" but since such individualized variations do not produce generalizable knowledge, the activity would be regarded as practice not research.

The "generalizable knowledge" definition works well for medical and behavioural studies pertaining to human health, which are commonly denominated "biomedical research" to indicate its relation to health. But the definition works less well in separating practice from research in the field of epidemiology. Many studies using the tools of epidemiology which are performed on a regular basis by public health agencies, such as routine surveillance for disease outbreaks, are correctly viewed as "practice" even though the information produced may contribute to generalizable knowledge. Thus, in carrying out their activities epidemiologists (and others examining the activities) need to apply careful judgment to determine whether the activity should be classified as research or practice. Of course, as explained more fully in these Guidelines, it does not necessarily follow that everything placed in the former category is problematic or is even subject to all the requirements for advance approval and individualized informed consent usually associated with research. Conversely, some activities that are routinely carried out by epidemiologists do raise ethical issues that may benefit from careful scrutiny or even reconsideration, even if they have long traditions and are sanctioned by regulations or statutes.

*Ethics and epidemiology.* Progress in medical care and disease prevention depends upon an understanding not only of physiological and pathological processes

but also of the social, cultural, economic, and other environmental determinants of health, including the effects of the health-care system and other social institutions. Producing that understanding requires performing research involving human subjects. Such research should be carried out only by, or strictly supervised by, suitably qualified and experienced investigators under accepted ethical guidelines.

Ethical guidelines assist both investigators and ethical review committees in acting responsibly. Investigators, with whom rests the primary duty to protect the rights and welfare of research subjects and to ensure the scientific quality of research, can benefit through better design and administration of their protocols, including the processes for obtaining consent and communicating their research findings, while ethical review committees can benefit through improved evaluation and oversight of studies. In their respective roles, each has a duty to see that research plans are transparent, that subjects' data and biological samples are actually used for valid studies, that study results are made publicly available, and that unnecessary administrative obstacles to research–should they occur–are effectively removed.

Because of their merely observational nature, epidemiological studies in the past were widely regarded as not raising any significant ethical issues and were commonly carried out without approval of an ethical review committee. However, recent years have brought increased attention to the ethical conduct of research generally, greater awareness of the potential harms to research subjects including non-physical harm from disclosures of health-related information and hence increased efforts to protect privacy. All of these have implications for observational epidemiological research. Investigators and review committees need to take differences between interventional and observational studies into consideration in designing and approving observational studies. In some cases, the differences can simplify the ethical review process; in others, additional considerations are raised.

The mere formulation of ethical guidelines for epidemiological research involving human subjects will hardly resolve all the moral doubts that can arise in association with such research. Nonetheless, the present Guidelines are intended at least to draw the attention of investigators, sponsors and ethical review committees to the need to consider carefully the ethical implications of research protocols and the manner in which research is conducted, and thus to conduce to high scientific and ethical standards in epidemiological research.

## INTERNATIONAL INSTRUMENTS AND GUIDELINES

The first official international statement on the ethics of medical research was promulgated in 1947 as part of the judgment of the court in Nuremberg that tried the Nazi physicians who had conducted atrocious experiments on unconsenting prisoners and detainees during the Second World War. The judges set forth ten conditions– which became known as the Nuremberg Code–for the ethical conduct of research involving human subjects, emphasizing the necessity of voluntary consent.

The Universal Declaration of Human Rights, adopted by the United Nations General Assembly in 1948 in the wake of the judgment in *The Doctors' Case*, states that "No one shall be subjected . . . to cruel, inhuman or degrading treatment or punishment" (Article 5). The International Covenant on Civil and Political Rights, approved by the General Assembly in 1966 to give the Declaration legal as well as moral force, explicates that this prohibition means that "In particular, no one shall be subjected without his free consent to medical or scientific experimentation." (Article 7). (Many countries have incorporated this provision or its equivalent into their constitution or public health laws and regulations.) Subsequent human rights instruments, which provide special protection to women (Convention on the Elimination of All Forms of Discrimination Against Women) and children (Convention on the Rights of the Child), reinforce the connection between human rights and the ethical principles that underlie a number of international guidelines for research with human beings.

The most prominent of these began taking shape in the 1950s, when the World Medical Association (WMA) began the process of articulating a set of duties for physicians conducting medical research. Though it drew on the Nuremberg Code, the WMA wanted a set of standards that was generated by the profession itself (free of any association with the wartime physician-criminals) and that encompassed research undertaken in the course of medical care. The resulting declaration, adopted at the WMA meeting in Helsinki in 1964, became a fundamental document in the field of research ethics and has influenced the formulation of international, regional and national legislation and codes of conduct. The Declaration, which has been amended several times, most recently in 2000 (Appendix 3), is a comprehensive international statement of the ethics of research involving human subjects. It sets out ethical

guidelines for physicians engaged in both clinical and nonclinical biomedical research.

Since the publication of the CIOMS 1993 Guidelines, several international organizations have issued ethical guidance on clinical trials. These have included, from the World Health Organization, in 1995, *Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products*; and from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in 1996, *Guideline on Good Clinical Practice*, designed to ensure that data generated from clinical trials are mutually acceptable to regulatory authorities in the European Union, Japan and the United States of America. The Joint United Nations Programme on HIV/AIDS published in 2000 the UNAIDS Guidance Document *Ethical Considerations in HIV Preventive Vaccine Research*; a revised version, *Ethical Considerations in Biomedical HIV Prevention Trials*, was produced by UNAIDS and WHO in 2007.

In 2001 the Council of Ministers of the European Union adopted a Directive on clinical trials, which became binding in law in the countries of the Union in 2004. The Council of Europe, with more than 40 Member States, has approved a Protocol on Biomedical Research (which was opened for ratification by Member States on 25 January 2005) to implement the provisions of its 1997 Convention on Human Rights and Biomedicine that relate to biomedical research.

## GENERAL ETHICAL PRINCIPLES

All research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficence and justice. It is generally agreed that these principles, which in the abstract have equal moral force, guide the conscientious preparation of proposals for scientific studies. In varying circumstances they may be expressed differently and given different moral weight, and their application may lead to different decisions or courses of action. The present guidelines are directed at the application of these principles to research involving human subjects.

***Respect for persons*** incorporates at least two fundamental ethical considerations, namely:

a) respect for autonomy, which requires that those who are capable of deliberation about their personal choices 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*** refers to the ethical obligation to maximize benefits and to minimize harms. 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 safeguard the welfare of the research subjects. Beneficence further proscribes the deliberate infliction of harm on persons; this aspect of beneficence is sometimes expressed as a separate principle, ***nonmaleficence*** (do no harm).

***Justice*** refers to the ethical obligation to treat each person in accordance with what is morally right and proper, to give each person what is due to him or her. In the ethics of research involving human subjects the principle refers primarily to ***distributive justice,*** which requires the equitable distribution of both the burdens and the benefits of participation in research. Differences in distribution of burdens and

benefits are justifiable only if they are based on morally relevant distinctions between persons; one such distinction is vulnerability. "Vulnerability" refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group. Accordingly, special provision must be made for the protection of the rights and welfare of vulnerable persons.

Sponsors of research or investigators cannot, in general, be held accountable for unjust conditions where the research is conducted, but they must refrain from practices that are likely to worsen unjust conditions or contribute to new inequities. Neither should they take advantage of the relative inability of low-resource countries or vulnerable populations to protect their own interests, by conducting research inexpensively and avoiding complex regulatory systems of industrialized countries in order to develop products for the lucrative markets of those countries.

In general, the research project should leave low-resource countries or communities better off than previously or, at least, no worse off. It should be responsive to their health needs and priorities in that any product developed is made reasonably available to them, and as far as possible leave the population in a better position to obtain effective health care and protect its own health.

Justice requires also that the research be responsive to the health conditions or needs of vulnerable subjects. The subjects selected should be the least vulnerable necessary to accomplish the purposes of the research. Risk to vulnerable subjects is most easily justified when it arises from interventions or procedures that hold out for them the prospect of direct health-related benefit. Risk that does not hold out such prospect must be justified by the anticipated benefit to the population of which the individual research subject is representative.

An issue, mainly for those countries and perhaps less pertinent now than in the past, has been the extent to which ethical principles are considered universal or as culturally relative – the universalist versus the pluralist view. The challenge to international research ethics is to apply universal ethical principles to biomedical research in a multicultural world with a multiplicity of health-care systems and considerable variation in standards of health care. The Guidelines take the position that research involving human subjects must not violate any universally applicable

ethical standards, but acknowledge that, in superficial aspects, the application of the ethical principles, e.g., in relation to individual autonomy and informed consent, needs to take account of cultural values, while respecting absolutely the ethical standards.

Finally, it is important to remember the basic distinction between legal norms and ethical norms. While the former are founded on the latter, there is no necessary one-to-one correspondence between each legal and ethical norm. A law may be regarded as unethical by some people (e.g., a law prescribing the death penalty for certain crimes) and likewise, an ethical norm may be regarded as unlawful in a country (e.g., one involving female genital mutilation). Thus it cannot be expected that ethical guidelines, which translate ethical principles into the form of recommendations (rather than of strict norms), will always coincide with legal prescriptions. This applies all the more to international guidelines which are issued in the context of legal dispositions varying from one country to another.

# THE GUIDELINES

## *Guideline 1*

## *Ethical justification and scientific validity of epidemiological research involving human beings*

**The ethical justification of epidemiological research involving human subjects is the prospect of discovering new ways of improving the health of individuals, groups and populations. Such research can be ethically justifiable only if it is carried out in ways that respect and protect, and are fair to, research subjects and that are morally acceptable within the communities in which the research is carried out. Moreover, because scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit, investigators and sponsors must ensure that proposed studies involving human subjects conform to generally accepted scientific principles and are based on adequate knowledge of the pertinent scientific literature.**

### *Commentary on Guideline 1*

*General considerations*. Among the essential features of ethically justified research involving human subjects**,** including research with identifiable human tissue or data, are that the research offers a means of developing information not otherwise obtainable, that the design of the research is scientifically sound, and that the investigators and other research personnel are competent. The methods to be used should be appropriate to the objectives of the research and the field of study. Investigators and sponsors must also ensure that all who participate in the conduct of the research are qualified by virtue of their education and experience to perform competently in their roles. These considerations should be adequately reflected in the research protocol submitted for review and clearance (Appendix 2 specifies the items to be included in a protocol, when relevant). Scientific review is discussed further in the Commentaries to Guidelines 2 and 3: *Ethical review committees* and *Ethical review of externally sponsored research.* Other ethical aspects of research are discussed in the remaining guidelines and their commentaries.

*Observational studies*. While observational research normally does not pose a risk of physical harm to individuals, this is not always the case, for several reasons. First, in some non-experimental studies researchers intervene physically with subjects, such as by taking blood or tissue samples. Second, even when an observational study involves only questionnaires or record-examination, subjects may be at risk of physical or psychological harm. For example, interviewing women in a study of domestic violence may expose them to the risk of further violence. A risk of psychological harm may be present when sensitive questions are asked, for instance asking parents about events surrounding a child's death, or details about sexual habits. Likewise, initiating research on workplace hazards may cause anxiety among both employees and employers. Even research limited to an examination of existing records may entail a risk for the group under investigation (such as stigmatization) or, without causing measurable harm, it may still wrong people by making use of information that they regard as private. Careful planning, open discussions with all concerned parties (such as representatives of workers and managers in occupational health research), vigorous efforts to protect confidential data, and pooling data to larger entities are all part of good study design.

## *Guideline 2*

## *Ethical review committees*

**All proposals to conduct epidemiological research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees. The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review. The investigator must obtain their approval or clearance before undertaking the research. The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring the progress of the study.**

### *Commentary on Guideline 2*

*Inclusion in, or exemption from, review.* Research involves human subjects when an investigator will directly obtain information from individuals or groups or will otherwise acquire identifiable private information about them. Proposals for epidemiological studies, like other research with human subjects, must usually undergo prior scientific and ethical review, although some observational studies, such as those utilizing publicly available or anonymous data, may not be subject to prior review and approval by an ethical review committee under the regulations of the local jurisdiction. When in doubt about whether or not a study involves elements that warrant ethical review, epidemiologists are encouraged to consult the ethical review committee or to submit their studies for review. For example, a study of sensitive topics or behavior (illicit drug use; domestic violence; etc.) may merit review because of its potential effects on a community or group even if the data were to be recorded anonymously. Even when an exemption is claimed, the research protocol should provide justification for the claimed exemption. A public health study not submitted to an ethical review committee should receive administrative confirmation by a competent authority that the study is exempt from review. Epidemiologists should keep in mind that scientific journals generally require that papers submitted for publication have received prior review by an ethical review committee.

*General observations.* Ethical and scientific review committees may function at the institutional, local, regional, or national level, and in some cases at the international level. The regulatory or other governmental authorities concerned should promote uniform standards across committees within a country, and, under all systems, sponsors of research and institutions in which the investigators are employed should allocate sufficient resources to the review process. Review committees may receive money for the activity of reviewing protocols, but under no circumstances may payment be conditioned on a review committee's approval or clearance of a protocol.

*Scientific review.* Scientific review and ethical review are intertwined: scientifically unsound research involving humans as subjects is *ipso facto* unethical in that it may expose them to risk or inconvenience to no purpose; even if there is no risk of injury, the wasting of subjects' and researchers' time in unproductive activities represents

loss of a valuable resource. Epidemiological research involving humans must conform to generally accepted scientific principles, and be based on a thorough knowledge of the scientific literature and other relevant sources of information, as well as adequate preparatory studies. Scientific review must consider, *inter alia*, the study design, including the provisions for avoiding or minimizing risk and for monitoring safety when applicable, as well as the scientific qualifications of the investigators (including education in the principles of research practice).

*Ethical review.* The ethical review committee is responsible for safeguarding the rights, safety, and well-being of the research subjects. Many ethical review committees consider both the scientific and the ethical aspects of proposed research; when the tasks are separated, the ethical review committee must verify that another competent expert body has determined that the research is scientifically sound. The ethical review committee should also ensure that provisions for monitoring of data and safety are in place, either through the committee itself or another body.

Once a research proposal has been found scientifically sound, the ethical review committee should consider whether any known or possible risks to the subjects are justified by the expected benefits, direct or indirect, and whether the proposed research methods will minimize harm and maximize benefit. (See Guideline 8: *Benefits, harms and risks of study participation.)* If the proposal is sound and the balance of risks to anticipated benefits is reasonable, the committee should then determine whether the procedures proposed for obtaining informed consent, when applicable (see Guideline 4), are satisfactory and the process for selecting subjects is equitable. The committee is also responsible for ensuring that all other ethical concerns arising from a protocol are satisfactorily resolved both in principle and in practice, for keeping records of its decisions, and for taking measures to follow up on the conduct of ongoing research projects.

*National (centralized) or local review.* Ethical review committees may be created under the aegis of national or local health administrations, national (or centralized) research councils or other nationally representative bodies. In a highly centralized administration a national, or centralized, review committee may be constituted for

both the scientific and the ethical review of research protocols. In countries where research is not centrally administered, ethical review is more effectively and conveniently undertaken at a local or regional level. The authority of a local ethical review committee may be confined to a single institution (such as a hospital, research institute, or university) or may extend to all institutions in which research is carried out within a defined geographical area.

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. The rules should protect the confidentiality of review-committee documents and discussions. The committee should provide its rules to prospective investigators, and should also never compel investigators to submit to unnecessary repetition of review.

*Committee membership*. Committees competent to review the scientific and/or ethical aspects of epidemiological research proposals have competence on all relevant topics; such committees must be multidisciplinary, including epidemiologists and other experts in the design and analysis of population health studies. It is important that at least some committee members (or experts co-opted on an *ad hoc* basis, as needed for particular studies) be knowledgeable and up-to-date about statistical methods as applied to epidemiology including sampling methodology in general, as well as about the populations being studied in particular (e.g., concerning the existence of subpopulations, social structure, hazards at work, etc.).

In addition to such experts, the membership should include other professionals such as physicians, nurses, lawyers, ethicists and clergy, as well as lay persons qualified to represent the cultural and moral values of the community and to ensure that the rights of the research subjects will be respected. Lack of formal education should not disqualify community members from joining in constructive discussion on issues relating to the study and the application of its findings, and when illiterate persons form the focus of a study they should either be considered for membership or invited to have their views expressed. Committees should include both men and women. A number of members should be replaced periodically, with the aim of blending the advantages of experience with those of fresh perspectives.

Committees that often review occupational health research should include

workers' representatives, and those that often review research proposals directed at specific diseases or impairments should invite or hear the views of individuals or bodies representing patients with such diseases or impairments. Similarly, for research involving such subjects as children, students, elderly persons or employees, committees should invite, or solicit the views of, their representatives or advocates.

*Multi-centre research.* Some research projects are designed to be conducted in a number of centres in different communities or countries. Generally, to ensure that the results will be valid, the study must be conducted in an identical way at each centre. Such studies include various kinds of epidemiological research and evaluations of health service programmes in addition to clinical trials. In multi-centre studies, local ethical or scientific review committees are not normally authorized to change inclusion or exclusion criteria or to make other, similar modifications. They should be fully empowered, however, to prevent a study that they believe to be unethical. Moreover, changes that local review committees believe are necessary to protect the research subjects should be documented and reported to the research institution or sponsor responsible for the whole research programme for consideration and due action, to ensure that all other subjects can be protected and that the research will be valid across sites.

To ensure the validity of multi-centre research, any change in the protocol should be made at every collaborating centre or institution, or, failing this, explicit inter-centre comparability procedures must be introduced; changes made at some but not all will defeat the purpose of multi-centre research. For some multi-centre studies, scientific and ethical review may be facilitated by agreement among centres to accept the conclusions of a single review committee; its members could include a representative of the ethical review committee at each of the centres at which the research is to be conducted, as well as individuals competent to conduct scientific review. In other circumstances, a centralized review may be complemented by local review relating to the local participating investigators and institutions. The central committee can review the study from a scientific and ethical standpoint, while the local committees verify the practicability of the study in their communities, including the infrastructures, the state of training, and ethical considerations of local significance.

In a large multi-centre epidemiological study, individual investigators will not have authority to act independently, with regard to data analysis or to preparation and publication of manuscripts, for instance. Such a trial usually has a set of committees which operate under the direction of a steering committee and are responsible for such functions and decisions. The function of the ethical review committee in such cases is to review the relevant plans with the aim of avoiding abuses.

*Research in emergency situations.* The emerging best practice for research conducted during an emergency–such as population studies of outbreaks of disease or of disasters (and relief efforts)–is to establish the basic research design for various categories of research prior to the emergency. Among other benefits, this permits prior ethical review of at least the major features of the research design. When prior review has not occurred, a review should be provided as quickly as possible. The special problems in obtaining informed consent in emergencies are addressed in the Commentary on Guideline 6.

*Sanctions.* Ethical review committees generally have no authority to impose sanctions on researchers who violate ethical standards in the conduct of research involving humans. They may, however, withdraw ethical approval of a research project if judged necessary. They should be required to monitor the implementation of an approved protocol and its progression, and to report to institutional or governmental authorities any serious or continuing non-compliance with ethical standards as they are reflected in protocols that they have approved or in the conduct of the studies. Failure to submit a protocol to the committee should be considered a clear and serious violation of ethical standards.

Sanctions imposed by governmental, institutional, professional or other authorities possessing disciplinary power should be employed as a last resort. Preferred methods of control include cultivation of an atmosphere of mutual trust, and education and support to promote in researchers and in sponsors the capacity for ethical conduct of research.

Should sanctions become necessary, they should be directed at the non-compliant researchers or sponsors. They may include fines or suspension of eligibility to receive research funding, to use investigational interventions, or to practise their

profession. Unless there are persuasive reasons to do otherwise, editors should refuse to publish the results of research conducted unethically and retract any articles that are subsequently found to contain falsified or fabricated data or to have been based on unethical research. Drug regulatory authorities should consider refusal to accept unethically obtained data submitted in support of an application for authorization to market a product. Such sanctions, however, may deprive of benefit not only the errant researcher or sponsor but also that segment of society intended to benefit from the research; such possible consequences merit careful consideration.

*Potential conflicts of interest.* To maintain a review committee's independence from the investigators and sponsors and to avoid conflict of interest, any member with a special or particular interest in a proposal (whether direct or indirect) should not take part in assessing the proposal if that interest could subvert the member's objective judgment. Members of ethical review committees should be held to the same standard of disclosure as scientific and medical research staff with regard to financial or other interests that could be construed as conflicts of interest. A practical way of avoiding such conflict of interest is for the committee to insist on a declaration of possible conflict of interest by any of its members. A member who makes such a declaration should then withdraw, when doing so is clearly appropriate, either at the member's own discretion or at the request of the other members. Before withdrawing, the member should be permitted to offer comments on the protocol or to respond to questions of other members.

Research sponsors (whether commercial enterprises, governments, or foundations) have good reasons to support studies that are ethically and scientifically acceptable, but cases have arisen in which the conditions of funding may have introduced bias. For example, an investigator may have little or no input into trial design, limited access to the raw data, or limited participation in data interpretation, or study results may not be published if they are unfavourable to the sponsor's product or activity. As the persons directly responsible for their work, investigators should not enter into agreements that interfere unduly with their access to the data or their ability to analyse the data independently, to prepare manuscripts, or to publish them.

Investigators must disclose potential or apparent conflicts of interest on their part to the ethical review committee or to other institutional committees designed to

evaluate and manage such conflicts. Guidance on mechanisms for ethical review committees to deal with conflicts of interest appears in Guideline 22. (See also *Multi-centre research*, above.)

## *Guideline 3*

## *Ethical review of externally sponsored research*

**An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards.**

### *Commentary on Guideline 3*

*Definition.* The term *externally sponsored research* refers to research undertaken in one country (the host) but sponsored, financed, and sometimes wholly or partly carried out by an external international or national organization or company with the collaboration or agreement of the appropriate authorities, institutions and personnel of the host country.

*Ethical and scientific review.* Committees in both the country of the sponsor and the host country have responsibility for conducting scientific and ethical review, as well as the authority to withhold approval of research proposals that fail to meet their scientific or ethical standards. As far as possible, there must be assurance that the review is independent and that there is no conflict of interest that might affect the judgment of members of the review committees in relation to any aspect of the research. When the external sponsor is an international organization, its review of the research protocol must be in accordance with its own independent ethical-review procedures and standards. Committees responsible for reviewing and approving proposals for externally sponsored research should have among their members or

consultants persons who are thoroughly familiar with the customs and traditions of the population or community concerned and sensitive to issues of human dignity.

Committees in the external sponsoring country or international organization have a special responsibility to determine whether the scientific methods are sound and suitable to the aims of the research; whether the drugs, vaccines, devices or procedures to be studied meet adequate standards of safety; whether there is sound justification for conducting the research in the host country rather than in the country of the external sponsor or in another country; and whether the proposed research is in compliance with the ethical standards of the external sponsoring country or international organization.

Committees in the host country have a special responsibility to determine whether the objectives of the research are responsive to the health needs and priorities of that country. The ability to judge the ethical acceptability of various aspects of a research proposal requires a thorough understanding of a community's customs and traditions. The ethical review committee in the host country, therefore, must have as either members or consultants persons with such understanding; it will then be in a favourable position to determine the acceptability of the proposed means of obtaining informed consent and otherwise respecting the rights of prospective subjects as well as of the means proposed to protect the welfare of the research subjects. Such persons should be able, for example, to indicate suitable members of the community to serve as intermediaries between investigators and subjects, and to advise on whether material benefits or inducements may be regarded as appropriate in the light of a community's gift-exchange and other customs and traditions.

When a sponsor or investigator in one country proposes to carry out research in another, the ethical review committees in the two countries may, by agreement, undertake to review different aspects of the research protocol. In short, in respect of host countries either with developed capacity for independent ethical review or in which external sponsors and investigators are contributing substantially to developing such capacity, ethical review in the external, sponsoring country may be limited to ensuring compliance with broadly stated ethical standards. The ethical review committee in the host country can be expected to have greater competence for reviewing the detailed plans for compliance, in view of its better understanding of the cultural and moral values of the population in which it is proposed to conduct the

research; it is also likely to be in a better position to monitor compliance in the course of a study. However, in respect of research in host countries with inadequate capacity for independent ethical review, full review by the ethical review committee in the external sponsoring country or international agency is necessary.

*Industry-sponsored research.* In industry-sponsored research on possible occupational hazards, the protection of confidential information on products and production processes should be respected. Such protection should not, however, prevail over the primary interests of identifying potential health effects and of communicating the research results to all involved parties and to the scientific community.

## *Guideline 4*

## *Individual informed consent*

**For all epidemiological research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law. Waiver of individual informed consent is to be regarded as exceptional, and must in all cases be approved by an ethical review committee unless otherwise permitted under national legislation that conforms to the ethical principles in these Guidelines.**

### *Commentary on Guideline 4*

*General considerations.* Voluntary informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation.

Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research. Informed consent embodies the individual's freedom of choice and respects the individual's autonomy.

As an additional safeguard, it must always be complemented by independent ethical review of research proposals. This safeguard of independent review is particularly important as many individuals are limited in their capacity to give adequate informed consent; they include young children, adults with severe mental or behavioural disorders, and persons who are unfamiliar with medical concepts and technology (See Guidelines 13, 14 and 15).

*Process.* Obtaining informed consent is a process that is begun when initial contact is made with a prospective subject and continues throughout the course of the study. By informing the prospective subjects**,** by repetition and explanation, by answering their questions as they arise, and by ensuring that each individual understands each procedure, investigators elicit their informed consent and in so doing manifest respect for their dignity and autonomy. Each individual must be given as much time as is needed to reach a decision, including time for consultation with family members or others. Adequate time and resources should be set aside for informed-consent procedures.

*Language.* Informing the individual subject must not be simply a ritual recitation of the contents of a written document. Rather, the investigator must convey the information, whether orally or in writing, in language that suits the individual's level of understanding. The investigator must bear in mind that the prospective subject’s ability to understand the information necessary to give informed consent depends on that individual's maturity, intelligence, education and belief system. It depends also on the investigator's ability and willingness to communicate with patience and sensitivity.

*Comprehension.* The investigator must then ensure that the prospective subject has adequately understood the information. The investigator should give each one full opportunity to ask questions and should answer them honestly, promptly and completely. In some instances the investigator may administer an oral or a written test or otherwise determine whether the information has been adequately understood. (See also Commentary on Guideline 6)

*Documentation of consent.* Consent may be indicated in a number of ways. The subject may imply consent by voluntary actions, express consent orally, or sign a consent form. As a general rule, the subject should sign a consent form, or, in the case of incompetence, a legal guardian or other duly authorized representative should do so. The ethical review committee may approve waiver of the requirement of a signed consent form if the research carries no more than minimal risk–that is, risk that is no more likely and not greater than that attached to routine medical or psychological examination–and if the procedures to be used are only those for which signed consent forms are not customarily required outside the research context. Such waivers may also be approved when existence of a signed consent form would be an unjustified threat to the subject's confidentiality. Particularly when the information is complicated, it is usually advisable to give subjects information sheets to retain; these may resemble consent forms in all respects except that subjects are not required to sign them. Their wording should be cleared by the ethical review committee. When consent has been obtained orally, for example in a telephone interview, investigators are responsible for providing documentation or proof of consent.

*Renewing consent.* When material changes occur in the conditions or the procedures of a study the investigator should once again seek informed consent from the subjects. For example, when a study itself (or another source) generates new information that would have to be disclosed were any subjects being newly recruited to the study, existing subjects should be given such information promptly and asked whether they agree to continue in the study.

In long-term studies involving active follow-up, subjects who do not wish to continue will simply stop participating, but in studies involving only passive follow-up it is appropriate to inform subjects periodically of the status of the study and to seek their agreement to continue having their on-going records incorporated into the data base. Prior to the initiation of such long-term studies (i.e., those lasting two or more quinquennia), the plans for such re-consenting should be presented to the ethical review committee responsible for reviewing and approving the study.

*Cultural considerations*. In some cultures an investigator may enter a community to conduct research or approach prospective subjects for their individual consent only

after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent. (To avoid a misunderstanding, the person from whom permission is sought should be informed in advance that consent will be still sought from individuals enrolling in research, lest this practice be seen as unanticipated disrespect for his or her authority.) In some populations the use of a number of local languages may complicate the communication of information to potential subjects and the ability of an investigator to ensure that they truly understand it. Many people in all cultures are unfamiliar with, or do not readily understand, scientific concepts such as those of placebo or randomization. Sponsors and investigators should develop culturally appropriate ways to communicate information that is necessary for adherence to the standard required in the informed consent process. Also, they should describe and justify in the research protocol the procedure they plan to use in communicating information to subjects. For collaborative research in developing countries the research project should, if necessary, include the provision of resources to ensure that informed consent can indeed be obtained legitimately within different linguistic and cultural settings.

*Consultation with community members.* Even when individualized consent is not feasible, investigators may be asked by the ethical review committee to ascertain the views of representative members of the relevant community on the proposed research. Consultation with the community should be sustained throughout the period of the study; eliciting community concerns may require study staff to mobilize the community and provide means for members to express their opinions. The opinions of persons in a position equivalent to those whose biological samples or records will be used in a study offer a relevant point for determining whether such a study would offend community norms of privacy and autonomy. Such efforts are not the same as obtaining permission from community leaders to undertake a study; rather they are aimed at obtaining the views of people who are in effect proxies for the potential subjects–for example, unions or other workers' organizations for studies involving occupational records, associations that represent population at high risk for disease (such as sex workers' groups, in the case of HIV infection), and patient organizations

for studies involving records or pathology specimens stored at a hospital. In designing their studies, researchers should be guided by this feedback in deciding whether, or to what extent, the persons whose records or specimens will be studied would be likely to object to such use if it were possible to ask them individually; likewise, ethical review committees may request that the researcher supply information from such community consultations as a part of a research proposal to use personally identifiable records or samples without individual informed consent. The process of community consultation, and the justification for using it, should be specified in the protocol so that the ethical review committee can evaluate what is proposed.

*Community review of, and permission for, studies.* Investigators carrying out epidemiological research sometimes include a process of review by representatives of the community in which it is proposed to conduct the study, particularly when the research originates outside that community or even outside the country in which the community is located. Such review can take the form of a "dialogue" with the community about the proposed study and its potential implications, or a more structured consultation that would document the concerns of a socially identifiable group. In some cases, formal approval may be legally required; for example, under US law, a Native American tribal council must formally approve any research conducted within tribal jurisdiction. In industry-based occupational epidemiology, the agreement and cooperation of employers and employees is a necessary requisite to the conduct of studies. Epidemiologists should usually follow the same approach when developing field investigations, especially when research findings may be presented or interpreted in ways that directly relate to a community or other identifiable group of people or in which the collectivity itself is the unit of analysis. Those consulted should be in a position to speak on behalf of the community or to reflect its views; researchers should have adequate time and resources to discern how the study population is organized socially and politically and which groups can best speak with authority for the population. Care should, of course, be taken to ensure that those consulted include all relevant groups and do not exclude, for instance, women or members of minority groups. As previously noted, plans for community review should be specified in the protocol, to allow their evaluation by the ethical review committee.

*Use of medical records and biological specimens collected for other purposes.* People have a right to know that their medical records or biological specimens may be used for research. Records and specimens taken in the course of clinical care, or for an earlier study, may be used for research without the consent of the patients/subjects only if an ethical review committee has determined that the research poses minimal risk, that the rights or interests of the patients will not be violated, that their privacy and confidentiality or anonymity are assured, and that the research is designed to answer an important question and would be impracticable if the requirement for informed consent were to be imposed. Appropriate standards and procedures are discussed more fully in Guideline 24 and its Commentary. (See also Guideline 18)

*Waiver of consent requirements in epidemiological studies.* Investigators should not initiate epidemiological research involving human subjects without first obtaining each subject's informed consent, unless they have received explicit approval to do so from an ethical review committee or the research activity is authorized by legislation or competent authorities in accord with the ethical principles in these Guidelines. Categories of epidemiological research for which consent may be waived include:

a. the use of personally non-identifiable materials;
b. the use of personally identifiable materials with special justification;
c. studies performed within the scope of regulatory authority;
d. studies using health-related registries that are authorized under national regulations; and
e. cluster-randomized trials.

The rules and processes for waiver of consent apply also to situations in which permission is obtained from appropriate surrogates for research involving subjects who lack the capacity to consent for themselves (see Guidelines 14 and 15).

*a. When personally non-identifiable materials are used.* As noted under Guideline 2, some epidemiological studies, for example those using publicly available data, may be exempt from ethical review and, *a fortiori*, from individual informed consent. In other cases, review may be appropriate but individual consent may not be relevant or required. For example, the individual consent requirement does not arise when the

materials used in the research are not personally identifiable (meaning that, by definition, the individuals concerned would be unknown to the researcher and hence could not be contacted to obtain consent).

*b. When personally identifiable materials are used.* Even when a study involves data or material that carry a person's name or that are linked by a code to a person, an ethical review committee may approve observational research using such data or material without requiring individual consent prior to the research. The committee may do so if it is convinced by the protocol that (a) subjects would be exposed to no more than minimal risk, and (b) either the study involves only publicly available data or the requirement of individual informed consent would make the conduct of the research impracticable.

An investigator who proposes not to seek informed consent for a non-interventional study that uses personally identifiable information which is not publicly available (including data derived from biological samples and medical records) must justify to an ethical review committee not obtaining consent; the committee should ensure that access to such information is strictly limited in time and extent for the specific research purposes, that allowing the investigator to use it will not compromise the interests or welfare of any persons identified by the data, that any risk of harm will be minimized, that the use accords with locally applicable legal requirements, and that there is no known objection of the individual to such use. (The obligation of institutions to make available means for people to opt out of having their stored biological material and associated records used for research is discussed in Guideline 24 and the associated Commentary.)

The most common justification for using records or samples collected in the past without consent is that it would be impracticable or prohibitively expensive to locate the persons whose samples or records are to be examined; this may happen when, for instance, the study involves reviewing hospital records or performing new tests on blood samples collected at a time when consent to future research uses of such samples was not usually sought (a point further elaborated under Guideline 24). On the other hand, the reluctance of individuals to agree to participate would not constitute impracticability; data from individuals who have specifically rejected such uses in the past may be used only with proper, official authorization in public health

emergencies. (The special circumstances of consent for research under emergency conditions is elaborated in the Commentary on Guideline 2.)

Implicit in the argument for use of personally identifiable material without consent is the claim that the value of the research and the unfeasibility of obtaining consent justify violating a person's interest in becoming a subject of research only with his or her knowledge and agreement. Thus, the task of the ethical review committee in each case is to evaluate the merits of this claim when set forth by an investigator: how important is the research and could the desired information be produced by another method, what would be the costs and burdens of contacting the persons whose data would be used in the study, how difficult would it be to meet those costs and burdens, and is the imposition of this difficulty justified by the nature of the interests that would be infringed or the potential harm created by allowing the investigator to proceed without consent?

The committee should also consider whether any mitigation–such as anonymizing the data–can be undertaken without seriously compromising the scientific merits of the proposed study. When research using personally identifiable data from records or samples collected in the past without an appropriate consent procedure is permitted without consent, the committee should ensure that the investigator (and sponsor) will strictly safeguard the confidentiality of subjects. For this purpose, up-to-date technical means of data encryption may be valuable for safeguarding the confidentiality of records.

Anonymization of samples and data will also make it impossible to convey to subjects any findings that might be relevant to the health of the person concerned or family members. Studies that could produce such findings should always include information about the circumstances, if any, under which such findings would be disclosed to the persons concerned or others. It is usually acceptable not to disclose such findings; indeed, it is often imprudent to convey individual findings in research because the significance of the finding will not be well established and the method used may not yet have met the standards used for clinically approved tests. If it is determined that the research is of a sort that could produce clinically significant findings, an alternative to irreversible anonymization would be to lodge the key to the coding system with an independent third party who would take on the responsibility

of notifying the persons concerned when a specified potential hazard has been identified.

*c. When studies are performed within the scope of regulatory authority.* Consent may also not be required for studies that involve data not publicly available but which are carried out under legislative or regulatory authority for public health, such as disease surveillance. The extent and limits of such permission are a matter of local law but epidemiologists must still consider whether, in a given case, it is ethical to use their public authority to access personal data for research purposes. When their use of such data does not clearly constitute a public health activity (e.g., when adverse reaction monitoring produces findings which raise a research issue the study of which would go beyond routine surveillance), the epidemiologists should seek individual consent for the use of the data or demonstrate that the research meets one of the other conditions for waiving informed consent, as explained in this Commentary. Even when individual consent is not required, the usual expectations of risk minimization, protection of confidentiality, and compliance with all other legal requirements still apply.

*d. Studies using health-related registries.* The creation and maintenance of health-related registries (e.g., cancer registries, databanks of genetic and other anomalies in newborn babies, etc.) provide a major resource for many public health activities, from disease prevention to resource allocation. Several considerations support the common practice of requiring that all practitioners submit relevant data to such registries: the importance of having comprehensive information to provide accurate information about an entire population; the scientific need to include all cases in order to avoid undetectable selection bias; and the general ethical principle that burdens and benefits should be distributed equitably across the population. Hence, registries that are established or officially recognized by governmental authorities usually involve mandatory rather than voluntary collection of data.

Studies using data from such registries (as well as studies that link data from several registries or that combine registry-data with information from publicly available sources) thus involve the use of data that have been compiled without the informed consent of the individuals involved. Such studies should be submitted to an

ethical review committee and permission should also be sought from the competent authority that is legally responsible for the maintenance and use of the registry. When an investigator plans to contact persons based on their inclusion in the registry (e.g., to obtain from them additional information for research purposes beyond the data supplied by the registry), the investigator should bear in mind that these persons may be unaware that their data were submitted to the registry or unfamiliar with the process by which investigators obtain access to the data. Investigators are cautioned to ensure that their access to the registry information is appropriately explained to the potential research subjects by the people who run the registry or other public authorities, preferably before the investigators approach the subjects.

*e. Cluster-randomized trials.* Epidemiological research can take the form of a trial in which an intervention is targeted to a whole group of people such as all the students in a school or all residents of a community, and in which the groups–rather than the individuals within the group–are randomly assigned to the different arms of the trial. Examples include a vaccination campaign applied at the school level, fluoridation of the drinking-water supply to prevent dental caries, a change in healthcare reimbursement policies, or a change in incineration practices at local waste disposal sites. In a cluster-randomized trial, individual persons usually do not have an opportunity to consent to the study itself but should typically still be made aware that it will take place. Depending upon the way the study is conducted, individuals may or may not be able to decline participation in the study. For example, parents could consent or not consent to their child's vaccination at school or a person could decide to drink bottled water rather than use water that may be fluoridated; conversely, it would be difficult for a person to change the air he or she breathed outside in a study comparing methods of incinerating waste, or for a person to move to a different jurisdiction where the experimental method for healthcare reimbursement is not being tested. As in all studies, investigators have a responsibility to describe in the protocol the information that will be provided to the decision-makers and to individuals within the clusters.

In a cluster-randomized trial, the investigator should identify an appropriate person or body (e.g., a community leader, headmaster, or local health council) that has authority to give permission for the cluster to participate in the study and to be

assigned on a random basis to one arm or another of the study. While this decision-maker may not have been appointed or elected for the specific purpose of giving permission for the cluster to participate in research, the scope of authority should encompass interventions of the type in question if provided outside of a research project; moreover, the decision-maker should ensure that the risks of participation in the study and the randomization are commensurate with the benefits for the cluster or for society. The decision-maker may choose to consult a wider group of community representatives or advisers before taking the decision to permit the study.

## *Guideline 5*

## *Obtaining informed consent:*

## *Essential information for prospective research subjects*

**Before requesting an individual's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand:**

1) **that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;**

2) **that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled;**

3) **the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care;**

4) **for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;**

5) **the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;**

6) **whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount;**

7) **that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status;**

8) **that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such non-disclosure);**

9) **any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner;**

10) **the direct benefits, if any, expected to result to subjects from participating in the research;**

11) **the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;**

12) **whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them;**

13) **any currently available alternative interventions or courses of treatment;**

14) **the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified;**

15) **the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;**

16) **policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject;**

17) **the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;**

18) **the possible research uses, direct or secondary, of the subject's medical records and of biological specimens taken in the course of clinical care (See also Guidelines 4 and 18 Commentaries);**

19) **whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed (See Guideline 4 Commentary);**

20) **whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products;**

21) **whether the investigator is serving only as an investigator or as both investigator and the subject's physician;**

22) **the extent of the investigator's responsibility to provide medical**

**services to the participant;**

23) **that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment;**

24) **in what way, and by what organization, the subject or the subject's family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation);**

25) **whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed;**

26) **that an ethical review committee has approved or cleared the research protocol.**

### *Commentary on Guideline 5*

The points specified in this Guideline–which were developed in the context of biomedical research–are generally relevant when obtaining informed consent for interventional research (especially population studies of drugs and devices) but are not all required in most observational studies. (In particular, items 4, 12, 13, and 21-24 are unlikely to be relevant.) Depending on the specifics of the study design, the investigator will need to justify to the ethical review committee why any particular items have been omitted from the consent process; a committee may, of course, decide that the researcher should be encouraged, as a prudential matter, to include some points that are not strictly speaking required. Alternatively, an ethical review committee may wish to provide investigators with a shorter list of points to be addressed in the consent process for observational studies.

Some of the points specified in this Guideline present special problems in the context of epidemiological research. The statement in Item #2 that individuals are "free to withdraw from the research at any time" rests on the principle that it is ethically unacceptable to force a person to participate in research. In epidemiological studies, a person's "withdrawal" from research can take several forms. The first, which is a subject's request that the gathering of new data about the subject cease (e.g., in a longitudinal study), must be honored, just as any other withdrawal from on-going participation in a study should be. The second could involve a request that the person's data (and perhaps biological materials) be removed from a database and/or repository. Such removal may be very difficult (or impossible if the data have been anonymized), would risk undermining the validity of studies using the database, and would typically seem disproportional to the individual's interest, since–unlike an on-going intervention study–the person does not bear any burden at present. If an investigator, with the approval of the ethical review committee, does not intend to honor requests to remove data and/or biological samples, this policy should be clearly stated in the consent document.

Item #7 requires two things: that subjects as a group be informed about the general findings of a study and that individuals be informed about any test results or other findings relevant to their personal health status. As noted in the Commentary to Guideline 4, when a study employs anonymization, which makes it impossible to notify individuals (and, in some cases, even identifiable groups of subjects) of research findings or personal test results, the ethical review committee should take this into account in deciding whether to approve the study. Even when they have not anonymized the data, epidemiologists have often not notified individual subjects of test results. In light of contemporary standards for informed consent, however, epidemiologists should make subjects aware of findings that are clinically relevant to their individual health. When (e.g., because of the scale of a particular study) an investigator does not plan to do so, he or she must obtain approval from the ethical review committee. In all cases, the extent to which findings will be disclosed to subjects as a group or as individuals should be clearly conveyed in the informed consent material.

## *Guideline 6*

## *Obtaining informed consent:*

## *Obligations of investigators and sponsors*

**Investigators have a duty to:**

- **refrain from unjustified deception, undue influence, or intimidation;**

- **seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of participation and has had sufficient opportunity to consider whether to participate;**

- **when individual consent is required, obtain from each prospective subject a signed form as evidence of informed consent– investigators should justify any exceptions to this general rule and obtain the approval of the ethical review committee (See Guideline 4 Commentary, *Documentation of consent*);**

- **renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate; and,**

- **renew the informed consent of each subject in long-term studies at pre-determined intervals, even if there are no changes in the design or objectives of the research.**

**The principal investigator has a non-delegable duty to ensure that all personnel working on the study comply with this Guideline.**

**Sponsors have a duty to ensure that these obligations are fulfilled.**

***Commentary on Guideline 6***

The investigator is responsible for ensuring the adequacy of informed consent from each subject, whether the investigator undertakes this task or delegates it to other members of the research team. The person obtaining informed consent should be knowledgeable about the research and capable of answering questions from prospective subjects. Investigators in charge of the study must make themselves available to answer questions at the request of subjects. Any restrictions on the subject's opportunity to ask questions and receive answers before or during the research undermines the validity of the informed consent.

*Consent by subjects enrolled by mail or electronic means.* In some epidemiological studies, no face-to-face contact occurs between investigators and subjects. For example, subjects may be asked to provide electronic authorization for the use of their personal data in a study, or subjects may be asked to complete a questionnaire over the Internet. When subjects are enrolled in such studies by mail or electronic means (e.g., e-mail, Internet, etc.), difficulties may arise in fulfilling investigators' duties to ensure that subjects are able to receive answers to any questions and to ascertain that subjects adequately understand relevant facts. Potential subjects enrolled in these ways should therefore be given a means (such as a toll-free phone number or email address) to enable them to pose questions to, and receive answers from, the research team concerning the study. Since investigators may not have direct contact, through such means of communication, with all potential subjects, it is especially important that the materials used for mail enrolment are worded carefully to maximize the chances that the subjects enrolled will have an adequate understanding of information relevant to their participation in the study. (see also Guideline 23)

*Withholding information and deception.* Sometimes, to ensure the validity of research, investigators withhold certain information in the consent process. For example, when tests will be performed to monitor subjects' compliance with a protocol, subjects may not be told the purpose of the testing, since if they knew their compliance was being monitored they might modify their behaviour and hence invalidate results. In most such cases, the prospective subjects are asked to consent to remain uninformed of the purpose of some procedures until the research is completed; after the conclusion of the study they are given the omitted information. More generally, when providing

certain information (e.g., regarding the study hypothesis) would jeopardize the validity of the research, subjects are sometimes not even told that some information has been withheld until after the research has been completed. Any withholding of information, and the procedures used to provide information subsequently, must receive the explicit approval of the ethical review committee based on the necessity of the withholding, the minimization of attendant risks to subjects, and the adequacy of the procedures for “debriefing” subjects after their participation in the study.

Active deception of subjects is considerably more controversial than simply withholding certain information. Lying to subjects is a tactic not commonly employed in biomedical research. Social and behavioural scientists, however, sometimes deliberately misinform subjects to study their attitudes and behaviour. For example, scientists have pretended to be patients to study the behaviour of health-care professionals and patients in their natural settings.

Some people maintain that active deception is never permissible. Others would permit it in certain circumstances. Deception is not permissible, however, in cases in which the deception itself would disguise the possibility of the subject being exposed to more than minimal risk. When deception is deemed indispensable to the methods of a study, the investigators must demonstrate to an ethical review committee that no other research method would suffice; that significant advances could result from the research; and that nothing has been withheld that, if divulged, would cause a reasonable person to refuse to participate. The ethical review committee should determine the consequences for the subject of being deceived, and whether and how deceived subjects should be informed of the deception upon completion of the research. Such informing, commonly called "debriefing", ordinarily entails explaining the reasons for the deception. A subject who disapproves of having been deceived should be offered an opportunity to refuse to allow the investigator to use information thus obtained. Investigators and ethical review committees should be aware that deceiving research subjects may wrong them as well as harm them; subjects may resent not having been informed when they learn that they have participated in a study under false pretences. In some studies there may be justification for deceiving persons other than the subjects by either withholding or disguising elements of information. Such tactics are often proposed, for example, for studies of the abuse of spouses or children. An ethical review committee must review and approve all proposals to

deceive persons other than the subjects. Subjects are entitled to prompt and honest answers to their questions; the ethical review committee must determine for each study whether others who are to be deceived are similarly entitled.

*Intimidation and undue influence.* Intimidation in any form invalidates informed consent. Prospective subjects who are patients often depend for medical care upon the physician/investigator, who consequently has a certain credibility in their eyes, and whose influence over them may be considerable, particularly if the study protocol has a therapeutic component**.** They may fear, for example, that refusal to participate would damage the therapeutic relationship or result in the withholding of health services. The physician/investigator must assure them that their decision on whether to participate will not affect the therapeutic relationship or other benefits to which they are entitled. In this situation the ethical review committee should consider whether a neutral third party should seek informed consent.

The prospective subject must not be exposed to undue influence. The borderline between justifiable persuasion and undue influence is imprecise, however. The researcher should give no unjustifiable assurances about the benefits, risks or inconveniences of the research, for example, or induce a close relative or a community leader to influence a prospective subject's decision. (See also Guideline 4: *Individual informed consent.)*

*Risks.* Investigators should be as objective as possible in discussing the details of the experimental intervention, the pain and discomfort that it may entail, and known risks and possible hazards. In complex research projects it may be neither feasible nor desirable to inform prospective participants fully about every possible risk. They must, however, be informed of all risks that a 'reasonable person' would consider material to making a decision about whether to participate, including risks to a spouse or partner associated with trials of, for example, psychotropic or genital-tract medicaments. (See also Guideline 8 Commentary, *Risks to groups of persons.*)

*Exception to the requirement of informed consent for interventional studies to include persons rendered incapable of informed consent by an acute condition.* Certain persons with acute conditions that render them incapable of giving informed consent

may be eligible for inclusion in a study concerning an acute condition in which the majority of prospective subjects will be capable of informed consent, and in which the investigational intervention would hold out the prospect of direct benefit and would be justified accordingly. When the investigation involves certain procedures or interventions that would not be of direct benefit yet carry no more than minimal risk (such as the collection of additional blood for research purposes), the initial protocol submitted for approval to the ethical review committee should anticipate that some persons may be incapable of consent, and should propose for such patients a form of proxy consent, such as permission of the responsible relative. When the ethical review committee has approved or cleared such a protocol, an investigator may seek the permission of the responsible relative and enrol such a person.

## *Guideline 7*

## *Compensation for participation*

**Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ("undue inducement"). All payments, reimbursements and medical services provided to research subjects must have been approved by an ethical review committee.**

### *Commentary on Guideline 7*

*Acceptable recompense.* Research subjects may be reimbursed for their transport and other expenses, including lost earnings, associated with their participation in research. Those who receive no direct benefit from the research may also receive a small sum of money for inconvenience due to their participation in the research. All subjects may receive medical services unrelated to the research and have procedures and tests performed free of charge.

*Unacceptable recompense.* Payments in money or in kind to research subjects should not be so large as to persuade them to take undue risks or volunteer against their better judgment. Payments or rewards that undermine a person's capacity to exercise free choice invalidate consent. It may be difficult to distinguish between suitable recompense and undue influence to participate in research. An unemployed person or a student may view promised recompense differently from an employed person. Someone without access to medical care may or may not be unduly influenced to participate in research simply to receive such care. A prospective subject may be induced to participate in order to obtain a better diagnosis or access to a drug not otherwise available; local ethical review committees may find such inducements acceptable. Monetary and in-kind recompense must, therefore, be evaluated in the light of the traditions of the particular culture and population in which they are offered, to determine whether they constitute undue influence. The ethical review committee will ordinarily be the best judge of what constitutes reasonable material recompense in particular circumstances. When research interventions or procedures that do not hold out the prospect of direct benefit present more than minimal risk, all parties involved in the research–sponsors, investigators and ethical review committees –in both funding and host countries should be careful to avoid undue material inducement.

*Incompetent persons.* Incompetent persons may be vulnerable to exploitation for financial gain by guardians. A guardian asked to give permission on behalf of an incompetent person should be offered no recompense other than a refund of travel and related expenses.

*Withdrawal from a study.* A subject who withdraws from research for reasons related to the study, such as unacceptable side-effects of the intervention being studied, or who is withdrawn on health grounds, should be paid or recompensed as if full participation had taken place. A subject who withdraws for any other reason should be paid in proportion to the amount of participation. An investigator who must remove a subject from the study for wilful noncompliance is entitled to withhold part or all of the payment.

## *Guideline 8*

## *Benefits, harms and risks of study participation*

**For all epidemiological research involving human subjects, the investigator must ensure that potential benefits and harms are reasonably balanced and risks are minimized.**

- **Interventions or procedures that hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual subject must be justified by the expectation that they will be at least as advantageous to the individual subject, in the light of foreseeable harms and benefits, as any available alternative. Risks of such 'beneficial' interventions or procedures must be justified in relation to expected benefits to the individual subject.**

- **Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be justified in relation to the expected benefits to society. The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained.**

### *Commentary on Guideline 8*

*Ethical grounding*. The Declaration of Helsinki in several paragraphs deals with the well-being of research subjects and the avoidance of harm, specifically: considerations related to the well-being of the human subject should take precedence over the interests of science and society *(Paragraph 5*); clinical testing must be preceded by adequate laboratory or animal experimentation to demonstrate a reasonable probability of success without undue risk (*Paragraph 11*); every project should be preceded by careful assessment of predictable harms and burdens in comparison with foreseeable benefits to the subject or to others (*Paragraph 16*); physician-researchers must be confident that the risks involved have been adequately assessed and can be satisfactorily managed (*Paragraph 17*); and the harms and burdens to the subject must be minimized, and reasonable in relation to the

importance of the objective or the knowledge to be gained (*Paragraph 18*).

Epidemiological studies may employ a variety of interventions of which some hold out the prospect of direct therapeutic benefit (beneficial interventions) and others are administered solely to answer the research question (non-beneficial interventions). Beneficial interventions are justified as they are in medical practice by the expectation that they will be at least as advantageous to the individuals concerned, in the light of both harms and benefits, as any available alternative. Non-beneficial interventions are assessed differently; they may be justified only by appeal to the knowledge to be gained, either "generalizable knowledge" (the usual objective of a research project) or more particularized findings, of use for example by public health officials.

Paragraphs 5 and 18 of the Declaration of Helsinki do not preclude well-informed volunteers, capable of fully appreciating risks and benefits of an investigation, from participating in research for altruistic reasons or for modest remuneration.

*Experimental studies of preventive interventions*. Epidemiologists carry out experimental studies, in particular randomized population trials, usually to test preventive intervention programmes, for instance administration of a vaccine or a drug, or an organized screening programme. Because they involve the totality of a population or a relevant segment of it (e.g., those believed to be at higher risk of the target disease), these interventions imply that everybody will be submitted to whatever inconvenience and potential harm the intervention entails, while only the minority (often, comparatively small), namely those who would have actually developed the disease, get the benefit of avoiding it thanks to the intervention (the same applies, although to a lesser degree, even when the intervention is concentrated on so-called "high risk" groups). This is an inherent problem of preventive programmes; both investigators and ethical review committees need to carefully weigh the potential harm and inconvenience to programme participants who may not receive any benefit from the programme, and the participants must receive clear and full information before giving their consent. Likewise, research may be conducted on a screening programme for a condition for which no effective treatment exists provided the results could be of sufficient direct relevance to the health of people

other than the participants in the study (for example, in developing a programme for a transmissible disease, whether contagious or genetic).

*Minimizing risk associated with participation in a randomized study.* In a randomized controlled study subjects risk being allocated to receive the intervention that proves inferior. They are allocated by chance to one of two or more intervention arms and followed to a predetermined end-point. (Interventions are understood to include new or established therapies, diagnostic tests and preventive measures.) An intervention is evaluated by comparing it with another intervention (a control), which is ordinarily the best current method, selected from the safe and effective treatments available globally, unless some other control intervention such as placebo can be justified ethically (see Guideline 11).

To minimize risk when the intervention to be tested is designed to prevent or postpone a lethal or disabling outcome, the investigator must not, for experimental purposes, withhold therapy that is known to be superior to the intervention being tested, unless the withholding can be justified by the standards set forth in Guideline 11. Also, the investigator must provide in the research protocol for the monitoring of research data by an independent board (Data and Safety Monitoring Board); one function of such a board is to protect the research subjects from previously unknown adverse reactions or unnecessarily prolonged exposure to an inferior therapy. Normally at the outset of a randomized controlled study, criteria are established for its premature termination (stopping rules or guidelines).

*Risks to groups of persons*. In order to achieve the social benefits anticipated from conducting research, results should be made public. Sometimes, however, research in epidemiology (as well as such other fields as genetics and sociology) may present risks to the interests of communities, societies, or racially or ethnically defined groups. Information might be published that could stigmatize a group or expose its members to discrimination. Such information, for example, could indicate that the group has a higher than average prevalence of alcoholism, mental illness or sexually transmitted disease, or is particularly susceptible to certain genetic disorders. Plans to conduct such research should be sensitive to such considerations, to the need to maintain confidentiality during and after the study, and to the need to publish the

resulting data in a manner that is respectful of the interests of all concerned, or in certain exceptional circumstances not to publish them. The ethical review committee should ensure that the interests of all concerned are given due consideration; often it will be advisable to have individual consent supplemented by community consultation. In assessing the harms and benefits that a protocol presents to a population, it is appropriate to consider the harm that could result from forgoing the research or from failing to publish the results.

[The ethical basis for the justification of risk is elaborated further in Guideline 9]

## *Guideline 9*

## *Special limitations on risk when research involves individuals who are not capable of giving informed consent*

**When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the potential harm from any research intervention that does not hold out the prospect of direct benefit for the individual subject should not be more than minimal.**

### *Commentary on Guideline 9*

*The minimal-risk standard.* Certain individuals or groups may have limited or no capacity to give informed consent either because, as in the case of prisoners, their autonomy is limited, or because they have limited cognitive capacity. Research involving such persons that does not aim to benefit them directly may occur only when its potential risks are found to be no more than minimal.

In addition, the ethical review committee must find: 1) that the research is designed to be responsive to the disease or condition affecting the prospective subjects or to conditions to which they are particularly susceptible; 2) that the objective of the research is sufficiently important to justify exposure of the subjects to the increased risk; and 3) that the interventions are reasonably comparable to the clinical interventions that the subjects have experienced or may be expected to

experience in relation to the condition under investigation. The requirement that the research interventions be reasonably comparable is intended to enable the subjects to draw on personal experience as they decide whether to accept or reject additional procedures for research purposes. Their choices will, therefore, be more informed even though they may not fully meet the standard of informed consent.

*Consent required when subject becomes capable of informed consent.* If such research subjects, including children, become capable of giving independent informed consent during the research, their consent to continued participation should be obtained.

(See also Guidelines 4, 13, 14 and 15.*)*

## *Guideline 10*

## *Research in populations and communities with limited resources*

**Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:**

- **the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and**

- **any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.**

### *Commentary on Guideline 10*

This Guideline is concerned with countries or communities in which resources are limited to the extent that the population is, or may be, vulnerable to exploitation by sponsors and investigators from the relatively wealthy countries and communities. This concern, which has arisen principally from experiences with clinical trials of new drugs, should not stand in the way of carrying out ethically sound epidemiological

studies in resource-limited setting. Such studies are, almost by nature, relevant to the health of the populations or communities in which they are conducted, and the information gathered in such studies can often be very important for improving population health in resource-poor countries and communities.

*Responsiveness of research to health needs and priorities*. To meet the ethical requirement that research be responsive to the health needs of the population or community in which it is carried, it is not sufficient simply to determine that a disease is prevalent in the population and that new or further research is needed: the ethical requirement of "responsiveness" can be fulfilled only if successful interventions or other kinds of health benefit are made available to the population. This is applicable especially to research conducted in countries where governments lack the resources to make such products or benefits widely available. Even when a product to be tested in a particular country is much cheaper than the standard treatment in some other countries, the government or individuals in that country may still be unable to afford it. If the knowledge gained from the research in such a country is used primarily for the benefit of populations that can afford the tested product, the research may rightly be characterized as exploitative and, therefore, unethical**.**

When an investigational intervention has important potential for health care in the host country, the negotiation that the sponsor should undertake to determine the practical implications of "responsiveness", as well as "reasonable availability", should include representatives of stakeholders in the host country; these include the national government, the health ministry, local health authorities, and concerned scientific and ethics groups, as well as representatives of the communities from which subjects are drawn and non-governmental organizations such as health advocacy groups. The negotiation should cover the health-care infrastructure required for safe and rational use of the intervention, the likelihood of authorization for distribution, and decisions regarding payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, when this economic information is not proprietary. In some cases, satisfactory discussion of the availability and distribution of successful products will necessarily engage international organizations, donor governments and bilateral agencies, international nongovernmental organizations, and the private sector. The development of a health-care infrastructure should be facilitated at the

onset so that it can be of use during and beyond the conduct of the research.

Additionally, if an investigational intervention has been shown to be beneficial, the sponsor should continue to provide it to the subjects after the conclusion of the study and pending its approval by a drug regulatory authority, when relevant. The sponsor is unlikely to be in a position to make a beneficial investigational intervention generally available to the community or population until some time after the conclusion of the study, as it may be in short supply and in any case cannot be made generally available before a drug regulatory authority has approved it.

When a study's expected outcome is scientific knowledge rather than a commercial product, such planning or negotiation is rarely, if ever, needed. There must be assurance, however, that the scientific knowledge developed will be used for the benefit of the population.

*Reasonable availability*. The issue of "reasonable availability" is complex and will need to be determined on a case-by-case basis. Relevant considerations include the length of time for which the intervention or product developed, or other agreed benefit, will be made available to research subjects, or to the community or population concerned; the severity of a subject's medical condition; the effect of withdrawing the study drug (e.g., death of a subject); the cost to the subject or health service; and the question of undue inducement if an intervention is provided free of charge.

In general, if there is good reason to believe that a product developed or knowledge generated by research is unlikely to be reasonably available to, or applied to the benefit of, the population of a proposed host country or community after the conclusion of the research, it is unethical to conduct the research in that country or community. This should not be construed as precluding studies designed to evaluate novel therapeutic concepts. As a rare exception, for example, research may be designed to obtain preliminary evidence that a drug or a class of drugs has a beneficial effect in the treatment of a disease that occurs only in regions with extremely limited resources, and it could not be carried out reasonably well in more developed communities. Such research may be justified ethically even if there is no plan in place to make a product available to the population of the host country or community at the conclusion of the preliminary phase of its development. If the concept is found to be

valid, subsequent phases of the research could result in a product that could be made reasonably available at its conclusion.

(See also Guidelines 3,12, 20 and 21.)

## *Guideline 11*

## *Choice of control in clinical trials*

**As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment".**

**Placebos may be used:**

- **when there is no established effective intervention;**

- **when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;**

- **when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.**

### *Commentary on Guideline 11*

The controversies that have arisen concerning placebo controls have centred largely on clinical trials of new drugs undertaken in resource-poor countries by investigators from resource-rich countries. Nonetheless, ethical issues can also arise when placebos are proposed as part of the design of interventional studies undertaken by epidemiologists.

*General considerations for controlled clinical trials.* The design of trials of

investigational diagnostic, therapeutic or preventive interventions raises interrelated scientific and ethical issues for sponsors, investigators and ethical review committees**.** To obtain reliable results, investigators must compare the effects of an investigational intervention on subjects assigned to the investigational arm (or arms) of a trial with the effects that a control intervention produces in subjects drawn from the same population and assigned to its control arm. Although randomization is the preferred method for assigning subjects to the various arms of a clinical trial, non-experimental methods, such as cohort and case-control studies to evaluate drugs and devices, may often be justified scientifically and ethically. Assignment to treatment arms by randomization, in addition to its usual scientific superiority, offers the advantage of tending to render equivalent to all subjects the foreseeable benefits and risks of participation in a trial.

A clinical trial cannot be justified ethically unless it is capable of producing scientifically reliable results. When the objective is to establish the effectiveness and safety of an investigational intervention, the use of a placebo control is sometimes much more likely than the use of an active control to produce a scientifically reliable result. In many cases the ability of a trial to distinguish effective from ineffective interventions (its assay sensitivity) cannot be assured unless the control is a placebo. If, however, an effect of using a placebo would be to deprive subjects in the control arm of an established effective intervention, and thereby to expose them to serious harm, particularly if it is irreversible, it would obviously be unethical to use a placebo.

*Placebo control in the absence of a established effective alternative.* The use of placebo in the control arm of a clinical trial is ethically acceptable when, as stated in the Declaration of Helsinki (Paragraph 29), "no proven prophylactic, diagnostic or therapeutic method exists." Usually, in this case, a placebo is scientifically preferable to no intervention. In certain circumstances, however, an alternative design may be both scientifically and ethically acceptable, and preferable; for example, in certain vaccine trials an investigator might choose to provide for those in the control arm a vaccine that is unrelated to the investigational vaccine.

*Placebo-controlled studies that entail only minor risks.* A placebo-controlled design may be ethically acceptable, and preferable on scientific grounds, when the condition

for which the intervention is being evaluated is only a small deviation in physiological measurements, such as slightly raised blood pressure or a modest increase in serum cholesterol, and if delaying or omitting an established effective intervention would cause only temporary discomfort (e.g., common headache) and no serious adverse consequences. Likewise, when the investigative intervention is aimed at a relatively trivial condition, such as the common cold or hair loss, and using a placebo for the duration of a trial would deprive control subjects of only minor benefits, it is not unethical to use a placebo-control design. Even if it were possible to design a so-called “non-inferiority”, or "equivalency", trial using an active control, it would still not be unethical in these circumstances to use a placebo-control design. The ethical acceptability of such placebo-controlled studies increases as the period of placebo use is decreased, and when the study design permits change to the active intervention (“escape treatment”) if intolerable symptoms occur. In any event, the ethical review committee must be fully satisfied that the risks of withholding such an intervention are truly minor and short-lived, that the safety and human rights of the subjects will be fully protected, that prospective subjects will be fully informed about alternative treatments, and that the purpose and design of the study are scientifically sound.

*Placebo control when active control would not yield reliable results.* Another rationale for using a placebo control rather than an established effective intervention is that the documented experience with the established effective intervention is not sufficient to provide a scientifically reliable comparison with the intervention being investigated; it is then difficult, or even impossible, without using a placebo, to design a scientifically reliable study. (When a researcher relies on this rationale, the ethical review committee has the option of seeking expert opinion as to whether use of an established effective intervention in the control arm would invalidate the results of the research.) This basis for depriving control subjects of an established effective intervention in clinical trials is, however, ethically acceptable only when doing so would not add any risk of serious, particularly irreversible, harm to the subjects. In some cases, the condition at which the intervention is aimed (for example, cancer or HIV/AIDS) will be too serious to deprive control subjects of an established effective intervention.

An exception to this general rule is applicable in some studies designed to develop a therapeutic, preventive or diagnostic intervention for use in a country or community in which established effective interventions used in other countries are not available, and are unlikely to become available in the foreseeable future, for economic or logistic reasons, when the purpose of such a study is to make a potentially effective and affordable alternative available to the population. An example might be an interventional epidemiological study of a simple method of water purification that could eliminate most pathogens responsible for serious disease in a country that is unable to afford more elaborate interventions which are effective in countries with greater resources. The scientific and ethical review committees must be satisfied that the established effective intervention cannot be used as comparator because its use would not yield scientifically reliable results that would be relevant to the health needs of the study population. This would be the case when existing data about the effectiveness and safety of the established effective intervention may have been accumulated under circumstances unlike those of the population in which it is proposed to conduct the trial (e.g., the disease or condition manifests itself differently in different populations, or other uncontrolled factors exist in the environment). In these circumstances an ethical review committee may approve a clinical trial in which the comparator is a placebo or no treatment or a local remedy. The ethical acceptability of such a proposed investigational intervention depends upon its being responsive to the health needs of the population from which the research subjects would be recruited and upon there being assurance that, if it proves to be safe and effective, it will be made reasonably available to that population.

*An "equivalency trial" as an alternative to a placebo-controlled trial.* An alternative to a placebo-control design would be an “equivalency trial”, which would compare an investigational intervention with an established effective intervention. Equivalency trials are not designed to determine whether an investigational intervention is superior to an established effective one but rather whether it is, in effectiveness and safety, equivalent, or almost equivalent, to the latter; it would be hazardous to conclude, however, that an intervention that meets this equivalency standard is better than nothing or whatever intervention is available in the country simply because the intervention used as the control was itself previously shown to be

better than a placebo, since there may be substantial differences between the results of superficially identical clinical trials carried out in different countries or at different times.

*Means of minimizing harm to placebo-control subjects.* Even when placebo controls are justified on one of the bases set forth in the Guideline, there are means of minimizing the possibly harmful effect of being in the control arm.

First, a placebo-control group need not be untreated. An add-on design may be employed when the investigational therapy and a standard treatment have different mechanisms of action. The treatment to be tested and placebo are each added to a standard treatment. Such studies have a particular place when a standard treatment is known to decrease mortality or irreversible morbidity but a trial with standard treatment as the active control cannot be carried out or would be difficult to interpret [*International Conference on Harmonisation* (*ICH) Guideline: Choice of Control Group and Related Issues in Clinical Trials, 2000*]. In testing for improved treatment of life-threatening diseases such as cancer, HIV/AIDS, or heart failure, add-on designs are a particularly useful means of finding improvements in interventions that are not fully effective or may cause intolerable side-effects. They have a place also in respect of treatment for epilepsy, rheumatism and osteoporosis, for example, because withholding of established effective therapy could result in progressive disability, unacceptable discomfort or both.

Second, as indicated in Guideline 8 Commentary, when the intervention to be tested in a randomized controlled trial is designed to prevent or postpone a lethal or disabling outcome, the investigator minimizes harmful effects of placebo-control studies by providing in the research protocol for the monitoring of research data by an independent Data and Safety Monitoring Board (DSMB). One function of such a board is to protect the research subjects from previously unknown adverse reactions; another is to avoid unnecessarily prolonged exposure to an inferior intervention. The board fulfils the latter function by means of interim analyses of the data pertaining to efficacy to ensure that the trial does not continue beyond the point at which an investigational therapy is demonstrated to be effective. Normally, at the outset of a randomized controlled trial, criteria are established for its premature termination (stopping rules or guidelines).

In some cases the DSMB is called upon to perform "conditional power calculations", designed to determine the probability that a particular clinical trial could ever show that the investigational therapy is effective. If that probability is very small, the DSMB is expected to recommend termination of the clinical trial, because it would be unethical to continue it beyond that point.

In most cases of research involving human subjects, it is unnecessary to appoint a DSMB. To ensure that research is carefully monitored for the early detection of adverse events, the sponsor or the principal investigator appoints an individual to be responsible for advising on the need to consider changing the system of monitoring for adverse events or the process of informed consent, or even to consider terminating the study.

## *Guideline 12*

## *Equitable distribution of burdens and benefits in the selection of groups of subjects in research*

**Groups or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. The exclusion of groups or communities that might benefit from study participation must be justified.**

### *Commentary on Guideline 12*

*General considerations:* Equity requires that no group or class of persons should bear more than its fair share of the burdens of participation in research. Similarly, no group should be deprived of its fair share of the benefits of research, short-term or long-term; such benefits include the direct benefits of participation as well as the benefits of the new knowledge that the research is designed to yield. When burdens or benefits of research are to be apportioned unequally among individuals or groups of persons, the criteria for unequal distribution should be morally justifiable and not arbitrary. In other words, unequal allocation must not be inequitable. Subjects should be drawn from the qualifying population in the general geographic area of the trial without regard to race, ethnicity, economic status or gender unless there is a sound

scientific reason to do otherwise.

In the past, groups of persons were excluded from participation in research for what were then considered good reasons. As a consequence of such exclusions, information about the diagnosis, prevention and treatment of diseases in such groups of persons is limited. This has resulted in a serious class injustice. If information about the management of diseases is considered a benefit that is distributed within a society, it is unjust to deprive groups of persons of that benefit. Such documents as the Declaration of Helsinki and the UNAIDS Guidance Document *Ethical Considerations in HIV Preventive Vaccine Research,* and the policies of many national governments and professional societies, recognize the need to redress these injustices by encouraging the participation of previously excluded groups in basic and applied biomedical research. [**NOTE**: ***Have epidemiologists' groups done likewise?***]

Members of vulnerable groups also have the same entitlement to access to the benefits of investigational interventions that show promise of therapeutic benefit as persons not considered vulnerable, particularly when no superior or equivalent approaches to therapy are available.

There has been a perception, sometimes correct and sometimes incorrect, that certain groups of persons have been overused as research subjects. In some cases such overuse has been based on the administrative availability of the populations. Research hospitals are often located in places where members of the lowest socioeconomic classes reside, and this has resulted in an apparent overuse of such persons. Other groups that may have been overused because they were conveniently available to researchers include students in investigators' classes, residents of long-term care facilities and subordinate members of hierarchical institutions. Impoverished groups have been overused because of their willingness to serve as subjects in exchange for relatively small stipends. Prisoners have been considered ideal subjects for Phase I drug studies because of their highly regimented lives and, in many cases, their conditions of economic deprivation.

Overuse of certain groups, such as the poor or the administratively available, is unjust for several reasons. It is unjust to selectively recruit impoverished people to serve as research subjects simply because they can be more easily induced to participate in exchange for small payments. A further injustice occurs when such people are called upon to bear the burdens of research while others who are better off

enjoy the benefits. However, although the burdens of research should not fall disproportionately on socio-economically disadvantaged groups, neither should such groups be categorically excluded from research protocols. It would not be unjust to selectively recruit poor people to serve as subjects in research designed to address problems that are prevalent in their group – malnutrition or poor living conditions, for example. Similar considerations apply to institutionalized groups or those whose availability to the investigators is for other reasons administratively convenient.

Not only may certain groups within a society be inappropriately overused as research subjects, but also entire communities or societies may be overused. This has been particularly likely to occur in countries or communities with insufficiently well-developed systems for the protection of the rights and welfare of human research subjects. Such overuse is especially questionable when the populations or communities concerned bear the burdens of participation in research but are extremely unlikely ever to enjoy the benefits of new knowledge and products developed as a result of the research. (See Guideline 10: *Research in populations and communities with limited resources.)*

## *Guideline 13*

## *Research involving vulnerable persons*

**Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied.**

### *Commentary on Guideline 13*

Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests.

*General considerations.* The central problem presented by plans to involve vulnerable persons as research subjects is that such plans may entail an inequitable distribution of

the burdens and benefits of research participation. Ethical justification of their involvement usually requires that investigators satisfy ethical review committees that:

- the research could not be carried out equally well with less vulnerable subjects;
- the research is intended to obtain knowledge that will lead to improved diagnosis, prevention or treatment of diseases or other health problems characteristic of, or unique to, the vulnerable class– either the actual subjects or other similarly situated members of the vulnerable class;
- research subjects and other members of the vulnerable class from which subjects are recruited will ordinarily be assured reasonable access to any diagnostic, preventive or therapeutic products that will become available as a consequence of the research;
- the risks attached to interventions or procedures that do not hold out the prospect of direct health-related benefit will not exceed those associated with routine medical or psychological examination of such persons unless an ethical review committee authorizes a slight increase over this level of risk (Guideline 9); and,
- when the prospective subjects are either incompetent or otherwise substantially unable to give informed consent, their agreement will be supplemented by the permission of their legal guardians or other appropriate representatives (Guidelines 14 and 15).

*Vulnerable groups*. Major classes of individuals conventionally considered vulnerable are those with limited capacity or freedom either to consent or to decline to consent. They include children, and persons who because of mental or behavioural disorders are incapable of giving informed consent. Less obvious as a vulnerable group are prospective subjects who are junior or subsidiary members of a hierarchical group; the quality of their consent requires careful consideration, since their agreement to volunteer may be unduly influenced, whether justified or not, by the expectation of preferential treatment if they agree or by fear of disapproval or retaliation if they refuse. Examples of such groups are medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and

members of the armed forces or police. Because they work in close proximity to investigators, they tend to be called upon more often than others to serve as research subjects, and this could result in inequitable distribution of the burdens and benefits of research.

Elderly persons are commonly regarded as vulnerable. With advancing age**,** people are increasingly likely to acquire attributes that define them as vulnerable. They may, for example, be institutionalized or develop varying degrees of dementia**.** If and when they acquire such vulnerability-defining attributes, and not before, it is appropriate to consider them vulnerable and to treat them accordingly.

Other groups or classes may also be considered vulnerable. They include residents of nursing homes, people receiving welfare benefits or social assistance and other poor people and the unemployed, patients in emergency rooms, some ethnic and racial minority groups, homeless persons, nomads, refugees or displaced persons, prisoners, patients with incurable disease, individuals who are politically powerless, and members of communities unfamiliar with modern medical concepts. To the extent that these and other classes of people have attributes resembling those of classes identified as vulnerable, the need for special protection of their rights and welfare should be reviewed and applied, where relevant.

Although, on the whole, investigators must study less vulnerable groups before involving more vulnerable groups, some exceptions are justified. In general, children are not suitable for Phase I drug trials or for Phase I or II vaccine trials, but such trials may be permissible after studies in adults have shown some therapeutic or preventive effect. For example, a Phase II vaccine trial seeking evidence of immunogenicity in infants may be justified when a vaccine has shown evidence of preventing or slowing progression of an infectious disease in adults, or Phase I research with children may be appropriate because the disease to be treated does not occur in adults or is manifested differently in children.

## *Guideline 14*

## *Research involving children*

**Before undertaking research involving children, the investigator must ensure that:**

- **the research might not equally well be carried out with adults;**
- **the purpose of the research is to obtain knowledge relevant to the health needs of children;**
- **a parent or legal representative of each child has given permission;**
- **the agreement (assent) of each child has been obtained to the extent of the child's capabilities; and**
- **a child's refusal to participate or continue in the research will be respected.**

### *Commentary on Guideline 14*

*Justifications for involving children in interventional studies.* The participation of children is indispensable for research into diseases of childhood and conditions to which children are particularly susceptible (*cf.* vaccine trials*),* as well as for clinical trials of drugs that are designed for children as well as adults. In the past, many new products were not tested for children though they were directed towards diseases also occurring in childhood; thus children either did not benefit from these new drugs or were exposed to them though little was known about their specific effects or safety in children**.** Now it is widely agreed that, as a general rule, the sponsor of any new therapeutic, diagnostic or preventive product that is likely to be indicated for use in children is obliged to evaluate its safety and efficacy for children before it is released for general distribution.

*Justifications for involving children in other epidemiological studies.* Observational epidemiological research, such as studies on how genetic and environmental factors present in childhood affect adult health, may be carried out even when the purpose is not "to obtain knowledge relevant to the health needs of children" provided that the other requirements are met. Since the potential benefits (in terms of etiological

knowledge derived from the study) are relevant to adults while the potential harm would affect the children, such studies are usually permissible only in the context of the extremely reduced risks found in observational research. A further justification would arise when the children in the study would also be potential beneficiaries of the study results when they become adults.

Research on occupational hazards for children at work, which would produce knowledge relevant to children's health but may not meet the other requirements (e.g., if it might instead be carried out with adults), should nonetheless be regarded as permissible and even necessary, if nothing else to document the persistence and extent of child labor practices.

*Assent of the child in studies for which competent subjects' consent is required.* The willing cooperation of the child should be sought, after the child has been informed to the extent that the child's maturity and intelligence permit. The age at which a child becomes legally competent to give consent differs substantially from one jurisdiction to another; in some countries the "age of consent" established in their different provinces, states or other political subdivisions varies considerably. Often children who have not yet reached the legally established age of consent can understand the implications of informed consent and go through the necessary procedures; they can therefore knowingly agree to serve as research subjects. Such knowing agreement**,** sometimes referred to as assent**,** is insufficient to permit participation in research unless it is supplemented by the permission of a parent, a legal guardian or other duly authorized representative.

Some children who are too immature to be able to give knowing agreement, or assent, may be able to register a 'deliberate objection', an expression of disapproval or refusal of a proposed procedure. The deliberate objection of an older child, for example, is to be distinguished from the behaviour of an infant, who is likely to cry or withdraw in response to almost any stimulus. Older children, who are more capable of giving assent, should be selected before younger children or infants, unless there are valid scientific reasons for involving younger children first.

A deliberate objection by a child to taking part in research should always be respected even if the parents have given permission, unless the child needs an intervention that is not available outside the context of research, the investigational

intervention shows promise of therapeutic benefit, and there is no acceptable alternative therapy. In such a case, particularly if the child is very young or immature, a parent or guardian may override the child's objections. If the child is older and more nearly capable of independent informed consent, the investigator should seek the specific approval or clearance of the scientific and ethical review committees for initiating or continuing with the investigational treatment. If child subjects become capable of independent informed consent during the research, their informed consent to continued participation should be sought and their decision respected.

A child with a likely fatal illness may object or refuse assent to continuation of a burdensome or distressing intervention. In such circumstances parents may press an investigator to persist with an investigational intervention against the child's wishes. The investigator may agree to do so if the intervention shows promise of preserving or prolonging life and there is no acceptable alternative treatment. In such cases, the investigator should seek the specific approval or clearance of the ethical review committee before agreeing to override the wishes of the child.

*Permission of a parent or guardian.* The investigator must obtain the permission of a parent or guardian in accordance with local laws or established procedures in all studies for which individual consent would be required from subjects capable of giving consent (see Guideline 4). It may be assumed that children over the age of 12 or 13 years are usually capable of understanding what is necessary to give adequately informed consent, but their consent (assent) should normally be complemented by the permission of a parent or guardian, even when local law does not require such permission. Even when the law requires parental permission, however, the assent of the child must be obtained.

In some jurisdictions, some individuals who are below the general age of consent are regarded as “emancipated” or “mature” minors and are authorized to consent without the agreement or even the awareness of their parents or guardians. They may be married or pregnant or be already parents or living independently. Some studies involve investigation of adolescents’ beliefs and behaviour regarding sexuality or use of recreational drugs; other research addresses domestic violence or child abuse. For studies on these topics, ethical review committees may waive parental permission if, for example, parental knowledge of the subject matter may place the

adolescents at some risk of questioning or even intimidation by their parents.

Because of the issues inherent in obtaining assent from children in institutions, such children should only exceptionally be subjects of research. In the case of institutionalized children without parents, or whose parents are not legally authorized to grant permission, the ethical review committee may require sponsors or investigators to provide it with the opinion of an independent, concerned, expert advocate for institutionalized children as to the propriety of undertaking the research with such children.

*Observation of research by a parent or guardian.* A parent or guardian who gives permission for a child to participate in research should be given the opportunity, to a reasonable extent, to observe the research as it proceeds, so as to be able to withdraw the child if the parent or guardian decides it is in the child's best interests to do so.

*Psychological and medical support.* Research involving children should be conducted in settings in which the child and the parent can obtain adequate medical and psychological support. As an additional protection for children, an investigator may, when possible, obtain the advice of a child's family physician, paediatrician or other health-care provider on matters concerning the child's participation in the research.

(See also Guidelines 8, 9 and 13.)

## *Guideline 15*

## *Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent*

**Before undertaking research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent, the investigator must ensure that:**

- **such persons will not be subjects of research that might equally well be carried out on persons whose capacity to give adequately**

**informed consent is not impaired;**

- **the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioural disorders;**
- **the consent of each subject has been obtained to the extent of that person's capabilities, and a prospective subject's refusal to participate in research is always respected, unless, in exceptional circumstances, there is no reasonable medical alternative and local law permits overriding the objection; and,**
- **in cases where prospective subjects lack capacity to consent, permission is obtained from a responsible family member or a legally authorized representative in accordance with applicable law.**

### *Commentary on Guideline 15*

*General considerations.* Most individuals with mental or behavioural disorders are capable of giving informed consent; this Guideline is concerned only with those who are not capable or who because their condition deteriorates become temporarily incapable. The investigator must obtain the approval of an ethical review committee to include such persons in research. They should never be subjects of research that might equally well be carried out on persons in full possession of their mental faculties, but they are clearly the only subjects suitable for a large part of research into the origins and treatment of certain severe mental or behavioural disorders.

*Consent of the individual in studies for which competent subjects' consent is required.* The willing cooperation of persons whose mental and behavioural condition interferes with their ability to consent should be sought to the extent that their mental state permits, and any objection on their part to taking part in any study that has no components designed to benefit them directly should always be respected. The objection of such an individual to an investigational intervention intended to be of therapeutic benefit should be respected unless there is no reasonable medical alternative and local law permits overriding the objection.

*Permission of a surrogate for a subject incapable of giving informed consent.* The investigator must obtain the permission of a surrogate in accordance with local laws or established procedures in all studies for which individual consent would be required from subjects capable of giving consent (see Guideline 4). The permission of an immediate family member or other person with a close personal relationship with the individual should be sought, but it should be recognized that these proxies may have their own interests that may call their permission into question. Some relatives may not be primarily concerned with protecting the rights and welfare of the patients. Moreover, a close family member or friend may wish to take advantage of a research study in the hope that it will succeed in "curing" the condition. Some jurisdictions do not permit third-party permission for subjects lacking capacity to consent. Legal authorization may be necessary to involve in research an individual who has been committed to an institution by a court order.

*Serious illness in persons who because of mental or behavioural disorders are unable to give adequately informed consent.* Persons who because of mental or behavioural disorders are unable to give adequately informed consent and who have, or are at risk of, serious illnesses such as HIV infection, cancer or hepatitis should not be deprived of the possible benefits of investigational drugs, vaccines or devices that show promise of therapeutic or preventive benefit, particularly when no superior or equivalent therapy or prevention is available. Their entitlement to access to such therapy or prevention is justified ethically on the same grounds as is such entitlement for other vulnerable groups.

Persons who are unable to give adequately informed consent by reason of mental or behavioural disorders are, in general, not suitable for participation in formal clinical trials except those trials that are designed to be responsive to their particular health needs and can be carried out only with them.

(See also Guidelines 8, 9 and 13.)

## *Guideline 16*

## *Women as research participants*

**Investigators, sponsors or ethical review committees should not exclude women of reproductive age from epidemiological research. The potential for becoming pregnant during a study should not, in itself, be used as a reason for precluding or limiting participation. However, a thorough discussion of risks to the pregnant woman and to her fetus is a prerequisite for the woman's ability to make a rational decision to enrol in an interventional study. In this discussion, if participation in the research might be hazardous to a fetus or a woman if she becomes pregnant, the sponsors/investigators should guarantee the prospective subject a pregnancy test and access to effective contraceptive methods before the research commences. Where such access is not possible, for legal or religious reasons, investigators should not recruit for such possibly hazardous research women who might become pregnant.**

### *Commentary on Guideline 16*

Women in most societies have been discriminated against with regard to their involvement in research. Women who are biologically capable of becoming pregnant have been customarily excluded from formal clinical trials of drugs, vaccines and medical devices owing to concern about undetermined risks to the fetus. Consequently, relatively little is known about the safety and efficacy of most drugs, vaccines or devices for such women, and this lack of knowledge can be dangerous.

A general policy of excluding from research women biologically capable of becoming pregnant is unjust in that it deprives women as a group of the benefits of the new knowledge derived from such studies. Further, it is an affront to their right of self-determination. It is particularly important that occupations that predominantly involve women workers are not excluded from epidemiological research on potential occupational hazards. Nevertheless, when given the opportunity to participate in research that could pose risks to the fetus, women of childbearing age should be helped to understand that such risk would arise if they become pregnant during the research.

Although this general presumption favours the inclusion of women in research,

it must be acknowledged that in some parts of the world women are vulnerable to neglect or harm in research because of their social conditioning to submit to authority, to ask no questions, and to tolerate pain and suffering. When women in such situations are potential subjects in research, investigators need to exercise special care in the informed consent process to ensure that they have adequate time and a proper environment in which to take decisions on the basis of clearly given information.

*Individual consent of women:* In research involving women of reproductive age, whether pregnant or non-pregnant, only the informed consent of the woman herself is required for her participation. In no case should the permission of a spouse or partner replace the requirement of individual informed consent. If women wish to consult with their husbands or partners or seek voluntarily to obtain their permission before deciding to enrol in research, that is not only ethically permissible but in some contexts highly desirable. A strict requirement of authorization of spouse or partner, however, violates the substantive principle of respect for persons.

A thorough discussion of risks to the pregnant woman and to her fetus is a prerequisite for the woman's ability to make a rational decision to enrol in a study. For women who are not pregnant at the outset of a study but who might become pregnant while they are still subjects, the consent discussion should include information about the alternative of voluntarily withdrawing from the study and, where legally permissible, terminating the pregnancy. Also, if the pregnancy is not terminated, they should be guaranteed a medical follow-up.

(See also Guideline 17.)

## *Guideline 17*

## *Pregnant women as research participants*

**Pregnant women should be presumed to be eligible for participation in epidemiological research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility.**

**Interventional studies should be performed in this population only if it is relevant to the particular health needs of a pregnant woman or her fetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity.**

### *Commentary on Guideline 17*

The justification of research involving pregnant women is complicated by the fact that it may present risks and potential benefits to two beings–the woman and the fetus–as well as to the person the fetus is destined to become. Even when evidence concerning risks is unknown or ambiguous, the decision about acceptability of risk to the fetus should be made by the woman as part of the informed consent process. Though this decision should be made by the mother, it is desirable in research directed at the health of the fetus to obtain the father's opinion as well, when possible.

Especially in communities or societies in which cultural beliefs accord more importance to the fetus than to the woman's life or health, women may feel constrained to participate, or not to participate, in research. Special safeguards should be established to prevent undue inducement to pregnant women to participate in research in which interventions hold out the prospect of direct benefit to the fetus. Where fetal abnormality is not recognized as an indication for abortion, pregnant women should not be recruited for research in which there is a realistic basis for concern that fetal abnormality may occur as a consequence of participation as a subject in research.

Investigators should include in protocols on research on pregnant women a plan for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child.

(See also Commentary on Guidelines 14 and 16.)

## *Guideline 18*

## *Safeguarding confidentiality*

**A healthcare provider should not submit any identifiable data about a patient to an investigator or to a database unless the patient permits such submission of data or it is authorized or mandated by law. The custodian of a database, and an investigator who receives data for research, must establish secure safeguards for the confidentiality of the data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality".**

### *Commentary on Guideline 18*

In addition to the requirements set forth in this Guideline, a growing body of laws have been adopted in many countries establishing detailed legal requirements regarding the protection of the confidentiality and security of health-related data.

*Confidentiality between investigator and subject.* Research relating to individuals and groups may involve the collection and storage of information that, if disclosed to third parties, could cause harm or distress. Investigators should arrange to protect the confidentiality of such information by, for example, omitting information that might lead to the identification of individual subjects, limiting access to the information, anonymizing data, or other means. During the process of obtaining informed consent the investigator should inform the prospective subjects about the precautions that will be taken to protect confidentiality.

The obligation to preserve confidentiality of research data encompasses all identifying information because the disclosure of such information can cause physical, psychological, social or economic harm to individuals, couples, families or other social groups or infringe their intimacy. One way of achieving confidentiality is to use only unidentifiable data; for instance, when testing unlinked anonymous blood samples for HIV infection or when unlinked anonymized or already partially aggregated data are provided by existing registries (e.g., of deaths) to the epidemiologist for descriptive studies.

When linked data and samples are used, epidemiologists customarily discard personal identifying information when consolidating data for purposes of statistical analysis; this also occurs when investigators have linked different sets of data regarding individuals with the consent of individual subjects. When personal identifiers remain on records used for a study, investigators should explain to ethical review committees why this is necessary and how confidentiality will be protected.

Participation in HIV/AIDS drug and vaccine trials may impose upon the research subjects significant associated risks of social discrimination or harm; such risks merit consideration equal to that given to adverse medical consequences of the drugs and vaccines. Efforts must be made to reduce their likelihood and severity. For example, subjects in vaccine trials must be enabled to demonstrate that their HIV seropositivity is due to their having been vaccinated rather than to natural infection. This may be accomplished by providing them with documents attesting to their participation in vaccine trials, or by maintaining a confidential register of trial subjects, from which information can be made available to outside agencies at a subject's request.

*Limits of confidentiality*. Prospective subjects should be informed of limits to the ability of investigators to ensure strict confidentiality and of the foreseeable adverse consequences of breaches of confidentiality. Some jurisdictions require the reporting to appropriate agencies of, for instance, certain communicable diseases or evidence of child abuse or neglect. Health authorities may have the legal right to inspect study records, and a sponsor's compliance audit staff may require and obtain access to confidential data. Although employers should be informed of occupational health study findings only at the group level, the risk exists, particularly in small organizations, that the employer will be able to identify the subjects. Pooling data from a number of comparable organizations may reduce–but not completely foreclose–this risk. Conversely, research that links data from different sources (e.g., health records, employment records, etc.) may increase the risk that individuals can be identified. These and similar limits to the ability to maintain confidentiality should be anticipated and disclosed to prospective subjects (see Guideline 5, #15).

*Data security.* Study materials and databases may contain data which besides being confidential also need to be ensured long life spans, which may in extreme cases cover several generations. Standards and methods need to be developed for the secure preservation of data that are, or could be, held for longitudinal studies. Investigators are responsible for ensuring data security and legitimate access to data by protecting them against physical injury, criminal action and during any change which may be associated with changes of technical systems. Several general principles are useful in judging the adequacy of data protection:

- Plans for data protection and custody of data, copies and backup facilities, whether in the hands of an institution or an individual investigator, should be outlined in the research plan and reviewed by the ethical review committee.
- Limitations on access and legal requirements for disclosure, if any, should be clearly outlined in the research plan.
- The level of identifiability should be appropriate to the scientific goals of the research, as well as appropriate to adequately protecting research subjects.
- The informed consent process should include a description of how data and/or samples will be handled and who will have access; when there will be different levels of data protection, the information should be explicit about this, explaining in general terms the modes of protection at each level.

*Confidentiality between physician and patient.* Physicians and other health care professionals record the details of their observations and interventions in medical records. Patients have the right to expect that these health-care professionals will hold all information about them in strict confidence and disclose it only to those who need, or have a legal right to, the information, such as other attending physicians, nurses**,** or other health-care workers who perform tasks related to the diagnosis and treatment of patients.

The use of such records in epidemiological studies without the informed consent of the patients concerned may be approved by an ethical review committee when this is

consistent with the requirements of applicable law and with the conditions discussed in the Commentary on Guideline 4, and provided that there are secure safeguards of confidentiality; information may also be provided without patient consent to a register or database when authorized or mandated by law. Access by researchers to patients' medical records must be approved in advance by an ethical review committee and supervised by a person who is fully aware of the confidentiality requirements. When the practice of collecting patient records for use in research without informed consent has been approved in a particular setting (such as a hospital or a clinic), patients should be notified of this practice; notification is usually by means of a statement in patient-information brochures. It should be made clear to persons that they have an option to restrict the secondary, research uses of information that is submitted for billing, prescribing, or other purposes and that if they choose to do so, the care provided will not be affected.

For populations covered by automated health databases, an ethical review committee with expertise regarding the scope of access researchers will have to the medical information and the types of research they want to conduct should ensure that confidentiality rules and procedures are in place and certify the public health value of the research (e.g., the Data Access Review Committee for the Canadian Saskatchewan Health database, the Scientific and Ethical Advisory Group for the UK General Practice Research Database). The ethical review committee should also determine how patients should be advised of such practices, usually by means of a statement in patient-information brochures, and the ethical or legal need to provide patients with the choice to "opt out" of secondary use of certain parts of their medical record.

When already existing collections of medical records that were assembled and stored without an explicit notification and consent procedure (including an

opportunity to “opt out”) offer important and otherwise unobtainable data, an ethical review committee needs to decide whether the use of such records is justified. Arguments pertaining to this decision are discussed within the more general framework of the waiving of consent in the Commentary on Guideline 4, under the section "*Waiver of consent requirements.*"

*Disclosure of test results to individuals*. When genetic or other diagnostic tests will be reported to the subject or to the subject’s physician, the subject should be informed that such disclosure will occur and that the samples to be tested will be clearly labeled. Investigators should not disclose results of such diagnostic tests to relatives of subjects without the subjects` consent. In places where immediate family relatives would usually expect to be informed of such results, the research protocol, as approved or cleared by the ethical review committee, should indicate the precautions in place to prevent such disclosure of results without the subjects’ consent; such plans should be clearly explained during the process of obtaining informed consent.

*Issues of confidentiality in genetic research.* An investigator who proposes to perform genetic tests of known clinical or predictive value on biological samples that can be linked to an identifiable individual must obtain the informed consent of the individual or, when indicated, the permission of a legally authorized representative. (Issues raised by research on stored samples are addressed in Guideline 24 and the associated Commentary.)

*Special confidentiality issues for groups in genetic research*. When unidentifiable biological samples (that is, those that have been fully anonymized and unlinked) are used in genetic research in a specific population or community, the results obtained cannot be fed back to individual participants, but in such cases research findings and advice to the relevant group may be communicated by suitable means. These

processes should be fully explained to the prospective subjects as part of informed consent (see Guideline 5).

Epidemiologists and ethical review committees should however be aware that, under specific circumstances, the genetic information gathered in a study (on pharmacogenetics or pharmacogenomics, for example) may have a significant impact on the subject and his/her family extending over generations, and in some instances on the whole population group to which the subject concerned belongs.

With genetic population studies, the possibility of new forms of discrimination based on genotype may emerge. If genetic variations in certain diseases or conditions are significantly more common in a particular community or ethnic group, this information may result in stigmatization and stereotyping and in discrimination in health care services or in the fields of life insurance, employment, reproductive rights, etc. The importance of confidentiality is heightened when genetic information might be used to discriminate or infringe the human rights, fundamental freedoms or dignity of individuals, families, groups or communities (see Guideline 8).

## *Guideline 19*

## *Right of injured subjects to treatment and compensation*

**Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation. Subjects must not be asked to waive the right to compensation.**

### *Commentary on Guideline 19*

Guideline 19 is concerned with two distinct but closely related entitlements. The first is the uncontroversial entitlement to free medical treatment and compensation for accidental injury inflicted by procedures or interventions performed exclusively to accomplish the purposes of research (non-therapeutic procedures). The second is the entitlement of dependants to material compensation for death or disability occurring

as a direct result of study participation. Implementing a compensation system for research-related injuries or death is likely to be complex, however.

*Equitable compensation and free medical treatment.* Compensation is owed to research subjects who are disabled as a consequence of injury from procedures performed solely to accomplish the purposes of research. Compensation and free medical treatment are generally not owed to research subjects who suffer expected or foreseen adverse reactions to investigational therapeutic, diagnostic or preventive interventions when such reactions are not different in kind from those known to be associated with established interventions in standard medical practice.

The ethical review committee should determine in advance: i) the injuries for which subjects will receive free treatment and, in case of impairment, disability or handicap resulting from such injuries, be compensated; and ii) the injuries for which they will not be compensated. Prospective subjects should be informed of the committee's decisions, as part of the process of informed consent. As an ethical review committee cannot make such advance determination in respect of unexpected or unforeseen adverse reactions, such reactions must be presumed compensable and should be reported to the committee for prompt review as they occur.

Subjects must not be asked to waive their rights to compensation or required to show negligence or lack of a reasonable degree of skill on the part of the investigator in order to claim free medical treatment or compensation. The informed consent process or form should contain no words that would absolve an investigator from responsibility in the case of accidental injury, or that would imply that subjects would waive their right to seek compensation for impairment, disability or handicap. Prospective subjects should be informed that they will not need to take legal action to secure the free medical treatment or compensation for injury to which they may be entitled. They should also be told what medical service or organization or individual will provide the medical treatment and what organization will be responsible for providing compensation**.**

*Obligation of the sponsor with regard to compensation.* Before the research begins, the sponsor, whether a pharmaceutical company or other organization or institution, or a government (where government insurance is not precluded by law), should agree

to provide compensation for any physical injury for which subjects are entitled to compensation, or come to an agreement with the investigator concerning the circumstances in which the investigator must rely on his or her own insurance coverage (for example, for negligence or failure of the investigator to follow the protocol, or where government insurance coverage is limited to negligence). In certain circumstances it may be advisable to follow both courses. Sponsors should seek adequate insurance against risks to cover compensation, independent of proof of fault.

## *Guideline 20*

## *Strengthening capacity for ethical and scientific review and epidemiological research*

**Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of epidemiological research proposed or carried out in their jurisdictions. In externally sponsored collaborative studies, sponsors and investigators have an ethical obligation to ensure that the research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct epidemiological research, and to provide scientific and ethical review and monitoring of such research.**

**Capacity-building may include, but is not limited to, the following activities:**

- **establishing and strengthening independent and competent ethical review processes/ committees**
- **strengthening research capacity**
- **developing technologies appropriate to public health, health care and epidemiological research**
- **training of research and health-care staff**
- **educating the community from which research subjects will be drawn.**

### *Commentary on Guideline 20*

External sponsors and investigators have an ethical obligation to contribute to a host country's sustainable capacity for independent scientific and ethical review and epidemiological research. Strengthening capacity for conducting epidemiological research, as well as for undertaking scientific and ethical review of epidemiological projects, should be regarded as a specific need in many countries, notably because adequate capacity for biomedical research does not automatically entail adequate capacity for epidemiological research. This further extends to capacity in very specialized domains of epidemiological research such as genetic, occupational or social epidemiology.

Before undertaking research in a host country with little or no such capacity, external sponsors and investigators should include in the research protocol a plan that specifies the contribution they will make. The amount of capacity building reasonably expected should be proportional to the magnitude of the research project. A brief epidemiological study involving only review of medical records, for example, would entail relatively little, if any, such development, whereas a considerable contribution is to be expected of an external sponsor of, for instance, a large-scale vaccine field-trial expected to last two or three years.

The specific capacity-building objectives should be determined and achieved through dialogue and negotiation between external sponsors and host-country authorities. External sponsors would be expected to employ and, if necessary, train local individuals to function as investigators, research assistants or data managers, for example, and to provide, as necessary, reasonable amounts of financial, educational and other assistance for capacity-building. To avoid conflict of interest and safeguard the independence of review committees, financial assistance should not be provided directly to them; rather, funds should be made available to appropriate authorities in the host-country government or to the host research institution.

(See also Guidelines 10 and 22.)

## *Guideline 21*

## *Ethical obligation of external sponsors*

## *to provide health-care services*

**External sponsors are ethically obliged to ensure the availability of:**

- **health-care services that are essential to the safe conduct of the research;**

- **treatment for subjects who suffer injury as a consequence of research interventions; and,**

- **services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.**

### *Commentary on Guideline 21*

Obligations of external sponsors to provide health-care services will vary with the circumstances of particular studies and the needs of host countries. Some types of interventional epidemiological studies are intended to find out whether a screening programme for a disease may lead to an improvement in prognosis, by means of early diagnosis and treatment. The intervention cannot be limited to administering a screening test and examining whether the disease has been detected at an earlier stage than through standard clinical practice, but should also include provision of the pertinent treatment.

The sponsors' obligations in particular studies should be clarified before the research is begun. The research protocol should specify what health-care services will be made available, during and after the research, to the subjects themselves, to the community from which the subjects are drawn, or to the host country, and for how long. In addition, investigators should specify what action if any they will take when medical conditions are detected within a study population that are not related to the study but that need treatment, for instance, obesity or hypertension when recruiting subjects in an observational cohort study of diet and cancer. The details of these arrangements should be agreed by the sponsor, officials of the host country, other interested parties, and, when appropriate, the community from which subjects are to be drawn. The agreed arrangements should be specified in the consent process and

document.

Although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so. Such services typically include treatment for diseases contracted in the course of the study. It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study.

The scope and limits of the obligation to ensure that subjects who suffer injury as a consequence of research interventions obtain medical treatment free of charge, and that compensation be provided for death or disability occurring as a consequence of such injury, are the subject of Guideline 19.

When prospective or actual subjects are found to have diseases unrelated to the research, or cannot be enrolled in a study because they do not meet the health criteria, investigators should, as appropriate, advise them to obtain, or refer them for, medical care. In general, also, in the course of a study, sponsors should disclose to the proper health authorities information of public health concern arising from the research.

The obligation of the sponsor to make reasonably available for the benefit of the population or community concerned any intervention or product developed, or knowledge generated, as a result of the research is considered in Guideline 10.

## *Guideline 22*

## *Disclosure and review of potential conflicts of interest*

**The investigator is responsible for ensuring that the materials submitted to an ethical review committee include a declaration of any potential conflicts of interest affecting the study. Ethical review committees should develop forms that facilitate the reporting of such potential conflicts and materials explaining their use for investigators. Ethical review committees should evaluate each study in the light of any declared conflicts and ensure that appropriate means of mitigation are provided. If a potentially serious conflict of interest cannot be adequately mitigated, the committee should not approve the project.**

### *Commentary on Guideline 22*

*Types of conflicting interests*. Conflicts can arise from a sponsor's interest in the study's outcome; such interests include those of a health ministry or other public agency and are not limited to commercial sponsors. Such conflicts may include a financial stake held by the investigator or senior members of the research team (as well as their close family members) in the sponsor of the research (such as an equity interest), payments to the investigator that depend on the rapidity with which subjects are recruited or certain results reported, restrictions on the investigator's freedom to analyze the data or publish research results, or dependence of a research centre on substantial, ongoing support from a particular sponsor, private or public.

*Potential conflicts of interest related to project support.* Epidemiological studies may receive funding from commercial firms. Such sponsors have good reason to support research methods that are ethically and scientifically acceptable, but cases have arisen in which the conditions of funding may have introduced bias. For example, investigators have sometimes had little or no input into study design, limited access to the raw data, or limited participation in data interpretation, and the results of some studies have not been published when they were unfavourable to the sponsor's product. (This risk of bias may also arise with other sources of support, such as government or foundations.) As the persons directly responsible for their work, investigators should not enter into agreements that interfere unduly with their access to the data or their ability to analyze the data independently, prepare manuscripts, or publish them. Investigators must also disclose potential or apparent conflicts of interest on their part to the ethical review committee or to other institutional committees designed to evaluate and manage such conflicts. Ethical review committees should therefore ensure that these conditions are met (see also the Commentary on Guideline 2, *Multi-centre research).*

*Institutional conflicts.* Officials overseeing research also need to be aware of – and, as necessary, take steps to mitigate – institutional conflicts of interest which may arise when a research centre derives substantial support (perhaps covering years of funding) from a single sponsor or handful of sponsors; in such circumstances, it may

be difficult for persons acting on behalf of the organization, including members of the ethical review committee, to reach judgments adverse to the sponsor's interests or wishes. The fact that the ethical review committee (or the institution where it operates) is paid a fee for reviewing a study does not present an inherent conflict of interest, provided that the fee is reasonably related to the costs of conducting the review, is not dependent on the outcome of the review, is uniform for all projects of comparable complexity, and is set and negotiated by persons other than those actually engaged in the ethical review process.

*Standardized disclosure*. Investigators will most likely come to recognize potential conflicts of interest if they are prompted to scrutinize research sponsorship as an expected part of preparing a description of their projects for the ethical review committee. Thus, the development of a standardized disclosure form and related educational and explanatory materials (by a committee or group of committees, such as a research ethics association) is recommended as a good way to ensure that investigators understand the potential for conflicts of interest and routinely report relevant facts about their own studies to review committees and in all publications. It is important that such a document provide a definition of potential conflict of interest. The explanatory materials should also help investigators to understand that a potential conflict of interest is not necessarily disqualifying but may be managed either through disclosure (both before the study, in consent materials, and when any results are reported) or other means.

*Mitigation of conflicts*. The means that ethical review committees may wish to consider for mitigating conflicts of interest include an agreed process for peer review of the study design, analysis, results, and interpretation; guarantees of the investigator's right to determine the scientific design and to use the data and publish results, free of undue restrictions from the sponsor; the existence of multiple sources of support for the study; etc. When appropriate, the committee may also require that potential conflicts of interest be part of the information provided in seeking subjects' consent to participate, beyond describing "the nature and sources of funding for the research", which is an element of informed consent under Guideline 5.

## *Guideline 23*

## *Use of the Internet in epidemiological research*

**If the Internet is used as a tool to identify respondents or to collect data in epidemiological research, the investigator must ensure that an appropriate informed consent procedure is applied and that data confidentiality is maintained.**

### *Commentary on Guideline 23*

There are several ways in which researchers can use the Internet while performing epidemiological research. First, while collecting data, researchers may use the Internet to actually perform the research itself (online research); visitors to sites may be enrolled as respondents and questionnaires may be made accessible through the Internet. In open Internet locations, investigators may observe, as a source of data, what others are saying and doing without necessarily interacting directly with other visitors to the site in question. (Such virtual "spaces" are public but may be regarded as private by users who are not adequately attentive to the ability of observers to "participate" invisibly.) Second, the Internet plays an increasingly important role for researchers in building databases; researchers may send electronic files containing the results of their research to other researchers for collaborative purposes or to aid in the construction of a centralized repository on information on a particular topic. This is the case, for instance, in multi-centre trials. Finally, after completion of the study, researchers may want to make some results available through the Internet. The principles of scientific validity of the study, informed consent, confidentiality, and balancing of potential benefit and harm are generally applicable to all of these uses of the Internet, but research using the Internet can have several unique features.

*Using the Internet to collect data and build databases*. Subjects' privacy, confidentiality and security are at stake when research is conducted through the Internet. Researchers should be explicit about their presence while doing online research and seek the informed consent of participants. As part of the informed consent process, participants should be informed of the means and degree of

protection applied to the data as well as where the data and their backup will be stored, for how long and who will have access to them. As no face-to-face contact takes place between participants and investigators, subjects' agreement to participate should be based on a clear disclosure of the purposes for which data are being collected and who (investigator and institution) is collecting or accessing them; the investigator is responsible for maintaining records that document informed consent. (see also Guideline 6)

Subjects' privacy, confidentiality and security are at stake when data are conveyed to others electronically. Researchers should make sure that confidentiality of information is guaranteed during data collection, transfer to other centres and the building of a common database. Registration forms and questionnaires with personal identifiers should receive a high degree of security. Passwords and the best available technology, such as encryption, should be used in order to make sure that only authorized persons are able to read the data.

*Results made available on the Internet.* After completion of a study, the accuracy and completeness of the information made available on the Internet become relevant. Researchers should be explicit in indicating whether the information provided is preliminary or definitive, and how complete it is.

*Electronic collection of health-related data through new technologies.* Subjects' privacy, confidentiality and security are also at stake when data are collected through electronic devices carried by or implanted in individuals. Epidemiological studies using such methods must attend to the resulting issues.

## *Guideline 24*

## *Use of stored biological samples and related data*

**When collecting and storing human biological samples (and related data, such as health or employment records) for future epidemiological research, the investigator must obtain the voluntary informed consent of the individual donor or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance**

**with applicable law. The consent should specify: the conditions and duration of storage; who will have access to the samples; the foreseeable uses of the samples, whether limited to an already fully defined study or extending to a number of wholly or partially undefined studies; and the intended goal of such use, whether only for research, basic or applied, or also for commercial purposes. The ethical review committee should satisfy itself that the proposed collection and storage protocol and the consent procedure meet these specifications.**

**The protocol of every study using stored human biological samples (and related data) must be submitted to an ethical review committee, which should satisfy itself that the proposed use of the samples comes within the scope specifically agreed to by the subjects.**

**For stored samples collected for past research, clinical or other purposes without informed consent to their use for research, the ethical review committee may consider waiving the consent if it proves materially unfeasible to obtain it, provided that it concludes that doing so would not harm the rights or welfare of the persons from whom the samples were collected.**

### *Commentary on Guideline 24*

Epidemiologists have long analyzed biological samples and are now increasingly using the tools of molecular genetics to understand the interaction of factors that contribute to disease. When combined with information from medical and other sources (such as dietary or occupational records), data from biological samples provide a powerful tool in deciphering the role of environmental and genetic factors in human health and disease. Consent to the use of samples collected and immediately analyzed for the purpose of a specific epidemiological study come under Guideline 4 and has been discussed in the Commentary on that Guideline.

Particular issues arise, however, for the use of stored samples, repositories of which are fast multiplying as a key resource for research, including in particular in the field of epidemiology. These issues are different in degree, if not in nature, from those concerning the use solely of recorded data, such as medical records. While from the

latter it is only possible to generate new information by linking different recorded data, for instance drug use with a subsequent health outcome, analytical determinations of all kinds carried out on biological samples can generate new data, and consequently new information, in a virtually limitless amount.

This inherent information-generating potential requires that strict measures be taken, to the satisfaction of the ethical review committee examining the protocol for establishment and management of a repository, for assuring not only the physical protection and maintenance of the samples but also appropriate confidentiality of the link between biological specimens and personal identifiers of the donating subjects. This responsibility falls upon the custodian of the repository. It is the responsibility of the person who obtains and submits the sample to a repository (e.g., a physician in the course of a diagnostic or screening procedure, or an epidemiologist in the course of a field study) to ensure that donors whose samples and related data will be stored have been informed about the potential future uses of such material, and that the samples will be stored and made available in accordance with conditions explicitly agreed by them (see Guideline 5, points 18-20). The informed consent should be reviewed and approved by the ethical review committee responsible for the repository, in addition to any review required by an ethical review committee at the institution where the samples are collected.

Three sources of stored samples are commonly in use:

a. repositories of samples collected and stored with informed consent for long-term, epidemiological studies (for example, so-called "population biobanks");
b. repositories of samples collected and stored in the context of a specific research [without explicit and fully-informed consent (in line with practices prevailing at the time)];
c. repositories of samples (typically surgically excised tissues, bioptic fragments, and leftover blood collected for diagnostic purposes) collected and stored in the context of routine clinical care or pathological or forensic examination.

*a. Repositories of samples collected at present and stored for long-term, epidemiological studies.* The value of repositories for longitudinal studies of specific diseases is now widely recognized; likewise, several large population biobanks are

being established to allow studies across many diseases, through correlations of genetic, environmental, occupational, and other health data. Such repositories share an important characteristic: the persons whose samples are stored explicitly agree to this future use through an informed consent procedure approved by an ethical review committee. However, since such future research inherently involves the testing of as-yet unformulated hypotheses and the carrying out of analytical determinations unforeseeable at the time samples are collected, the information disclosed must of necessity lack much of the specificity usually expected in an acceptable informed consent process.

The ideal and most direct way out of this dilemma is to seek from the participants a new consent each time a new hypothesis is going to be tested, a procedure which, though cumbersome, may be feasible in studies where participants are contacted and followed up at regular intervals (say, every one or two years). Even this procedure, however, leaves out people who die in the interval, a feature that may seriously bias the study results; it will be up to the ethical review committee, notably in the light of the response obtained from the subjects who are actually requested to give a new consent, to advise for or against the use of the samples from deceased persons. A second best approach is to make the consent given at enrolment specific enough regarding the type of factors and health endpoints to be investigated in the future (even if any actual hypotheses cannot be indicated, being as yet unknown) to constitute the basis for a genuinely "informed" agreement on the part of donors. This solution may be the only practicable one in studies where subjects are "passively" followed up, for instance through disease registries, but are not contacted by the investigators. A third conceivable solution would be consent to an open-ended donation of the sample to be used for biomedical and epidemiological research, conditional upon the approval of an ethical review committee. This solution is highly debatable and [likely to be] unacceptable under the ethical standards applied in several countries. It may also be deceivingly simple because it implies that, in order to give a current informed consent, the participant should in any case be made aware (unless he/she explicitly refuses) of the spectrum of studies that the blanket formula "biomedical or epidemiological research" encompasses and which kind of studies, if any, it excludes.

In no case can a clearance given by an ethical review committee to establish a

repository also be regarded as a clearance to carry out an actual study using the samples in the repository; a new clearance is required after scientific and ethical review of every specific study protocol.

Especially in the context of repositories established for longitudinal study of a particular disease, the informed consent should clearly stipulate what return of information–if any–derived from analysis of the samples is foreseen, should the subject so wish. In general, information of uncertain scientific validity or meaning would not qualify for transmission to the participant. It may also be reasonable to consider not all health-related information generated by the investigations conducted on the biological samples but only information potentially beneficial to the subject and/or his/her relatives, for example diagnostic information on gene variants or phenotypic traits established as relevant to health, particularly when amenable to some form of beneficial intervention or information on markers of an infectious disease or of a harmful environmental exposure, especially if avoidable.

*b. Repositories of samples collected and stored in the past with no informed consent in the context of research.* When already existing repositories of biological samples collected and stored without an explicit consent procedure offer important and otherwise unobtainable data, an ethical review committee needs to decide whether the use of such samples is justified in the absence of explicit consent. Arguments pertaining to this decision are discussed within the more general framework of waiving of consent in the Commentary on Guideline 4, under the section "*Waiver of consent requirements*".

*c. Repositories of routinely collected samples.* Secondary use of samples collected in the context of clinical or preventive (screening) practice does not raise ethical objections if the informed consent by the patient makes clear that samples can also be used in the future for research purposes, provided these are explicitly specified. Given the likelihood that such materials will be of interest to future researchers, it would be good clinical practice to insist that patients always be offered several options: to have their samples used only for their own treatment or benefit and then discarded; to allow stored samples to be used for research directly related to the condition for which they have been treated; or to allow stored samples to be used for unrelated research, with

or without personal identifiers (as noted above, this blanket option would be unacceptable under the ethical standards applied in several countries). These options may be presented during a conversation with the patient or in an information document upon admittance to the hospital. It should be made clear to persons, that it is reasonable to choose to "opt out" and that such a choice will not adversely affect the care provided to them. (Of course, if the person allows future studies using identifiable samples which then generates new information of definite clinical value to that person, ordinary good practice dictates that the person be contacted again even if years have elapsed in between). In any case, the person should be told that any research uses of the stored samples will be subject to approval by the relevant ethical review committee. Consent for each study to be conducted with samples collected routinely without explicit consent for future research use must be sought. Only if this is unobtainable, such as if the patient proves after a reasonable attempt to contact him to be untraceable or is dead, may an ethical review committee consider the option of allowing the use of the samples for projects which cannot be carried out in alternative ways; these conditions are likely to hold, for example, for "historical" collections of samples stored when contemporary informed consent policies were not applied.

*Genetic research.* When individual consent or permission has not been obtained to perform a genetic test that is of known predictive value or that gives reliable information about a known heritable condition, the investigator must see that biological samples are fully anonymized and unlinked before performing the test; this ensures that no information about specific individuals can be derived from such research or passed back to them.

When biological samples are not fully anonymized and when it is anticipated that there may be valid clinical or research reasons for linking the results of genetic tests to research subjects, the investigator in seeking informed consent should assure prospective subjects that their identity will be protected by secure coding of their samples (encryption) and by restricted access to the database, and should explain this process to them.

(See also Guidelines 5, 6 and 7.)

## *Appendix 1:*

## Glossary

This glossary defines terms used in the text of the Guidelines and Commentaries. Several definitions are based on, or adapted from, those found in John Last's *Dictionary of Epidemiology*, 4th ed. (Oxford University Press) to which the reader is more generally referred for terms encountered in epidemiological study protocols and reports. Within a definition *italicized words* refer to other terms found in the glossary.

**Analytic study.** An epidemiological study to test the hypothesis that a *factor* is the cause of an health effect, for instance that the *factor* causes a disease or that it prevents a disease. The commonest types of analytic studies are *case-control, cohort* and *cross-sectional studies.* Analytic studies are contrasted with *descriptive studies,* which do not test hypotheses. In addition to these types of studies, all of which are *observational,* analytic studies also encompass *interventional studies.*

**Anonymous.** A record, biological sample or item of information that in no circumstance can be linked to an identified person.

**Benefit.** A favourable consequence arising from a study, for example the demonstration that a vaccine is effective in a *randomized controlled trial* or the identification of a workplace hazard in an *observational study.* Benefits are often contrasted to "risks" (as in a "risk/benefit ratio") but the term "risk" is ambiguous because it connotes both an adverse consequence and the probability of its occurrence (i.e., *risk* in the formal epidemiological meaning). To avoid this ambiguity, the term "risk" is better replaced by "harm" when the consequence is certain or has already occurred, or "potential harm" when it remains a possibility. In the context of planned research, the balance to be struck is thus between potential benefits (to society and possibly to the subjects) and potential harms (principally to subjects), paying attention both to the type and magnitude of these benefits and harms and the probability that they will occur. Potential benefits and harms "to subjects" may not be restricted to them, but may extend to their family members or, more generally, to a group to which

they belong. For instance, findings of a higher than average prevalence of certain genetic traits or diseases among study subjects may offer a means of early assessment and prevention (a benefit for the group of which they are a part) but may also stigmatize the family or the group in the eyes of others (a harm for the group).

**Case-control study.** An *observational study* comparing cases with a disease (for example, lung cancer) with non-diseased control subjects from the same population as the cases being studied. The relationship of a *factor* (for example, tobacco smoking) to the disease (here, lung cancer) is examined by comparing how frequently the *factor* or its different levels (the number of cigarette smoked) is present among cases and among controls. Information about the *factor(s*) of interest be gathered by interviewing people or by consulting existing records, for example, prescription records for a study of adverse effects of a drug.

**Cluster sampling.** A method of selecting subjects from a population in which each unit selected is a group of subjects (e.g., all children in a school or all people in a town district) rather than an individual. Clusters are usually selected through *random sampling.*

**Cohort study.** An *observational study* in which the occurrence of a disease or other health condition is recorded in any designated group of subjects who are followed up over a period of time, usually years or, in some studies, decades. At the start of the observation, the subjects are classified according to the *factor(s)* whose relation with the disease is being investigated. For example, blood pressure may be used to classify subjects in a study of coronary heart disease; the study would consist of comparing the frequency with which coronary heart disease occurred subsequently in subgroups of subjects with different blood pressure levels. In some cohort studies, the subjects are contacted and asked questions and/or undergo measurements and blood tests by the investigator at the time of enrolment in the cohort and at fixed intervals thereafter, while in other studies the cohort can be formed using existing records (e.g., hospital or employment records) with no technical need to contact the subjects.

**Competent person.** A person capable of understanding the meaning of the information she is presented with and of taking decisions based on it. Certain persons, such as children up to a specified age are typically deemed by the law to be legally incompetent, while others, including people whose mental capacity or thought processes are impaired by mental or physical illness, can be found by a court or other body to be incompetent to make some or all decisions.

**Control (noun and adjective).** Designates the group of subjects against which the group(s) of subjects of interest in a study are compared. For example in a *case-control study* the subjects with the disease of interest, say lung cancer, may be compared with subjects without the disease, the control or *reference group,* to find out whether the former were more frequently exposed than the latter to carcinogenic fumes. In a *randomized controlled trial (RCT)* of a new drug, the subjects given the intervention being studied are compared with the "control" subjects who receive a routinely used drug or, under certain circumstances, a *placebo*.

**Control (verb).** In public health, "to control" means to prevent a disease (or its causal factors) or to treat it .A disease which can be prevented or treated, or both, is "controllable". In the analysis of an epidemiological study, control means to remove the influence of those factors such as age and gender that may be differently distributed in two groups of subjects which are being compared so as to avoid having those factors distort the comparison of the two groups, for instance of their respective death rates.

**Cross-sectional study.** An *observational study* in which the presence of a disease (or other health condition) and the presence of factor(s) of interest are simultaneously ascertained at a point in time in order to examine their relationship. The ascertainment is often carried out in random representative samples of a population. For example, a factor such as blood pressure and a health condition as defined by an electrocardiogram may be measured in subjects selected at random within each age- and sex-specific stratum of a population.

**Descriptive study.** An *observational study* portraying the occurrence of a disease or of other health-related events in relation to geographical areas, calendar periods and demographic characteristics of populations, such as age, sex, educational level, occupation, socioeconomic conditions, etc. These studies can be carried out as "ad hoc" research investigations or as institutional and regular activities of disease surveillance within public health practice. In both contexts they contribute to generating hypotheses on the *factors* potentially determining the observed disease patterns. These hypotheses can then be tested in *analytic studies* whose results may in turn be used to verify how much the factors account for the disease patterns. Descriptive studies usually make use of individual records as available in existing databases or registries (of deaths, of notifiable communicable diseases, of cancer, etc.) and do not require identification of the persons to whom the records belong.

**Factor.** Generically any event, characteristic or other definable entity potentially or actually capable of affecting health or contributing to a health-related condition. Factors include age, sex, body characteristics (such as height, weight, blood pressure, genetic traits, etc.), economic status, occupation, residence, and a wide range of personal behaviour and environmental causes external to the body including diet, drugs, etc.

**Genetic epidemiology.** The branch of epidemiology dealing with biologically inherited causes of health and diseases. It is a bridging discipline between epidemiology and genetics, and it encompasses the study of the interactions between genes and environmental factors in disease causation.

**Harm.** An adverse consequence arising from a study, as opposed to a *benefit.* A potential harm is often referred to as a *risk*," but that term is ambiguous because it encompasses both the magnitude and the probability of a harm occurring.

**Information.** Items of knowledge contained in materials, namely *records* (e.g., from hospitals, interviews, recorded measurements on people, etc.) or *biological sample*s which can be tested in the laboratory for a variety of components. Records and biological samples may or may not be identified as belonging to a particular person

and may or may not be linked to each other for the purpose of a study. The combinations of these different possibilities in various contexts (epidemiology, clinical trials, and genetic research) have been classified and labeled in different ways. In the present document, two major categories of information and materials have been utilized: *(personally) identifiable information***,** which refer to, or can provide a link to, a particular person and *(personally) non-identifiable information,* which cannot be linked to a person. The two types of information respectively derive from *(personally) identifiable material* and *(personally) non-identifiable material* .

**Identifiable material.** This includes three types of materials:

- *Nominal record or sample*: records and samples that carry the person's name or unique identifier, such as a social security number.
- *Linked, coded record or biological sample*: a record or sample that does not carry a name but is coded and thus, by possessing or by "breaking" the coding system, could be linked to the person to whom the record refers or from whom the sample was obtained. Depending on the circumstances, the code may be known only to the person concerned or the key to the code may be held by the person who collected the material (such as the physician of the person concerned), by the repository where the record or sample is held, and/or by an investigator who is using the material in a study.
- *Linked, double-coded record or sample*: similar to a *linked, coded record or biological sample* except that two different codes are used for each record or sample; one key, which connects the codes on different samples and records (and allows data derived from analysing samples to be compared to data from records), is created by the repository and used by investigators, while a separate coding system that links each record or sample to the person concerned is held by a third party (such as the physician who submitted the record or sample) and is not available to the investigator. Although double-coding makes linking samples or records to a particular person much more difficult, the existence of the codes means that such linkage might occur, either accidentally or through diligent effort.

**Intervention.** An intentional change induced by the investigator in the status of the study subjects in order to investigate its effects on health. Examples are the administration of a drug, vaccine, or health education programme. In contrast, procedures used to acquire data, such as administering a questionnaire, conducting an interview, taking a blood sample or performing an X-ray, are not regarded as "interventions" in the technical sense because they are not performed in order to produce a measurable effect on the subject.

**Interventional or intervention study.** An epidemiological study based on an *intervention;* synonymous with "experimental study". Such studies test the effects of interventions (often termed "treatments" in the technical literature, not to signify that they are therapeutic but that they change the circumstances) which are assigned to subjects in a population following a study protocol. For example, an intervention would be a screening test for early recognition and management of a disease to be compared with no screening or with screening with lesser frequency; or a treatment could be a vaccine to prevent a disease of viral origin to be compared with no vaccine or a different vaccine. Whenever possible, subjects are assigned interventions at random (a *randomized controlled trial*). Random allocation means that, other than the intervention itself, all possibly relevant factors (both those already known to affect the outcomes being studied and those not yet identified) are on average equally distributed between groups receiving the different modalities; consequently, assuming the sample size is large enough to yield statistically significant results, random allocation ensures that any observed difference in outcomes can be confidently regarded as a real effect of the intervention.

**Investigation.** A study carried out for research purposes. It may also denote a study carried out for clinical diagnostic purposes and, sometimes, a specific diagnostic procedure (e.g., a breast echography, colonoscopy, or CT investigation).

**Linked, coded record or biological sample.** A type of *identifiable material.*

**Linked, double-coded record or biological sample.** A type of *identifiable material.*

**Minimal risk**. In this expression "risk" is taken in its common meaning of a possible but not certain adverse effect (on health). Minimizing risk implies reducing to the feasible minimum the number and magnitude of such possible effects as well as the probability that they will occur. A study is often said to involve "minimal risk" when the potential harms involved are comparable to those as experienced in "ordinary life" by a person of a given age and gender or by an apparently healthy person undergoing routine medical surveillance.

**Molecular epidemiology.** The use in epidemiological studies of techniques of molecular biology, better understood as a level and method of measurement rather than a branch of epidemiology with substantive research content.

**Nominal record or sample.** A type of *identifiable material.*

**Non-identifiable material.** Includes *unlinked records or biological samples* that were either collected on an *anonymous* basis or have been made anonymous (anonymized) in such a way that they do not carry any direct or indirect personal identifier . For these materials, no link is possible between the records or samples and the identity of the person who was the source of the record or sample.

**Observational study.** Synonymous of non-experimental study. An epidemiological study that does not involve an *intervention*. Observational studies have a wider range of applicability than *intervention studies* as they can be employed to investigate both putative hazardous or beneficial *factors* (e.g., in the environment, in diet), whereas, for obvious ethical reasons, intervention studies are typically limited to potentially beneficial factors. The results of observational studies, however, cannot usually be regarded with the same degree of confidence than the results from intervention studies. In observational studies the groups differently exposed to a *factor* (for example subjects with a high and low consumption of fats) may also differ in other factors, some of which are unknown and uncontrollable and may be the real cause of an observed effect (for example myocardial infarction). Therefore no single study can as a rule be regarded as providing firm evidence on the causal role, either hazardous or protective, of a factor. Multiple studies, carried out in different settings and

producing consistent results, are necessary and should therefore not be considered as redundant or unethical.

**Placebo.** An inert medication or procedure given to "please" subjects so that they think they are receiving an active treatment for their condition. The effects, beneficial and sometimes even adverse, observed following the administration of a placebo are usually attributed to psychological processes (e.g., "the power of suggestion").

**Publicly available record or information.** Any record or information, whether carrying personal identifiers or not, that the law treats as publicly accessible, such as a telephone directory, registry of deaths, or, in a number of countries, the register of nominal tax records. Since anyone can use these records, no special authorization or permission of any type - legal and/or ethical - is required for epidemiologists to consult them.

**Random allocation, random assignment or randomization.** Allocation of subjects to groups, for example to two pharmacological treatments, by a procedure that gives each subject the same probability of being assigned to either of the groups. Nowadays this is usually implemented by the use of a computer-generated sequence of random numbers; for example, each successive subject would assigned to one intervention if the corresponding random number is an even number and to the other if it is an odd number. Random allocation guarantees that all factors capable of influencing the study outcome (e.g., disease duration), other than the intervention being studied, are on average equally distributed between the two groups. Random allocation is the defining feature of a *randomized controlled trial.*

**Randomized controlled trial (RCT).** An *intervention study* involving *random allocation* of the subjects to different treatment modalities (*factors*); "randomized population trial" or "randomized prophylactic trial" are equivalent terms used for trials carried out to test a preventive measure in a healthy population.

**Random sampling.** A method of selecting units from a population in which each unit of the population has a known probability of selection. The unit can be the individual or, in *cluster sampling*, a group of individuals.

**Register and Registry.** A register is an ordered collection of records, for instance of births or of deaths. A registry is an organized system to develop, maintain and use one or more registers, for example a national registry may keep the registers of births and deaths. By extension the institution responsible for the system is also often called a registry (e.g., a cancer registry).

**Risk.** The probability that an event, favourable or adverse, will occur within a defined time interval. Although often contrasted to *benefit* (as in a "risk/benefit ratio"), the term "potential harm" is better for that context, leaving "risk" in its formal epidemiological sense to express the probability of a (typically adverse) event or outcome.

**Social epidemiology.** The branch of epidemiology dealing with socially relevant variables in relation to health. These variables characterize either the place of persons in society (e.g., gender, education, income, profession) or the structure and function of social institutions (e.g., family, school, government).

**Trial.** A generic term that in a clinical context denotes a research activity involving the administration of an intervention to humans to evaluate its safety and efficacy.

**Unlinked record or biological sample.** A *non-identifiable material.*

## *Appendix 2.*

## Items to be included in a protocol (or associated documents) for epidemiological research involving human subjects

This comprehensive checklist essentially reproduces Appendix 1 of the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Since interventional epidemiological studies, such as a population-randomized controlled trial of a new vaccine, are similar to biomedical trials, this checklist is applicable; however, in observational studies, a number of items will not be relevant. In all cases it is up to the principal investigator to judge which items are pertinent - and to what extent - to a given study; likewise, the ethical review committee must be satisfied that the items included meet the requirements of the present Guidelines.

1. Title of the study;

2. A summary of the proposed research in lay/non-technical language;

3. A clear statement of the justification for the study, its significance in development and in meeting the needs of the country/population in which the research is carried out;

4. The investigators` views of the ethical issues and considerations raised by the study and, if appropriate, how it is proposed to deal with them;

5. Summary of published studies and of ongoing research pertinent to the topic, including relevant animal, preclinical and clinical studies;

6. A statement that the principles set out in these Guidelines will be implemented;

7. An account of previous submissions, if any, of the protocol for ethical review and their outcome;

8. A brief description of the site(s) where the research is to be conducted, including

information about the adequacy of facilities for the safe and appropriate conduct of the research, and *relevant* demographic and epidemiological information about the country or region concerned;

9. Name and address of the sponsor;

10. Names, addresses, institutional affiliations, qualifications and experience of the principal investigator and other investigators;

11. The objectives of the study, its hypotheses or research questions, its assumptions, and its variables;

12. A detailed description of the design of the study, including whether it is an observational or interventional study, and if the latter, a description, among other things, of how subjects will be assigned to treatment groups (including the method of randomization, if used), and whether the study will be blinded (single blind, double blind) or open;

13. The number of research subjects needed to achieve the study objective, and how this was statistically determined;

14. The criteria for inclusion or exclusion of potential subjects, and justification for the exclusion of any groups on the basis of age, sex, social or economic factors, or for other reasons;

15. The justification for involving as research subjects any persons with limited capacity to consent or members of vulnerable social groups, and a description of special measures to minimize risks and discomfort to such subjects;

16. The process of recruitment, e.g., advertisements, and the steps to be taken to protect privacy and confidentiality during recruitment;

17. Description and explanation of any interventions (the method of treatment

administration, including route of administration, dose, dose interval and treatment period for investigational and comparator products used);

18. When relevant, the plans and justification for withdrawing or withholding standard measures in the course of the research, including any resulting risks to subjects;

19. Any other treatment that may be given or permitted, or contraindicated, during the study;

20. Clinical and laboratory tests and other tests that are to be carried out on subjects or on biological samples obtained from the subjects;

21. The standardized case-report forms to be used, description and evaluation of the methods and frequency of measurement in gathering data from subjects, follow-up procedures, and, if applicable, the measures proposed to determine the extent to which subjects actually use or are exposed to the intervention;

22. Rules or criteria according to which subjects may be removed from the study or clinical trial, or, in a multi-centre study, a centre may be discontinued, or the study may be terminated;

23. Methods of recording and reporting adverse events or reactions, and provisions for dealing with complications;

24. The known or foreseen risks of adverse reactions, including the risks attached to each proposed intervention and to any drug, vaccine or procedure to be tested;

25. For research carrying more than minimal risk of physical injury, details of plans, including insurance coverage, to provide treatment for such injury, including the funding of treatment, and to provide compensation for research-related disability or death;

26. Provision for continuing access of subjects to the intervention after the study, indicating its modalities, the individual or organization responsible for providing it or paying for it, and for how long it will continue;

27. For research on pregnant women, a plan, if appropriate, for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child;

28. The potential benefits of the research to subjects and to others;

29. The expected benefits of the research to the population, including new knowledge that the study might generate;

30. The means proposed to obtain individual informed consent and the procedure planned to communicate information to prospective subjects, including the name and position of the person responsible for obtaining consent;

31. When a prospective subject is not capable of informed consent, satisfactory assurance that permission will be obtained from a duly authorized person, or, in the case of a child who is sufficiently mature to understand the implications of informed consent but has not reached the legal age of consent, that knowing such child's agreement, or assent, will be obtained, as well as the permission of a parent or a legal guardian or other duly authorized representative*;*

32. An account of any economic inducements or other remuneration to prospective subjects for participation, and of any financial obligations assumed by the subjects, such as payment for medical services;

33. Plans and procedures, and the persons responsible, for communicating to subjects information arising from the study (on harm or benefit, for example), or from other research on the same topic, that could affect subjects' willingness to continue in the study;

34. Plans to inform subjects about the results of the study;

35. The provisions for protecting the confidentiality of personal data, and respecting the privacy of subjects, including the precautions that are in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives without the consent of the subject;

36. Information about how the code, if any, for the subjects' identity is established, where it will be kept and when, how and by whom it can be broken in the event of an emergency;

37. Any foreseen further uses of personal data or biological materials;

38. A description of the plans for statistical analysis of the study, including plans for interim analyses, if any, and criteria for prematurely terminating the study as a whole if necessary;

39. Plans for monitoring the continuing safety of drugs or other interventions administered for purposes of the study or trial and, if appropriate, the appointment for this purpose of an independent data-monitoring (data and safety monitoring) committee;

40. A list of the references cited in the protocol;

41. The source and amount of funding of the research: the organization that is sponsoring the research and a detailed account of the sponsor's financial commitments to the research institution, the investigators, the research subjects, and, when relevant, the community;

42. The arrangements for dealing with financial or other conflicts of interest that might affect the judgement of investigators or other research personnel: informing the institutional conflict-of-interest committee of such conflicts of interest; the communication by that committee of the pertinent details of the information to the

ethical review committee; and the transmission by that committee to the research subjects of the parts of the information that it decides should be passed on to them;

43. The time schedule for completion of the study;

44. For research that is to be carried out in a developing country or community, any contribution that the sponsor will make to capacity-building for scientific and ethical review and for biomedical research in the host country, and an assurance that the capacity-building objectives are in keeping with the values and expectations of the subjects and their communities;

45. Particularly in the case of an industrial or commercial sponsor, a contract stipulating who possesses the right to publish the results of the study, and a mandatory obligation to prepare with, and submit to, the principal investigators the draft of the text reporting the results;

46. In the case of a negative outcome, an assurance that the results will be made available, as appropriate, through publication or, if relevant to the type of study, by reporting to the drug registration authority;

47. Circumstances in which it might be considered inappropriate to publish findings, such as when the findings of an epidemiological, sociological or genetics study may present risks to the interests of a community or population or of a racially or ethnically defined group of people, and the procedures by which such a determination would be made; and

48. A statement that any proven evidence of falsification of data will be dealt with in accordance with the policy of the sponsor or of the legal authorities to take appropriate action against such unacceptable procedures.

## *Appendix 3.*

# WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

## Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

### A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse

consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially

important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. (See footnote)

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. (See footnote)

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

**Note**: **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

**Note**: **Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

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## *Appendix 4.*

## Members of the CIOMS/WHO Core Group established to carry out drafting of the provisional text of Guidelines

VALLOTTON, Michel B. (Chairman)
Professor, Swiss Academy of Medical Sciences and President, CIOMS

CAPRON, Alexander (Principal Rapporteur)
Professor of Law and Medicine, University of Southern California, Los Angeles, CA, USA, formerly Director, Department of Ethics, Trade, Human Rights and Health Law, WHO

SARACCI, Rodolfo (Co-rapporteur)
Director of Research in Epidemiology, National Research Council, Pisa, Italy and formerly Chairman, Ethical Review Committee, International Agency for Research on Cancer, WHO, Lyon, France

FARLEY, Tim
Coordinator, Controlling Sexually Transmitted and Reproductive Tract Infections, Department of Reproductive Health and Research, WHO

FLUSS, Sev S. (Secretary)
Senior Adviser, CIOMS

IDÄNPÄÄN-HEIKKILÄ, Juhana E.
Professor, Senior Adviser and formerly Secretary-General, CIOMS

KREUTZ, Gottfried
Professor, Secretary-General, CIOMS

MATSUDA, Ichiro
Professor, Science Council of Japan

PETERSON, Herbert
Professor, Chair, Department of Maternal and Child Health, University of North Carolina, Chapel Hill, NC, USA, and formerly Coordinator, Promoting Family Planning, Department of Reproductive Health Research, WHO

RANTANEN, Jorma
Professor, formerly Director-General, Institute of Occupational Health, Helsinki, Finland, and President, International Commission on Occupational Health

van DELDEN, Johannes J.M.
Professor of Medical Ethics, University of Utrecht, Netherlands, Royal Netherlands Academy of Arts and Sciences

VAYENA, Effy
Technical Officer, Department of Reproductive Health and Research, WHO