CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects

Revised draft, January 2002

(This draft revision of the Guidelines is presented in preparation for the CIOMS Conference to be held at WHO in Geneva, 27 February to 1 March 2002, to review and, as far as possible, endorse the draft Guidelines.)

The Council for International Organizations of Medical Sciences (CIOMS) presents here the draft International Ethical Guidelines for Biomedical Research Involving Human Subjects revised in the light of the comments submitted on the draft placed on this website in June 2001. CIOMS has greatly appreciated the contribution of the many organizations and individuals who have commented, many of them extensively, some critically, and not a few whose views opposed one another's. Submissions came mostly from developed countries. All comments were reviewed by an electronic drafting group of eight experts from Africa, Asia, Europe, Latin America and the United States, who interacted with one another and with the CIOMS secretariat.

The purpose of this draft is to elicit comments on issues that commentators believe should be raised at the forthcoming conference. Given the short interval between this posting and the opening of the conference on 27 February, which CIOMS regrets, those who wish to comment are invited to do so without delay and in any case by 20 February, so that the issues they raise and that are not already provided for in the provisional conference programme may receive due consideration.

Comments, whether general or on specific guidelines, should be submitted to CIOMS by e-mail. Otherwise they may be sent by air-mail or fax [(+41-22) 791 31 11] to CIOMS, c/o WHO, Avenue Appia, CH-1211 Geneva 27, Switzerland

Titles and Categories of Draft Guidelines

Ethical Justification

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Ethical Review

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Informed Consent

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Guideline 21: Obligations of external sponsors to provide health-care services

Guideline 1: Ethical justification of biomedical research involving human subjects.

Sponsors and investigators 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. The methods to be used should be appropriate to the objectives of the research and the field of study. Sponsors and investigators must also ensure that all personnel 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 approval to scientific and ethical review committees and funding agencies.

Commentary on Guideline 1

The most important requirements for ethical justification of research involving human subjects are that the scientific design of the programme must be adequate to achieve the objectives of the research and the investigators and other personnel must be competent. Scientific review is discussed further in the Commentaries to Guidelines 2 and 3: *Ethical review committees* and *Ethical review of externally sponsored research.* The protocol designed for submission for approval to scientific and ethical review committees and funding agencies should include, when relevant, the items specified in Appendix I.

Guideline 2: Ethical review committees

All proposals to conduct research involving human subjects must be submitted for review and approval of their scientific merit and ethical acceptability to one or more scientific and ethical review committees. These committees must be independent of the research team and not in a position to derive direct financial or other material benefit from the research. The researcher must obtain such approval before undertaking the research. The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.

Commentary on Guideline 2

Provision must be made for independent ethical review wherever research is conducted. Ethical review committees may function at the institutional, local, regional, or national level, and in some cases at the international level. Uniform standards should be promoted across committees within a country and, under all systems, sufficient resources should be allocated to the review process.

Scientific review. According to the Declaration of Helsinki (*Paragraph* 11), medical research involving humans must conform to generally accepted scientific principles, and be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, where appropriate, animal experimentation. Scientific review must include consideration of the study design and of whether appropriate safety monitoring is included. Committees competent to review and approve scientific aspects of research proposals must be multidisciplinary**.**

Ethical review. The responsibility of the ethical review committee is to safeguard the rights, safety, and well-being of all research participants. Scientific review and ethical review cannot be clearly separated: 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, wasting of participants' time in unproductive activities represents loss of a valuable resource. Normally, therefore, an ethical review committee considers both the scientific and the ethical aspects of proposed research. It must ensure that a proper scientific review is carried out, or verify that a competent expert body has confirmed that the research is scientifically sound. Also, it considers provisions for monitoring of data and safety (data and safety monitoring).

If an ethical review committee finds a research proposal scientifically sound, or verifies that a competent expert body has found it so, it should then 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. If the proposal is sound and the risk/benefit ratio sufficiently favourable, the committee should then determine whether the procedures proposed for obtaining informed consent are satisfactory, and whether the procedures proposed for selection of subjects are equitable.

Risks and benefits. The Declaration of Helsinki forbids the imposition of unwarranted risks on human research subjects. *Paragraph* 18 requires that " the importance of the objective outweighs the inherent risks and burdens to the subject." The need for means of preventing or treating serious infections or diseases, for example, is obvious justification of research aimed at developing such treatment or prevention.

As the Declaration of Helsinki states (*Paragraph* 11), clinical testing must be preceded by adequate laboratory, and, where appropriate, animal experimentation, to demonstrate a reasonable probability of success without undue risk. "*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"* (Declaration of Helsinki, *Paragraph* 16). "*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." (Declaration of Helsinki, *Paragraph* 5). This, however, does not preclude well-informed volunteers, capable of fully appreciating risks and benefits of an investigation, from participating in research for altruistic reasons.

[The ethical basis for the justification of risk is elaborated further in Guideline 4]

National (centralized) or local review. Ethical review committees may be created under the aegis of national or local health administrations, national (or centralized) medical 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 medical research is not centrally directed, protocols are more effectively and conveniently reviewed from the ethical standpoint at a local or regional level. The competence of a local ethical review committee may be confined exclusively to a single research institution or may extend to all biomedical research involving humans undertaken within a defined geographical area. The basic responsibilities of local ethical review committees are:

- to verify that a competent expert body has assessed all proposed interventions, and particularly the administration of drugs and vaccines or the use of medical devices or procedures under development, as acceptably safe to be undertaken in humans;
- to verify that a competent expert body has found the proposed research to be scientifically sound or to determine that it is so;
- to ensure that all other ethical concerns arising from a protocol are satisfactorily resolved both in principle and in practice;
- to consider the qualifications of the researchers and the conditions of the research site with a view to ensuring the safe conduct of the trial; and
- to keep records of previous decisions and to take measures to follow up on the conduct of ongoing research projects.

Committee membership. National or local ethical review committees should be so composed as to be able to provide complete and adequate review of the research activities referred to them. There should be a strong presumption in favour of including as members physicians, scientists and other professionals, such as nurses, lawyers, ethicists and clergy, as well as lay persons qualified to represent the cultural and moral values of the community. The membership should include both men and women.

Committees that often review research directed at specific diseases or impairments, such as HIV/AIDS or paraplegia, should invite or hear the views of individuals or bodies representing patients with such diseases or impairments. Similarly, in the case of such research subjects as children, students, elderly persons or employees, committees should invite or hear the views of their representatives or advocates.

Membership should be rotated periodically with the aim of blending the advantages of experience with those of fresh perspectives. Independence from the researchers and avoidance of conflict of interest are maintained by

excluding from the assessment of a proposal any member with a special or particular, direct or indirect, interest in it that could subvert objective judgment. Appointed members of ethical review committees should be held to the same standard of disclosure as scientific and medical staff of trials concerning financial and other interests that could be construed to be 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 member, to consider whether to ask the member to leave the discussion, and to invite the member to make a statement before leaving.

A national or local ethical review committee responsible for reviewing and approving proposals for externally sponsored research should have among its 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. When uneducated or illiterate persons form the focus of a study they should also be considered for membership.

Need for particularly stringent review requirements. The requirements of review committees should be particularly stringent when the proposed research is to involve children, persons with mental or behavioural disorders, communities unfamiliar with modern medical concepts and procedures, and other vulnerable social groups such as poor, uneducated or illiterate people, or when prospective subjects are pregnant or nursing women; and also when it carries substantial risk from interventions or procedures that do not hold out the prospect of direct health-related benefit for the individual participants. In considering such proposals the review committee should be especially attentive in determining that research participants are to be selected in a way that is both equitable and likely to minimize risk to them.

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 clinical trials, research designed for the evaluation of health service programmes, and various kinds of epidemiological research. For such studies, local ethical or scientific review committees are not normally authorized to change doses of drugs, to change inclusion or exclusion criteria, or to make other similar modifications. They should be fully empowered 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 trial 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 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. In some multi-centre studies, scientific and ethical review may be facilitated, where practicable, by agreement among institutions to accept the results of review by a single review committee, whose members could include representatives of ethical review committees at each of the places in which the research is to be conducted, as well as individuals competent to conduct scientific review. In other circumstances, a centralized review should be

complemented by local review relating to the participating investigators and institutions. The central committee could review the study from a scientific and ethical standpoint, and the local committees could verify the practicability of the study in their region/country, including the existing infrastructure, the state of training and ethical considerations of local significance.

In largemulti-centre trials, individual investigators will not have authority to act independently, with regard, for instance, to data analysis or to preparation and publication of manuscripts. Such trials usually have formal boards for monitoring of data and safety (Data and Safety Monitoring Boards) and publication committees which decide for the group what will be published and when. The function of the ethical review committee in such cases is to review the relevant plans with the aim of avoiding abuses *(Appendix: Protocol Item 32).*

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 therapies, or to practise medicine. Editors should consider refusal to publish the results of research conducted unethically. Drug regulatory authorities should consider refusal to accept unethically obtained data submitted in support of an application for marketing authorization of 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 related to project support. Increasingly, biomedical studies receive funding from commercial firms. While these sources of support may be rigorously supportive of acceptable scientific methodologies, there are instances in which the conditions of funding have the potential to bias and otherwise discredit the research. It may happen that investigators have little or no input into trial design, limited access to the raw data, or limited participation in data interpretation, or the results of a clinical trial might not be published if they are unfavourable to the sponsor's product. This risk of bias may also be associated 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 with their access to the data or their ability to analyse the data independently, to prepare manuscripts, or to publish them. Investigators must also disclose potential or apparent conflicts of interest to the ethical review committee. Ethical review committees should therefore ensure that these conditions are met. See also *Multi-centre research*, above.

Another potential conflict of interest to be considered for disclosure is investment of the sponsor (e.g., university) or investigator in a company whose product is being tested or service on company advisory committees. Usually determinations about such disclosure are made by an institutional conflict-of-interest committee.

Guideline 3: Ethical review of externally sponsored research

An external sponsoring agency and individual investigators should submit the research protocol to ethical and scientific review in the country of the sponsoring agency, and the ethical standards applied should be no less exacting than they would be for research carried out in that country. Appropriate authorities of the host country, including an independent national or local ethical review committee or its equivalent, should ensure that the proposed research is responsive to the health needs and priorities of the country and meets the requisite ethical standards.

Commentary on Guideline 3

Definition. The term *externally sponsored research* refers to research undertaken in a host country but sponsored, financed, and sometimes wholly or partly carried out by an external international or national agency or pharmaceutical 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 sponsoring agency and the host country have responsibility for conducting both 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 between the members of the review committees and the research. When the external sponsor is an international agency its review of the research protocol must be in accordance with its own independent ethical-review procedures and standards.

Committees in the external sponsoring country or international agency have a special responsibility to determine whether the scientific methods are sound and suitable for 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 sponsoring agency or in another developed country; and whether the proposed research is in compliance with the broadly stated ethical standards of the external sponsoring country or international organization.

Committees in the host country have the special responsibility to determine whether the objectives of the research are responsive to the health needs and priorities of the host 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, so that it may evaluate the proposed means of obtaining informed consent and otherwise respecting the rights of prospective subjects as well as 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 researchers 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 researcher 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 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 in 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. In host countries with inadequate capacity for independent ethical review, however, full review by ethical review committees in both the external sponsoring country or international agency and the host country is necessary.

When externally sponsored research is initiated and financed by an industrial sponsor such as a pharmaceutical company, it is in the interest of the host country to require that the research proposal be submitted with the comments of a responsible authority of the initiating country, such as a health administration, research council, or academy of medicine or science, or with the approval of an independent ethical review committee in the same country.

Guideline 4: Individual informed consent

For all biomedical research involving humans the researcher 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. Waiving of informed consent is to be regarded as uncommon and exceptional, and must in all cases be considered and approved by an ethical review committee.

Commentary on Guideline 4

General considerations. 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. (See Guideline 5, *Obtaining informed consent: Essential information for prospective research subjects;* Guideline 6, *Obtaining informed consent: Obligations of sponsors and investigators;* and Guideline 7, *Inducement to participate.)*

Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research. Informed consent protects 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 sophisticated medical concepts and technology (See Guidelines 13, 14,15).

Process. Obtaining informed consent is a process that is begun when initial contact is made with a prospective participant and continues throughout the course of the study. By informing the participants**,** by repetition and explanation, by answering their questions as they arise, and by ensuring that each participant understands each procedure, the research team elicits the informed consent of participants and in so doing manifests respect for their dignity. (Appendix 1, item 26)

Language. Informing the individual participant must not be simply a ritual recitation of the contents of a written document. Rather, the researcher must convey the information, whether orally or in writing, in language that suits the individual's level of understanding. The researcher must bear in mind that the prospective participant`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 researcher's attitude, and ability and willingness to communicate with patience and sensitivity.

Comprehension. The researcher must then ensure that the prospective participant has adequately understood the information. The researcher should give the prospective participant full opportunity to ask questions and should answer them honestly and promptly**.** In some instances the researcher may administer an oral or a written test or otherwise determine whether the information has been adequately understood.

Documentation of consent. Consent may be indicated in a number of ways. The subject may imply consent by his or her 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 the waiving 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 subjects' confidentiality. In some cases, particularly when the information is complicated, it is 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.

Waiver of the consent requirement. When the research design involves no more than minimal risk and it is not practicable to obtain informed consent from each subject (for example, where the research involves only excerpting data from subjects' records) the ethical review committee may waive some or all of the elements of informed consent. Investigators should never initiate research involving human subjects without obtaining each subject's informed consent, however, unless they have received explicit approval to do so from an ethical review committee.

Renewing consent. When material changes occur in the conditions or the procedures of a study, the researcher should once again seek informed consent from the subjects. For example, new information may have come to light, either from the study or from outside the study, about the risks or benefits of products being tested or about alternatives to them. Subjects should be given such information promptly. In many clinical trials, results are not disclosed to subjects and researchers until the study is concluded. This is ethically acceptable if the findings are monitored by a data and safety monitoring board, and an ethical review committee has approved their non-disclosure.

Cultural considerations. In some cultures or groups, a researcher 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 other 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. In some situations, the use of many local languages among the population of potential subjects or their limited acquaintance with scientific concepts, such as the concept of placebo or randomization, complicates the process of communicating information and ensuring that they truly understand it. Sponsors and researchers 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 procedures they plan to use in communicating information to participants. For collaborative research in developing countries the research project should, if necessary, include the resources to ensure that informed consent can indeed be obtained legitimately within different linguistic and cultural settings.

Consent to use for research purposes biological materials (including genetic material) from subjects in clinical trials: Consent forms for the research protocol should include a separate section for subjects in clinical trials who are requested to provide their consent for the use of their biological specimens for research. Separate consent may be appropriate in some cases (e.g., if researchers are requesting permission to conduct basic research which is not a necessary part of the clinical trial), but not in others (e.g., the clinical trial requires the use of participants' biological materials).

Use of medical records and biological specimens: Medical records and biological specimens that are taken in the course of clinical care may be used for research without the consent of the patients/subjects only if an ethical review committee has decided that the protocol poses minimal risk, that the rights or interests of the patients will not be violated, and that the research is designed to answer an important question and could not practicably be conducted if the requirement for informed consent were to be imposed. Refusal or reluctance of individuals to agree to participate would not be evidence of impracticability sufficient to warrant waiving informed consent. Records and specimens of individuals who have specifically rejected such uses in the past may be used only in the case of public health emergencies**.** (See Guideline 18 Commentary, *Confidentiality between physician and patient)*

Secondary use of research records or biological specimens: Researchers may want to use records or biological specimens that another researcher has created or collected. This raises the issue of whether the records or specimens contain personal identifiers, or can be linked to such identifiers, and by whom (See also *Guideline 18: Safeguarding confidentiality*). If informed consent or permission was required to authorize the original collection or creation of such records or specimens for research purposes, secondary uses are generally constrained by the conditions specified in the original consent. Consequently, it is essential that the original consent process anticipate, to the extent that this is feasible, any foreseeable plans for future use of the records or specimens for research. Thus, in the original process of seeking informed consent the researcher should discuss with, and, when indicated, request the permission of, prospective subjects as to: i) whether there will or could be any secondary use and, if so, whether such secondary use will be limited with regard to the types of study that may be performed on such materials; ii) the conditions under which researchers will be required to contact the research subjects for additional authorization for secondary use; iii) the researchers' plans, if any, to destroy or to strip of personal identifiers the records or specimens; and iv) the rights of subjects to request destruction or anonymization of biological specimens or records or any of their component parts that they might consider particularly sensitive such as photographs, videotapes or audiotapes.

Guideline 5: Obtaining informed consent: Essential information for prospective research subjects

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

1) that each individual is invited to participate in research, the reasons for selecting the individual, 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

researcher and the subject, and the aspects of the protocol that are incremental in that they would not be part of routine medical care;

4) for controlled trials, an explanation of features of the research design (e.g., randomization, double-blind), 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 and the possibility of early termination of the trial or of the individual's participation in it;

6) whether monetary 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, participants will be informed of the results;
8) 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;

9) the direct benefits to participants expected to result from the research;

10) the expected benefits of the research to the community or larger society, or contributions to scientific knowledge;

11) whether and 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;

12) any alternative, currently available, procedures or courses of treatment and their potential benefits and risks;

13) 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;

14) the limits, legal or other, to the researchers' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;

15) when appropriate, policy with regard to the disclosure and 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 without the consent of the subject;

16) the nature and sources of funding of the research, the sponsors of the research, the institutional affiliation of the investigators, and financial incentives to the investigators;

17) the possible research uses, direct or secondary, of the participant`s medical records and of biological specimens taken in the course of clinical care (See also Guidelines 4 and 17 commentaries);

18) whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage and possible future use, and that participants have the right to decide about such future use, to refuse storage, and to have the material destroyed (See Guideline 4 Commentary);

19) whether commercial products may be developed from biological specimens;

20) whether the researcher is serving only as a researcher or as both researcher and the subject`s health-care professional;

21) the extent of the researcher's responsibility to provide medical services to the subject;

22) that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, and whether there is any uncertainty regarding funding of such treatment.

23) whether the subject or the subject`s family or dependants will be compensated for disability or death resulting from such injury;

24) when applicable, in a particular country, that the right to compensation is not legally acknowledged; and,

25) that the research protocol has been approved by an ethical review committee.

Guideline 6: Obtaining informed consent: Obligations of sponsors and investigators

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

Commentary on Guideline 6

The researcher is responsible for ensuring the adequacy of informed consent from each subject. The person obtaining consent should be knowledgeable about the research and capable of answering questions from prospective subjects. Researchers in charge of the study must make themselves available to answer questions at the request of subjects. Any restriction of the subject's opportunity or right to ask questions and receive answers before or during the research undermines the validity of the informed consent.

In some types of research, potential subjects should receive counselling about risks of acquiring a disease unless they take precautions. This is especially true of HIV/AIDS vaccine research (see UNAIDS, Guidance Point 14, pp. 38-39).

Withholding information and deception. Sometimes, to ensure the validity of research, researchers withhold certain information in the consent process. In biomedical research, this typically takes the form of withholding information about the purpose of specific procedures. For example, subjects in clinical trials are often not told the purpose of tests performed to monitor their compliance with the protocol, 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. In other cases, because a request for permission to withhold some information would jeopardize the validity of the research, subjects are not told that some information has been withheld until the research is completed. Any such procedure must receive the explicit approval of the ethical review committee.

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 researcher 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 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 is ordinarily offered an opportunity to refuse to allow the researcher to use information obtained from studying the subject. Researchers 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/researcher, 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 researcher 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 it should be a neutral third party who seeks 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 3: *Individual informed consent.*

Risks. Investigators should be completely objective in discussing the details of the experimental intervention, the pain and discomfort that may be anticipated, 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 18 Commentary, *Risks to groups of persons.*)

Exceptions to the requirement for informed consent in emergencies. There are two classes of emergency investigational therapy in which the requirement for informed consent may be waived. The first consists of studies of emergency situations in which the researcher anticipates that many subjects will be unable to consent: a patient requires treatment, and this affords the investigator an opportunity to study a new treatment, even in an emergency context. The second is so-called compassionate or humanitarian use of an investigational new therapy: the individual patient requires prompt treatment that is of necessity an investigational treatment.

Exceptions to the consent requirement in studies of emergency situations in which the researcher anticipates that many subjects will be unable to consent. Research protocols are sometimes designed to address, as a necessary characteristic of the research population, particular conditions occurring suddenly and rendering the patients/subjects incapable of giving informed consent. Examples are head trauma, cardiopulmonary arrest and stroke. The investigation cannot be done with patients who can give informed consent in time and there may not be time to locate a person having the authority to give permission. In such circumstances it is often necessary to proceed with the research interventions very soon after the onset of the condition in order to evaluate an investigational therapy or develop the desired knowledge. As this class of emergency exception can be anticipated, the researcher must secure the review and approval of an ethical review committee before initiating the study. If possible, an attempt should be made to identify a population that is likely to develop the condition to be studied. This can be done readily, for example, if the condition is one that recurs periodically in individuals; examples include grand mal seizures and alcohol binges. In such cases, prospective subjects should be contacted while fully capable of informed consent, and invited to consent to their involvement as research subjects during future periods of incapacitation. If they are patients of an independent physician who is also the physician-researcher, the physician should likewise seek their consent while they are fully capable of informed consent. In all cases in which approved research has begun without prior consent of patients/subjects incapable of giving informed consent because of suddenly occurring conditions, they should be given all relevant information as soon as they are in a state to receive it, and their consent to continued participation should be obtained as soon as is reasonably possible**.**

The conditions to be satisfied before the ethical review committee may approve a plan to proceed without prior informed consent are the following :

Reasonable efforts will be made to locate an individual who has the authority to give permission on behalf of incapacitated patients. If such a person can be located and refuses to give permission, the patient may not be enrolled as a subject.

The risks of all interventions and procedures will be justified as required by Guideline 9 (*Justification of risk in research involving individuals who are not capable of giving informed consent).*

The researcher and the ethical review committee should agree to a maximum time of involvement of an individual without obtaining either the individual's informed consent or authorization according to the applicable legal system if the person is not able to give consent. If by that time the researcher has not obtained either consent or permission owing either to a failure to contact a representative or a refusal of either the patient or the person or body authorized to give permission the participation of the patient as a subject must be discontinued. The patient or the person or body providing authorization should be offered an opportunity to forbid the use of data derived from participation of the patient as a subject without consent or permission

Where appropriate, plans to conduct emergency research without prior consent of the subjects should be publicized within the community in which it will be carried out. In the design and conduct of the research, the ethical review committee, the investigators and the sponsors should be responsive to the concerns of the community. If there is cause for concern about the acceptability of the research in the community there should be a formal consultation with representatives designated by the community. The research should not be carried out if it does not have substantial support in the community concerned. (See Guideline18 Commentary, *Risks to groups of persons*.)

Emergency exception for compassionate or humanitarian use of an investigational new therapy. This second class of emergency exception is for so-called compassionate or humanitarian use of an investigational therapy: a patient requires treatment, and there is no other therapy available that is known to be equally or more suitable for the individual patient. Though this investigational therapy is not strictly research, in some countries drug regulatory agencies require that its use be reviewed by an ethical review committee as though it were research.

Such an exception to the requirement of informed consent may be justified only in circumstances in which all three of the following conditions are met: 1) the individual patient requires prompt treatment with the investigational drug or procedure to prevent death or serious disability; 2) no established treatment that is widely believed to be equally effective or superior is available; and 3) the individual patient is unable to give informed consent and no third party having the authority to give permission can be located in time for the investigational therapy to have its desired effect. In such circumstances the physician may proceed without informed consent. Within one week of having used this emergency exception, the physician should report to the ethical review committee the details of the case and the actions taken. An independent health-care professional should confirm in writing the treating physician's judgment that the emergency exception was justified according to the three specified criteria; this confirmation should also be submitted within one week.

Guideline 7: Inducement to participate

Subjects may be paid or otherwise rewarded for inconvenience and time spent; they may also receive free medical services. 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 to be provided to research subjects should be approved by an ethical review committee.

Commentary on Guideline 7

Acceptable recompense. Research subjects may have their transport and other expenses reimbursed and receive a modest allowance for inconvenience due to their participation in the research. Also, during the course of the research, investigators may provide them with medical services and the use of facilities, and perform procedures and tests 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. When there is minimal or no risk attached to a research intervention, 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. In studies in which there is more than minimal risk, all parties involved in the research - sponsors, researchers and ethical review committees - in both funding and host countries should be careful to avoid undue material inducements.

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 remuneration except a refund of out-of-pocket expenses, namely an amount comparable to that paid to research subjects for transport and related expenses. (For research involving children, see Guideline 14).

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

Guideline 8: Benefits and risks of study participation.

For all biomedical research involving humans, the researcher must ensure that there is a reasonable balance of potential benefits and risks. 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 risks 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 (generalizable

knowledge). The risks presented by such interventions must be: (i) minimized; and (ii) reasonable in relation to the importance of the knowledge to be gained.

Commentary on Guideline 8

The Declaration of Helsinki requires a careful evaluation of the harms and benefits of study participation: "*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" (Paragraph 16).* Physician-researchers must similarly "*abstain from engaging in research projects involving human subjects unless [the researchers] are confident that the risks involved have been adequately assessed and can be satisfactorily managed" (Paragraph 1).*

Clinical research often employs a variety of procedures of which some hold out the prospect of direct therapeutic benefit (beneficial procedures) and others are administered solely to answer the research question (non-beneficial procedures). Beneficial procedures 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 risks and benefits, as any available alternative.

Non-beneficial procedures are evaluated differently; they may be justified only by appeal to the knowledge to be gained. In evaluating the risks and benefits that a protocol presents to a population, it is appropriate to consider the harm that could result from forgoing the research.
The Declaration of Helsinki (Paragraph 18) requires that *"the importance of the objective outweighs the inherent risks and burdens to the subject."* This is understood as requiring that (i) the risks be minimized, and (ii) the risks be reasonable in relation to the knowledge to be gained.

Minimizing risk associated with participation in a randomized controlled trial.
In randomized controlled trials participants risk being allocated to receive the treatment 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 either new or established therapies, diagnostic tests and preventive measures.) The 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 in a randomized controlled trial is designed to prevent or postpone a lethal or disabling outcome, the investigator must not, for purposes of conducting the trial, withhold therapy that is known to be superior to the intervention being tested. Also, the investigator must provide in the research protocol for the monitoring of research data by an independent data-and-safety-monitoring board; one function of such a board is the protection of the research subjects from previously unknown adverse reactions or unnecessarily prolonged exposure to an inferior or less well tolerated therapy. Normally at the outset of a randomized controlled trial, criteria are established for its premature termination (stopping rules or guidelines).

Guideline 9: Justification of risk in research involving individuals who are not capable of giving informed consent.

When research involves participants who are unable to consent, the risk from procedures or interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them, and when, for scientific reasons, the research cannot be conducted with individuals capable of giving consent.

Commentary on Guideline 9

The low-risk standard: In research involving persons who are unable to consent, or whose capacity to make an informed choice may not fully meet the standard of informed consent, the employment of interventions or procedures that do not hold out the prospect of direct benefit for the individual subject requires careful ethical justification. When the risks of such interventions or procedures do not exceed those associated with routine medical or psychological examination of such persons, there is no requirement for special substantive or procedural protections apart from those generally required for all research involving members of the particular class of persons. When the risks are in excess of those, the requirements for justification are more stringent. In such cases the ethical review committee must find: 1) that the research is designed to be responsive to the disease affecting the prospective participants or to conditions to which they are particularly susceptible; 2) that the risks of the research interventions or procedures are only slightly greater than those associated with routine medical or psychological examination of such persons for the condition or set of clinical circumstances under investigation; 3) that the object of the research is sufficiently important to justify exposure of the research participants to the increased risk; and 4) that the procedures or interventions themselves present experiences to the subjects that are reasonably commensurate with those inherent in their actual clinical situations.

If such research participants, including children (Guideline 14), become capable of giving independent informed consent during the course of the research, their informed consent to continued participation should be obtained and respected

There is no precise definition of a "slight or minor increase" above the risks associated with routine medical or psychological examination of such persons. The meaning of this standard is inferred from what various research ethics committees have reported as having met that standard. Examples include the performance of additional lumbar punctures or bone-marrow aspirations on children with conditions for which such examinations are regularly indicated in clinical practice. The requirement that the object of the research be relevant to the disease or condition affecting the prospective participants rules out the use of such procedures or interventions in healthy children

The requirement that the procedures or interventions themselves must present experiences to the subjects that are reasonably commensurate with those inherent in their actual clinical situations is intended to enable them to draw on personal experience as they decide 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.

(See also Guidelines 4, *Individual informed consent*; 13, *Research involving vulnerable persons;* 14, *Research involving children;* and 15, *Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent.)*

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 researcher 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

The ethical requirement that research be responsive to the health needs of the population or community in which it is carried out calls for an interpretation of what is needed to fulfil the requirement**.** It is not sufficient simply to determine that a disease or condition is prevalent in the population concerned and that new or further research is needed: the ethical requirement of "responsiveness" can be fulfilled only if successful interventions or other benefits resulting from such research are made available to the population. This is especially the case when research is conducted in countries where governments lack the resources to make such products 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**.**

Sponsors should ensure that research subjects and the communities from which they are recruited are not made worse off as a result of the research (apart from justifiable risks of research interventions) for example, by the diversion of scarce local resources to research activities.

To address the ethical requirement of responsiveness to the health needs of the population or community concerned, a process of planning and

negotiation should commence before the research begins. It should set out the criteria for an equitable and just process by which decisions about post-trial availability will be made. It should end with "prior agreement," a term that refers generally to arrangements that are made before research begins, that are kept under review as the research progresses, and that lay out a realistic plan for making the proposed research product available to the host country, after the study is completed, within a specified time-frame if possible. There can be a substantial delay between the completion of a study and the time when a product or intervention can receive regulatory approval and be made available to research participants.

When a research study relates to a product or intervention that has important potential for health care in the host country, the negotiation should include representatives of stakeholders in the host country, such as the national government, the health ministry, local health authorities, and concerned scientific and ethics groups, as well as representatives of the communities from which participants are drawn and non-governmental organizations such as health advocacy groups. The discussions should cover the health-care infrastructure required for safe and rational use of the intervention or product, the likelihood of authorization for distribution, and decisions regarding payments, royalties, subsidies, technology and intellectual property, as well as distribution costs. 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, sponsors should continue to provide beneficial study interventions to all study participants at the conclusion of the study.

For minor research studies and when the outcome of research is in the form of scientific knowledge rather than a commercial product or intervention, such complex 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.

In general, if there is good reason to believe that a product developed or knowledge generated by a research programme is unlikely to be reasonably available to, or applied to the benefit of, the population of a proposed host country or community at 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. For example, as a rare exception, research designed to develop 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 that could not be carried out reasonably well in developed or more developed communities, 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 the development of a product that could be made reasonably available at its conclusion.

(See also Guidelines 3: *Ethical review of externally sponsored research;* 12:

Equitable distribution of burdens and benefits; 20: *Strengthening capacity for ethical and scientific review and biomedical research;* and 21: *Obligations of external sponsors to provide health-care services.)*

Guideline 11

Explanatory Note on Guideline 11: This Guideline is controversial. At three points alternate language is presented, and an addition is proposed to the first paragraph of the Commentary. The Guideline will be revised to put it in final form after the Conference adjourns on March 1, 2001. This process will require the development of conforming amendments depending on which of the alternates are chosen.

Guideline 11: Control groups in clinical trials

In a controlled trial of a new treatment or a new diagnostic or preventive procedure, its benefits, risks, burdens and effectiveness should be tested against those of the best current treatment or procedure. Placebo may be used as a comparator, however, if there is no proven best treatment or procedure that can be used as a comparator, or if its use carries no additional risk of serious or irreversible harm to the subjects. Any other proposal to use a control other than the best current method requires a sound scientific and ethical reason.

Proposed alternate language: Delete the third (last) sentence of the Guideline.

Commentary on Guideline 11

General considerations. Studies of investigational therapeutic or preventive methods should make use of control arms only when there is sound scientific reason to compare the effects of an investigational method with the effects of a method considered standard treatment, no treatment, or placebo. The study should be designed such that the foreseen benefits and risks to the research participants are considered equivalent in all arms. At the same time, the study design should have the promise of yielding scientifically valid results of benefit to the population in which the research takes place. In studies where the foreseen benefits or risks are considered greater in one or more arms, or where the 'best proven therapeutic method' is withheld from subjects in all arms, sound scientific and ethical justification should be provided in the research protocol. These factors should be clearly communicated to the ethical review committees as well as to prospective subjects in the informed-consent procedure.

Proposed addition: *The provisions of this guideline should not be considered as impediments to research into methods that may be better suited to the existing infrastructure in developing countries than the best current treatment or procedure used in industrialized countries.*

Placebo-controlled trials. The Declaration of Helsinki, Paragraph 29, states: "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." In October 2001 the World Medical Association Council issued a "note of clarification" on Paragraph 29 (see Appendix):

The present guideline endorses the intent of the clarification. It is, however, more restrictive and requires more stringent justification of exceptions to the general rule regarding control groups in controlled clinical trials.

There are two sound scientific and ethical reasons for departing from the principle regarding placebo-controlled studies stated in the Declaration of Helsinki and repeated in this Guideline:

> (1) Withholding the best current treatment will result in only temporary discomfort and no serious adverse consequences.
>
> (2) A comparative study of two active treatments will yield no reliable scientific results, or results that would not be beneficial to the community from which the subjects are drawn.

Proposed alternate language: *(Insert the word, 'and' at the end of the first criterion.)*

> *(1)Withholding the best current treatment will result in only temporary discomfort and no serious adverse consequences; and,*
>
> *(2)A comparative study of two active treatments will yield no reliable scientific results, or results that would not be beneficial to the community from which the subjects are drawn.*

These reasons apply when the condition for which patients/subjects are randomly assigned to placebo or active treatment is only a small deviation in physiological measurements, such as a slight elevation of blood pressure or a modest increase in serum cholesterol; in such circumstances, placebo-controlled studies may be ethical if delaying or omitting available treatment may cause only temporary discomfort and no serious adverse consequences. The researcher, however, must ensure that the safety, integrity and human rights of the patients/subjects are protected, that they are fully informed about alternative treatments, that the purpose and design of the study are scientifically sound, and that an independent ethical review committee has reviewed the study plan and given a favourable opinion. Examples of such studies are clinical trials of analgesics, hypnotics, drugs to relieve anxiety, anti-emetics, antihistamines, cough medicines, or substances or interventions designed to facilitate the cessation of smoking or prevent diseases caused by smoking or other harmful habits related to lifestyle. In many of those conditions, a comparative study of two treatments will yield no reliable scientific results.

The ethical and scientific acceptability of placebo-controlled studies increases when the placebo exposure period is limited and the study design permits change to active treatment (escape treatment) if intolerable symptoms persist (*WHO Good Clinical Practice Guidelines, 1995*).

A lack of sensitivity of the testing method (poor assay sensitivity) favours a placebo-controlled study design rather than a study comparing a known standard treatment or intervention with a new treatment or intervention being tested.

Control other than best current treatment or placebo. There are circumstances in which a control other than the best current method or standard treatment may be ethically justified. Sponsors and researchers in technologically developed countries, for instance, may propose to collaborate with counterparts in other countries to develop inexpensive alternatives to expensive therapies that are recognized as the "best current therapeutic method". In some such cases it may be appropriate to compare the new, inexpensive alternative with a locally available method or product rather than with the locally unavailable 'best proven therapeutic method.' Although there is no general agreement on this point, there are commentators who have concluded that in such circumstances use of a control other than the best current method is justified if: 1) the scientific and ethical review committees in both the country of the sponsoring organization and the host country determine that use of the best current method as a control would be likely to invalidate the results of the research or make the results inapplicable in the host country; 2) plans to make the therapeutic product reasonably available in the host country or community are securely established; 3) a process of planning and negotiation, including justification of a study in regard to local health-care needs, has taken place with the health authorities in the host country before the research begins; and 4) there is little or no likelihood that the results of the research would be applicable to the practice of medicine in the country of the sponsoring agency.

Proposed alternate language *(to replace the preceding paragraph- Control other than best current treatment or placebo):*

A proposal to use a control other than the best current method or standard treatment can be ethically justified only by applying to it the same requirement as for a placebo control: use of a control other than the best current treatment will result in only temporary or no discomfort and no serious adverse consequences.

Placebo "add-on" studies. A placebo-control group need not be untreated. In so-called "add-on studies" 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 trials are a particularly useful means of finding improvements in treatment or interventions that are not fully effective or may cause intolerable side-effects. Such studies also have a place in respect of treatment for epilepsy, rheumatism and osteoporosis, for example.

The UNAIDS (Joint United Nations Programme on HIV/AIDS) Guidance Document Ethical Considerations in HIV Preventive Vaccine

Research, May 2000 (Guidance point 11, commentary) advises as follows:

> A vaccine with proven efficacy in preventing infection or disease from HIV does not currently exist. Therefore, the use of a placebo control arm is ethically acceptable in appropriately designed protocols. In an effort to address the concern of lack of benefit to those randomly placed in a placebo group arm, it is recommended that the provision to these persons of another vaccine, such as for hepatitis B or tetanus, be considered.
>
> **End of Guideline 11**

The following will be printed in the Appendix immediately following the 2000 version of the Declaration of Helsinki:

"The WMA is concerned that paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It 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."

Guideline 12: Equitable distribution of burdens and benefits

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 individuals who 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, including 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. Participants 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. In some cases exclusion was based on judgments that the group was vulnerable (children, for example). Pre-menopausal women were excluded for more complex reasons: they were considered potentially vulnerable in that they might become pregnant, but also because cyclical changes in various physiological or biochemical measurements made it less convenient to use them as research subjects. Users of illicit drugs were excluded on grounds of their probable non-compliance with the necessarily rigid regimens of clinical trials.

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, and the policies of many national governments and professional societies, recognize the need to redress these injustices by encouraging the inclusion of previously excluded groups of people as participants in basic and applied research.

Members of vulnerable groups also have the same entitlement to access to the benefits of investigational agents 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. The location of research hospitals in places where members of the lowest socioeconomic classes reside has resulted in an apparent overuse of such persons. Other groups of people that may have been overused because they were conveniently available to researchers include students in the researchers' 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. In the past, prisoners were considered ideal subjects for Phase I drug studies because of their highly regimented lives and 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. In most cases, these people would be called upon to bear the burdens of research so that others who are more wealthy could 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, for example.

Similar considerations apply to institutionalized groups or those whose availability to the researchers is for other reasons administratively convenient.

Not only may certain groups within a society be inappropriately over-used as research subjects, but also entire communities or societies may be over-used. 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 over-use is especially problematic 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 3: *Ethical review of externally sponsored research* (*Commentary , Ethical and scientific review);* and 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. Classes of individuals conventionally considered vulnerable are those with limited capacity or freedom to consent or to decline to consent. They are the subject of specific guidelines in this document (Guidelines 14, 15) and include children, and persons who because of mental or behavioural disorders are incapable of giving informed consent. Ethical justification of their involvement usually requires that researchers 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; 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.

Other vulnerable social groups. The quality of the consent of prospective subjects who are junior or subordinate members of a hierarchical group requires careful consideration, as their agreement to volunteer may be unduly influenced by the expectation, whether justified or not, of preferential treatment 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 researchers or disciplinary superiors, 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.

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.
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.

Persons who have serious, potentially disabling or life-threatening diseases are highly vulnerable**.** Drugs and other therapies that have not yet been licensed for general availability because studies designed to establish their safety and efficacy remain to be completed are sometimes made available to such persons.. This is compatible with the Declaration of Helsinki, which states in Paragraph 32: " In the treatment of a patient, where proventherapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering". Such measures, commonly called 'compassionate use', are not properly regarded as research; however these measures should generally be made the object of research, designed to evaluate their safety and efficacy.

Although, on the whole, it is required that research be conducted on less vulnerable groups before involving more vulnerable groups, some exceptions are justified. In general, children are not suitable subjects for Phase I drug trials or for Phase I or II vaccine trials, but in some cases such trials may be

permissible after studies in adults have shown some degree of therapeutic or preventive effect. For example, a Phase II vaccine trial seeking evidence of immunogenicity in infants may be justified in the case of a vaccine that has shown evidence of preventing or slowing progression of an infectious disease in adults. In some cases it is appropriate to carry out Phase I research in children because the disease to be treated does not occur in adults or because it is manifested differently in children.

Guideline 14: Research involving children

Before undertaking research involving children, the researcher must ensure that:

- **children will not be involved in research that might 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 guardian of each child has given permission;**
- **the consent of each child has been obtained to the extent of the child's capabilities;**
- **a child's refusal to participate in research must always be respected unless, according to the research protocol, the experimental intervention shows promise of therapeutic benefit and there is no acceptable alternative therapy.**

See also Guideline 8: Benefits and risks of study participation; *Guideline 9:* Justification of risk in research involving individuals who are not capable of giving informed consent; *and Guideline 13:* Research involving vulnerable persons.

Commentary on Guideline 14

Justification of the involvement of children. 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 without any knowledge on specific effects and side-effects 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.

Consent of the child. 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 may be able to register a 'deliberate objection', an expression of disapproval or refusal of a proposed procedure. The deliberate objection of a four-year-old 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 knowledgeable agreement (assent) should be selected before younger children or infants, unless there are important scientific reasons related to age for involving younger children first. A deliberate objection by a child to taking part in research should always be respected even if the parent has given permission, unless the experimental 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 objections of the child. If such child participants become capable of giving independent informed consent during the course of the research, their informed consent to continued participation should be obtained and respected.

Permission of a parent or guardian. The researcher must obtain the permission of a parent or guardian in accordance with local laws or established procedures. 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 should normally be complemented by the permission of a parent or guardian, even when local law does not require it. Even when the law requires it, however, the assent of the child must always 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 investigations of adolescents' beliefs and behaviour regarding sexuality or use of recreational drugs; other research addresses domestic violence or child abuse. In studies on these topics, when they involve questionnaires or interviews only, 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 informed consent from children in institutions, such children should not be subjects of research unless researchers can consult an independent, concerned, expert advocate for institutionalized children who may be involved in research.

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 observe the research as it proceeds, so as to be able to withdraw the child from the research 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, a researcher 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.

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 researcher 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 there is no reasonable medical alternative and local law permits overriding the objection;**
- **in cases where prospective subjects lack capacity to consent, permission is obtained from a responsible relative or a legally authorized representative in accordance with applicable law.**

See also Guidelines 8: *Benefits and risks of study participation*; 9: *Justification of risk in research involving individuals who are not capable of giving informed consent*; and 13: *Research involving vulnerable persons.*

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 of exacerbations of their disorder are temporarily incapable. 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. The investigator must obtain the approval of an ethical review committee to include in research persons who by reason of mental or behavioural disorders are not capable of giving adequately informed consent. The willing cooperation of such persons 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. The agreement of an immediate family member or other person with a close personal relationship with the individual should be sought, but (is sometimes) may be of doubtful value, especially as 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 affliction. 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 (See Guideline 13**:** *Research involving vulnerable persons.*)

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.

Guideline 16: Women as research participants

Researchers, sponsors or ethical review committees should not exclude women of reproductive age from biomedical 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 potential 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 clinical study. In this discussion, if the research might be hazardous to a pregnant woman or to her fetus, the sponsors/ investigators should guarantee the prospective subject a pregnancy test and access to effective contraceptive methods. Where such access is not possible, for legal or religious reasons, researchers 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. Thalidomide, for example, caused much more extensive damage than it would have if its first administration to such women had been part of a formal, carefully-monitored clinical trial.

A general policy of excluding from such clinical trials women biologically capable of becoming pregnant is unjust in that it deprives women as a class of persons of the benefits of the new knowledge derived from the trials. Further, it is an affront to their right of self-determination. Nevertheless, although women of child-bearing age should be given the opportunity to participate in research, they should be helped to understand that the research could include risks to the fetus 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 participants in research, researchers 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 spousal authorization, however, violates the substantive principle of respect for persons, which requires equal respect to women as persons.

A thorough discussion of potential 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 clinical study. For women who are not pregnant at the outset of a study but who might become pregnant while they are still participants, 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: **Pregnant women as research participants.**

Guideline 17: Pregnant women as research participants.

Pregnant women should be presumed to be eligible for participation in biomedical research. Researchers 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. In all cases, risks to women and fetuses should be minimized. Even when evidence concerning risks is unknown or ambiguous, the decision about acceptability of risk should be made by the woman as part of the informed consent process.

Research in this group should be performed only if it is relevant to a pregnant woman's particular health needs 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 carcinogenicity.

Commentary on Guideline 17

The justification of research involving pregnant woman as subjects 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. Though the decision about acceptability of risk should be made by the mother as part of the informed consent process, it is desirable, when possible, also to obtain the father´s opinion.

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 participate in research in which there are interventions or procedures that hold out the prospect of direct benefit to the fetus. Where fetal abnormality is not recognized as ground for abortion, pregnant women should not be recruited for research programmes in which there is a realistic basis for concern that fetal abnormality may occur as a consequence of participation as a subject in research.

Guideline 18: Safeguarding confidentiality

The researcher must establish secure safeguards of the confidentiality of participants' research data. Participants should be told of the limits, legal or other, to the researchers' ability to safeguard confidentiality and of the possible consequences of breaches of confidentiality.

Commentary on Guideline 18

Confidentiality between researcher 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. Researchers 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 researcher should inform the prospective subjects about the precautions that will be taken to protect confidentiality.

Prospective subjects should be informed of limits to the researchers' ability

to ensure strict confidentiality and of the foreseeable adverse social 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. These and similar limits to the ability to maintain confidentiality should be anticipated and disclosed to prospective subjects.

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, participants 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 participants, from which information can be made available to outside agencies at a participant's request.

Confidentiality between physician and patient. Patients have the right to expect that their physicians 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. A treating physician should not disclose any identifying information about patients to an investigator unless each patient has given consent to such disclosure and unless an ethical review committee has approved such disclosure. Physicians and other health care professionals record the details of their observations and interventions in medical and other records. Epidemiological studies often make use of such records. For such studies it is usually impracticable to obtain the informed consent of each identifiable patient; an ethical review committee may waive the requirement for informed consent when this is consistent with the requirements of applicable law. *(See* Guideline 4 and Commentary*: Waiver of the consent requirement.)* In institutions in which records may be used for research purposes without the informed consent of identifiable patients, it is advisable to notify patients generally of such practices; notification is usually by means of a statement in patient-information brochures.

For research limited to patients' medical records, access must be approved by an ethical review committee and must be supervised by a person who is fully aware of the confidentiality requirements.

[See also Guideline 4 Commentary: *Consent to use of biological materials (including genetic material) for research.]*

Risks to groups of persons. Research in certain fields may present risks to the interests of communities, societies or racially or ethnically defined groups of people. Examples of such fields are epidemiology, genetics and sociology. Information could be published that could stigmatize a group or expose its members to discrimination; for example, it could indicate, rightly or wrongly, 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 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.

Issues of confidentiality in genetic research: The informed consent of the prospective subject is required for the performance of genetic tests of known clinical or predictive value on biological samples that can be linked to the individual. Conversely, unless specific individual consent is obtained, where a genetic test is of known predictive value or gives reliable information about a known heritable condition, DNA samples must be fully anonymized and unlinked before testing; this ensures that no information about specific individuals can be derived from such research or passed back to them.

When 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 participants, the investigator seeking informed consent should explain to the prospective participants the system by which their identity will be protected by secure coding of their DNA samples (encryption) and by restricted access to the database.

When it is clear that for medical, and possibly research, reasons the results of genetic tests will be reported to either the participant or the participant`s clinician, the participant should be informed that the samples to be tested will be clearly labelled.

Researchers should not disclose results of diagnostic genetic tests to relatives of subjects**.** In places where immediate family relatives would usually expect to be informed of results of a subject's diagnostic genetic tests, the research protocol, as approved by the ethical review committee, should indicate the precautions that are in place to prevent such disclosure of results without the consent of the subject; such plans should be clearly explained during the informed consent process.

Where there is no participant involvement and individual privacy is assured, and subject to specific guidelines regarding research using existing records and biological samples, it is ethically acceptable to use samples for genetic research that could generate stigmatizing data about disease frequency in a community or sub-population without the renewal of the consent of the research participant. [See also Guideline 4 Commentary: *Consent to use of biological (including genetic) material for research*; *Use of medical records and biological specimens;* and *Secondary use of research records or specimens*.]

Studies of genetic variation, when they are concerned with genotypic variants that may or may not be linked with disease, should be conducted only after consultation with the communities or sub-populations that may be liable to stigmatization or otherwise harmed as a result of the information obtained; the communities or sub-populations concerned must have appropriate and identifiable advocates. They do not have the right, however, to deny individuals the authority to decide whether or not to participate in such studies. In all cases the consent of the prospective individual subjects

must be obtained.

Guideline 19: Right of subjects to compensation

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 material compensation. The right to compensation may not be waived.

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. The implementation of the compensation system for research-related injuries or death is liable to be complex.

Accidental injury. Accidental injury due to procedures performed exclusively to accomplish the purposes of research rarely results in death or in permanent or temporary impairment, disability or handicap. These are much more likely to result from investigational diagnostic, preventive or therapeutic interventions. In general, however, death or serious injury is less likely to result from such interventions performed in the course of properly designed, conducted and sanctioned studies than from similar standard interventions in routine medical practice. Usually, human research subjects are in exceptionally favourable circumstances in that they are under close and continuing observation by qualified researchers alert to detecting the earliest signs of untoward reactions.

Equitable compensation and free medical treatment. Compensation is owed to participants 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 from investigational therapies or other procedures performed to diagnose or prevent disease. Such reactions are not different in kind from those that occur in medical practice.

When, as in the early stages of drug testing, it is unclear whether a procedure is performed primarily for research or for therapeutic purposes, 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 review committee's decisions, as part of the process of informed consent (Guideline 5, items 22, 23: *Obtaining informed consent: Essential information for prospective research subjects)*. As an ethical review committee cannot make such advance determination in respect of unexpected or unforeseen adverse reactions, they must be

presumed compensable and should be reported to the committee for prompt review as they occur.

Subjects should not be required to waive their rights to compensation or to show negligence or lack of a reasonable degree of skill on the part of the researcher in order to claim free medical treatment or compensation. The informed consent process or form should contain no words that would absolve a researcher 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.

Obligation of the sponsor to pay. The sponsor, whether a pharmaceutical company, a government or an institution, should agree, before the research begins, to provide compensation for any physical injury for which subjects are entitled to compensation, or to come to an agreement ahead of time with the investigator concerning the situations 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 both. Sponsors should seek to obtain adequate insurance against risks to cover compensation, independent of proof of fault.

Guideline 20: Strengthening capacity for ethical and scientific review and biomedical research

Many countries lack the capacity to ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. Sponsors and investigators have an ethical obligation to see that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical 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**
- **strengthening research capacity**
- **developing technologies appropriate to health-care and biomedical research**
- **training of research and health-care staff**
- **educating the community from which research participants will be drawn.**

Commentary on Guideline 20

It is an important secondary objective of externally sponsored collaborative research to help develop a host country's sustainable capacity for independent scientific and ethical review and to carry out independent biomedical research. When a host country has little or no such capacity, an

indispensable preliminary to initiating a research programme on the part of external sponsors and investigators is a plan whereby they undertake to assist in the development of such capacity. (See Guideline 10*: Research in populations and communities with limited resources.*) The specific capacity-building objectives should be determined and achieved through a process of dialogue and negotiation among the various partners from host and sponsor countries. Accordingly, external sponsors are expected to employ and, if necessary, train local individuals to function as researchers, 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 to ensure the independence of committees, such assistance should not be provided directly to committees; rather, funds should be made available to appropriate authorities in the host-country government or in the host research institution.

Apart from contributing to capacity for ethical and scientific review, this provision reduces the risk of exploitation of countries that lack developed regulatory systems or ethical review arrangements.

Guideline 21: Obligations of external sponsors to provide health-care services

External sponsors are ethically obliged to provide health-care services:

- **when the health-care services are essential to the conduct of the research;**
- **when subjects require treatment for injury suffered as a consequence of research interventions;**
- **when the services 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.**

External sponsors incur obligations to provide health-care services:

- **when the sponsor has undertaken to make specified health-care services available to the research subjects even though the services are not, strictly speaking, essential to the conduct of the research;**
- **when the services are a specified part of the contribution that a sponsor has undertaken to make to the community's capacity to provide health-care facilities and personnel as a part of capacity-building for ethical and scientific review and biomedical research;**

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. The sponsors' obligations in particular studies should be clarified before the research is begun. The research protocol should specify what, if any, resources, facilities, assistance and other goods or services will be made available, during and after the research, to the community from which the subjects are drawn and to the host country, and for how long. 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 ethical review committee in the host country should determine whether any or all of these details should be made a part of the consent process.

Health-care services that are essential to the conduct of the research include, but are not limited to, the clinical facilities in which to conduct the research, which may be a hospital or an outpatient facility; the study drugs or vaccines; and the professional staff. By prior agreement the sponsoring agency may agree to maintain, in the host country, after the research has been completed, under specified conditions, health services and facilities established for purposes of the study. These may be made part of a sponsor `s contribution to a community's sustainable capacity for ethical and scientific review and biomedical research. (See Guideline 20*: Strengthening capacity for ethical and scientific review and biomedical research.)*

Although sponsors are, in general, not obliged to provide services or health-care facilities or personnel 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 during 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.

In certain circumstances, it may be considered an ethical obligation to provide such services. When, for instance, subjects suffer from diseases that are related to the research, such as participants in HIV preventive vaccine trials who contract HIV/AIDS and its associated complications, or subjects of studies that monitor HIV progression, the sponsor is expected, as an ethical obligation, to provide care and treatment, in a form determined by prior agreement, through a host/community/sponsor dialogue (UNAIDS Guidance Document, point 16).

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, is the subject of Guideline 19, on the scope and limits of such obligations.

Investigators should refer for health-care services subjects or prospective subjects who are found to have diseases unrelated to the research; also, if appropriate, they should advise prospective subjects to seek medical care if they are rejected as research subjects because they do not meet health criteria for admission to the investigation. In general, also, in the course of a study, sponsors should disclose to the proper host-country authorities information arising that relates to the health of the country or community.

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: *Research in populations and communities with limited resources.*

APPENDIX I

Items to be included in a protocol (or protocol annexes) for biomedical research involving human subjects.

1. Title of the study;

2. 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, its objectives, its hypotheses or research questions, its assumptions, its variables, and any foreseen risks;

3. Information on previously published research on the topic;

4. An account of previous submissions of the protocol for ethical review and their outcome;

5. A brief description of the site(s) where the research is to be conducted, and *relevant* demographic and epidemiological information about the country or region concerned;

6. Name and address of the sponsor;

7. Name*s*, address*es*, institutional affiliations*,* qualifications and experience of the principal investigator (as in multi-centre studies) and of the other investigators;

8. A detailed description of the type of trial or study (randomized, blinded, open), the design (parallel groups, cross-over technique), the blinding technique (double-blind, single-blind), and the method of randomization;

9. The number of participants needed to achieve the study objective, determined on a statistical basis;

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

11. The process of recruitment, the methods and timing of allocation of

subjects to investigational groups, and the steps to be taken to protect privacy and confidentiality during recruitment;

12. Description of, and justification of, all interventions, including route of administration, dose, dose interval and treatment period for investigational and comparator products used;

13. Plans, or justification, for withdrawing or withholding standard therapies in the course of the research, including any resulting risks to subjects;

14. Any other treatment that may be given or permitted, or contraindicated, at the same time;

15. Clinical and laboratory tests, pharmacokinetic analysis, or other tests that are to be carried out;

16. Samples of the standardized case-report forms to be used, the methods of recording therapeutic response (description and evaluation of methods and frequency of measurement), the follow-up procedures, and, in a drug trial, the measures proposed to determine the extent of compliance of subjects with the treatment;

17. Rules or criteria according to which the investigator may remove subjects from the study or clinical trial;

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

19. The risks of adverse reactions, including the risks attached to each proposed intervention and to any drug, vaccine or procedure to be tested, and the results of relevant laboratory and animal research;

20. For research carrying more than minimal risk of physical injury, an account of plans, if any, to provide treatment for such injury, including provisions for the funding of such treatment, and to provide compensation for research-related disability or death;

21. Medical care to be provided to participants after the study, and the modalities of such treatment;

22. The resources, facilities, assistance and other goods or services that will be made available, during and after the research, to the community from which the subjects are drawn and to the host country;

23. The expected benefits of the research to subjects and to others;

24. The expected benefits to the population, including new knowledge that might be generated as a result of the study;

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

26. The means proposed to obtain individual informed consent and the procedures planned to communicate information to prospective subjects, including the name and position of the person responsible for obtaining consent, or, when a prospective subject is not capable of informed consent, satisfactory assurance that permission will be obtained from a duly authorized person*;*

27. An account of any economic or other inducements or incentives to prospective subjects to participate, such as offers of cash payments, gifts, or free services or facilities, and of any financial obligations assumed by the subjects, such as payment for medical services;

28. 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;

29. Plans to inform subjects ultimately about the results of the study;

30. The provisions for protecting the confidentiality of personal data, and respecting the privacy of participants, 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;

31. Any foreseen further uses of research results/personal data/biological materials;

32. A description of the plans for statistical analysis of the study, including calculation of its statistical power, and, derived from such calculation, criteria for prematurely terminating the study as a whole if necessary;

33. Plans for monitoring the continuing safety of drugs or other interventions administered for purposes of the study or trial(data safety monitoring) and the appointment for this purpose of an independent data-safety-monitoring

board;

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

35. The organization that is sponsoring the research and a detailed account of the sponsor's financial commitments to the research institution, the researchers, the research subjects, and, when relevant, the community;

36. Information on the source and amount of funding of the research;

37. An account of financial or other conflicts of interest that might affect the judgement of investigators or other research personnel;

38. Information about the adequacy of facilities for the safe and appropriate conduct of the research;

39. A statement that the principles set out in these Guidelines or in the Declaration of Helsinki will be implemented;

40. Information about how the code 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;

41. The time schedule for completion of the study;

42. Instructions for staff involved in the trial, including how they are to be informed about the way the trial is to be conducted and about the procedures for drug use and administration, and other interventions;

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

44. The contribution that the research 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 participants and their communities;

45. When the protocol serves as a contract, statements regarding financing, insurance, liability, and delegation or distribution of responsibilities, including arrangements for publication of the results or other plans for making available both positive and negative outcomes, and assurance that investigators performing the study will be free to publish their results;

46. A contract stipulating who possesses the right to publish the results, and a mandatory obligation to prepare with, and submit to, the principal investigators the draft version of the text reporting the results of the study, as well as to make available to the principal investigators a statistical analysis with the raw data;

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