3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

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PROPOSED INTERNATIONAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Council for International Organizations of Medical Sciences and World Health Organization, 1982

Preamble

All advances in medical practice are dependent upon an understanding of relevant physiological and pathological processes and must necessarily, in the last resort, be tested for the first time on human subjects. It is in this sense that the term "research involving human subjects" is used.

The context in which such research is undertaken is wide and includes:

- studies of a physiological, biochemical, or pathological process, or of the response to a specific intervention—either physical, chemical, or psychological—in healthy subjects or patients under treatment;
- prospective controlled trials of diagnostic, prophylactic, or therapeutic measures in larger groups of patients, with a view to demonstrating a specific response against a background of individual biological variation;
- studies in which the consequences of specific prophylactic or therapeutic measures are determined within communities.

Research involving human subjects is thus defined for the purposes of these guidelines as any study involving human subjects, and directed to the advancement of biomedical knowledge, that cannot be regarded as an element in established clinical management or public health practice, and that involves either:

- physical or psychological intervention or assessment, or
- generation, storage, and analysis of records containing biomedical information referrable to identifiable individuals.

Such studies include not only planned interventions on human subjects but research in which environmental factors are manipulated in a way that could place incidentally exposed individuals at risk.

The terms of reference are framed broadly, in order to embrace field studies of pathogenic organisms and toxic chemicals under investigation for medical purposes. Analogous risks are recognized to arise in research directed to other objectives, but nonmedical research does not fall within the scope of this document.

Research involving human subjects should be carried out only by appropriately qualified and experienced investigators in accordance with an experimental protocol that clearly states: the aim of the research; the reasons for proposing that it should be undertaken on human subjects; the nature and degree of any known risks; the sources from which it is proposed that subjects should be recruited; and the means proposed for ensuring that their consent is adequately informed. The protocol should be scientifically and ethically appraised by a suitably constituted review body independent of the investigators.

The guidelines proposed below will offer some countries nothing that is not already in force in one form or another. They have been framed with special reference to the requirements of developing countries and elaborated in the light of replies to a questionnaire received from 45 national health administrations and 91 medical faculties in countries in which medical research involving human subjects is as yet undertaken on a limited scale and/or in the absence of explicit national criteria for protecting such subjects from involuntary abuse. The replies were received from a total of 60 developing countries.

International Declarations

1. The first international declaration on research involving human subjects was the Nuremberg Code of 1947, which was a by-product of a trial of physicians for having performed cruel experiments on prisoners and detainees during the Second World War. The Code lays particular stress on the "voluntary consent" ("informed consent" is now the usual term) of the subject, which is stated to be "absolutely essential."

2. In 1964, the World Medical Association (WMA), at its 18th World Medical Assembly, adopted the Declaration of Helsinki ("Helsinki I"), which was a set of rules to guide physicians engaged in clinical research, both therapeutic and nontherapeutic. At its 29th World Medical Assembly in 1975, the WMA revised this Declaration ("Helsinki II"), broadening its scope to include "biomedical research involving human subjects." Some important new provisions in the revised Declaration were that experimental protocols for research involving human subjects "should be transmitted to a specially appointed independent committee for consideration, comment and guidance" (article I, 2); that such protocols "should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with" (article I, 12); and that reports on "experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication" (article I, 8).

3. Both the Nuremberg Code and the original Declaration of Helsinki of

1964 have been superseded by "Helsinki II," the full text of which is appended.[3] This is the basic document in its field, and has been widely accepted as such.

4. These guidelines take account of the distinction made in "Helsinki II" between medical research combined with professional care (clinical research) and nontherapeutic (nonclinical) biomedical research.

5. While the general principles laid down in "Helsinki II" may be regarded as of universal validity, their modes of application in various special circumstances must necessarily vary. The purpose of the present guidelines is, therefore, not to duplicate or amend these principles, but to suggest how they may be applied in the special circumstances of many technologically developing countries. In particular, the limitations of the informed consent procedure are emphasized, and issues specific to research involving communities rather than individual subjects are addressed.

Consent of Subjects

6. "Helsinki II" requires (article I, 9) that human subjects should not be used in medical research unless "freely given informed consent" has been elicited after having been adequately informed of the "aims, methods, anticipated benefits, and potential hazards" of the experiment and informed that they are free to abstain or to withdraw from participation at any time. Of itself, however, informed consent offers an imperfect safeguard to the subject, and it should always be complemented by independent ethical review of research proposals. Moreover, there are many individuals, including children, adults who are mentally ill or defective, and those who are totally unfamiliar with modern medical concepts, who are incapable of giving adequate consent and from whom consent implies a passive and uncomprehending participation. For such groups, in particular, independent ethical review is imperative.

Children

7. It is axiomatic that children should never be the subjects of research that might equally well be carried out on adults. However, their participation is indispensable for research on diseases of childhood and conditions to which children are particularly susceptible. The consent of a parent or other legal guardian, after a full explanation of the aims of the experiment and of possible hazards, discomfort, or inconvenience, is always necessary.

8. To the extent that is feasible, which will vary with age, the willing cooperation of the child should be sought, after he or she has been frankly informed of any possible discomfort or inconvenience. Older children may be assumed to be capable of giving informed consent, preferably also with the consent of the parent or other legal guardian.

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[3]See pages 604–609 in this volume.

9. Children should in no circumstances be the subjects of research holding no potential benefit for them unless with the objective of elucidating physiological or pathological conditions peculiar to infancy and childhood.

Pregnant and Nursing Women

10. While no special problems of eliciting informed consent exist in the case of pregnant and nursing mothers as such, they should in no circumstances be the subjects of nontherapeutic research that carries any possibility of risk to the fetus or neonate, unless this is intended to elucidate problems of pregnancy or lactation. Therapeutic research is permissible only with a view to improving the health of the mother without prejudice to that of the fetus or nursling, to enhancing the viability of the fetus, or to aiding the nursling's healthy development or the ability of the mother to nourish it adequately.

Research directed to induced termination of pregnancy, or undertaken in anticipation of termination, is an issue that is dependent upon national legislation and religious and cultural precepts, and, therefore, does not lend itself to an international recommendation.

Mentally Ill and Mentally Defective Persons

11. Substantially similar ethical considerations apply to the mentally ill and the mentally defective as to children. They should never be the subjects of research that might equally well be carried out in adults in full possession of their intellectual faculties, but they are clearly the only subjects available for research into the origins and treatment of mental disease or disability.

12. The agreement of the immediate family—whether spouse, parent, adult offspring, or sibling—should be sought, but is sometimes of doubtful value, especially as mentally deranged or defective patients are sometimes regarded by their families as an unwelcome burden. Where a subject has been compulsorily committed to an institution by a court order, it may be necessary to seek legal sanction before involving the subject in experimental procedures.

Other Vulnerable Social Groups

13. The quality of the consent of candidate subjects who are junior or subordinate members of a hierarchically structured group requires careful consideration, as willingness to volunteer may be unduly influenced by the expectation, whether justified or not, of adventitious benefits. Examples of such groups are medical and nursing students, subordinate laboratory and hospital personnel, employees of the pharmaceutical industry, and members of the armed forces.

Subjects in Developing Communities

14. Rural communities in developing countries may not be conversant with the concepts and techniques of experimental medicine. It is in these communities that diseases not endemic in developed countries exact a heavy toll of illness, incapacity, and death. Research on the prophylaxis and treatment of such diseases is urgently required, and can be finally carried out only within the communities at risk.

15. Where individual members of a community do not have the necessary awareness of the implications of participation in an experiment to give adequately informed consent directly to the investigators, it is desirable that the decision whether or not to participate should be elicited through the intermediary of a trusted community leader. The intermediary should make it clear that participation is entirely voluntary, and that any participant is free to abstain or withdraw at any time from the experiment.

Community-based Research

16. Where research is undertaken on a community basis—for example, by experimental treatment of water supplies, by health services research, or by large-scale trials of new insecticides, of new prophylactic or immunizing agents, and of nutritional adjuvants or substitutes—individual consent on a person-to-person basis may not be feasible, and the ultimate decision to undertake the research will rest with the responsible public health authority.

17. Nevertheless, all possible means should be used to inform the community concerned of the aims of the research, the advantages expected from it, and any possible hazards or inconveniences. If feasible, dissenting individuals should have the option of withholding their participation. Whatever the circumstances, the ethical considerations and safeguards applied to research on individuals must be translated, in every possible respect, into the community context.

Review Procedures

18. The provisions for review of research involving human subjects are influenced by political institutions, the organization of medical practice and research, and the degree of autonomy accorded to medical investigators. Whatever the circumstances, however, a dual responsibility exists within society to ensure that:

- all drugs and devices under investigation in human subjects meet adequate standards of safety;
- the provisions of "Helsinki II" are applied in all biomedical research involving human subjects.

Assessment of Safety

19. Authority to assess the safety and quality of new medicines and devices intended for use in man is most effectively vested in a multidisciplinary advisory committee operative at the national level. Clinicians, clinical pharmacologists, pharmacologists, toxicologists, pathologists, pharmacists, and statisticians have important contributions to offer to these assessments. Many countries at present lack resources to undertake independent assessments of technical data according to procedures and standards now considered mandatory in many highly developed countries. Improvement in their capability to subserve this function is dependent, in the short term, on more efficient exchange of relevant information internationally.

Ethical Review Committees

20. It is not possible to draw a clear dividing line between scientific review and ethical review, for an experiment on human subjects that is scientifically unsound is *ipso facto* unethical, in that it may expose the subjects to risk or inconvenience to no purpose. Normally, therefore, ethical review committees consider both scientific and ethical aspects. If a review committee finds a research proposal scientifically sound, it will then consider whether any known or possible risk to the subject is justified by the expected benefit and, if so, whether the proposed procedure for eliciting informed consent is satisfactory.

21. In a highly centralized administration, a national review committee may be constituted to review research protocols from both scientific and ethical standpoints. In countries where medical research is not centrally directed, protocols are more effectively and conveniently reviewed from the ethical standpoint at local or regional levels. The basic responsibilities of locally operative ethical review committees are twofold:

- to verify that all proposed interventions, and, particularly, the administration of drugs under development, have been assessed by a competent expert body as acceptably safe to be undertaken in human subjects.
- to ensure that all other ethical considerations arising from a protocol are satisfactorily resolved both in principle and in practice.

22. Review committees may be created under the aegis of national or local health administrations, of national medical research councils, or of other nationally representative medical bodies. The competence of committees operating on a local basis may be confined exclusively to a specific research institution or it may extend to all biomedical research involving human subjects undertaken within a defined geographical area.

23. Local review committees act as gatherings of the investigators' peers

and should be so composed as to provide complete and adequate review of the research activities referred to them. The membership may include other health professionals, particularly nurses, as well as laymen qualified to represent community, cultural, and moral values. Independence from the investigators is maintained by precluding any member with a direct interest in a proposal from participation in its assessment.

24. The requirements of review committees should be particularly stringent in the case of proposed research involving children, pregnant and nursing women, the mentally ill or mentally defective persons, members of developing communities unfamiliar with modern clinical concepts, and any invasive nontherapeutic research.

Information to be Provided by Investigators

25. Whatever may be the pattern of the procedure adopted for ethical review, it should be based on a detailed protocol comprising:

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

26. There should also be included information to establish:

- the safety of each proposed intervention and of any drug or device to be tested, including the results of relevant laboratory and animal research;
- the presumed benefits and potential risks of participation;
- the means proposed to elicit informed consent or, when this is not possible, satisfactory assurance that the guardian or family will be appropriately consulted and the rights and welfare of each subject will be adequately protected;
- evidence that the investigator is appropriately qualified and experienced, and commands adequate facilities for the safe and efficient conduct of the research;
- provisions that will be made to protect confidentiality of data;
- the nature of any other ethical considerations involved, together with an indication that the principles enunciated in "Helsinki II" will be implemented.

Externally Sponsored Research

27. The term externally sponsored research is here used to refer to research undertaken in a host country but initiated, financed, and sometimes wholly or partly carried out by an external international or national agency with the collaboration or agreement of the appropriate authorities of the host country.

28. Such research implies two ethical imperatives:

- The research protocol should be submitted to ethical review by the initiating agency. The ethical standards applied should be no less exacting than they would be for research carried out within the initiating country.
- After ethical approval by the initiating agency, the appropriate authorities of the host country should, by means of an ethical review committee or otherwise, satisfy themselves that the proposed research meets their own ethical requirements.

Where externally sponsored research is initiated and financed by a pharmaceutical manufacturer, it is in the interest of the host country to require that it should 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.

29. An important secondary objective of externally sponsored research should be the training of the health personnel of the host country to carry out similar research projects independently.

Compensation of Research Subjects for Accidental Injury

30. Reports of accidental injury to subjects volunteering to participate in therapeutic or nontherapeutic research resulting in temporary or permanent disability, or even death, are exceedingly rare. In fact, human subjects of medical research are usually in exceptionally favorable circumstances, in that they are under close and continued observation by highly qualified investigators who are alert to detect the earliest signs of untoward reactions. Such conditions are less likely to occur in routine medical practice.

31. However, any volunteer subjects involved in medical research who may suffer injury as a result of their participation are entitled to such financial or other assistance as would compensate them fully for any temporary or permanent disability. In the case of death, the dependents should be eligible for appropriate material compensation.

32. Experimental subjects should not, in giving their consent to participation, be required to waive their rights to compensation in the case of an accident; nor should they be required to show negligence or lack of a reasonable degree of skill on the part of the investigator. Support is increasing for a system of insurance against risks, financed either by public or private funds or both, the injured party having only to show a causal relationship between the investigation and his injury. For research spon-

sored by pharmaceutical manufacturers, the manufacturers themselves should assume responsibility in case of accidents. This is particularly necessary in the case of externally sponsored research when the subjects are not protected by social security measures.

Confidentiality of Data

33. Research may involve the collection and storage of data relating to individuals, which, if disclosed to third parties, might cause harm or distress. Consequently, arrangements should be made by investigators to protect the confidentiality of such data, as for example by omitting information which might lead to the identification of individual subjects, by limiting access to the data, or other appropriate means.

INTERNATIONAL GUIDING PRINCIPLES FOR BIOMEDICAL RESEARCH INVOLVING ANIMALS

Council for International Organizations of Medical Sciences

Preamble

Experimentation with animals has made possible major contributions to biological knowledge and to the welfare of man and animals, particularly in the treatment and prevention of diseases. Many important advances in medical science have had their origins in basic biological research not primarily directed to practical ends, as well as from applied research designed to investigate specific medical problems. There is still an urgent need for basic and applied research that will lead to the discovery of methods for the prevention and treatment of diseases for which adequate control methods are not yet available—notably the noncommunicable diseases and the endemic communicable diseases of warm climates.

Past progress has depended, and further progress in the foreseeable future will depend, largely on animal experimentation which, in the broad field of human medicine, is the prelude to experimental trials on human beings of, for example, new therapeutic, prophylactic, or diagnostic substances, devices, or procedures.

There are two international ethical codes intended principally for the guidance of countries or institutions that have not yet formulated their own ethical requirements for human experimentation: the Tokyo revision of the Declaration of Helsinki of the World Medical Association (1975), and the Proposed International Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences and the World Health Organization (1982). These codes recognize that while experiments involving human subjects are a *sine qua non* of medical progress, they must be subject to strict ethical requirements. In order to ensure that such ethical requirements are observed, national and institutional ethical codes have also been elaborated with a view to the