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PAHO GUIDELINES AND REVIEW PROCEDURES FOR THE PROTECTION OF HUMAN SUBJECTS IN MEDICAL INVESTIGATION

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Background

Recognizing that medical progress thoughout history has and will continue to require human experimentation, there has been during the past several decades a growing concern over the adoption of measures that assure the safe and responsible involvement of human subjects in all types of biomedical experimentation.

In view of the widely accepted principle that suitable animal models are not always available for some kinds of diagnostic and therapeutic research, many government agencies, international organizations, research institutions, scientific groups, etc., have established guidelines and procedures to standardize and regulate research efforts that require human participation as research subjects.

Codes of Ethics

Until 1947 when the Nuremberg Code was promulgated as a judicial decision of the case U.S. vs. Karl Brandt, et al, ethical codes and physician oaths did not relate specifically to research in humans.

The Nuremberg code stemed from a trial for crimes against humanity of a group of doctors who performed medical experiments on prisoners in concentration camps during the II World War. The 10 principles of this Code are, therefore, applicable to non-clinical research on healthy subjects under some form of restraint and do not refer to clinical research on patients. The most important principles formulated in this Code are: the need for the voluntary consent of the human subject; the

subject's right to withdraw from the experiment; the Investigators' obligation to terminate the experiment when the procedure is likely to result in injury, disability or death to the subject; the need for justification of proposed procedure in terms of anticipated benefits to society; prior experimentation on animals; guarantees against unnecessary suffering; involvement of qualified scientists.

A number of other codes have been promulgated since 1947, but the Helsinki Declaration adopted in 1964 by the World Medical Association is perhaps the most widely aclaimed and adopted code of basic ethical principles that govern modern research involving human subjects. A major feature of the Helsinki Declaration is the elucidation of rules governing clinical research combined with patient care and of non-therapeutic clinical research.

In 1975, in Tokyo, the Helsinki Declaration was amended to include, among others, the recommendation that the ethical aspects of research protocols be reviewed by an independent committee. Al full text of the Helsinki Declaration appears as Attachment I.

The Role of WHO/PAHO

Concern regarding international aspects of bioethics and human rights has been voiced by WHO's governing bodies, through several resolutions, such as EB55.R65 on health aspects of human rights in the light of scientific and recent technological developments and, more particularly, resolutions WHA29.64, WHA30.40 and WHA31.35, drawing attention to the importance of the ethical issues within the context of biomedical research and inviting the Director-General to study and to

prepare recommendations on these issues.

In response to these mandates, the Council for International Organizations of Medical Sciences (C.I.O.M.S.), established by WHO and UNESCO, has been collaborating with WHO since 1976 in matters of medical ethics by conducting limited surveys and a comparative analysis of procedures adopted by some countries with formal ethical review committees. In July 1978, CIOMS with WHO initiated a project for the development of guidelines to assist developing countries in the establishment of mechanisms that would ensure observance of the principles of medical ethics in biomedical research. Attachment II presents the objectives, plan of work and general characteristics of this project.

In compliance with the Pan American Health Organization's governing bodies resolutions, the PAHO Research Ethics Review Committee (RERC) was established on 1 March 1974. The present revision stems from a recommendation of the PAHO Advisory Committee on Medical Research at its XIX Meeting in 1979.

The PAHO Research Ethics Review Committees

General Guidelines

The PAHO Research Ethics Review Committee (RERC) was established at Headquarters to provide a mechanism for the assessment of ethical implications of research projects. In addition, similar committees have been established in PAHO affiliated centers in which research involving human subjects is carried on.

Until WHO officially adopts the general guidelines and principles

being developed in collaboration with CIOMS, these committees are guided by the principles established by the Helsinki Declaration of the World Medical Association and by the Standards of Conduct for Research carried outby or under the auspices of the World Health Organization. In addition, committees are instructed to comply with principles, practices, and rules applicable within the country of research. When research is funded by other agencies, the committees must also comply with the standards set by the grantor regarding humans as subjects of research.

In addition, the PAHO committees must take into consideration that ethical review of clinical proposals constitutes a mechanism for the protection of the individual subject; an important protection for the investigator and for the granting agency; and an important element for the protection of a nation, particularly in the developing world.

In order to enable the committees to make an indepth assessment of the above considerations, the revised procedures expand the composition of the committees to include lay representatives, who are able to reflect cultural and social attitudes regarding ethical issues. Additionally, investigators from outside of the Organization are added to the review groups. When the research involves women, the review committee should also make an effort to include women participants.

In sum, PAHO committees in the field and at Headquarters review all proposals to assess ethical implications, such as:

1) the dangers, if any, to the subject's health as a consequence of the proposed investigation;

2) the inviolability of his/her rights as an independent and free individual;

3) the appropriateness of the methods used to obtain informed consent, either verbal or written and if such consent seems appropriate;

4) the risks and potential benefits of the investigations, with respect to medical progress and national interests; and

5) compliance with principles practices and rules within the country or countries where research projects are to be carried out.

All PAHO sponsored research, whether the Organization is directly responsible by conducting the study or indirectly by providing financial support or technical cooperation, is subject to ethical review by the field as well as Headquarters committees. As to the type of research, the review requirements extends not only to clinical pharmacology and drug trials, but to all forms of clinical research including studies in the area of therapy, diagnosis, prevention or behavioral sciences.

Informed consent

"Voluntary consent" is a principle adopted by all codes of ethics and has, throughout the years, remained unchallenged. The definition of "informed consent", however, has proven to be a highly debated issue, particularly in regard to its validity. Until clearer guidelines are established, the PAHO Review Committees in assessing this issue will focus on the appropriateness of the process whereby the experimental subject is informed before he signs the consent form.

Membership

One of the major changes in the revised procedures of the PAHO Ethics Review Committees concern their composition. Since many of the issues facing the Ethics Review Committees demand judgement requiring thorough familiarity and knowledge of local attitudes and customs, it is proposed that the composition of all PAHO Committees include lay membership and whenever possible, of women, particularly if the experiment involve women.

The Core Committee at Headquarters will include two PAHO staff members; two clinical researchers from the Washington, D.C. area hospitals; one member of the PAHO Advisory Committee on Medical Research; one member from an international organization, the diplomatic or scientific community; and one member from an institute of bioethics, such as the Kennedy Institute of Georgetown University Bioethics Institute. The Committee will be served by a chairman and a secretary appointed by the PAHO Director. The members will also be designated by the PAHO Director on the recommendation by the ACMR, Technical Units or government bodies.

In addition, the Secretary will maintain an updated list of other individuals from throughout the Region who may be invited to serve on an ad-hoc basis to review proposals of their expertise. The list should include various scientific specialists, laypeople from the community, religious leaders, hospital administrators, nurses, dentists, psychologists, lawyers, and others.

As to the field or regional centers review committees, it is recommended that the core group be composed of two staff members who are

independent of the project or of the Principal Investigator and three other individuals derived from outside the organization of the research worker and representing social or religious organizations, governmental and clinical research groups.

Members should be appointed for periods of no less than four years.

Review of the Proposal

The proposals should be reviewed at a meeting so that all members may offer and discuss their different point of view. Only in exceptional circumstances should the review of the proposal be conducted by mail. The Headquarters Research Ethics Review Committee (HRERC) will schedule three meetings per year. The dates will reflect the deadlines for proposal submission of the larger research funding institutions. Nevertheless, applications must be submitted to the HRERC at least three months before they are due at the funding agency.

The field or centers RERC should schedule their meetings well in advance of the due dates for the review of the proposals at Headquarter; the number of sessions per year should reflect the needs of the individual center.

The agenda will include an annual progress review of each ongoing study previously approved as well as all new research proposals involving human subjects.

Information required

In addition to such fundamental information as is required of granting agencies -background, statement of problem, design, purpose, methods, procedure, personnel, local, equipment, budget, etc.- all

proposals seeking PAHO sponsorship, whether conducted in the field or at Headquarter's installations or in independent institutions, must provide, if man is an experimental subject, sufficient detail so as to make possible the sound assessment of ethical implications, such as:

1) A description of the characteristics of the proposed subject population and the rationale for using in this population special subjects, such as fetuses, pregnant women, children, the mentally disabled, prisoners, or other subjects whose ability to give voluntary informed consent may be in question;
2) An assessment of any potential risks -physical, psychological, social, legal or other- and of the likelihood and seriousness of such risks. If methods of research create potential risks, a description of other methods, if any, that were considered and why they will not be used;
3) A description of consent procedures to be followed, including how and by whom documentation of informed consent will be obtained;
4) The procedures (including confidentiality safeguards) for protecting against or minimizing potential risks and an assessment of their likely effectiveness;
5) An assessment of the potential benefits to be gained by the individual subject, as well as of the benefits which may accrue to society in general as a result of the planned work;
6) An evaluation of the risk-benefit ratio;
7) When physical or psychological risks to human subjects are involved, a statement on the extent to which the principal

investigator will be responsible for their medical care, and how potential subjects will be selected from a population available.

The applications forwarded to the HRERC will also include the written approval of the field or center review committee stating the criteria and guidelines followed as well as a summary of the deliberations and conclusions.

Finally, recognizing that prime responsibility for the welfare of subjects involved in medical research rests with the institutions undertaking the studies and the appropriate governmental authorities, the current WHO Manual provisions require that, before supporting any research activity, technical units ensure that the proposal has been authorized by national health authorities and that it has been reviewed by an appropriate committee, either at the institutional or governmental level, which will be responsible for ensuring that the ethical principles involved will be carefully adhered to.

Committees' decision

The PAHO Research Ethics Review Committees are advisory panels to the Director of the field office or regional center, and in the case of the Headquarters Committee to the PAHO Director.

Their conclusions recommend approval, rejection or discontinuation of a research proposal involving human subjects.

Review Procedures

1) Research worker submits his proposal to field or center Research Ethics Review Committee (RERC).

2) Field or Center RERC reviews the application as to the safeguard and right of human subjects involved in the research.

2.A) If such safeguards have not been considered or are unsatisfactory, the proposal is returned to the research worker for necessary amendments.

2.B) If the safeguards put forth are accepted, the proposal is channeled to the Secretary of the PAHO Headquarter's Research Ethics Review Committee with the clearance report.

3) When the cleared research proposal reaches Washington, the Secretary of the RERC studies it and takes the following steps:

3.A) If no human subjects are involved in the proposed study, he prepares the certification as required by the funding agency and gives clearance to continue the processing of the application through the corresponding Budget and Finance Office.

3.B) If human subjects are involved, but the information is insufficient, he writes to the Principal Investigator with a copy to the field or center RERC requesting him to submit the needed clarifications.

3.C) If the documentation is complete, sends documentation to all the core Committee members and to those selected from the ad-hoc list, and schedules the review for the next session.

4) After consideration of the project by the Headquarters RERC:

4.A) If the HRERC endorses the project, prepares the necessary certification and gives clearance to continue the

processing of the application through the office of Budget and Finance.

4.B) Returns the proposal to the Investigator through the center or field RERC if the guarantees, given by the latter, are not accepted or endorsed.

Finally, it is the Council's opinion that any account of investigations on human subjects should make clear that the appropriate requirements have been fulfilled and, further, that no paper should be accepted for publication if there are any doubts that such is the case.

The progress of medical knowledge has depended, and will continue to depend, in no small measure upon the confidence which the public has in those who carry out investigations on human subjects, be these healthy or sick. Only insofar as it is known that such investigations are submitted to the highest ethical scrutiny and self-discipline will this confidence be maintained. Mistaken, or misunderstood, investigations could do incalculable harm to medical progress. It is our collective duty as a profession to see that this does not happen and so to continue to deserve the confidence that we now enjoy.

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EXPERIMENTAL RESEARCH ON HUMAN BEINGS

British Medical Association

1963

1. New drugs or other therapy should not be prescribed unless prior investigation as to the possible effects upon the human body has been fully adequate.

2. Before a new drug is used in treatment, the clinician should ensure that the distributors of the drug are reputable and the claims made for the products include reference to independent evidence of its effects.

3. No new technique or investigation shall be undertaken on a patient unless it is strictly necessary for the treatment of the patient, or, alternatively, that following a full explanation the doctor has obtained the patient's free and valid consent to his actions, preferably in writing.

4. A doctor wholly engaged in clinical research must be at special pains to remember the responsibility to the individual patient when his experimental work is conducted through the medium of a consultant who has clinical responsibility for the patient.

5. The patient must never take second place to a research project nor should he be given any such impression. Before embarking upon any research the doctor should ask himself these questions:

a. Does the patient know what it is I propose to do?
b. Have I explained fully and honestly to him the risks I am asking him to run?
c. Am I satisfied that his consent has been freely given and is legally valid?
d. Is this procedure one which I would not hesitate to advise, or in which I would readily acquiesce, if it were to be undertaken upon my own wife or children?

[*British Medical Journal Supplement* 2 (1963): 57. Reprinted with the permission of the British Medical Association.]

DECLARATION OF HELSINKI

World Medical Association

1964 and 1975

The first document reproduced below, which offers recommendations for conducting experiments using human subjects, was adopted in 1962 and revised by the 18th World Medical Assembly at Helsinki, Finland, in 1964. The second document is the Declaration of Helsinki as revised by the 29th World Medical Assembly in Tokyo in 1975. Revisions in the second document are noted in italics.

1. The Helsinki Declaration of 1964

Introduction

It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of The World Medical Association binds the doctor with the words: "The health of my patient will be my first consideration" and the International Code of Medical Ethics which declares that "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest."

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to each doctor in clinical research. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and the clinical research, the essential object of which is purely scientific and without therapeutic value to the person subjected to the research.

I. Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.

5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

II. Clinical Research Combined with Professional Care

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, reestablishing health, or alleviating suffering.

If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient.

2. The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

III. Non-Therapeutic Clinical Research

1. In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out.

2. The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor.

3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.

3b. The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise fully his power of choice.

3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.

4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.

4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued.

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

2. The Helsinki Declaration of 1975

Introduction

It is the mission of the medical doctor to safeguard the health of the people. His *or her* knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of The World Medical Association binds the doctor with the words "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies a fortiori to biomedical research.

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

In the field of *biomedical* research a fundamental distinction must be recognized between *medical* research in which the aim is essentially *diagnostic or* therapeutic for a patient, and *medical* research, the essential object of which is purely scientific and without *direct diagnostic or* therapeutic value to the person subjected to the research.

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

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, The World Medical Association has prepared the following recommendations as a guide to every doctor in *biomedical* research *involving human subjects. They should be kept under review in the future.* It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. *Biomedical* research *involving human subjects* must conform to *generally accepted* scientific principles and should be based on *adequately performed* laboratory and animal experimentation *and on a thorough knowledge of the scientific literature.*

2. *The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.*

3. *Biomedical* research *involving human subjects* should be conducted only by scientifically qualified persons and under the supervision of a *clinically*

competent medical *person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.*

4. *Biomedical* research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every *biomedical* research project *involving human subjects* should be preceded by careful assessment of *predictable* risks in comparison with foreseeable benefits to the subject or to others. *Concern for the interests of the subject must always prevail over the interests of science and society.*

6. *The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.*

7. *Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.*

8. *In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.*

9. *In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely given informed consent, preferably in writing.*

10. *When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.*

11. *In the case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.*

12. *The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.*

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the doctor must be free to use a new *diagnostic or* therapeutic measure, if in his *or her* judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. *The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.*

3. *In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.*

4. *The refusal of the patient to participate in a study must never interfere with the doctor–patient relationship.*

5. *If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.* (I, 2).

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent

that medical research is justified by its *potential diagnostic or* therapeutic value for the patient.

III. Non-therapeutic Biomedical Research Involving Human Subjects (Non-clinical Biomedical Research)

1. In the purely scientific application of *medical* research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom *biomedical* research is being carried out.

2. *The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.*

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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ETHICAL GUIDELINES FOR CLINICAL INVESTIGATION

American Medical Association

1966

At the 1966 Annual Convention of its House of Delegates, the American Medical Association endorsed the ethical principles set forth in the 1964 Declaration of Helsinki *of the World Medical Association. The 1966 Ethical Guidelines for Clinical Investigation, which are printed below, were intended to enlarge on the Nuremberg Code and the Declaration of Helsinki, as well as on the fundamental concepts found in the AMA* Principles of Medical Ethics. *In 1974, when asked to establish mechanisms and procedures to protect the rights of the institutionalized in clinical investigations, the AMA House of Delegates reaffirmed the 1966 guidelines; emphasized the ethical responsibility of each investigator; endorsed the principle that precautions must be taken to protect the rights of subjects whose ability to consent knowingly and voluntarily is impaired; and affirmed the goal of establishing uniformity of standards and procedures for medical experimentation throughout the world.*

1. A physician may participate in clinical investigation only to the extent that his activities are a part of a systematic program competently designed, under accepted standards of scientific research, to produce data which is scientifically valid and significant.

2. In conducting clinical investigation, the investigator should demonstrate the same concern and caution for the welfare, safety and comfort of the person involved as is required of a physician who is furnishing medical care to a patient independent of any clinical investigation.

3. In clinical investigation *primarily for treatment—*

A. The physician must recognize that the physician-patient relationship exists and that he is expected to exercise his professional judgment and skill in the best interest of the patient.

B. Voluntary consent must be obtained from the patient, or from his legally authorized representative if the patient lacks the capacity to consent, following: (a) disclosure that the physician intends to use an investigational drug or experimental procedure, (b) a reasonable explanation of the nature of the drug or procedure to be used, risks to be expected, and possible therapeutic benefits, (c) an offer to answer any inquiries concerning the drug or procedure, and (d) a disclosure of alternative drugs or procedures that may be available.

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTÉ

Attachment II

ACMR21/79.7

ENGLISH ONLY

RESTRICTED

ADVISORY COMMITTEE ON MEDICAL RESEARCH

Twenty-first Session

Geneva, 19 - 22 November 1979

Agenda item 8.5

ETHICAL REVIEW PROCEDURES FOR RESEARCH INVOLVING HUMAN SUBJECTS

1. Introduction

At its twentieth session in 1978 the Advisory Committee on Medical Research in its consideration of the ethical aspects of WHO's research activities, recommended for support a project to be carried out by WHO Headquarters and the Council of International Organizations of Medical Sciences (CIOMS), in order to develop guidelines to assist developing countries in evolving mechanisms that would ensure observance of the principles of medical ethics in biomedical research (ACMR20/78 Report, page 19).

Concern regarding international aspects of bioethics and human rights has been voiced in recent years in WHO's governing bodies, the significant decisions being embodied in resolution EB55.R65 on health aspects of human rights in the light of scientific and technological developments and, more particularly, resolutions WHA29.64, WHA30.40 and WHA31.35, in which the World Health Assembly has drawn attention to the importance of the ethical issues arising within the context of biomedical research and has invited the Director-General to study, to prepare recommendations on these issues, and to report on progress to the Executive Board and the World Health Assembly.

CIOMS, on its part, has already collaborated with WHO in matters of medical ethics and, as noted by the ACMR at its twentieth session, has prepared a limited survey and comparative analysis of procedures adopted by some countries that have already established formal ethical review committees. The necessary funding for such a project has now been secured and work has commenced on the project on the basis of the project proposal submitted to the donors (Annex 1). The duration of the project is approximately two years, the work to be completed in 1981.

In the preliminary planning phase of the project, the following matters have been considered:

(a) The revision of the project time-table and objectives;

(b) Reporting to funding agencies;

(c) Reporting on data already collected;

(d) Case studies of research in developing countries;

(e) Selection of consultants for field investigation;

(f) Preparation of a field investigation schedule and briefing of consultants.

This report has consequently been prepared for the ACMR at the conclusion of the first planning phase of the project.

2. Objective of the study and plan of action

The objective of the study is described succinctly in paragraph 2 of the project proposal. This is to develop " . . . guidelines for the establishment of national ethical review procedures for research involving human subjects.

These guidelines will enable countries to:

a. define a national policy on the ethics of medical and health research and to adopt ethical standards appropriate to their specific local needs, and

b. establish adequate mechanisms for ethical review of research activities involving human subjects."

The steps that are proposed to achieve this objective are indicated in paragraph 3 of the project proposal. Two major activities are envisaged for the remainder of 1979 and the first months of 1980. Further information will be gathered and analysed on existing national policies, codes and review mechanisms and the possibility of illustrating the impact of these instruments by use of case studies will be explored. In addition, information on the situation as it now stands in developing countries, and on their needs in this connexion, will be canvassed (see target time schedule, Annex 2). Consultants will be identified and approached following consultation with WHO's Regional Offices, the ACMR and other interested parties. Additional information will be obtained from other countries by correspondence or through case studies, on as broad a basis as possible.

At this stage the attention of the ACMR is drawn particularly to the following matters, which will be outlined seriatim:

(i) Special characteristics of research carried out in developing countries which have relevance to the selection of appropriate controls.

(ii) Data collected on existing systems of ethical/legal review of research involving human subjects.

(iii) The scope and content of questionnaire surveys, case surveys, and consultant briefings to be adopted in compiling country status reports.

3. Research carried out in developing countries

3.1. General characteristics

The amount of research being carried out in developing countries and involving human subjects appears to be increasing. These activities are frequently sponsored and conducted by external agencies including international organizations, nationally-based funding agencies, foundations, research councils, universities and research-based pharmaceutical companies, and they may be directed to:

(a) Specific priority issues within a country or groups of countries in such areas as primary health care, nutrition, tropical diseases, family planning, maternal and child health and environmental health.

(b) Issues having no specific relevance to the country in which the research is undertaken including clinical trials of new drugs with a market potential located predominantly in the industrialised countries.

External sponsorship of research has a number of important social and ethical implications:

- there may be no long-term commitment to subjects.

- there may be no tangible commitment to the host country and its scientific community (in terms of training and service).

- the research may not be necessarily related to local or even regional health needs.

- in the absence of a national - or internationally-based - inventory of research that is accessible to the host country, there is a risk of fragmentation of effort and duplication of research.

- when investigators and sponsors are externally-based they are less likely to have adequate insight into local mores, customs and legal systems.

3.2. Specific characteristics

The ethical issues associated with research activities carried out in developing countries are fundamentally the same as those of research undertaken in the industrialised world: they relate to respect for human dignity and the protection of the rights and welfare of human subjects. There are, however, both qualitative differences and differences of scale in the problems that are encountered.

3.2.1. Problems inherent in the selection and recruitment of subjects

(i) Underprivileged subjects are particularly vulnerable to exploitation since, through lack of sophistication and educational opportunity, they may be persuaded to accept unreasonable inconvenience and discomfort and even risks by:

- the offer of small monetary or other rewards.

- the abuse of trust.

(ii) Institutionalised subjects, because of their dependent status, are similarly vulnerable. Special consideration needs to be accorded to:

- the chronically ill.

- the mentally handicapped.

- institutionalised children.

(iii) Research may be undertaken in a region where a high incidence of the target disease may be considered to condone inclusion of untreated control groups in circumstances where this would otherwise be considered unacceptable.

(iv) The objective of the study (particularly if it is directed to an analysis of community, rather than individual, responses), the characteristics of the target population, or the structure of the society from which subjects are drawn can each on occasion frustrate all possibility of eliciting freely-given and informed consent independently from every individual subjected to, or incidentally affected by, the proposed intervention.

3.2.2. Assessment of potential risk and benefit

Assessment of the potential risk and benefit of a proposed experimental intervention is particularly onerous when both the disease under consideration and the treatment offered each carry substantial risk. The development of new prophylactic measures can raise particularly fraught considerations.

3.2.3. Lack of accountability

A lack of accountability may arise when research is sponsored by external agencies that operate beyond the effective ambit of local jurisdiction. This may prejudice the rights of subjects insofar that their recourse to any form of compensatory process in connexion with injury resulting from the research may be frustrated.

3.2.4. Apportionment of responsibility and liability

Responsibilities and liabilities of sponsors, investigators, local review committees, and responsible national authorities are frequently ill-defined, particularly when research is funded or planned externally. This confusion can only operate counter to the interest of subjects involved. Some research activities in developing countries, whether directed to a public health issue or some other objective, fall outside a strict definition of clinical research, but nevertheless place individuals or human populations at risk. Experimental use of insecticides in vector control trials are a case in point,and in the course of this project it will be necessary to determine the extent to which these activities should fall to consideration, and whether the health aspects should, as in clinical research, be subject to ethical review.

4. Data collected on existing systems of ethical/legal review of research involving human subjects

In many developed countries research involving human subjects is now constrained by a variety of statutory and administrative provisions. Different approaches can be identified, although they are frequently interrelated and share the common objective of safeguarding the welfare and rights of the individual subject. The statutory instruments are highly selective in their impact on the conduct of clinical investigators since, for the most part, they relate to research concerned with new drugs and devices. In some instances these instruments explicitly address ethical issues and impose relevant requirements. More frequently, however, ethical considerations are implicit in the elaboration of safety standards and other provisions aimed to ensure that the research is based upon sound scientific methodology. More widely-ranging restraints are commonly exercised through a process of self-regulation by the scientific medical community, either through the adoption of ethical codes or declarations, or through the development of ethical principles and guidelines by national or international professional groups, or by the establishment of peer review procedures and, particularly, ethical review committees.

The adoption of ethical standards by a professional body provides a framework of reference for the investigator while leaving him free to exercise his own judgement. Such standards also serve to guide funding agencies, and to assist peer review groups, administrative bodies and courts.

The manner in which such measures can be adapted to national requirements is determined to a large extent by considerations of constitutional law and custom and by the nature of the political and social system. Consequently it is not feasible to devise a set of universally applicable guidelines or mechanisms suited to the needs of all developing countries.

It is, however, of value to enumerate the elements that might be included, on the basis of present day experience, in a comprehensive integrated system of control applicable in a defined instance such as new drug development:

(i) A set of legal regulations providing norms for the safety and efficacy of drugs.

(ii) A requirement for independent approval of all research on human subjects by an ethical review committee as a matter of general policy and not merely linked to conditions imposed by funding agencies. A specific requirement for independent

approval by an ethical review committee on pharmaceutical drug trials could be provided in the drug regulations themselves.

(iii) Incorporation of ethical standards relating to the protection of human subjects within the drug regulations themselves that are comparable to and consonant with standards developed by professional groups (international and national codes, declarations and guidelines) and applied by funding agencies.

Existing data collated by CIOMS in its preliminary study indicate that three distinctive approaches can be discerned in provisions relating to ethical review of research involving human subjects:

(1) Self-regulation by the medical profession without any formal mechanisms created expressly for the purpose, but associated with a strict appreciation of what is acceptable, such as the total prohibition of the use of healthy volunteers and limitations on the individuals authorized to conduct research.

(2) Regulation by ethical review committees. Although this mechanism has only recently been evolved, it is now quite widely used. In the form of peer review, the responsibility for ethical determination passes from the individual investigator to the group that may be constituted to include lay representatives, in order to reflect the views of the community as a whole.

(3) Regulation from within the national administration. This may be exercised within the national civil service, with the advice of such bodies as national scientific councils, academies of medicine, and statutory advisory committees charged to undertake specialised technical assessments. Central direction of research is implied in this mechanism which may include formal delegation of responsibility for specific protocols to officially designated centres.

Irrespective of the mechanisms used, the scientific medical literature of a number of countries indicates that several issues highly relevant to the current project remain the subject of controversial debate. These include:

(a) ethical issues relating to controlled clinical trials.

(b) use of special categories of subjects - pregnant women and women of child-bearing age, minor children, incompetent adults, prisoners and detainees, citizens of third states.

(c) the validity of informed consent.

(d) the control of clinical studies, and particularly drug trials, conducted abroad, and applicability of domestic regulations (relating to drug safety, for instance) to studies conducted abroad.

(e) financial protection of subjects, compensation and insurance, strict liability and product liability.

5. Scope and content of additional material to be gathered and collated

5.1. Questionnaire survey

A questionnaire directed to responsible administrative authorities will be prepared in collaboration with WHO Regional Offices, and in accordance with appropriate consultant advice. The endorsement of the ethics sub-committee of the ACMR will be sought prior to its circulation.

The objective of the questionnaire will be to establish the present extent of any central direction or control of research involving human subjects within countries and the extent to which such measures are considered feasible and desirable. In particular the following points will be addressed:

5.1.1. Whether any centralised record exists to

- indicate the amount and type of research involving human subjects that is undertaken.
- identify the sources from which these studies are funded.
- inform the local scientific community of the results of research that has been undertaken.

5.1.2. The nature of any constraint that the administration imposes upon research undertaken within the country with a view to ensuring that

- it is directed to priority issues.
- the protocols meet accepted ethical criteria.

5.1.3 The mechanism, statutory or otherwise, by which this responsibility is discharged.

5.2. Analysis of case studies/ Reports of consultants

This work will be directed to the identification and characterisation of specific problems relating to research undertaken in developing countries as they are perceived locally; to identify approaches that have been successfully utilised to resolve them; and to explore the importance of cross-cultural factors in this context.

The preparatory briefing of consultants selected to undertake field studies will be based upon an extended analysis of points raised in section 3. of this report, while case material will be drawn from published literature and canvassed from bodies, operating either nationally or internationally, that are concerned with the sponsorship and assessment of research in these countries.

PROJECT PROPOSAL

FROM

WORLD HEALTH ORGANIZATION

AND

COUNCIL OF INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES

TO

FOR THE DEVELOPMENT OF GUIDELINES
FOR THE ESTABLISHMENT OF ETHICAL REVIEW PROCEDURES
FOR RESEARCH INVOLVING HUMAN SUBJECTS

MARCH 1978

CONTENTS

GUIDELINES FOR THE ESTABLISHMENT OF ETHICAL REVIEW PROCEDURES FOR RESEARCH INVOLVING HUMAN SUBJECTS

SUMMARY

Over the past decade, considerable attention has been directed in industrialized countries to the rights and welfare of human subjects involved in research. National and international codes of ethics have been formulated, institutional ethical review committees have been created, and, in some cases, clinical trials of medicinal products have been subjected to detailed and complex statutory controls.

Since an increasing amount of research--much of it externally planned--is conducted in developing countries, there is a pressing need to consider how such mechanisms for the protection of human subjects might be adapted and evolved for the developing world with its unique socio-economic circumstances, educational opportunities, and cultural factors. Pure biomedical research frequently involves consideration of risk and benefit to individuals of a different order to those encountered in industrialized states and, on occasion, the interventions involved--particularly those relating to environmental factors--affect large communities. Moreover, studies are not always related to the control of the major endemic diseases and health requirements of the developing countries and there appears to be a trend for the initial trials of any new drug to be undertaken in countries without strong regulatory authorities.

The above considerations underscore the need to establish a specific set of guidelines for ethical review procedures, based on a wide body of experience for application at the national and institutional levels of developing countries. This proposal aims to establish such a set of guidelines.

I. INTRODUCTION

As a direct consequence of the efforts of industrialized nations to satisfy their health and welfare needs, research activities have increased progressively over the past decades and in many of these countries this evolution has resulted in a parallel development of mechanisms that protect the rights and welfare of human subjects involved in these studies.

Research programmes are now being planned and implemented in many developing countries, but these programmes are still frequently planned and sponsored from the outside and not always related to national priorities. The disease burden of many parts of the world affects whole populations and research attempting to develop mechanisms to combat this burden will involve large groups of people. In addition, health is more and more frequently perceived as one of the major factors involved in the development process as a whole since the manipulation of environmental systems by man-made lakes in the tropics has an impact on the health of large population groups with important ethical implications.

In drug research, ethical issues are related not only to the trials of products developed specifically to combat endemic diseases in developing countries, but also to the trials of drugs for non-endemic diseases undertaken on the populations of nations where strong regulatory constraints do not exist. Ethical considerations are also linked to the problems of quality control, distribution, conservation, and importation of drugs.

The growing concern for human rights and welfare in research has been partially met both on the international scene and in a number of national contexts. At the international level, a number of ethical codes have been adopted and have received widespread support. However, by their very nature international declarations can only be general and they present a number of weaknesses such as a lack of definition of the terms used and the absence of provisions concerning the concrete implementation of the principles they enounce. International codes do not offer, therefore, adequate protection either to the human subjects that are involved in or affected by the research or to the investigators and sponsors responsible for that research. Specific mechanisms are needed to apply the general principles of international ethical codes to actual local situations in health research. Developed countries have responded with mechanisms such as regulatory constraints and ethical review committees. However, most developing countries have no experience or programme in this area of vital importance to their populations.

2. OBJECTIVE OF THE STUDY

The study will develop guidelines for the establishment of rational ethical review procedures for research involving human subjects.

These guidelines will enable countries to:

a. define a national policy on the ethics of medical and health research and to adopt ethical standards appropriate to their specific local needs, and

b. establish adequate mechanisms for ethical review of research activities involving human subjects.

3. STEPS TO ACHIEVE THE OBJECTIVE

The guidelines will be developed through the following steps:

(a) gathering of all possible available information on international and national policies and ethical codes regarding human experimentation and their related legislation;

(b) gathering all information on existing systems of ethical review mechanisms in those countries where they have been established;

(c) carrying out a comparative analysis of the structure and functioning of the different national systems;

(d) determining by means of national status reports the specific needs of developing nations so that the proposed guidelines will reflect not only the developments that have taken place in the industrialized countries but also the different conditions and circumstances in which research is conducted in other parts of the world;

(e) developing and providing an on-going international exchange of information on existing or planned structures or mechanisms to assist in the possible improvement of national or institutional ethical review systems.

4. ISSUES TO BE CONSIDERED IN THE GUIDELINES

4.1. General issues

4.1.1. National health needs and research. Every country attempts to define its national health needs and to develop research oriented towards meeting these needs. In developing countries, more and more research will be aimed at responding to needs in areas such as primary health care, nutrition, tropical diseases, maternal and child health, environmental health, etc., areas which concern whole populations and which for research frequently require control groups towards which ethical obligations should be fulfilled.

4.1.2. National research policy. Implicit in a national health policy is the need for countries to define a health research policy and programmes and to adopt appropriate legislation regulating conditions for conducting research.

4.1.3. Research conducted by outside groups. Although national research programmes are increasing in number, a substantial proportion of research undertaken in developing countries is still planned and conducted by outside groups, often under the sponsorship or financial dependence of foreign agencies[1], and one can reasonably ask which codes or guidelines are followed by these outside groups.

4.2. Specific issues

4.2.1. Informed consent. Informed consent is a crucial issue of ethics. The existing ethical codes stress the need for informed consent obtained from the subjects of the research and the debate continues as to the exact meaning of such a concept. The issue is extremely complex and the manner of conveying research protocol information sometimes can be questioned. This is particularly true in instances in which the research subjects are retarded persons, young children, prisoners, students or individuals of lesser educational attainment who present greater vulnerability to exploitation. In developing countries, this issue presents even greater difficulties. Here it might be illusory to place in the notion of informed consent the same meaning of absolute individual choice and liberty as in highly developed settings. When a whole population is concerned, when the nature of educational attainment is measured by different criteria than those of the investigator, when the socio-cultural background of the people concerned is radically different from the background of the investigator, often expatriate, the issue of the conveyance of the information to the subjects presents a complexity that is difficult to solve. In some instances, the involvement of a personality particularly trusted by a group, such as the consent of a village leader, may

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[1] This problem was described by Dr Lambo at a Round Table Conference of CIOMS in 1967 on "Biomedical Science and the Dilemma of Human Experimentation" during which he explained that 60-80% of all material and financial support for clinical and other research projects in the medical sciences in some developing nations came from outside sources.

be the only way to reach a population where individual consent could never be obtained because of cultural barriers.[2]

4.2.2. Recruitment of subjects. Ethical problems arise in the recruitment of the subjects and in determining the ethnic, social, and geographical criteria governing the selection procedures. The issues of incentives for participation in research and remuneration also have ethical implications linked to the cultural and socio-economic circumstances of the area in which the project is to be carried out.

4.2.3. Assessment risk/benefit. In developing countries, clinical trials of new drugs and other research efforts are increasingly aimed at the development of the means to combat diseases which create different and greater health risks than those diseases facing most populations of the developed countries. The assessment of risks and benefits will have to take such factors into account when decisions regarding trials of new drugs are considered.

4.2.4. Quality control of drugs. Most developing nations are almost totally dependent on the importation of the drugs required for their health care needs. The control of the quality of these imported drugs presents a very real ethical issue for the countries.

5. CURRENT STATUS OF ETHICAL CODES AND GUIDELINES

In highly industrialized countries with long traditions of scientific activities, there has been considerable concern for the protection of the rights of human subjects in research. This concern was initially limited to special groups such as individuals under some form of confinement. The coverage was gradually extended to subjects of medical experiments in hospitals and more recently to individuals involved in field trials of new biologicals[3] and it was expressed in a number of international codes to provide guidance to investigators. The first code of this nature is the Nuremberg Code, promulgated in 1947.[4] More recently, the World Medical Association adopted the Helsinki Declaration, amended in Tokyo in 1975.[5]

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[2] For a discussion of specific problems encountered by clinical research investigators in developing countries, see the presentation of Dr Lambo at the CIOMS Round Table Conference on "Biomedical Science and the Dilemma of Human Experimentation", 1967, in which he describes the philosophy of the dignity and rights of human beings in an African country as being radically different from the Western tradition.

[3] Diana Crane, "Sociological Perspectives on Biologicals Research in Human Populations". Paper presented at the International Conference on the Individual and the Community in the Research, Development and Use of Biologicals, Geneva, Switzerland, 2-5 March 1976.

[4] Nuremberg Code, promulgated in a judicial decision on August 1947, in the case US vs. Karl Brandt et al.

[5] Declaration of Helsinki, "Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects". Adopted by the 18th World Medical Assembly, Helsinki, Finland 1964, and revised by the 29th World Medical Assembly, Tokyo, Japan, 1975.

It has become clear, however, that these guidelines are unable to offer the type of protection that is called for.[6] Todays research shows a complexity that cannot be met by codes which are by nature very general. Other national devices are necessary to complement and to implement these general principles. A number of countries have created such mechanisms. In the United States of America for example, a review of the ethical implications of biomedical and behavioural research projects has been required by the Department of Health, Education, and Welfare for all applicants of funds from the US Public Health Service since 1966.[7] A similar system operates in Great Britain and applies to all research funded by the British Medical Research Council or conducted within the National Health Service.[8] Similarly, in Sweden all research projects sponsored by the Swedish Medical Research Council are reviewed by an ethical review committee.[9] The movement to establish such independent ethical review bodies for medical research has gained considerable impetus from the adoption by the World Medical Association of an amendment to its Declaration of Helsinki which endorses the use of such bodies on a worldwide basis.[10] It should be noted also that the World Medical Association adopted at the same time the important principle that the results of medical research should not be accepted for publication in a scientific or medical journal unless the work has been previously reviewed and approved by an independent review panel.[11] The European Medical Research Council has recommended that the setting up of ethical advisory committees should be encouraged following the guidelines formulated by the Helsinki/Tokyo Declaration.

A certain number of countries have developed other means to ensure the protection of the rights and welfare of human subjects involved in research, through the promulgation of governmental regulations which include ethical requirements for clinical trials of pharmaceutical products and in some instances for all human experimentation.[12]

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[6] Diana Crane, see Supra. Clarence Blomquist, "Ethical Guidelines for Biomedical Research" in Annals of Clinical Research 7: 291-294, 1975.

[7] Code of Federal Regulations 45 CFR 46 "Protection of Human Subjects".

[8] National Health Service Circular of June 1975 (HSC (IS) 153) of the Department of Health and Social Security to all Regional Health Authorities, Area Health Authorities, and Boards of Governors: "Supervision of the Ethics of Clinical Research Investigations and Fetal Research".

[9] Policy of the Swedish Medical Research Council, described by Dr B. Gustafsson in "Committees on Medical Ethics in Sweden", paper presented at the Scientific Session of the Xth General Assembly of CIOMS, November 1976.

[10] Declaration of Helsinki, Basic Principles, Paragraph 2.

[11] Declaration of Helsinki, Basic Principles, Paragraph 8.

[12] See as an example the German Democratic Republic Regulations of 17 May 1976 "Control of pharmaceutical products: pre-clinical testing and clinical trials" governing the testing of medicaments for use in human medicine.

6. APPROACHES/METHODOLOGY

6.1. Gathering of information

6.1.1. Information on international ethical codes and national and/or ethical guidelines will be obtained by direct contact with Departments of Health, Medical Research Councils, professional associations, etc. Complementary to this information will be the review of the pertinent literature concerned with the content and adequacy of existing principles, guidelines, and statutes at the international and national levels.

6.1.2. Individual analyses of the concepts used in the general declarations of principles such as informed consent and their adaptation to specific research situations (for example trials of new vaccines) will be obtained from ethicists and scientists directly involved in research.

6.1.3. Existing national legislations and/or regulations governing research in general or trials of new pharmaceutical products will be collected by correspondence with health authorities and regulatory agencies of the countries concerned.

6.1.4. Information on existing ethical review mechanisms is absolutely crucial for this project. A pilot study, undertaken by the Council of International Organizations of Medical Sciences (CIOMS), provides an initial insight into a number of existing systems in Great Britain, the United States of America, and Sweden. This was obtained by visits, correspondence with health authorities, and the circulation of a questionnaire to the chairmen of a number of institutional ethical review committees.

The present study requires the expansion of this data to include other countries and an in-depth analysis of the material. This will require:

a. the identification of all the countries where ethical review systems have been established;

b. additional visits to a number of key countries and interviews with health authorities responsible for national research policy, research investigators, and members of review committees;

c. the wide circulation of a revised questionnaire to selected institutional committees.

6.2. National status reports

Four special consultants will prepare national status reports reflecting conditions in countries where no formal procedures exist for the protection of the rights of human beings involved in research. These reports will describe particular national circumstances, areas in which and by whom research is being conducted or is most likely to be undertaken and reflect particular national problems. The consultants will describe other possible approaches to the issue and their appropriateness when confronted to particular social, economic, cultural conditions. The national status reports will provide a basis for international discussion of appropriate mechanisms to be offered to countries.

6.3. Comparative analysis

A comparative analysis will be made between the critical elements constituting the various ethical review systems considered. This comparative analysis will concern itself with:

6.3.1. The organization, operation, and funding of national research programmes.

6.3.2. Policies on the protection of human subjects in research.

6.3.3. Legislation or regulations governing medical research and/or clinical trials of new drugs with particular emphasis on ethical requirements for the protection of human subjects.

6.3.4. Ethical review committees or other ethical review mechanisms: their establishment, structure, and membership.

6.3.5. The functioning of these committees: procedures and monitoring practices, efficiency and effectiveness.

6.4. Preparation of proposed guidelines

The guidelines will reflect both the experience gained in countries where for a number of years mechanisms to prevent the exploitation of human beings have been developed and the particular needs of countries where for historical, economic, social or cultural reasons whole populations may become at risk because of the type and magnitude of the research to be undertaken there. The purpose of the guidelines is not to impose any particular system but to assist appropriate authorities in the development of national procedures.

It is proposed to convene two or, if necessary, three meetings of expert advisers to participate in the drafting of the guidelines. The first meeting will analyse the available material and offer suggestions as to the formulation and content of the guidelines.

A first draft of guidelines will then be widely circulated to health authorities, research institutions, concerned individuals for their reactions and suggestions.

A second meeting will be convened to formulate the final version of the guidelines.

7. PROJECT EXECUTION

The project will be undertaken jointly by the World Health Organization (WHO) and the Council of International Organizations of Medical Sciences (CIOMS).

7.1. WHO

In accordance with a series of Resolutions adopted over the past two years by the World Health Assembly and the Executive Board, considerable emphasis has been placed upon the need for increased technical cooperation between WHO and Member States. An immediate consequence of this policy has been an increase in the level of direct support of research programmes undertaken at the country level. This change presents a number of challenges including the definition of practicable policies and procedures to ensure that, at all times, the welfare of subjects involved in research sponsored by the Organization is adequately considered and appropriately protected. WHO has therefore a major interest and commitment to the project, particularly in relation to its own review procedures. While the guiding principles for research performed under the auspices of the Organization have been laid down and developed from time to time by the World

Health Assembly and the Executive Board, the technicalities of the general conditions for research contracts and the provisions relating to ethical aspects of research have been developed at Secretariat level, and the Secretariat Committee on Research Involving Human Subjects (SCRIHS) was created by the Director-General in 1967:

(i) to establish a set of guiding principles for WHO's own use as regards research carried out by WHO staff members or with WHO's support;

(ii) to advise him, in the light of those principles, on all research proposals posing ethical problems.

The rules of procedure of the Committee are now under review, and information collected during the course of the proposed project would have considerable influence in determining WHO's executive responsibility in this regard.

Support for a collaborative approach between WHO and CIOMS is embodied in Resolution WHA 30.32 adopted by the 30th World Health Assembly which requests the Director General to collaborate with other relevant organizations of the United Nations system and with CIOMS and the World Medical Association to elaborate principles of medical ethics.

CIOMS preliminary activities in this field have received full endorsement of the WHO Advisory Committee on Medical Research (ACMR). In the Report to the Director General on its 19th session held in June 1977, an account of the collaborative efforts in the field of biomedical ethics between the ACMR and CIOMS is presented. This joint effort is further emphasized in the Report by the Director General on Development and Coordination of Biomedical and Health Services Research to the 61st session of WHO Executive Board in January 1978 (Document EB 61/23).

7.2. CIOMS

Over the past decade, the CIOMS has been actively engaged in the exploration of moral and ethical issues raised by scientific and technological advances in the field of biology and medicine. The Council organized a number of Round Table Conferences, many of which dealt with medical ethics: in 1967, "Biomedical Science and the Dilemma of Human Experimentation"; in 1970, "Medical Research, Priorities and Responsibilities"; in 1974, "Protection of Human Rights in the Light of Scientific and Technological Progress in Biology and Medicine"; in 1977, "Trends and Prospects in Drug Research and Development". The proceedings of these conferences were published and represent a major contribution to the world literature in this field. Several recommendations were formulated as a result of these debates, encouraging and urging the CIOMS to develop an active programme in the field of ethics as related to health issues. As early as 1967, a resolution, unanimously adopted by the CIOMS General Assembly, expressed this concern in the following terms:

"3. to urge member organizations constantly to consider the ethical issues in biomedical investigations involving human subjects in order to create in each discipline the necessary climate of opinion for sharpening the ethical guidelines in biomedical research;

4. to invite the Executive Committee to establish a commission with membership drawn from member organizations and institutions of biomedical research in order to submit its views and offer recommendations from time to time on the ethics in biomedical research."

Another resolution, adopted by the Executive Committee of CIOMS at its 45th session in 1969 further encouraged the establishment of a CIOMS Study Committee on Medical Research who could: "(iii) express views on ethical problems related with research involving human subjects." In 1974, a resolution was adopted by the Conference on "National and international considerations of ethical canons for medical-scientific investigations to protect the welfare and human rights of concerned participants." The Conference also reaffirmed the "need for CIOMS and its parent organizations, UNESCO and WHO, in conjunction with other national and international bodies concerned about the subject to explore possibilities of establishing an international nongovernmental body to explore and study the moral and social issues raised by new and forthcoming developments in biology and medicine." Finally, another resolution was adopted by the Xth CIOMS General Assembly in November 1976 urging CIOMS to develop its programme on biomedical ethics and endorsing the establishment of an Advisory Committee for Biomedical Ethics.

A CIOMS Advisory Committee on Bioethics was established with a wide-ranging represent-:ation. The membership will be expanded further to include individuals from Asia and Latin America.

No.	ACTIVITIES DESCRIPTION	1979 Jan.-March	1979 April-June	1979 July-Sep.	1979 Oct.-Dec.	1980 Jan.-March	1980 April-June	1980 July-Sep.	1980 Oct.-Dec.	1981 Jan.-March	1981 April-June	1981 July-Sep.	1981 Oct.-Dec.
1	Programme planning			▬									
2	ACMR Meeting 19-22 November				*								
3	Selection of countries for status reports				▬	▬							
4	Exploration of sources of case material and consultative procedures				▬	▬							
5	Selection and recruitment of consultants and briefing				▬	▬							
6	Questionnaire survey through Regional Offices				▬	▬							
7	Literature search			▪▪▪	▪▪▪	▪▪▪	▪▪▪	▪▪▪	▪▪▪	▪▪			
8	Analysis of existing systems and applicability to developing countries			▪▪▪	▪▪▪	▪▪▪	▪▪▪	▪▪▪	▪▪▪	▪▪			
9	Field investigations					▬	▬	▬					
10	Analysis of questionnaires, case material and country status reports							▬	▬	▬			
11	First draft of report								▬	▬			
12	Consultative meeting									*			
13	Second draft of report									▬	▬		
14	Circulation of report for comments										▬	▬	
15	Final draft											▬	
16	Publication												