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PROPOSED INTERNATIONAL GUIDELINES

for

Biomedical Research Involving Human Subjects

Geneva, 1982

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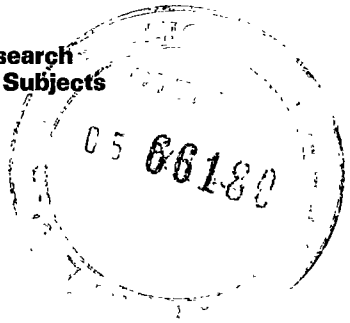

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Biomedical Research Involving Human Subjects

A joint project of the
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INTRODUCTION

Over the past years, CIOMS has provided a forum for discussion of moral and ethical issues of the application of new scientific and technological knowledge to the practice of medicine.

The international guidelines for biomedical research involving human subjects that are now proposed are the results of a study initiated in 1976 by CIOMS in collaboration with WHO. They were drawn up after a series of extensive consultations with individual experts, representing a wide variety of backgrounds, and are based on the replies to a questionnaire received from national health administrations and medical faculties in many developing countries. The original version of the guidelines received, during 1980, the benefit of the comments of an ad hoc WHO/CIOMS working group, of the WHO Advisory Committee on Medical Research, and of a CIOMS Round Table Conference held in Mexico City.

The fundamental ethical principles that guide the conduct of biomedical research involving human subjects, and on which these guidelines are based, are embodied in the World Medical Association's Declaration of Helsinki, as revised by the 29th World Medical Assembly in Tokyo in 1975. The guidelines, which have been drawn up in the form of a general survey followed by specific recommendations, are intended to indicate how these principles can be effectively applied, particularly in developing countries, taking into account socio-economic circumstances, national legal provisions and administrative arrangements.

The guidelines, in their present form, were endorsed in September 1981 by the 56th Session of the CIOMS Executive Committee and in October 1981 by the 23rd Session of the WHO Advisory Committee on Medical Research, and recommended for wide distribution as a consultative document to ministries of health, medical research councils, medical faculties, relevant non-governmental organizations, and medical journals as well as any other interested institutions, including research-based pharmaceutical companies.

Comments on these proposed guidelines are welcomed and should be directed to:

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GENERAL SURVEY

The generalized application of experimental scientific method to biomedical research is a product of the present century. Many fundamental discoveries were made before this time, but the sustained progress subsequently achieved in patient care and preventive medicine through application of scientific principles to medical practice offers incontestable evidence of the value of contemporary biomedical research techniques.

Much basic and developmental biomedical research can be undertaken successfully in animal models. However, absolute reliance cannot at present be vested in these models as indicators of physiological, pharmacological or toxicological responses in man, and all innovative diagnostic, prophylactic or therapeutic measures need ultimately to be evaluated in human subjects.

In the past such studies have been undertaken predominantly in highly-developed countries and directed to diseases of global relevance. However, wide acceptance of the need for increased collaboration with developing countries and awareness of the communicable diseases, malnutrition and unconstrained population growth now endemic in these areas raise the prospect that more applied biomedical research will henceforth be undertaken in these countries.

Untoward pressures may also arise, however, for research unrelated to local priority issues to be transferred to these areas. As research and development costs rise to inhibitory levels in more developed countries, a tendency for work to be

undertaken wherever it can be done least expensively and with least restriction is liable to gather momentum.

Consideration is thus required in developed and developing countries alike as to whether prevailing legal provisions and administrative arrangements ensure that the human rights and welfare of subjects involved in biomedical research are adequately considered and protected in conformity with the ethical principles prescribed in the Declaration of Helsinki of the World Medical Association, as revised by its 29th World Medical Assembly in 1975. Since, in the final resort, the ethical conduct of biomedical research on human subjects is the responsibility of the investigator, provision should be made in medical education to develop students' awareness of this imperative.

SPECIFIC CONSIDERATIONS APPLYING TO RESEARCH IN DEVELOPING COUNTRIES

The ethical implications of research involving human subjects are identical in principle wherever the work is undertaken: they relate to respect for human dignity, and protection of the rights and welfare of human subjects. In particular, assessment of inherent risks is a pre-eminent concern. A number of subsidiary considerations, however, have particular relevance to work undertaken in developing countries.

External sponsorship: Research activities in developing countries are frequently sponsored - and sometimes administered or conducted - by

external agencies including international organizations or nationally-based funding agencies, such as foundations, research councils, universities and research-based pharmaceutical companies.

Support from these sources is essential if required research is to be fostered on an adequate scale in the developing world, but external sponsorship carries certain implications that require careful preliminary assessment:

- the investigation may subserve external rather than local interests.
- foreign investigators and sponsors may not possess adequate insight into local mores, customs and legal systems.
- the absence of any long-term commitment to subjects involved in the research, and withdrawal of out-posted personnel on completion of their task, may result in local disillusionment.
- lack of accountability may deprive subjects of any form of compensation for incidental injury.

If externally-sponsored research is undertaken, whenever feasible, through the agency of - or in collaboration with - an established local institution, and if some tangible commitment can be offered simultaneously to the host country and its scientific community in terms of service and training, these difficulties may frequently be overcome. Nonetheless, national medical manpower is a scarce and extremely valuable resource in developing countries and the mobilization of highly-trained personnel for research

activities is most readily justified when the objectives are clearly attuned to important issues of local relevance.

Assessment of risks and benefits: Few developing countries command the resources or expertise - notably in toxicology or clinical pharmacology - to support the complex regulatory apparatus now considered mandatory for new drug development in industrialized countries. However, it is essential that drugs of potential value against diseases endemic in these countries be tested within the populations at risk. Decisions relating to their investigation and subsequent use should be made in the light of local judgement and experience, and directed to practicable options rather than unattainable ideals. The community itself should be equitably represented in the planning of such investigations, but international advisory bodies can offer a valuable resource to developing countries faced with such responsibilities.

In many instances, particularly in the developing world, both the disease under investigation and the candidate treatment may carry material risk. Without a full assessment of these risks no investigation involving human subjects is warranted. Proposed interventions must be justifiable in terms of the declared objectives. The experimental design must offer every practicable safeguard to the subjects and ensure that a statistically valid result will be obtained efficiently from the smallest possible number of subjects. When trials are prolonged and conducted under double blind conditions, patients' interests can be subserved by predetermining circumstances that would justify a break in coding, and by

arranging for a biostatistician to oversee trends and to alert the investigator on any cause to conclude the trial prematurely.

Subjects who are otherwise beyond the reach of organized medical care should benefit from the treatment of incidental illness and, whenever feasible, a new treatment that is shown to be of value should remain available to the community in which it has been tested.

INFORMED CONSENT

The involvement of human subjects in biomedical research must be contingent, whenever feasible, upon freely-elicited informed consent and upon liberty to withhold or withdraw collaboration at any stage without fear of prejudice. No alternative basis exists for effectively protecting the freedom of choice of the individual and ensuring that such research finds acceptance with opinion at large.

Nonetheless, there are circumstances in which the procedure of consent provides inadequate protection of subjects:

- some important categories of individuals, including children and mentally incapacitated patients, are incompetent to provide legally valid consent. Moreover, elimination of any suggestion of coercion or exploitation may be difficult when subjects are drawn from classes of individuals who, either directly or indirectly, are in a dependent or subordinate relationship to the investigator.

- unjustifiable assurances may be given, inadvertently or otherwise, concerning risks or inconvenience, and consent may be elicited by reward or other inducement that exceeds reasonable compensation for services rendered. It is axiomatic that consent should operate to protect the interests of the subject, and not to reduce the legal liability of the investigator.

- provision of comprehensive information on every possible risk arising from participation in a study may not be feasible. An adverse effect may occur that was unanticipated by the investigator and, possibly, totally unpredictable. More frequently, the potential subject may be unable adequately to comprehend the implications of the proposal. In some communities the very concept of experimental evaluation of therapy is alien and inconsistent with cultural precepts. Consent can then merely signify innate confidence in the judgement of the investigator.

Ideally, each potential research subject should possess the intellectual capacity and insight to provide valid informed consent, and enjoy the independence to exercise absolute freedom of choice over the extent of the collaboration without fear of discrimination. However, many investigations, and particularly those intended to subserve the interests of underprivileged communities and vulnerable minorities including children and the mentally ill, would be debarred if these preconditions were accepted as mandatory criteria for recruitment.

It is consequently of prime importance to consider whether research involving such subjects can be vindicated and, if so, by what mechanism their welfare can be protected and the ethical propriety of the research be assured.

Research involving children

Children should never be involved as subjects in research that could be appropriately undertaken in adults.

However, the results of much research undertaken in adults cannot be extrapolated freely to apply to younger individuals. Unique physiological adjustments occur during transition from intrauterine life, while the physiology and pathology of physical and mental processes, and particularly of growth, maturation and degeneration, are manifestly age-dependent.

Furthermore, some important childhood diseases are virtually incompatible with survival into adult life. In other instances infants are highly vulnerable to conditions, including diarrhoea, mulnutrition and malaria, that are better tolerated within the adult population. Improved management of these conditions is unlikely to occur save from results of research undertaken in the population at risk. More commonly, however, trials are undertaken in children simply and necessarily to identify suitable dosage regimens for drugs that are of established value in adults. Even in the case of drugs or vaccines intended ultimately for use in children, safety and efficacy studies in adults should be well advanced before tests are contemplated in younger

subjects. There is no merit, however, in unduly delaying such tests when these are appropriate: marketed drugs will otherwise be used in children without the benefit of knowledge obtained from appropriately designed clinical studies.

In such circumstances, the proposition that either therapeutic or non-therapeutic research on children is inherently unethical becomes untenable. In the vast majority of situations, however, no intervention can be countenanced that involves any predictable risk to health or prospect of unreasonable psychological disturbance, physical discomfort or pain.

Strong justification is always required for any invasive procedure, including even blood sampling in children, but very small quantities of biological fluids or tissues may often be obtained incidentally and innocuously for research purposes when such materials are in any event required for diagnosis or routine management. The same reservation also applies to the use of X-rays or radioactive isotopes for research purposes. The International Commission on Radiological Protection, however, considers that exposure could be justified in some situations provided the total additional radiation lies within the limits of variation in natural exposure.

With rare exceptions - such as a comparison of two alternative emergency treatments - the understanding and agreement of parents or guardians are essential when a child is involved as a research subject and, if possible, the informed consent of the child should also be obtained. Consent should, as far as is practicable, be regarded as a decision

of the family.

Research involving pregnant and nursing women

The deliberate exposure of a fetus to the uncertain consequences of an experimental intervention unrelated to the pregnancy is unacceptable save in circumstances in which the mother's life is at issue. To avert all possibility of fetal damage, it is frequently prudent specifically to exclude from clinical investigations any woman who is, or is likely to become, pregnant. Analogous considerations arise, particularly in drug trials, in relation to nursing mothers.

Knowledge concerning the potential teratogenic effects of drugs under development is at present obtained exclusively from the results of studies in several animal species. Direct information on any possible hazard they may represent to the human fetus can only emerge from epidemiological data subsequently obtained under routine conditions of use.

Different considerations apply to research directed specifically to sustaining normal pregnancy. Nonetheless, teratogenic and latent carcinogenic changes have been reported in individuals exposed *in utero* to hormones administered both for diagnostic and therapeutic purposes. There is therefore a special need for extensive preliminary investigation and authoritative independent consideration of possible adverse consequences of any proposed experimental intervention contemplated in pregnant subjects.

Research involving the mentally ill

Medical research has brought benefits

to the mentally ill in the form of new psychotropic drugs, which have reduced the morbidity associated with the psychoses, the mortality resulting from depression and the need for long-term institutional care.

As human psychiatric disease does not occur in animals, and because many psychoactive agents have little effect on the behaviour and mood of normal individuals, a clear indication of the therapeutic potential of these substances can usually be obtained only from investigations on subjects drawn from precisely-defined groups of patients.

Although freely-elicited informed consent must remain the ideal objective for all research involving human subjects, the capacity of schizophrenic, severely depressed or mentally defective patients to collaborate on these terms is inevitably compromised and often completely lacking. In some instances a second clinician's opinion of the patient's competence to provide consent can be sought, and the participation of individual patients should, where applicable, be contingent upon the consent of the legal guardian.

Research involving prisoners

The services of volunteer prisoners for biomedical research are utilized in very few countries, and even in these is the subject of controversy.

Protagonists of the use of prisoners argue that the subjects are particularly suitable in that they are living in a standard physical - and, indeed, psychological - environment; that they have the time to participate in long-term experiments that is not available to socially active populations; and that

the prisoners themselves regard such participation as a means of escaping from the tedium of prison life, or demonstrating their social worth, and of earning a small income.

Antagonists claim that the consent of members of a captive population cannot be valid in that it is influenced by the hope of adventitious benefits such as earlier parole, and that it is purchased by this and other expectations rather than given freely.

Although the use of prisoners for biomedical research is not explicitly debarred by any of the international declarations when all appropriate safeguards are followed, arguments on both sides are persuasive and such contradictory ethical evaluations provide no basis for an international recommendation. However, where the use of prisoners as research subjects is permissible, this is perhaps deserving of special rules providing for independent monitoring of projects.

Community-based research

The provision of basic prophylactic care on a community basis is the aim and the obligation of every public health service. These measures, moreover, are often accorded force of law on the thesis that any incidental infringement of individual liberties is decisively outweighed by benefit to the community as a whole. In some instances this care commits individuals, either singly or collectively, to exposure to biologically active substances. Compulsory vaccination and implementation of vector control programmes offer obvious examples, while addition of iodide to table salt, of vitamins to staple foods, of nitrite to meat products and of

fluoride to public water supplies further illustrates the scope of such provisions. The benefits are incontestable, but apprehension concerning risks - both hypothetical and apparent - has, on occasion, obstructed their acceptance.

Wherever interventionist public health policies are accepted as a function of government, a complementary need to assess and to monitor the consequences of such measures from the time they are planned - and for as long as they remain in operation - must be accepted, not only by the responsible authorities, but by the community at large. Observations on considerable numbers of subjects are usually required if reliable estimates of performance, both beneficial and adverse, are to be obtained. Moreover, these effects may be measurable only in terms of a collective response and comparisons between treated and untreated communities may be required to discern them.

These considerations apply with even greater force in many developing countries where comparative field trials undertaken on a community basis frequently offer the only practicable means of objectively determining policies relating to issues as diverse as nutritional requirements, environmental and/or occupational health regulations, vaccination programmes and other measures applied in the control of communicable disease.

When it is impracticable to elicit adequately-informed consent from every individual implicated in a field study, investigations can only proceed upon the basis of meticulous assessment, competent technical

advice, and an acceptable procedure for delegation of the power of consent from the individual subject to an independent representative body charged to protect community interests.

The precise mechanisms through which delegation of consent is achieved will be influenced by political philosophy, the nature and inter-relationships of governmental and professional institutions, the degree of centralization of administrative processes, the structure of society, cultural precepts, and the degree of sophistication of the communities directly involved in the matters at issue. The responsibility for such community-based studies must rest, directly or indirectly, with government agencies. Having regard to the inherent difficulties, community-based research should be entertained only when the expectation of benefit to the community is adequately secure and when smaller-scale studies would not produce a conclusive result.

INDEPENDENT PROSPECTIVE REVIEW

The limited application of the informed consent procedure, and its vulnerability to abuse, render it inadequate as an exclusive means of protecting the human rights and welfare of research subjects, and it fails most decisively when the population from which the subjects are drawn is most vulnerable.

Even when valid consent is obtainable, both the subjects and the investigator should have assurance to proceed in the knowledge that the research is sanctioned by representative professional and, where appropriate, lay opinion. This requires an independent impartial prospective review of all protocols

with the aim of establishing that:

- the objectives of the research are directed to a justifiable advancement in biomedical knowledge that is consonant with prevailing community interests and priorities.
- the interventions are justifiable in terms of these objectives; the required information cannot be obtained from animal models; and the study has been designed with a view to obtaining this information from as few subjects as possible who will be exposed to a minimum of risk and inconvenience.
- the responsible investigator is appropriately qualified and experienced, and commands facilities to ensure that all aspects of the work will be undertaken with due discretion and precaution to protect the safety of the subjects.
- adequate preliminary literature research and experimental studies have been undertaken to define, as far as practicable, the risks inherent in participation.
- every effort will be made to inform prospective subjects of the objectives and consequences of their involvement, and particularly of identifiable risks and inconvenience.
- any arrangement to delegate consent has adequate justification, and appropriate safeguards will be instituted to ensure that the rights of the subjects will be in no way abused.
- appropriate measures will be adopted to ensure the confidentiality of data generated in the course of the research.

The size, composition and terms of reference of existing ethical review committees vary within wide limits. Two principles, however, generally determine representation:

- committees must command the technical competence and judgement to attempt to reconcile the physical and psychological consequences of participation with both the welfare of the subjects and the objectives of the investigation.
- they may also, with advantage, accommodate respected lay opinion in a manner that provides effective representation of community as well as medical interests.

Where administrative functions are highly centralized, and research activities are concentrated predominantly or exclusively in officially-designated specialized centres, an integrated national review mechanism may be practicable. Through appropriate organization of sub-committees, a centralized committee may itself possess the full range of specialized competence to assess all technical information bearing upon the safety of the proposed interventions, as well as the complementary ethical considerations.

Where research activities are conducted more diffusely within the medical community a need emerges to dissociate these two functions. A centralized committee of experts is still best equipped to provide an authoritative technical pronouncement on the safety and efficacy of investigational agents including new drugs and devices, whereas it might not be suitably constituted to consider large numbers of research protocols generated by every clinician with

a research interest working under its aegis. In any case, peripheral committees, operating on an institutional or regional basis, are inherently better placed through awareness and understanding of local factors, not only to assess the ethical aspects of individual studies, but also, after initial review, to maintain their ethical concern with projects, whether by monitoring, receiving progress reports or requiring further periodical review.

Although the organization of ethical review committees in many countries has been determined by official policy, professional organizations have a responsibility to recommend appropriate standards of operation and to assume a harmonizing role. In particular, bodies representative of pediatricians, psychiatrists and many other clinical specialties are uniquely qualified to address the problems of research involving individuals lacking the capacity to offer informed consent. Not least, sponsoring agencies, which also have a strong vested interest in developing and maintaining acceptable ethical standards, might advantageously demand evidence of independent committee review as a mandatory pre-condition of funding.

COMPENSATION FOR PERSONAL INJURY

Accidents resulting in serious disability or death are rarely encountered in medically-oriented research involving human subjects. On the occasion that such an event does occur, the subject, or the dependants, may qualify for an *ex gratia* payment, or they may have the right to institute proceedings on grounds of negligence in a court of law. In

either case the outcome is uncertain, and the process of litigation, which readily becomes protracted and embittered, can also be unreasonably detrimental to the reputation of the investigator.

Such provisions are widely regarded as inadequate and inappropriate in most cases, and alternative systems have recently been advocated or introduced in several countries. These are based on two principles:

- strict liability which is determined by the courts, not on the basis of negligence, but solely on the ability of the claimant to prove association of cause and effect.
- no-fault compensation, which provides for claims to be made on a similar basis against an insurance fund derived from public or private sources and administered by an arbitration board.

Ideally - save, perhaps, when punitive damages are considered appropriate in cases of gross negligence - all disability should be compensated on an equitable basis regardless of its cause. This is likely to remain an impracticable objective in the majority of countries for the foreseeable future. Nonetheless, natural justice demands that every subject participating in medical research should have automatic entitlement to reasonable and expeditious compensation for any injury sustained as a result of participation. It is inevitable that such provision will create anomalies, but this objection cannot negate the obligation adequately to protect those who have offered their services to the general benefit of the community.

PROPOSED GUIDELINES

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 non-medical 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 non-therapeutic. 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. 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 non-therapeutic (non-clinical) 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 it 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.

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 non-therapeutic 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 multi-disciplinary 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 level. The basic responsibilities of locally operative ethical review committees are two-fold:

- 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 non-therapeutic 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 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 non-therapeutic research and resulting in temporary or permanent disability, or even death, are excessively rare. In fact, human subjects of medical research are usually in exceptionally favourable 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 dependants 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 sponsored 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.

DECLARATION OF HELSINKI

Recommendations guiding medical doctors in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and As Revised by the 29th World Medical Assembly, Tokyo, Japan, 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 interest 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 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 and 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 wellbeing of the subject.

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