

## 17. Ethical Issues

Ethical concern should be at the heart of all research involving mothers and children. Even though most teaching and research institutions as well as hospitals have ethical committees whose job it is to scrutinize and discuss all research proposals before sanctioning research, it would be useful for all investigators to bear in mind the following general principles while formulating research plans. These principles are:

- The proposed research should have the ultimate prospect of benefiting children and their families. Obviously not all research conducted on children can be expected to be of direct benefit to the subjects on whom it is performed. For example, methods of assessing normal growth and development, assessing diagnostic methods, or the use of placebo in controlled clinical trials. Such research is not necessarily unethical, even though it is of no intended benefit to the subjects.
- Research is not undertaken primarily for financial or professional advantage.
- The research is well designed and properly conducted with an appropriate number of subjects so that the results are meaningful.
- The results are properly reported to the medical scientific community.

The general ethical requirements of medical research have been outlined in the Declaration of Helsinki issued by the World Medical Association. This document has received worldwide acceptance as the basis for ethical research. The relevant sections of this document are reproduced below, and the full document in Appendix 17.1

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### **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 that should be transmitted to a specially appointed 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 the medically qualified person and never rest on the subject of the research, even though consent has been given.
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 their research doctors are obliged to preserve the accuracy of their 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 a doctor who is not engaged in the investigation and who is completely independent of this official relationship should obtain the informed consent.
11. 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.

### **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 clinical study, every subject including those of a control group, 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 the proposal should be stated in the research protocol for transmission to the independent committee.
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.

### **Children as subjects of research**

Children, as subjects of research are different from adults. Being unable to express their fears or defend their interests, their parents or legal guardians must consent to participate in the research. Sometimes this would involve painful procedures, or hospitalization. In some cases it may need repeated attendance at outpatient clinics with long waits and exclusion from play activities. Secondly, unlike adults children are not able to challenge researchers when there is breach of confidentiality. For all these reasons it is important that concern for the interest of the subjects must take precedence over that of science and the community.

As medical science progresses a number of new therapies, vaccines and procedures are coming into vogue. Just as it is mandatory to test all new treatments after adequate research in the laboratory and on volunteers, so also it is necessary that all new innovations should have been proven to work on adults before trying them on children. When a choice of age groups is feasible, older children should be the subjects of new and experimental interventions before trying them on younger children, infants and

newborns. It is a good practice to make sure that the immediate and long term effects of new procedures have been fully ascertained before attempting them on children. The reason is to ensure that unknown long-term effects and complications of new treatments have had time to be detected. An example is the use of cadaveric growth hormone for the treatment of growth failure. The treatment was hailed as an advance in the 1970's only to discover some 10 to 20 years later that some of the subjects so treated went on to develop the Cruetzfeld - Jacob disease.

### **Potential benefits and harm.**

In assessing the potential benefits of proposed research the following questions need to be considered:

#### *Magnitude of the problem.*

- How common is the problem?
- How severe is the condition which the research seeks to alleviate?
- How would the knowledge gained be utilized?

#### *Probability of success.*

- How likely is the research to achieve its aim?

#### *Beneficiaries.*

- Who are the intended beneficiaries?
- Will the beneficiaries be the subjects participating in the research, or others?

#### *Resources.*

- Will the potential benefit of a proposed treatment be limited because of costs?

**Assessment of potential harm** is performed by reviewing the following:

#### *Types of intervention.*

- How invasive is the procedure? Children's responses are varied, unpredictable, and often alter as they grow. Hence generalization is not always possible or easy.

*Magnitude of the harm.*

- How severe will be the harm due to the research procedure? Sometimes the potential for harm is latent e.g. in pre-symptomatic diagnosis of a genetic disorder. Those diagnosed positive may have their choice of careers and opportunities restricted.

*Probability.*

- How likely is the harm to occur?
- How long lasting is it likely to be?

*Equity.*

- Are the proposed subjects being used for the research because of easy access? e.g. inmates of a mental disability institution?

*Reporting.*

- If evidence of harm emerges during a study will it be terminated, and results reported?

**Painful Procedures.**

All research on human subjects is a form of intrusion, and as such painful. The adverse effects vary according to the procedure. These may be classified as follows:

*Minimal.* For example, during questioning; measuring; observing; collecting stool and urine samples (though not by needle aspiration); collecting extra amount of blood for research purposes during venepuncture which was needed as part of treatment.

*Low.* For example, causing brief pain or tenderness, as with injections and taking samples of blood.

*High.* For example, doing biopsy; arterial punctures; blood vessel cannulation. Such procedures are justified only when research is combined with treatment intended to benefit the individual concerned.

It would be unethical to subject people to more than minimal risks when the research offers no obvious benefit to them. High risks are acceptable with severe or chronic diseases. Even then the harm should be balanced against the effects and outcome of the disease.

In the case of children there are additional considerations concerning their families, in terms of distress and anxiety caused, costs of travel and time away from work, and general inconvenience.

**Care in the design and conduct of medical research** Any research which is badly planned and poorly executed is unethical. It is unreasonable that children and mothers should be subjected to potential risks, inconvenience, or intrusion of privacy if the study is lacking scientific quality or efficient organization including logistics. In the design of a study there are three main pitfalls which the researcher should avoid. These are:

- Bias. Avoidance of bias is as much a scientific issue as an ethical one. Biased studies lead to erroneous conclusions and have a potential for harm.
- Inadequate sample size. The conclusions become unreliable, especially in the case of clinical trials, making the study worthless.
- No resulting report or communication. If the findings of a study do not get communicated to the scientific community the inconvenience suffered by the patients and parents has been in vain.

### **Informed Consent**

Consent refers to the positive agreement to participate. Informed consent means that consent has been given on the basis of full information being made available to the participants. In the case of children, because of their immaturity valid parental consent is necessary. However, where a child has sufficient understanding and intelligence to follow what is being proposed by the research, refusal to participate ought to be taken seriously. But how does one assess a child's ability to understand the investigative procedure being proposed? In different countries there would be different legal interpretations. In general, a reasoned refusal to participate in the proposed research would be considered legally binding. On the other hand, observational research, or compiling information from medical records and laboratory tests already carried out during previous hospitalization is considered permissible and does not require consent, provided full confidentiality is maintained.

The minimum basic information researchers must provide when obtaining consent includes the following:

- A statement describing the research, its purpose, the expected duration of subjects' participation, and the procedures to be undertaken.
- A description of any benefits that may be reasonably expected and any possible risk or discomfort.
- A statement that participation is voluntary, and that refusal to participate would not incur any penalty or denial of benefit.

Consent which is given under pressure, or because of financial inducement cannot be valid. In pursuing the aim of informed consent researchers should be prepared to discuss with the subjects and their families the purpose of the research; whether they stand to benefit directly from it, and all the relevant terms which the lay person is not likely to understand. Subjects should be aware that they are free to refuse participation, and to withdraw any time in spite of signing a consent form. In no way should

such action prejudice their right to treatment. During the course of the research the investigators should be available to respond with full explanations to questions from the participants and their families. Every attempt should be made to allay their anxieties in an informative manner.

Consent cannot be considered a once and for always phenomenon. The subjects' commitment can falter over a long period of participation. Explanations on matters, however trivial, may be needed from time to time and members of the research team should make sure that these are provided unstintingly.

### **Maintenance of confidentiality**

It is not uncommon for parents to expect detailed feedback from time to time. At the same time the researcher must ensure complete confidentiality. Modern technology makes it possible for information stored in data banks to be accessed by third parties. It is likely that the investigators' data are of interest to other agencies, and due care should be exercised in safeguarding data stored on computers.

## Appendix 17.1

### World Medical Association Declaration of Helsinki

#### Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964; amended by the 29th WMA General Assembly, Tokyo,

Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong,

September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA

General Assembly, Edinburgh, Scotland, October 2000

#### A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research that ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who maybe subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on

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

## **B. Basic principles for all medical research**

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

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

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

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

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

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

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

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

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

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

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

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

minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

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

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

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

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

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

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

### **C. Additional principles for medical research combined with medical care**

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

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

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

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

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or

have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, reestablishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.