

Workshop

Declaration of Helsinki

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The Doctors Trial

(The Medical Case of the Subsequent Nuremberg Proceedings)

- Nuremberg 12/1946 - 8/1947
 - An American military tribunal opened legal proceedings against 20 leading Nazi physicians and three administrators for their participation in war crimes and crimes against humanity
 - 16 accused were found guilty
 - 7 of them were sentenced to death
- The court claimed 10 basic principles on “Permissible Medical Experiments” (on humans) later known as “**Nuremberg Codex**”

Nuremberg Codex

1. The voluntary consent of the human subject is absolutely essential. [Additional comments]
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Time line

- 1947 Nuremberg Codex
- **1964 Declaration of Helsinki**
- **1975 - Revision of Tokyo**
- 1983 - Revision of Venice
- 1989 - Revision of Hong Kong
- 1996 - Revision of Somerset-West
- **2000 - Revision of Edinburgh**

Reasons for Revision

- Issues of clinical research in developing countries
- Increase of transparency
- Clarification on use of placebo

What has changed?

A point by point comparison

Formal Structure

2000

1996

A. Introduction

Provision 1-9

Introduction

Provision 1-8

B. Basic Principles for all
Medical Research

Provision 10-27

I. Basic Principles

Provision 1-12

C. Additional Principles for
Medical Research combined
with Medical Care

Provision 28-32

Note of Clarification
on Paragraph 29

II. Medical Research combined
with Professional Care

Provision 1-6

III. Non-therapeutic Biomedical
Research involving Human
Subjects

Provision 1-4

Same Title - New Addressee

2000

World Medical Association
Declaration of Helsinki

Ethical Principles for
Medical Research
Involving Human
Subjects

1996

World Medical Association
Declaration of Helsinki

**Recommendations guiding
Physicians** in
Biomedical Research
Involving Human
Subjects

Introduction (A1)

2000

1996

A1

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.**

Introduction #8

Because it is essential that the results of laboratory experiments be applied to human beings for further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research **involving human subjects.**

...

Introduction (A2)

2000

1996

A2

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**.

Introduction #1

It is the **mission** of the physician to **safeguard** the health of the people.

His or her knowledge and conscience are dedicated to the fulfillment of this **mission**.

Introduction (A3)

2000

1996

A3

Introduction #1

The Declaration of Geneva of the World Medical Association binds the physician with the words,

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„The health of my patient will be my first consideration,"

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and the International Code of Medical Ethics declares that,

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„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."

„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.“

Introduction (A4)

2000

1996

A4

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

Introduction #5

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

Introduction (A5)

2000

1996

A5

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.

I.5

S2 Concern for the interests of the subject must always prevail over the interests of science and society.

III.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.

Introduction (A6)

2000

1996

A6

Introduction #3

The **primary** purpose of medical research involving human subjects is to improve **prophylactic, diagnostic and therapeutic procedures** and the understanding of the aetiology and pathogenesis of disease.

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.

Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

Introduction (A7)

2000

A7 In current medical practice
and in medical research,
most prophylactic,
diagnostic and therapeutic
procedures involve risks
and burdens.

1996

Introduction #4

In current medical practice
most diagnostic, therapeutic
or prophylactic procedures
involve hazards.

This applies especially to
biomedical research.

Introduction (A8)

2000

1996

A8 Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights.

no counterpart

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 may be 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.

Introduction (A9)

2000

1996

A5

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.

Introduction #8 ...

S4 Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

S3 It must be stressed that the standards as drafted are only a guide to physicians all over the world.

Basic Principles for all Medical Research (B10)

2000

B10 It is the duty of the physician in medical research to protect the **life, health, privacy, and dignity** of the human subject.

1996

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

Basic Principles for all Medical Research (B11)

2000

B11 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.

1996

I.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.

Basic Principles for all Medical Research (B12)

2000

1996

B12

Introduction 7

Appropriate 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.

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.

Basic Principles for all Medical Research (B13)

2000

B13 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.

1996

III.1 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol

which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor

provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

Basic Principles for all Medical Research (B14)

2000

B14 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.

1996

I.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**.

Basic Principles for all Medical Research (B15)

2000

B15 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.

1996

I.3 **B**iomedical 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.

Basic Principles for all Medical Research (B16)

2000

B16 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.

1996

I.5 Every **bio**medical research project involving human subjects should be preceded with careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. (S1)

Basic Principles for all Medical Research (B17)

2000

B17 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**.

1996

I.7 Physicians should abstain from engaging in research projects involving human subjects unless they are **satisfied** that the **hazards** involved **are believed to be predictable**.

Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

Basic Principles for all Medical Research (B18)

2000

B18 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.

1996

I.4 **Bi**omedical 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.**

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

Basic Principles for all Medical Research (B19)

2000

B19 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.

1996

no counterpart

Basic Principles for all Medical Research (B20)

2000

B20 The subjects must be volunteers and informed participants in the research project.

1996

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

I.9 ... 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. (S2)

Basic Principles for all Medical Research (B21)

2000

B21 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.

1996

I.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.

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

Basic Principles for all Medical Research (B22)

2000

B22 In any research on human beings, each potential subject must be adequately informed of the aims, methods, **sources of funding, 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.

1996

I.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 physician should then obtain the subject's freely-given informed consent, preferably in writing.

Basic Principles for all Medical Research (B23)

2000

B23 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.

1996

I.10 When obtaining informed consent for the research project the physician 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 physician who is not engaged in the investigation and who is completely independent of this **official** relationship.

Basic Principles for all Medical Research (B24)

2000

B24 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.

1996

I.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. (S1)

Basic Principles for all Medical Research (B25)

2000

B25 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.

1996

I.11 ... Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian. (S2)

Basic Principles for all Medical Research (B26)

2000

B26 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.

1996

II.5 If the physician 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.**

Basic Principles for all Medical Research (B27)

2000

1996

B27 Both authors and publishers have ethical obligations.

I.8

In publication of the results of research, the investigators are obliged to preserve the accuracy of the results.

In publication of the results of his or her research, the physician is 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.

Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

Additional Principles for Medical Research combined with Medical Care (C28)

2000

C28 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.

1996

II.6 The physician **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.

Additional Principles for Medical Research combined with Medical Care (C29)

2000

C29* 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.

1996

II.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.

II.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.

This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

*See note of clarification

Note of Clarification on Paragraph 29*

- The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, **a placebo-controlled trial may be ethically acceptable, even if proven therapy is available**, under the following circumstances:
 - Where for **compelling and scientifically sound methodological reasons** its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
 - Where a prophylactic, diagnostic or therapeutic method is being investigated **for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.**
 - All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

*Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Additional Principles for Medical Research combined with Medical Care (C30)

2000

C30 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.

1996

No counterpart

Additional Principles for Medical Research combined with Medical Care (C31)

2000

1996

C31 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.

II.4 The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

Additional Principles for Medical Research combined with Medical Care (C32)

2000

C32 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, re-establishing 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.

1996

II.1 In the treatment of the **sick person**, the physician must be free to use a new diagnostic and therapeutic measure, if in **his or her** judgement it offers hope of saving life, re-establishing health or alleviating suffering.

What is really new?

New Addressee

- Now addressed to **all persons** working in medical research involving humans not only physicians
 - Also applicable for research on **identifiable human material or data**
- Nevertheless many paragraphs only address physicians

Clinical and non-Clinical Research

- Differentiation between clinical (therapeutic) and non-clinical (non-therapeutic) research defined less strictly
 - Most provisions relate to all medical research, only section C deals with medical research combined with medical care
 - no special focus on non-therapeutic research

Vulnerable Populations (A8)

- Definition according to the Declaration
 - Subjects who cannot give or refuse consent for themselves
 - e.g. minors, mentally/physically incapable persons ...
 - Subjects who may be subject to giving consent under duress
 - persons in institutions (prison, military)
 - persons in special relationship to the investigator (B23)
 - Subjects who will not benefit personally from the research
 - e.g. healthy volunteers
 - Subjects for whom the research is combined with care
 - Patients
- Issues
 - Based on the new definition almost every trial participant is member of a vulnerable population -> no special protection to specific populations

Role of IEC/IRB

- IEC approval required (where appropriate)
- Monitoring of ongoing trials by IEC
- Obligation to provide monitoring information to the IEC
 - especially any serious adverse events
- The researcher should also submit to the IEC information regarding
 - funding, sponsors
 - institutional affiliations
 - other potential conflicts of interest
 - incentives for subjects

Informed Consent

- Subject must be informed about
 - aims, methods,
 - sources of funding
 - 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 right to withdraw without reprisal
- Patients have to be informed which aspects of the care are related to research
 - Additional lab tests, X-rays etc.
- Clarification on non-written consent
 - consent must be documented and witnessed

Transparency

- Results - positive as well as negative - should be published (or made publicly available)
- Study designs should be publicly available
- Publication should include
 - Sources of funding
 - institutional affiliations
 - any possible conflicts of interest

Premature Study Termination

- Physicians should cease any investigation in case of a
 - negative risk/benefit consideration
 - **conclusive proof of positive and beneficial results**
- **Long term trials?**
- **Interim Analysis?**

Research Population and Benefit

B19: “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.”

C30: “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.”

Distributive Justice

- “No research in the poor for the rich” / “Ethical export”
- “Who took part must have access”

Legally Incompetent Subjects

- Research permitted if
 - the research is necessary to **promote the health** of the **population represented**
 - and **this research cannot instead** be performed on **legally competent persons**
- **Restriction on “therapeutic research only” has been dropped!**
- Research without prior informed consent
 - if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population
 - if conditions are documented in the protocol and protocol is IEC approved
 - Informed consent must be obtained as soon as possible
 - Comatose patients ...

Control Treatment

- “The benefits, risks, burdens and effectiveness of a **new method should be tested against those of the best current** prophylactic, diagnostic, and therapeutic **methods**”
 - What is the best current method?
 - Only regionally available methods?
 - Which standard must apply: national/international?

Use of Placebo

- Placebo-controlled trial acceptable even when proven therapy is available

“Where for **compelling and scientifically sound methodological reasons** its use is necessary to determine the **efficacy or safety** of a prophylactic, diagnostic or therapeutic method;

or

Where a prophylactic, diagnostic or therapeutic method is being investigated **for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.**”

- *Proposal for proper conduct*

- Where for **compelling and scientifically sound methodological reasons** its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method **and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.**

International Status of the DoH

- Unanimously adopted by all member organizations of the WMA at the 52nd WMA general assembly in Edinburgh, October 2000, including the German Medical Association (Bundesärztekammer)
- No official status under international law

Current National Status

- Currently the German Medical Association's professional code of conduct does not refer to the Declaration of Helsinki
("Musterberufsordnung" der BÄK)
- Some federal medical associations' professional codes of conduct refer to the 1996 revision (LÄK Nordrhein and others)