Overview of International Guidelines in Research Ethics

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I. Framework for Analysis

Ethical guidelines for research were "born in scandal and reared in protectionism"

--Carol Levine,1988

“Medicine's worst corruption had occurred among its best technicians.”

--Leo Alexander, 1947

II. Pre-Nuremberg Research Scandals

1796: Edward Jenner (discovered smallpox vaccine) -injected healthy eight-year-old James Phillips first with cowpox then three months later with smallpox

1845-1849: J. Marion Sims, "father of gynecology"

-- performed multiple experimental surgeries on enslaved African women without the benefit of anesthesia.

-- After suffering unimaginable pain, many lost their lives to infection.

II. Pre-Nuremberg Research Scandals, continued

1900: Walter Reed

-- injected 22 Spanish immigrant workers in Cuba with the agent for yellow fever paying them $100 if they survive and $200 if they contract the disease.

1906: Dr. Richard Strong, Harvard professor of tropical medicine

--experimented with cholera on prisoners in the Philippines killing thirteen.

II. Pre-Nuremberg Research Scandals, continued

1932-1941 Japanese Kwantung Army Unit 731

--1932: Kwantung invaded Manchuria.

--1938: Japan established Unit 731, a biological-warfare unit disguised as a water-purification unit.

--1940: Poisonous gas experiments on 16 Chinese prisoners by exposing them to mustard gas in a simulated battle situation.

--1940-1941: Unit 731 used aircraft to spread cotton and rice husks contaminated with the black plague in central China. About 100 people died.

Nuremberg War Crimes

- Nazi doctors' trials for medical experiments
- Conducted among civilians and Allied forces under the custody of the German Reich
- Without subject consent
- Committed murders, brutalities, cruelties, tortures, atrocities and other inhuman acts

Principles of Research Ethics

Nuremberg Code 1947

- Informed consent
- Requirement of prior animal experiment
- Anticipated scientific findings to result from the experiment
- Only qualified scientist
- Avoidance of physical and mental suffering
- No death or disabling injury

DECLARATION OF HELSINKI

--The Nuremberg Code had little or no influence on the actual conduct of research.

--The medical and research community realized that the Code did not provide adequate guidance for most of the research activities carried out by medical doctors

DECLARATION OF HELSINKI,

In 1953, the WMA Committee on Medical Ethics recognized that:

1. Need for professional guidelines designed by physicians for physicians (Nuremberg Code, formed by jurists for use in a legal trial)

2.Experiments must be classified into two groups:

a) “Experiments in new diagnostic and therapeutic methods”, and

b) “Experiments undertaken to serve other purposes than simply to cure an individual"

Declaration of Helsinki WMA

- World Medical Association created in London in 1946: resolution for guidelines for human experimentation
- Need for guidelines designed by MDs for MDs.
- 1964: Investigators asked to sign that research was conducted in accordance with D.H.
- 1975 : Protocol should be submitted to a specially appointed independent committee

Declaration of Helsinki WMA

- 1996 –Every patient, including control group should be assured of the best proven diagnostic and therapeutic methods.
- Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects
- 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.

Declaration of Helsinki WMA

- Primary purpose of medical research is to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.
- Most procedures involve risks and burdens
- Ethical standards that promote respect for all human beings and protect their health and rights.

Declaration of Helsinki WMA

- Research with humans should be based on the results from laboratory and animal experiments
- Research proposals should be reviewed by an independent committee
- Informed consent from research participants is necessary
- Research should be conducted by medically/scientifically qualified individuals
- Risks should not exceed benefits

Declaration of Helsinki WMA 2000

Informed consent: special cases

- MD should be cautious if the subject is in a dependent relationship with the MD or may consent under duress
- Legally incompetent, physically or mentally incapable of giving consent or legally incompetent minor – consent from the legally authorized representative
- Assent from subject (minor child) if able, in addition to consent of representative

Declaration of Helsinki WMA 2000

Medical Research Combined with Medical Care

- Only when the research is justified by its potential value.
- Benefits, risks, burdens, effectiveness of a new method should be tested vs current methods
- After study, patients should have access to the best proven methods identified by study

Declaration of Helsinki WMA 2000

- MD should fully inform patients aspects of the care related to the research. Refusal of patient must never interfere with the MD-patient relationship
- Where proven methods do not exist or ineffective, MD must be free, with consent of patient, to use unproven or new measures if in the MD's judgment, it offers hope of saving life

Declaration of Helsinki WMA 2000

Par 29 This does not exclude the use of placebo or no treatment in studies where no proven prophylactic, diagnostic and therapeutic method exists.

2001 Clarification : Extreme caution must be taken in making use of placebo controlled trials and in general, this methodology should only be used in absence of existing proven therapy. It may be ethically acceptable:

- for compelling and scientifically sound reasons, its use is necessary to determine efficacy or safety of method
- where method is being investigated to a minor condition and no additional risk of safety or irreversible harm

Origin of US Guidelines
Tuskegee Syphilis Experiment

- US Public Health Service study on natural history of syphilis from 1932-1972
- Studied illiterate 399 black sharecroppers from Alabama
- Informed that they were being treated with ‘bad blood’ and were given token doses of medicine
- Data to come from autopsies of these men

US Guidelines - Belmont Report (1979)

- Report of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Summarized the issues into 3 principles
  - Autonomy/ respect for persons
  - Beneficence/ Non Maleficence
  - Justice

CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (1982, 1993, 2002)

- Council for International Organizations of Medical Sciences (CIOMS) with WHO
- Purpose: how the ethical principles set forth in Helsinki Declaration can be applied
- Dealt with special circumstances of developing countries

CIOMS International Ethical Guidelines for Biomedical Research 2002

1. Ethical Justification and scientific validity of biomedical research involving human beings
2. Ethical review committees
3. Ethical review (local) of externally sponsored research
4. Individual informed consent

CIOMS International Ethical Guidelines for Biomedical Research

5. Obtaining informed consent: Essential information for prospective research subjects
6. Obtaining informed consent: Obligations of sponsors and investigators
7. Inducement to participate
8. Benefits and risks of study participation

CIOMS International Ethical Guidelines for Biomedical Research

13. Research involving vulnerable persons
14. Research involving children
15. Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent
16. Women as research subjects
17. Pregnant women as research participants

CIOMS International Ethical Guidelines for Biomedical Research

18. Safeguarding confidentiality
19. Right of injured subjects to treatment and compensation
20. Strengthening capacity for ethical and scientific review and biomedical research
21. Ethical obligation of external sponsors to provide health-care services.

GOOD CLINICAL PRACTICE

A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical data

- Ensure that participants' rights and safety are adequately protected
- Ensure quality and integrity of data

WHO Operational Guidelines For Ethics Committees That Review Biomedical Research 2000

- to contribute to the development of quality and consistency in the ethical review of biomedical research
- Defines
  - Membership requirements,
  - Training of members
  - Operating ERC guidelines
  - Meeting requirements
  - Knowledge of ethical issues
  - Independence from influences

Ethical Research

- Requires scientific validity and careful thought and planning to protect human subjects.