

Module II: The Trial Landscape

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- The history of clinical trials
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- **Research ethics**
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Research Ethics

The History of Research Ethics - overview

- Hundred years ago no regulations
- No consumer regulations - no Research Ethics Committees
- Twentieth century: many medicines and vaccines developed
- However many studies were made on marginal groups such as prisoners and children.
- Test subjects were involved without being informed.
- As a consequence of those unethical clinical studies we have nowadays well defined rules and regulations for the conduct of ethical human experimental studies.
- Ethics Committee Approval and Informed Consent

Research Ethics

The History of Research Ethics - Milestones



Research Ethics

Unethical medical research – 1840-1910

- 1847: J. Marion Sims, “the father of gynecology” performed experimental surgeries on enslaved African women without the benefit of anesthesia. Many lost their lives to infection.
- 1896: Dr. Arthur Wentworth performed spinal taps on 29 children at Children’s Hospital, Boston, to determine if the procedure was harmful.
- 1897: Italian bacteriologist Sanarelli injected five subjects with bacillus searching for a causative agent for yellow fever.
- 1900: Walter Reed injected 22 Spanish immigrant workers in Cuba with the agent for yellow fever paying them \$100 if they survived and \$200 if they contracted the disease.
- 1906: Dr. Richard Strong, a professor of tropical medicine at Harvard, experimented with cholera on prisoners in the Philippines killing thirteen.

Research Ethics

Unethical medical research – 1910-1940

- 1915: A doctor in Mississippi, working for the U.S. Public Health Office produced Pellagra in twelve Mississippi inmates in an attempt to discover a cure for the disease.
- 1920: Testicular transplant experiments on five hundred prisoners at San Quentin.
- 1931: Lubeck, Germany, 75 children died from paediatrician's experiment with tuberculosis vaccine.
- 1931: Dr. Cornelius Rhoads, a pathologist, conducted a cancer experiment in Puerto Rico. Dr. Rhoads purposely infected his Puerto Rican subjects with cancer cells. Thirteen of the subjects died.
- 1939: Twenty-two children living at the Iowa Soldiers' Orphans' Home in Davenport were the subjects of the “monster” experiment that used psychological pressure to induce children who spoke normally to stutter.

Research Ethics

Unethical medical research – World War II

There were many unethical clinical research trials during the World War II.

- One example: An Office of Scientific Research and Development was established in the US to combat diseases such as dysentery, influenza and malaria, diseases that commonly affect soldiers.
- One of the research teams created a potential vaccine for dysentery. To test it the researchers used orphans and mentally retarded individuals in institutions. The orphans developed high fevers, thus proving that the vaccine did not work.
- Another research team gave psychotic patients with malaria.

Research Ethics

The History of Research Ethics - Milestones

EU Directive 2001/20/EC 2004
Clinical Trials Harmonisation

ICH GCP Guideline 1996
Drug Development Harmonisation

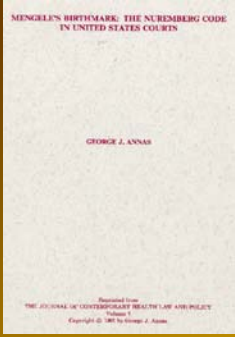
Belmont Report 1979
Unethical US Studies

Declaration of Helsinki 1964
The Nuremberg Trial

The Nuremberg Code 1947
German Physicians War Crimes

Research Ethics

The Nuremberg Code - 1947



Research Ethics

The Nuremberg trial - 1946

- High-Altitude Experiments
- Freezing Experiments
- Malaria Experiments
- Lost Gas Experiments
- Sulfanilamide Experiments
- Bone, Muscle, and Nerve Regeneration and Bone Transplantation Experiments
- Sea-water Experiments
- Epidemic Jaundice Experiments
- Sterilization Experiments
- Spotted Fever (Fleckfieber) Experiments
- Experiments with Poison
- Incendiary Bomb Experiments



Research Ethics
The Nuremberg Code – the 10 items

Permissible Medical Experiments

1. Voluntary consent of the subject
2. The experiment should yield fruitful results
3. Animal experimentation to justify the study
4. Avoid all unnecessary physical/mental suffering/injury
5. No experiment so death or disabling injury will occur
6. Risk never exceeds the importance of the benefit
7. Proper preparations to protect against injury, disability, or death
8. Only by scientifically qualified persons
9. The human subject should be at liberty to stop the experiment
10. The scientist must terminate the experiment if it is likely to result in injury, disability, or death

Research Ethics
The Japanese World War II experiments

From *Eubios Journal of Asian and International Bioethics* 10 (2000), 179-180. The article was written by a Japanese academic, Dr. Takashi Tsuchiya.

- From 1933 to 1945, Japanese doctors in China performed cruel experiments on Chinese, Russians, Mongolians, and Koreans. Most of the doctors who performed human experiments and vivisections were academic researchers leading Japanese medical schools.
- Unit 731, a biological-warfare unit was a huge compound with more than 150 buildings outside the city of Harbin, China.

Research Ethics
The Japanese World War II experiments

In his article Dr. Tsuchiya classified the experiments and vivisections under four categories:

1. Vivisections for training newly employed army surgeons
 - At army hospitals in China, army surgeons did many vivisections on Chinese prisoners. This surgical practice was purportedly part of the training program of newly employed army surgeons.
2. Intentional infection of diseases
 - Researchers infected prisoners with many kinds of diseases, for example, plague, cholera, epidemic hemorrhagic fever, tuberculosis, typhoid, tetanus, anthrax, typhus, and dysentery. The subjects were dissected after their death or vivisected to death.

Research Ethics

The Japanese World War II experiments

3. Trials of non-standardised treatments

- Vaccines in the development stage were tried directly on prisoners, with no prior trials on animals. Another example was horse blood transfusion.

4. Learning tolerance of the human body

- Experiments studied how much air could be injected intravenously, how much poison gas inhaled, how much bleeding brought prisoners to death, how many days prisoners could live with no food or water, or how high electric current or voltage human beings could bear. There were also many trials of weapons with human subjects.

The Japanese medical doctors involved in these experiments have not been taken to court, so the allegations have not been exposed for the public as they were during the Nuremberg trial.

Research Ethics

The History of Research Ethics - Milestones

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Research Ethics

Declaration of Helsinki

The Declaration of Helsinki was revised in 1975, 1983, 1989, 1996 and 2000 by the World Medical Association.

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

Research Ethics
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Research Ethics
Vulnerable populations – after 1945

- 1945: Malaria experiment on 800 prisoners.
- 1950: Infects 200 women prisoners with viral hepatitis.
- 1956: Tests experimental polio vaccine on 133 prisoners.
- 1962-1966: A total of 33 pharmaceutical companies tested 153 experimental drugs at one prison.
- 1962-1980 Pharmaceutical companies conduct phase I safety testing of drugs almost exclusively on prisoners.
- 1969. Investigational drugs tested on mentally disabled children. No institutional approval.
- 1969: 70 poor women - half received oral contraceptives the other placebo. No informed consent.

Research Ethics
Government initiated research – after 1945

- 1946-1953: Atomic Energy Commission sponsored study: residents were fed Quaker Oats breakfast cereal containing radioactive tracers.
- 1947: The CIA study: of LSD as a potential weapon. Human subjects - both civilian and military – were used with and without their knowledge.
- 1949-1953: Atomic Energy Commission studies: mentally disabled school children fed radioactive isotopes.
- 1966: U.S. Army introduces bacillus globigii into New York subway tunnels in a field study.

Research Ethics

Tuskegee Syphilis Study (1932-1972)

The Tuskegee syphilis study is one of the most widely cited examples of research in which human subjects were not adequately protected. This provided the impetus for federal regulations that now restrict the treatment of human subjects in research in the US. The Belmont Report was published in 1978.

- During a research project conducted by the US Public Health Service, 600 low-income African-American males, 400 of whom were infected with syphilis, were followed for 40 years.
- The subjects were not told about their disease.
- Even though penicillin became available in the 1950s, the study continued until 1972 with participants being denied treatment.
- Perhaps as many as 100 died of syphilis during the study.
- The study was stopped in 1973 only after its existence was publicized.

Research Ethics

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Research Ethics

The History of Research Ethics - Milestones

ICH GCP Guideline 1996

IRB/IEC

- Responsibilities
- Composition
- Functions and Operations
- Records

Research Ethics
The History of Research Ethics - Milestones

ICH GCP Guideline 1996

Responsibilities

- EC.....responsibility is to ensure the protection of the rights, safety and well-being of human subjects in a trial ...
- EC review documents: protocol/amendment(s); written informed consent form; recruitment procedures (advertisements); written information to subjects; Investigator's Brochure; safety information; payments/compensation to subjects; investigators CV; any other documents
- Reasonable time for review; GCP Qualification of investigator; Continuing review, at least once per year; Review payments

Research Ethics
The History of Research Ethics - Milestones

ICH GCP Guideline 1996

Composition

- five or more; one lay person; one independent of institution; list of members + qualifications

Functions and Operations

- perform its functions according to written standard operating procedures (SOPs); maintain written records of its activities; make its decisions at announced meetings

Records

- retain all relevant records for at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies)

Research Ethics
The History of Research Ethics - Milestones

ICH GCP Guideline 1996

The informed consent to be provided to subjects should include explanations in 20 points:

1. That the trial involves research.
2. The purpose of the trial.
3. The trial treatment(s) and the probability for random assignment to each treatment.
4. The trial procedures to be followed, including all invasive procedures.
5. The subject's responsibilities.
6. Those aspects of the trial that are experimental.

Etc.

Research Ethics
The History is not over

India, 2004:

- Erythromycin, was placed in the wombs of 790 women to test the drug as a contraceptive.
- The trials were conducted between 1999 and 2002.
- First group was given a 500 mg tablet, while the second group received ten 50 mg tablets.
- A year later, 35 percent of women in the first group and 28 percent in the second group had become pregnant.
- The doctors did not have permission

Conclusion
Research Ethics

The three international Guidelines for the prevention of unethical clinical research

- The Nuremberg Code (1947)
- The Declaration of Helsinki (1964)
- The ICH GCP Guideline (1996)
