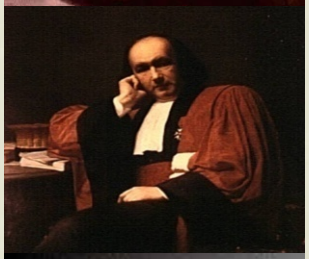
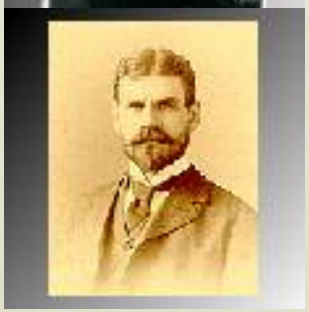
History of research Ethics

Origin of International Guidelines

History of Medical Research

Pre WWII





Edward Jenner (1789)
Smallpox Vaccine

Claude Bernard (1865)
Ethical Maxims

Louis Pasteur (1885)
Rabies Vaccine

Walter Reed (1900)
Yellow Fever

During World War II

- Nazi doctors conducted as many as 30 different type of experiments on concentration-camp inmates
- performed these studies without the consent of the victims
- Who suffered indescribable pain, mutilation, permanent disability, or in many cases death as a result

The International Military Tribunals in Nuremberg 1946

The Nuremberg Military Tribunals in 1946

- 23 German physicians
- “performing medical experiments upon concentration camp inmates and other living human subjects, without their consent, in the course of which experiments the defendants committed the murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts.”

Nazi Doctors Trial

- 11 supplemental trials
- 23 Nazi physicians were charged with conducting inhuman experiments on German civilians and nationals of other countries
- 16 defendants were convicted
- 7 were sentenced to death

The Nuremberg Code

- 1947
  - Developed by International Military Tribunal
  - The judgment included a set of standards knows as the Nuremberg Code, an ethical yardstick.
  - First internationally recognized code of research ethics

The Nuremberg Code (1947)

As part of the verdict, the Court enumerated some rules for "Permissible Medical Experiments", now known as the “Nuremberg Code”. These rules include:

- **voluntary consent**
- **benefits outweigh risks**
- **ability of the subject to terminate participation**

http://www.hhs.gov/ohrp/references/nurcode.htm

Nuremberg Code (1947)

- Informed consent from volunteers must be obtained without coercion.
- Human experiments should be based upon prior animal experimentation.
- Anticipated results should justify the experiment.
- Only qualified scientists should conduct research.
- Physical and mental suffering should be avoided.
- There should be no expectation of death or disabling injury from the experiment.

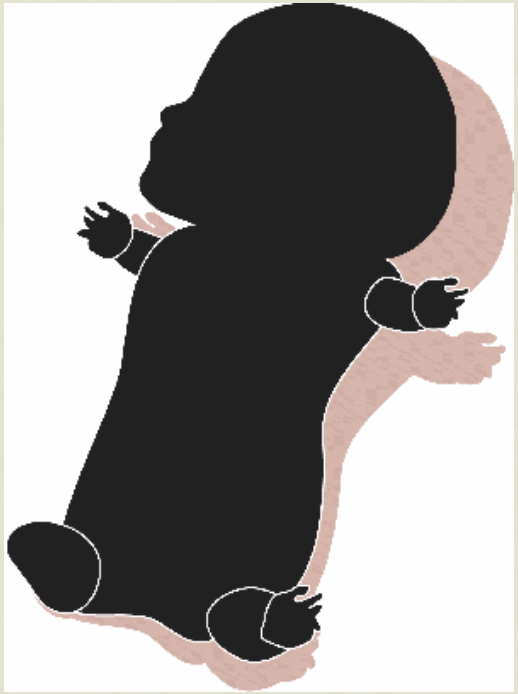
Study at Jewish Chronic Disease Hospital New York 1960's

- 22 Elderly patients
- some with dementia, some spoke only Yiddish
- The participants were not informed that the injected material contained live cancer cells
- No review committee and no approval was sought from attending MDs providing care.
- Need for informed consent in research
- guardians not asked for permission
- consent deceptive, inadequate, & not translated

Lerner BH. Sins of omission – cancer research without informed consent. NEJM 2004; 351(7):628-630.

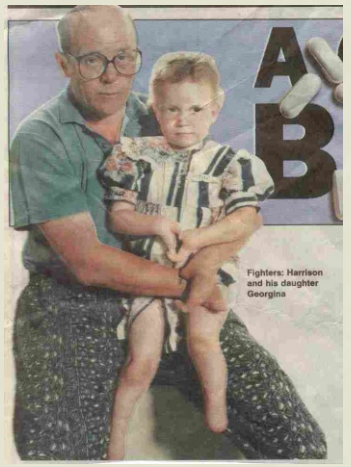
The Thalidomide Study 1961

- Thalidomide was approved as a sedative in Europe in the late 1950's.
- The FDA never approved the drug, but samples were sent to US doctors.
- By 1961 thalidomide was shown to be very harmful to the fetus, interfering with the normal development of arms and legs.



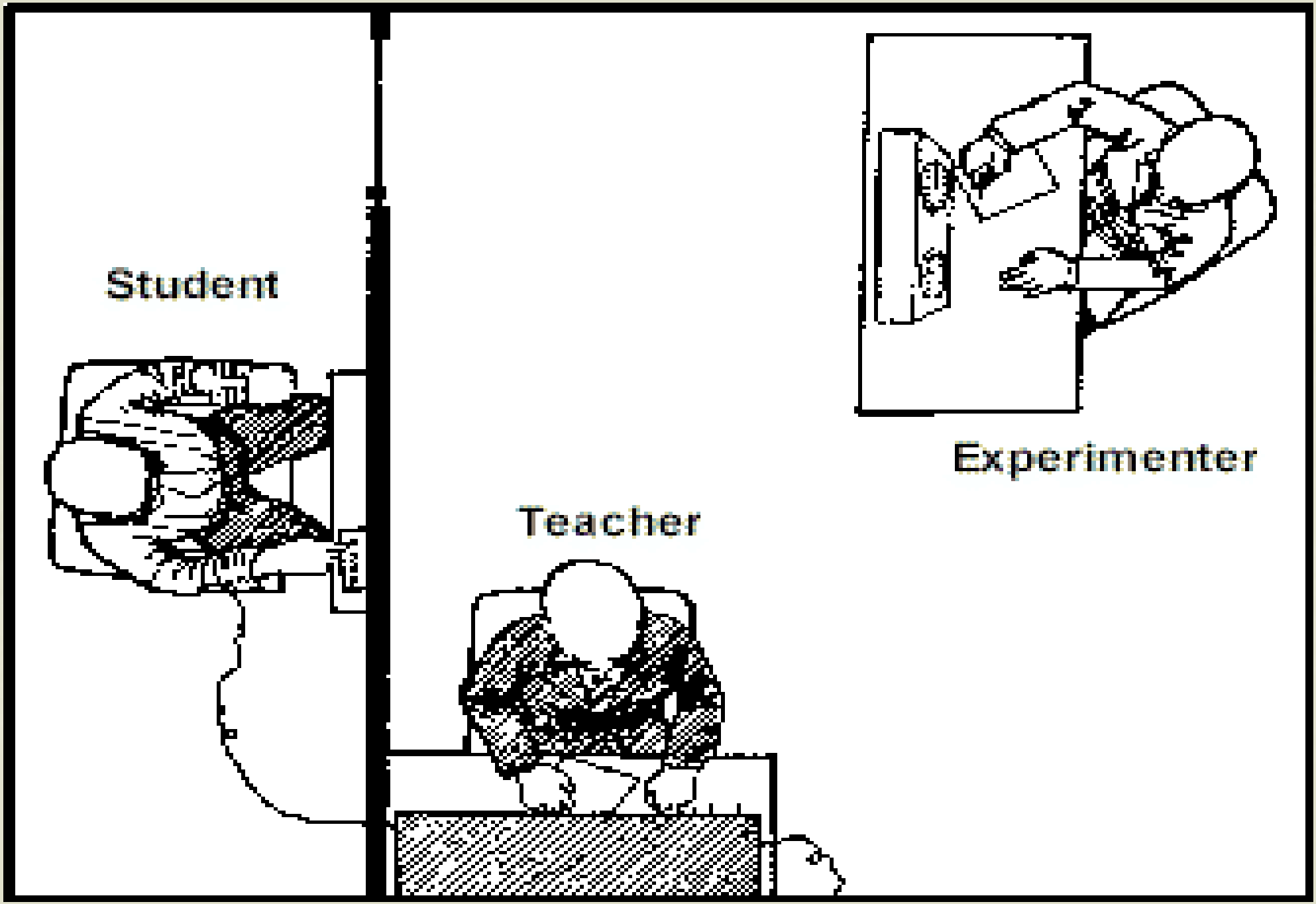
The Thalidomide Study Results

- These events lead to the passage of the Drug Amendments of 1962 to the Food, Drug and Cosmetic Act
- This was the first US statues that required subjects be informed of a drugs experimental nature and to consent before starting the research study



The Milgram Study (1963)

- The study was on obedience and humans' response to authority.
- The subjects were deceived as to the nature of the study and were told it was a teacher / learner experiment.
- The "teachers" were told to give the "subject" an electrical shock for missed answers.


Student
Teacher
Experimenter

Criticism of the Milgram Study

- Informed consent had not been obtained because of the Deception
- Federal regulations specifically allow for deception in research, but only in limited conditions and only with IRB approval
- Extreme psychological stress experienced by most subjects

Declaration of Helsinki (1964)

- **Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964**
- **Revised by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, and in Hong Kong in 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996** and 2000 (Edinburgh, Scotland). added by the WMA General Assembly, Washington 2002.
- **It is the mission of the physician to safeguard the health of the people**
- **Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects**

Declaration of Helsinki

- **Respect for Persons** – people are not a means to an end; researchers have duty to protect life, health, privacy and dignity of research participants
- **Standard of care** must be best available, even for control group
- Proxy consent and assent for vulnerable populations
- Placebo

Declaration of Helsinki (1964)

- **“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…**

- **In any medical study, every patient, including those of a control group, if any, should be assured of the best proven diagnostic therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.”**

Willowbrook Hepatitis Study
(1956-1972)

- 800 Children - Willowbrook State School for the Mentally Retarded
- Newly admitted mentally disabled children were inoculated with infectious hepatitis
- Objective: to determine the period of infectivity for the disease
- Researchers injected students with mild form of hepatitis
- Parents were not informed of the risks
- Benefit of study for participants: better hospital facilities and care for the children
- coercion of parents

Beecher Article

"Ethics and clinical research"

Henry K. Beecher

New Engl J Med 274 (1966):1354-60

- **22 published medical studies presenting risk to subjects without their knowledge or approval**
- **Published in some of the most prestigious journals and conducted at some of the most prestigious institutions**
  - **perform heart catheterizations on patients getting a bronchoscopy [look at breathing passages through a tube]**
  - **placebo control groups in life-threatening diseases with known effective treatments – several**
  - **randomize soldiers with strep throat to penicillin vs. treatments known-to-be-ineffective [ineffective treatment may lead to rheumatic heart disease]**

Public Health Service Policy 1966

- NIH Director and Surgeon General requested that the National Advisory Health Council review human subject protections
- Council recommended prior institutional review for PHS supported research to:
  - Protect of the rights and welfare of the subjects
  - Assure appropriate methods of informed consent
  - Determine acceptable balance of risks and benefits
- Adopted as Public Health Service policy in 1966
- Beginnings of the Institutional Review Board (IRB)

U.S. Federal Regulations Policy and Guidelines

- **DHHS - 45 CFR Part 46 (The Common Rule)**
- **FDA - 21 CFR (First developed and promulgated 1962-1966)**
  - **Part 50 (Informed Consent)**
  - **Part 56 (IRBs)**
  - **Part 312 (Drugs)**
  - **Part 812 (Devices)**
- **Department of Education**
  - **34 CFR Part 97**
- **NIH assurance (FWA)**

DEPARTMENT OF HEALTH & HUMAN SERVICES

The main elements of the Common Rule

- requirements for assuring compliance by research institutions;
- requirements for researchers obtaining and documenting informed consent;
- requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping.
- additional protections for certain vulnerable research subjects-- pregnant women, prisoners, and children

45CFR.46 Protection of Human Subjects

- Composition and function of a local institutional review board (IRB)
- Criteria for IRB approval of proposals
- Requirements regarding informed consent

The Tuskegee Study of Untreated Syphilis in the Negro Male

Tuskegee Syphilis Experiment
(1932-1972)

- US Public Health Service study on natural history of syphilis
- 399 black men with syphillis were recruited. they were mostly illiterate
- They were not Informed about their disease, the nature of the study, the risk to the partner
- Offers for free examination ,medicines, insurance, hot meal, transportation.
- No treatment for the disease.

Second phase began in 1933

- To strengthen validity and gain more data
- A control group of 201 black men were added
- An autopsies of deceased subjects
- No informed about the purpose of the study
- Government doctors were examining people for bad blood

Syphilis Study

The rationale published by the investigators for their decision regarding the lack of treatment provided to the infected "Negro" population:

- **"...Such individuals seemed to offer an unusual opportunity to study the untreated syphilitic patients from the beginning of the disease to the death of the infected person. An opportunity was also offered to compare the syphilitic process uninfluenced by modern treatment with the results attained when treatment had been given."**

"Sometimes, with the best of intentions, scientists and public officials and others involved in working for the benefit of us all, forget that people are people. They concentrate so totally on plans and programs, experiments, statistics - on abstractions - that people become objects, symbols on paper, figures in a mathematical formula or impersonal 'subjects' in a scientific study."

***Atlanta Constitution*, 1972**

New York Times Reported Tuskegee case in 1972

- Several bills to regulate research were introduced in congress in 1973
- Senator Edward Kennedy held hearings on Experimentation with human subjects, the study was stopped and treatment was given as needed
- Government would pay all medical expenses for the survivors, their wives and children who were born with congenital syphillis

1997

- President Clinton issued a formal apology to the subjects and their families.

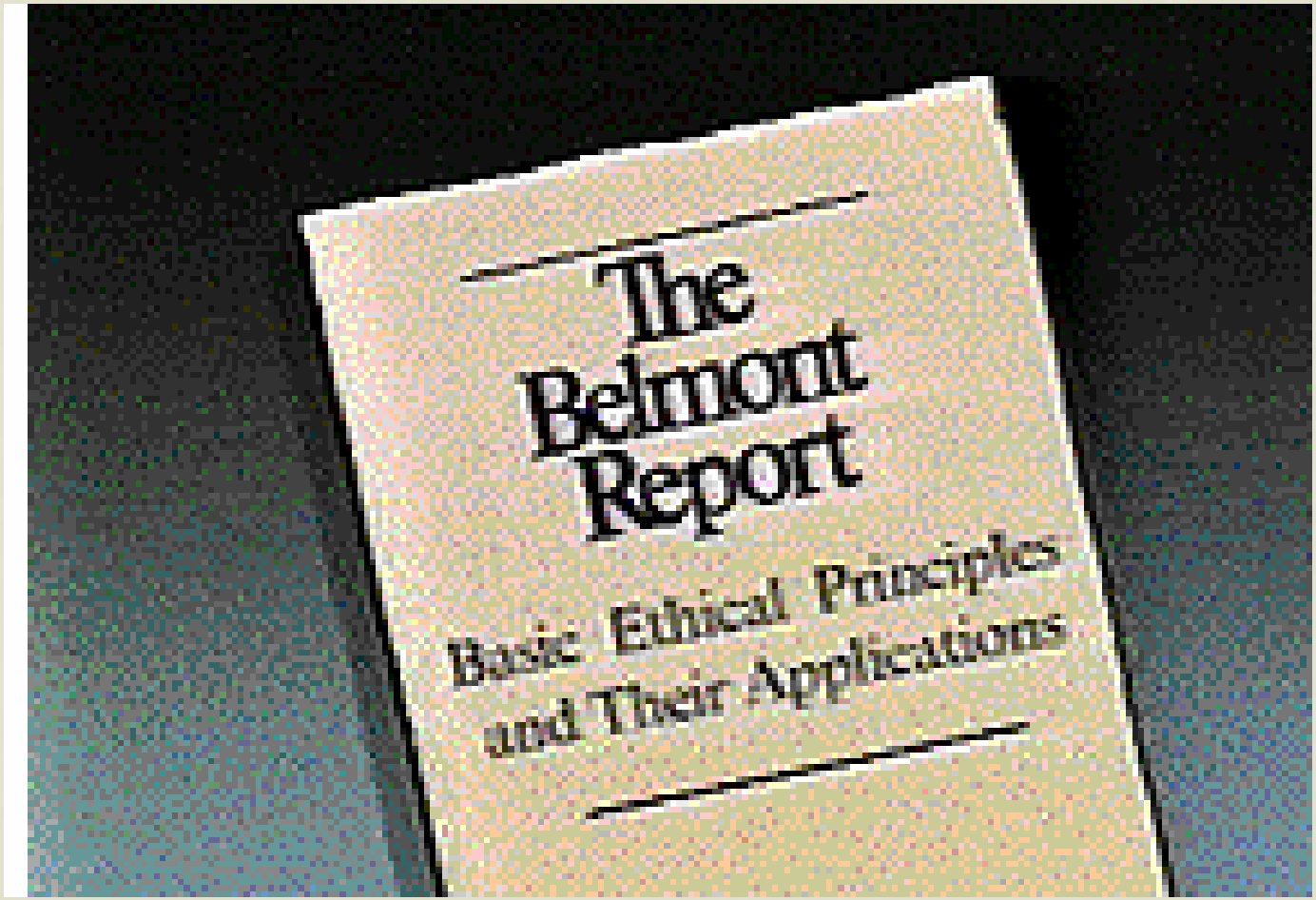
1974 The National Research Act

- Regulations for the protection of human subjects
- Requirement for informed consent
- Review research by the institutional review boards
- Created the commission for the protection of human subjects of Biomedical and Behavioral research

The Commission

- Identifying the basic ethical principles
- Develop guidelines to assure that the research is conducted in accordance with those principles
- Consider the boundaries between medical practice and research
- Role of assessment of risk and benefit
- Selection of subjects
- Nature and definition of informed consent

1979 National commission wrote the “Belmont Report”



The Belmont Report

Basic Ethical Principles:

- **Respect for Persons**
  - **Individual autonomy**
  - **Protection of individuals with reduced autonomy**
- **Beneficence**
  - **Maximize benefits and minimize harms**
- **Justice**
  - **Equitable distribution of research costs and benefits**

CIOMS/WHO Guidelines

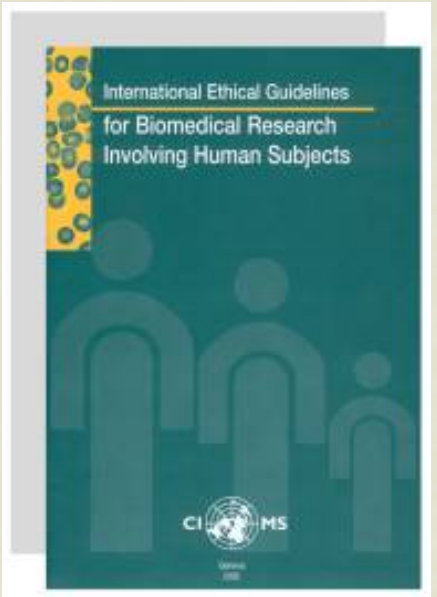
Council for International Organizations of Medical Sciences

- **Their scope reflects the changes, the advances and the controversies that have characterized biomedical research ethics.**

- **CIOMS Guidelines are designed to be of use to countries in defining national policies on the ethics of biomedical research involving human subjects,**

CIOMS/WHO Guidelines

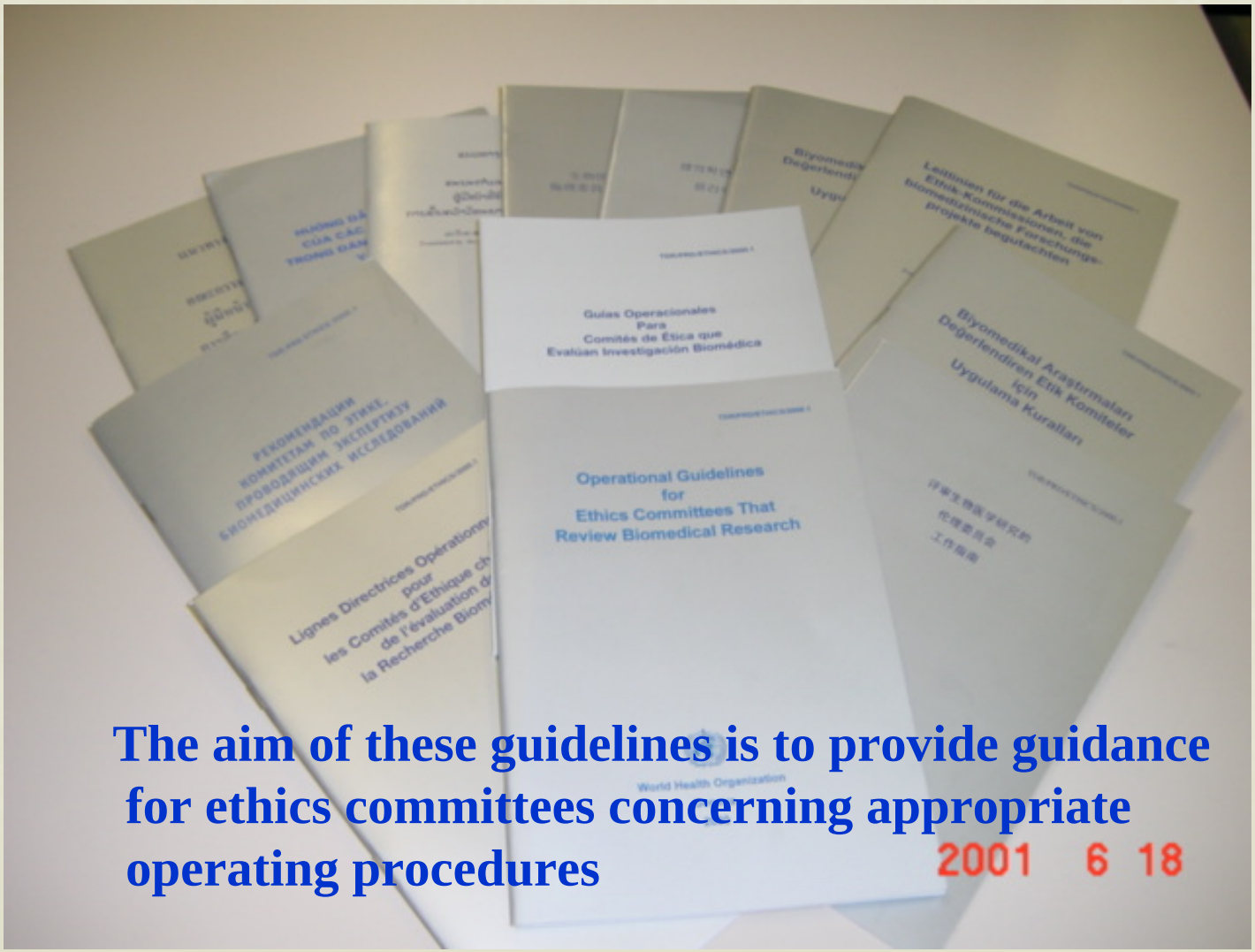
- provides guidance for the proper application of the principles of the Declaration of Helsinki and focuses particularly on research sponsored by or initiated in developed countries and carried out in developing countries.
- The CIOMS-WHO Guidelines added, among other things, a requirement for review and approval of all proposed research by an "ethical review committee"



Other Guidelines

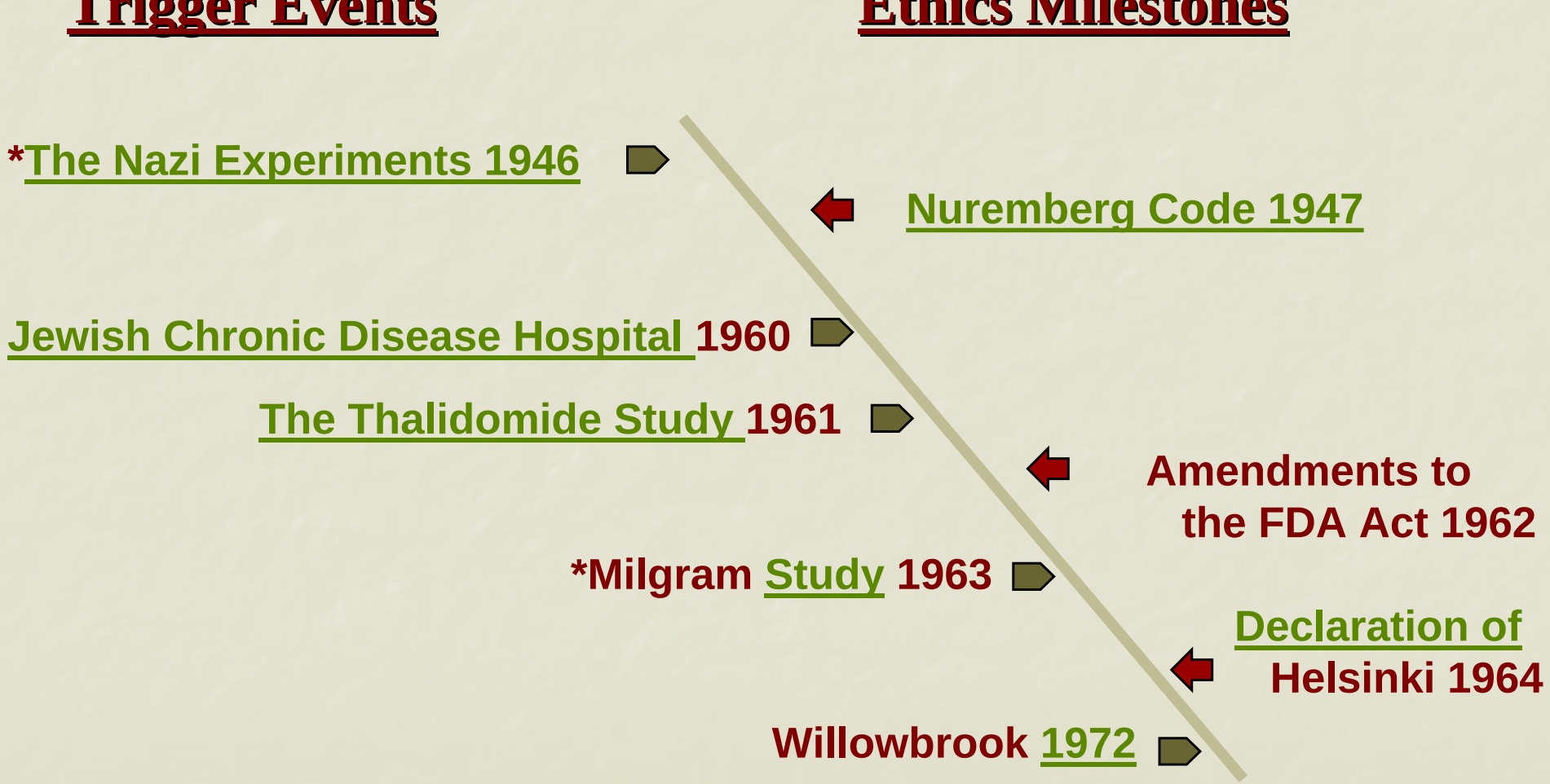
- ICH GCP Guideline 1996
- UNAIDS guidance document: Ethical consideration in HIV Preventive Vaccine research, 2000
- WHO Operational Guidelines for Ethics Committees that review Biomedical research, 2000
- WHO Surveying and Evaluating Ethical Review practices,2002

Operational Guidelines for Ethics Committees That Review Biomedical Research



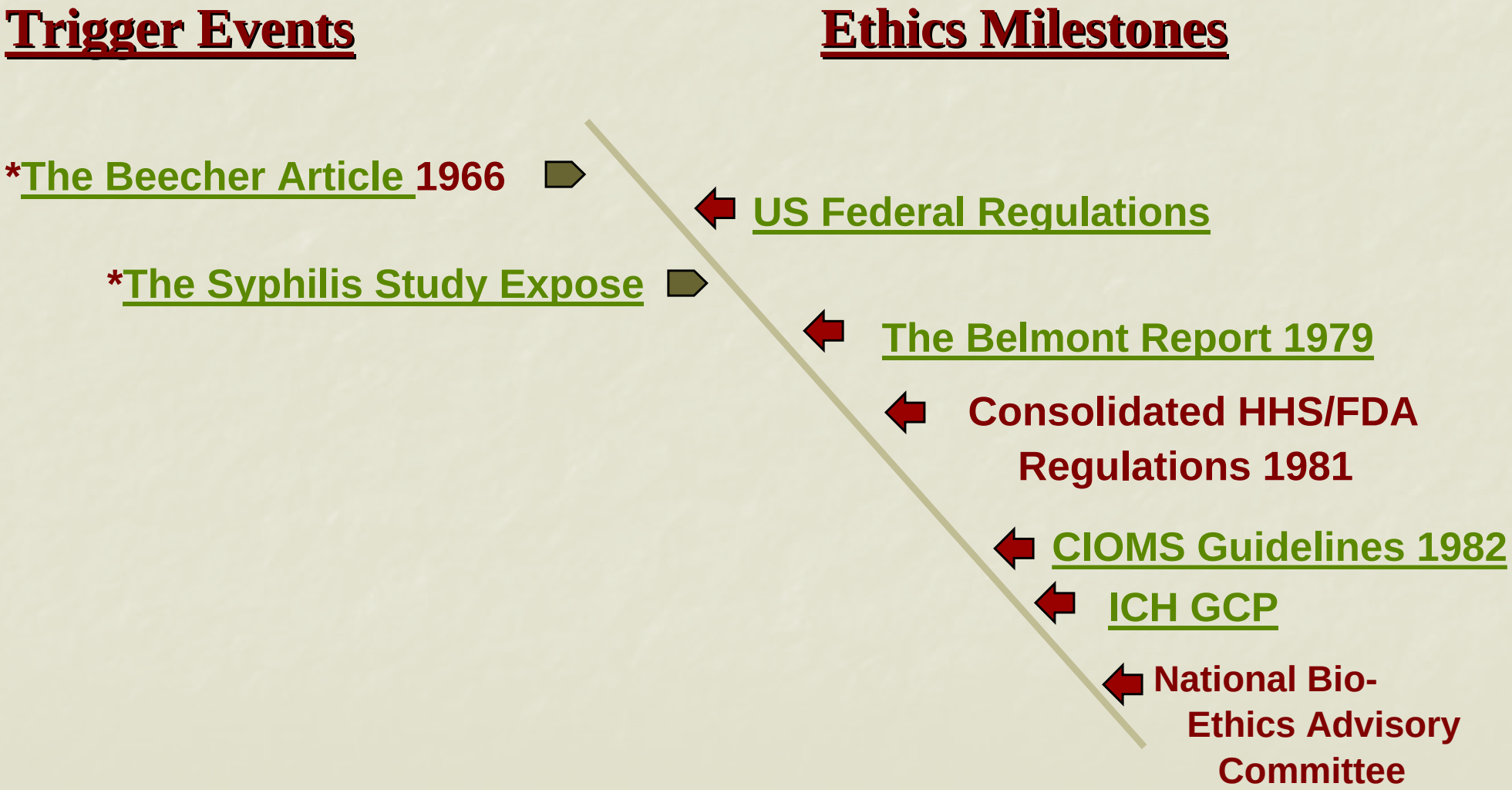
The aim of these guidelines is to provide guidance for ethics committees concerning appropriate operating procedures

Research Ethics Milestones



*From "Protecting Study Volunteers in Research" Dunn & Chadwick

Research Ethics Milestones



Basic Research Ethics Documents

Developed to observe the "rules of the road" for research involving human participants

The Evolution of Research Ethics

Codes, guidelines and regulations developed to observe the rules of the road for research involving human participants.

The Nuremberg Code

- Informed consent is absolutely essential
- Qualified researchers use appropriate research designs
- Favorable risk/benefit ratio
- Participant must be free to stop at any time

Webshots

The Declaration of Helsinki

- "The well-being of the subject should take precedence over the interests of science and society"
- Consent should be in writing
- Use caution if participant is in dependent relationship with researcher
- Limited use of placebo
- Greater access to benefit

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research:

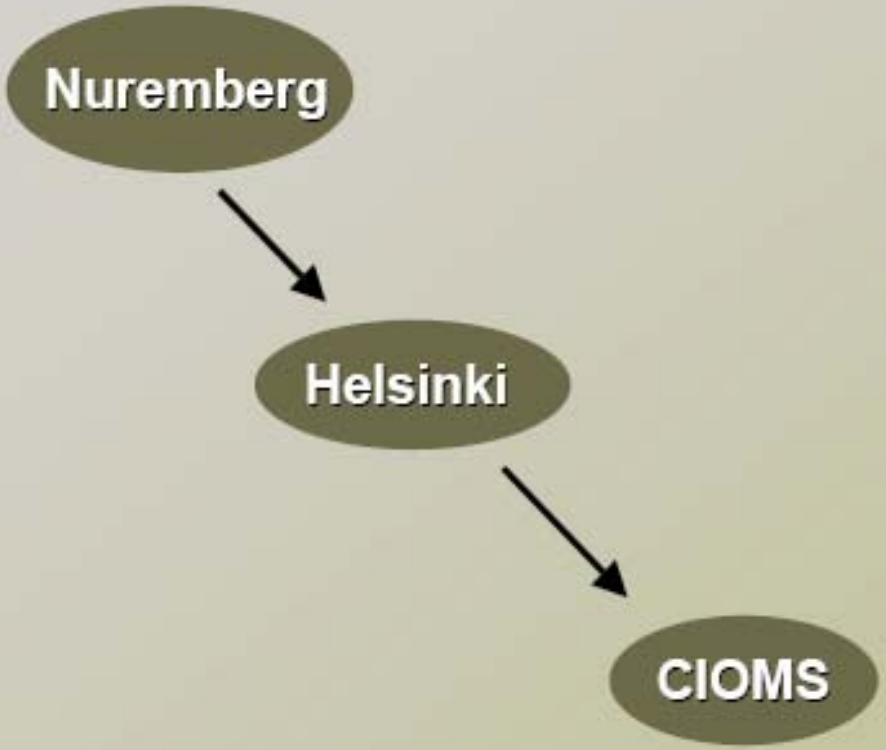
- Respect for persons
- Beneficence
- Justice

FHI / N. Herndon

The U.S. Code of Federal Regulations (also called *The Common Rule*)

- Prior approval by ethics committee
- Written informed consent and documentation
- Equitable recruitment of research participants
- Special protection for vulnerable groups
- Continuing review of approved research

Council for International Organizations of Medical Science (CIOMS) Guidelines



- informed consent
- research in developing countries
- protection of vulnerable populations
- distribution of the burdens and benefits
- role of ethics committees

International Conference on Harmonisation (ICH)

- Standardize drug development and approval process
- Protocol development standards
- Review by ethics committee
- Researcher responsibilities
- Sponsor responsibilities

National Bioethics Advisory Committee (NBAC)

Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries

- Responsive to local needs
- Community involvement
- Placebo use only when justified
- Access to benefits
- Focus on informed consent

From Fundamental Ethical Principles to Local Guidelines

Local Regulations and Guidelines

- Many countries now have national guidelines
- Rapid growth of research on a global scale
- Greatest need is in developing countries

Summary—Principles and Foundations of Research Ethics

- All codes and regulations advocate 3 fundamental principles:
  - — respect for persons
  - — beneficence
  - — justice
- Research is a privilege, not a right
- The well-being of the participant is paramount