



# Protecting Human Participants in Research: Historical and Ethical Perspectives

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# Early Protections

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- Self-experimentation
- Great attention to minimization of risk
- Distinctions between normal volunteers and patient-subjects with respect to consent



# Nazi Experiments

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- Military
  - Hypothermia
  - High Altitude
- Social
- Other



# Nuremberg Code

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- Voluntary Consent
- Anticipate scientific benefits
- Benefits outweigh risks
- Animal experiments first
- Avoid suffering
- No intentional death or disability
- Protection from harm
- Subject free to stop
- Qualified investigators
- Investigators stop if harm occurs



# Declaration of Helsinki

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- Issued by the World Medical Association in 1964
- Major revisions in 1975, 1983, 1989, 1996, 2000 (with 2 later clarifications regarding placebos and access to effective therapies following research), and 2008
- Three part document
  - Introduction
  - Basic principles
  - Research combined with clinical care



# US Scandals

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- Medical Research
  - Willowbrook Hepatitis Experiments
  - Jewish Chronic Disease Hospital
- Behavioral Research
  - Obedience to Authority
  - Tearoom Trade Study



# Willowbrook Hepatitis Experiments

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- ❑ Inoculation and injection of hepatitis
- ❑ Institutionalized children
- ❑ Admission through the research unit



# Jewish Chronic Disease Hospital Cancer Experiments

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- Injection of live cancer cells
- Hospitalized elderly patients
- Patients not told of live cancer cell injection



# Ethics and Clinical Research

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- Henry Beecher
- Chronicles 22 ‘unethical’ studies, from publications in respected medical journals
- Published in the *NEJM* June 1966



## US Public Health Services Study of Untreated Syphilis in the Negro Male

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- ❑ Often referred to as the “Tuskegee Syphilis Study”
- ❑ Poor, rural community
- ❑ Initiated as a natural history study when there were no effective treatments,
- ❑ Promise of “funeral benefits”
- ❑ Effective treatment (penicillin) arose in course of study, but not made available to subjects



# National Commission Belmont Principles

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- Respect for Persons
- Beneficence
- Justice



# Respect for Persons

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- Philosophical principle of autonomy
- Political principle of liberty
- The right to be left alone



# Beneficence

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- *Beneficentia* = Favor, benefit
- In health care, an obligation to improve health
- In research, an obligation to maximize benefits and minimize risks



# Justice

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- Fairness
- Treat equals as equals
- Originally conceived as protection, now as access



# Three Pillars of Protection

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- Investigators and sponsors
- Informed consent
- Oversight



# Investigators and Sponsors

## Good Clinical Practice

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- Protection of participants
- Credibility of results



# Credible Results

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- Scientific design
- Responsible conduct of research
- Responsibilities of sponsors
- Responsibilities of investigators



# Informed Consent

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- Two senses of consent
- The process of consent
  - Threshold
    - Decision-making capacity
    - Voluntariness
  - Information
    - Disclosure
    - Understanding
  - Consent



# The Need for Oversight

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- Many research scandals emanated from practices that did not meet current standards and prospective review might have avoided the occurrence
- Independence may serve as a check on the enthusiasm of investigators and sponsors
- Randomization with blinding poses special issues for providing protection for those enrolled in these trials and in properly interpreting adverse events



# Oversight

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- Institutions
- Federal agencies
- Accrediting bodies (eg, AAHRPP)
- DMCs
- IRBs



# Concluding Comments

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- The regulation of research ethics is a public activity
- Attention to the ethics of research is essential to respect those who choose to participate
- Although investigators and sponsors retain significant moral responsibility for protecting the rights and interests of participants in research, ‘external’ bodies are positioned to provide additional protection