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Ethical issues confronting clinical research: How did we get here?

Sarah Fowler-Dixon
Washington University School of Medicine in St. Louis

ETHICAL ISSUES CONFRONTING CLINICAL RESEARCH

How did we get here?

Sarah Fowler-Dixon, Ph.D.

Education Specialist

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http://medschool.wustl.edu/hsc/

314-633-7456

How Did We Get Here?

- War Research
- Drug Trials
- Questionable Ethics In Trials
- Tuskegee
- Harmonization
- Scenarios

WAR RESEARCH

- 1946 AMA Code of Ethics
  - response to concerns about research abuses
- 1947 Nuremberg Code
  - in reaction to WWII atrocities
  - 10 principles set by Nuremberg Military Tribunal
    - No more war crimes
    - Informed consent necessary

ETHICAL CODES

- 1964 Declaration of Helsinki
  - rules for therapeutic and non-therapeutic research
  - legal guardians can grant permission
  - waiver of consent is permissible in therapeutic trials

DRUG USE

- 1938 FDA
  - in response to 107 human deaths attributed to a liquid preparation of the first sulfa drug used to treat certain infectious bacteria, including pneumonia and strep throat.
  - Law requires evidence of drug safety prior to marketing

INVESTIGATION

- 1961 First investigator investigation by FDA
  - Found that investigator fabricated results of 25 drug trials done for different companies on adults, infants, and children

DRUG TRIALS REGULATIONS

- 1963 Certification of Informed Consent (FDA)
  - certification that informed consent will be obtained required of investigators conducting drug trials

- 1963 Investigational Drug Regulations
  - IND application established
  - Protocol, names and qualifications of investigators, study sites must be submitted to FDA

DRUG TRIALS REGULATIONS

- 1972 FDA monitoring by drug study sponsors
- 1988 Guidelines for Monitoring Clinical Investigations
  - FDA requires QA audits

THALIDOMIDE TRIAL

- 1962 Kefauver-Harris Amendments to FDA
  - result of thalidomide trial that caused infant deformities when taken by pregnant women
  - Drug efficacy must be proven prior to marketing
  - Informed Consent is necessary
  - Adverse Events must be reported

PROTECTIONS WOMEN

- 1975 HHS Special protections for Pregnant Women
  - trial must meet mother's health needs
  - minimal risk to fetus

- 1977 FDA Inclusion of Women
  - women of childbearing potential must be excluded from phase I and early phase II studies unless have a life-threatening disease
  - revised 1993 "reasonable" number included

PROTECTIONS MINORS

- 1983 HHS Special Protections for Children

- 2002 Best Pharmaceuticals for Children Act
  - drugs already on the market will be carefully studied in children

QUESTIONABLE ETHICS

- 1966 Beecher article
  - 22 examples of unethical or questionably ethical studies including Willowbrook State School in New York
    - retarded children are made to ingest hepatitis virus
- 1966 AMA adopts ethical guidelines for clinical investigations

REGULATORY RESPONSE

- 1966 HHS policy of independent review
  - HHS funded research must have an independent review made by “institutional associates” that includes methodology and informed consent

- FDA requires consent in all non-therapeutic drug studies

REGULATORY RESPONSE

- 1967 FDA creates division of Scientific Investigation
  - prison based research
  - IND/IDE research
  - suspect list
- 1967 FDA permits oral consent
- 1971 FDA requires IRB review
  - for studies on institutionalized subjects

TUSKEGEE

- 1972 Details of Tuskegee emerge
- 1972 OPRR established within NIH
  - to protect participants
  - becomes OHRP in 1999
- 1974 National Research Act
  - establishes National Commission for the Protection of Human Subjects in Biomedical & Behavioral Research
  - in reaction to Tuskegee

ETHICAL & FEDERAL CODES

- 1974 HHS requires informed consent for all federally funded studies
- 1975 Declaration of Helsinki signed by 34 nations
  - treatment of participants in biomedical research
  - PI responsible for trial conduct
- 1976 FDA Expands Bioresearch Monitoring
  - 1977 Bioresearch Monitoring Program

FROM THE DOH

- 1978 Protections for Prisoners
  - prisoner advocate must review research
  - OPRR approval necessary
  - risks can be no greater than for non prisoners
  - no special advantages to prisoners

- 1979 Belmont Report
  - Respect for Persons
  - Beneficence
  - Justice

HARMONIZATION

- 1981 President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research
  - recommends uniform federal regulatory system

- 1990 International Conference on Harmonization (ICH)
  - Europe, Japan, and US create guidelines for drug trials across borders

- 1991 Common Rule (45 CFR 46) - now 18

Do the Federal and Ethical Codes governing research assist the PI in these Scenarios?

SCENERIO 1

- A PI is performing a clinical trial of a new drug. Preliminary data shows that the drug appears to be failing to provide any benefit and has some unexpected side effects.
  - Should the trial be continued?
  - Should the unexpected side effects be reported as SAEs?
  - Should participants be informed of this preliminary information?

- Should the trial be continued?
  - depends on data and adverse events
  - quite often early results show no benefits

- Should the unexpected side effects be reported as SAEs?
  - unanticipated
  - life-threatening
  - death

- Should participants be informed of this preliminary information?
  - Any adverse event that would cause a participant to reconsider study participation should be reported to the participant in the form of a consent addendum.

SCENERIO 2

- The researcher's retired father owns stock in the drug company. The company asks the researcher to delay reporting the results until after the company's annual meeting in 2 months because of a concern about a drop in the stock price.
  - Should the trial be stopped?
  - Is there a financial conflict of interest?
  - Should the PI withhold reporting results?
    - How could this affect participants?

- Should the trial be stopped?
  - The drug company wants to withhold information. There may a real problem with this trial.

- Should the PI withhold reporting results?
  - How could this affect participants?
    - Withholding information could cause real harm to the participants.

- Is there a financial conflict of interest?
  - If the aggregate amount of the stock is $10,000 or more.
    - Participants should be aware of COI.

REFERENCES

- Reference INFORMED CONSENT by Getz & Borfitz
- Reference SAEM