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

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ETHICAL ISSUES CONFRONTING CLINICAL RESEARCH

How did we get here?

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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?

SCENARIO 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.

SCENARIO 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