Regulation and Oversight of Research with Children

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History

- **Henry K Beecher, MD: "Ethics and Clinical Research" NEJM, 1966.**

  - **22 examples of published studies in which investigators "endangered the health or the life of their subjects" without permission.**
    - **Example 3: Chloramphenicol for typhoid fever: 23 additional subjects died in placebo control group**

Tuskegee 1932 -- 1972

The Belmont Report (1979)
Ethical Principles

- ✓ Respect for Persons
  Requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.
- ✓ Beneficence
  An obligation to maximization of benefits and reduction of risk.
- ✓ Justice
  Who ought to receive the benefits or research and bear its burdens?

A Brief History

- “The Common Rule” adopted by federal 17 agencies that conduct human subjects research
  - 45CFR46 Subpart A
- FDA regulations 21CFR50
  - Relevant to human subjects research under FDA regulation (drugs and devices)
  - Identical to 45CFR46 with a few exceptions

Mechanisms for Human Subject Protections

- Peer review: Institutional Review Boards (IRBs)
  - Multidisciplinary panels
  - Lay participation
- Informed consent
- Professional integrity

IRBs

- Review boards can be organized at several levels
  - Academic Institution
  - Public Health Institution (Health Department, NIH Agency)
  - Research Organization (A central IRB for a research collaborative)
  - Commercial IRBs (Western IRB)
- Institutions sign a Federal Wide Assurance (FWA) that commits the institution to follow federal regulations governing human subjects research
  - IRB can defer oversight authority to a separate IRB

IRBs

- Federal regulations provide a floor for IRB policies and procedures
  - IRBs may be more stringent than required by the regulations
  - May create local policies and procedures for domains not covered by the regulations
- Local interpretation of regulations is appropriate as they apply to individual studies
    - Is a genetic test minimal risk in a protocol?
    - Considerable variation between IRBs documented

Exempt Research (46.101b)

- Research conducted in established or commonly accepted educational settings...
- Research involving the use of educational tests…
- Research involving the use of educational tests (cognitive, diagnostic, aptitude achievement), survey procedures, interview procedures,..
- Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study ... public benefit or service programs...

What is Research?

- *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
- “Innovative therapy” -- novel therapy by a physician in the attempt to benefit the individual patient
- “Quality Assurance/Quality Improvement” -- grey line between research and QA/QI

Human Subjects

- *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains
- (1) Data through intervention or interaction with the individual, or (2) Identifiable private information
    - Medical records
    - Tissue samples
    - Databases containing individually identifiable data

Vulnerable Populations

- **Subpart B**: Additional Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research
- **Subpart C:** Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- **Subpart D**: Additional Protections for Children Involved as Subjects in Research
- **? Subpart ?** Individuals with impaired decision-making capacity

45CFR46
Subpart D

- 4 Categories of approvable research with children

45CFR46

- 404 Research not involving greater than minimal risk

45CFR46

- 405 Research involving greater than minimal risk but offering prospects of direct benefit to the individual subject
  - The risk is justified by the anticipated benefit to the subjects
  - Risk/benefit ratio at least as good as available alternative approaches
  - Adequate provisions for solicitation of assent and parental permission

45CFR46

- 406 Greater than minimal risk and no prospect of direct benefit but likely to yield generalizable knowledge about the subject's disorder or condition
  - Must only be a "minor increase over minimal risk"
    - Not defined in the regulations
  - Knowledge of vital importance
  - Procedures are reasonably commensurate with subject's actual or expected treatment
  - Adequate provision for assent/permission

45CFR46

- 407 Not otherwise approvable research. Must be approved by Secretary of HHS and expert panel

Parental Permission

- Parent consent required
  - One parent for 404, 405
  - Two parents for 406, 407
- Child assent generally required
  - IRB to determine age for assent
  - Assent can be waived for beneficial research

Waiver of Consent

- Waiver of Consent possible under 45CFR46 but NOT under FDA counterpart
- 4 Criteria for Waiver (45CFR46.116d)
  - **(1) The research involves no more than minimal risk to the subjects;**
  - **(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;**
  - **(3) The research could not practicably be carried out without the waiver or alteration; and**
  - **(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.**

Case

- An investigator wishes to use 200,000 residual NBS samples to assess the population prevalence of a condition that is under consideration for a NBS panel.
- She also wishes to identify screen positive children and assess their health status through interviews and review of their medical records
  - Human subjects research?
  - Prospect of direct benefit to participants?
  - Minimal risk?
  - Parental consent necessary?

- QUESTIONS?