Clinical Research Involving Vulnerable Populations

Ethical and Regulatory Considerations

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Historical Background

- Nearly all examples of injustice in human research, stemming from Goldberger's 1915 prisoner study on pellagra through the and Tuskegee syphilis and San Antonio contraceptive studies of the 60's and 70's exploited vulnerable individuals.

Historical Background

- Since 1947, public response to human research injustice has led to the establishment of ethical codes, declarations, reports, and regulations to protect vulnerable populations in research.
- Current ethical and regulatory guidance:
  - Declaration of Helsinki
  - Belmont Report
  - Common rule

Definitions

- Vulnerability
  - Those who are relatively (or absolutely) incapable of protecting their own interests.*

* Guideline 13 of the Council for International Organizations of Medical Sciences International Guidelines for Biomedical Research Involving Human Beings, 2002

Belmont Report

- Vulnerable populations as those groups that might "**bear unequal burdens in research**" because of their "**ready availability in settings where research is conducted**", such as prisons, hospitals, institutions, and camps.
- Called for extra protection for these groups

Helsinki Declaration (2008)*

- 9. “Medical research is subject to ethical standards that promote respect for all human subjects…Some research populations are particularly vulnerable and need special protection”

* Addresses vulnerability in 6 articles

Helsinki Declaration

- 17. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit….
- 27. For a research subject who is legally incompetent….these groups should not be included in research unless the research is necessary to promote the health of the population represented….

Who is Vulnerable?

- Pregnant Women
- Human fetuses and neonates
- Prisoners
- Children and Adolescents
- Persons who are:
  - Physically handicapped
  - Mentally disabled
  - Economically disadvantaged
  - Educationally disadvantaged
- Elderly
- Staff and students

Vulnerability

- Subtle Forms
  - Patients not benefiting from standard therapy
    - Vulnerable to therapeutic misconception
  - Female partners of study subjects who become pregnant and need to be followed
- Not so Subtle Forms
  - Populations of Sub-Saharan Africa
    - Explicitly recognized in Helsinki # 8 and CIOMS # 10 and 13
    - Medically disadvantaged (orphan diseases)
    - Economically disadvantaged
    - Incompetent minors

Identifying Vulnerability

- Group Membership
- Individual

Identifying Vulnerability: Group Classification

- Advantages
  - Easier to identify group's vulnerability
  - Easier to mandate special protections
  - Easier to comply with regulations calling for appropriate informed consent

Identifying Vulnerability: Group Classification

- Disadvantages
  - Overlooks individual variation
  - Members may belong to multiple groups
  - Status of an individual may change
  - Group labeling can be stigmatizing

Identifying Vulnerability

- Ethical Dilemma
  - Protecting subjects based on their classification as "vulnerable" does not show respect for autonomy.*
    - It denies the individual the opportunity to evaluate risks in light of their own priorities.

* Rhodes, R. Rethinking Research Ethics. AJOB 2010; 10: 19-36

Exploitation of Human Vulnerability

- Coercion
- Deception
- Undue Inducements

Exploitation of Human Vulnerability

- Coercive Research
  - Aims are achieved through blatant or subtle threat of harm perceived as greater than compliance
  - Most of the historical abuses involving human experimentation involved coercive research
  - Subtle coercion is not absent from research today (Tangwa, 2009)

Exploitation of Human Vulnerability

- Deceptive Research
  - Subject is made to misunderstand a situation
  - “therapeutic misconception”
  - Different from scientifically justified “deception” research in the social sciences

Exploitation of Human Vulnerability

- Inducive Research
  - Undue inducements are intended to encourage a person from doing something they would no otherwise do.
  - Exploits the economically disadvantaged
  - Common practice in research conducted in developing countries

Regulatory

- 45 CFR 46 and its subparts
- 21 CFR 50, 56, and its subparts

45 CFR 46 Subpart B

- Research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates
  - 10 specific criteria must be met
    - Preclinical data identifying risk
    - No inducements to terminate pregnancy
    - Researcher has no role in determining viability
    - Etc.

Fetal Tissue
NIH Revitalization Act of 1993

- The attending physician must disclose in writing:
  - Any interest in the research to be conducted with the tissue, and
  - Any known medical risks to the donor or risks to her privacy associated with the research.

45 CFR 46.303 (Subpart C)

- What is a “prisoner”?
  - any individual involuntarily confined or detained in a penal institution
  - parolee
  - wards of the court

45 CFR 46 Subpart C

- Research Involving Prisoners
  - At least one member of the IRB will be a prisoner or a prisoner representative with “appropriate” background
  - The proposed research must be directly related to prison environment…or research improving the health or well-being of the subject.
  - Free of coercion
  - No special treatment; e.g. a parole board cannot consider study participation when determining parole

Prisoner Research - Controversy

- 45 CFR 46 Subpart C requires that prisoner research must meet specific criteria.
- IOM (2006) argues that the category-based approach is too subjective and should be replaced by risk-benefit criteria.
- Others argue that the Common Rule ensures adequate protection*
  - Adherence to Common Rule should protect prisoners against coercion, undue inducements, and exploitation.

* Chwang, E. Against risk-benefit review of prisoner research. Bioethics. 2010; 24: 14-22

45 CFR 46 Subpart D

- Research Involving Children or Adolescents
  - IRB must document:
    - the specific risk determination (sections 404-407) under which the approval is given.
    - the conditions of parental and child or adolescent assent.

Ethics – some issues

- Scientific justification for enrolling vulnerable subjects
  - Direct benefit (Helsinki)
  - Benefits to society (Belmont)
- Determining capacity
- Equitable recruitment – who decides?

Harmonizing Ethics with Regulations: Respect

- Ethics:
  - Individuals should be treated as autonomous agents
  - Persons with diminished autonomy and thus in need of protection are entitled to such protections
- Practice
  - By informed consent procedures that ensure subjects understand:
  - Clear description of the purpose of the research
  - The risks and benefits that participation is voluntary

Harmonizing Ethics with Regulations: Justice

- Ethics:
  - Equal distribution of benefits and burdens (risks) of research
- Practice:
  - By IRB review of study design and recruitment
  - Justification of enrolling from vulnerable populations

Ethical Issues – Research involving children

- Background
  - Society wants to spare children from potential risks involved in research
  - Most medicines given to children have not been subjected to randomized efficacy trials
  - 70% of children with cancer are enrolled in NCI clinical trials

Ethical Issues – Research involving children

- Ethical Challenges
  - Emancipated minors
    - Effectively an adult in the eyes of the law
  - Disclosure of confidential information to parents (pregnancy, drug use)
  - Enrolling minors who are wards of the court

Ethical Issues – Research involving children

- Waiving informed consent
  - IRBs can waive parental permission
    - For minimal risk research
    - When getting permission could jeopardize the safety of the child
    - Emergency, life-threatening situations
  - IRBs can waive child assent – only if research holds promise of direct benefit to the child
    - Limited capability
    - Special circumstances

Ethical Issues – Research Individuals with Mental Illness

- Background
  - Of the 10 leading causes of disability worldwide, 5 are psychiatric conditions (ICMR)
  - Current management of mental illness (dementia, depression, psychosis) is extremely costly to society.
  - As society ages, the need for more research on causes and treatment of age-related cognitive illness will also increase.

Ethical Issues – Research Individuals with Mental Illness

- Ethical Challenges
  - Evaluating capacity to make an informed decision to participate in research
  - Withdrawal or delay of ongoing treatment
  - Placebo trials
  - Outpatient trials
  - Surrogate consent
  - Decline in mental status while in a trial
  - Research in the emergency setting

Decisional capacity

- Decisional capacity in the research context has been interpreted by the APA as requiring the ability to:
  - evidence a choice;
  - understand relevant information;
  - appreciate the situation and its likely consequences; and
  - manipulate information rationally.

When enrolling subjects with diminished cognitive capacity…

- IRBs need to develop policies and procedures for:
  - Surrogate consent
  - Consent for placebo-controlled trials involving psychiatric patients
  - Ongoing consent (re-consent)
  - Documenting subject's capacity to provide informed consent : a post-consent quiz.

Surrogates Decision-Making

- Surrogates
  - Are persons who make decisions for an incompetent patient
  - Are committed to the welfare of the patient
  - Possess an ability to make a reasoned judgment

Surrogates Decision-Making

- Ethical Challenges - 1
  - How is this person identified?
    - hierarchy, convenience
  - Who decides when there are opposing decisions by different surrogates?
  - How is the ability/capacity of the surrogate evaluated?

Surrogates Decision-Making

- Ethical Challenges - 2
  - Should policy makers (IRBs?) define limits on the kinds of research risks that the surrogate can accept on behalf of the patient?
    - Study has direct benefit to patient
    - Minimal risk
    - High likelihood that society would benefit

Cultural Differences – Informed Consent *

- Where community is more important than the individual, how do people made decisions related to participation in research?
- An interview study was conducted on Haryana, India
  - Interviewed the youngest married male member of family; if not available, then youngest married female
- Questions pertained to participation in a variety of studies; surveys, blood draw, vaccine trial; drug trial.

* De Costa et l., J Med Ethics, 2004;30: 318-323

Cultural Differences – Informed Consent *

- Men (n=50)
  - 90% reported themselves to be decision makers regarding their own participation
  - 10% reported elder members of extended family as deciding for them
- Women (n=7)
  - 3 said they decide form themselves
  - 2 said their husbands decide
  - 2 said their mother-in-law decides

* DeCosta et l., J Med Ethics, 204;30: 318-323

How can we guarantee that vulnerable subjects are protected?

- Don't include them in research
  - NIH guidelines requires inclusion
- Include them only in minimal risk research
  - Violates the spirit of Helsinki
- Include them only if scientifically justified
  - Violates ethical principle of justice

Balancing Regulations with Ethics

- Regulations want *both* to protect and include vulnerable subjects
  - Places pressure on IRBs to monitor enrollment; educate researchers
  - Places pressure on researchers to be inclusive
  - Policies need to encourage research without being overly protective

Innovative approaches for dealing with questionable decisional capacity

- Who
  - Early Alzheimer's or mild dementia
  - End-stage liver disease
  - Schizophrenia
  - Mild retardation

Obtaining informed consent from cognitively impaired subjects

- How
  - Move beyond printed consent forms to multimedia consent
  - Focus on the *process* of informed consent

IRB
ETHICS & HUMAN RESEARCH

MARCH-APRIL 2009 • VOLUME 31, NUMBER 2

Reformed Consent:
Adapting to New Media and Research Participant Preferences

BY JAMES HENRY, BARTON W. PALMER, LAWRENCE PALINKAS, DANIELLE KUKENE GLORIOSO, MICHAEL P. CALIGIURI, AND DILIP V. JESTE

The principle of respect for persons clearly demands that investigators communicate with potential research participants in a way that fosters comprehension of the information relevant to deciding whether to enroll in a particular study.[1] Federal regulations governing research with humans require documentation of [illegible] comprehension of key information.[5]

Because of their statutorily mandated status, signed printed consent forms are likely to remain a component of the consent process for the foreseeable future. However, the use of printed forms does not preclude the use of additional materials during the consent