

# Ethical Issues in Research with “Vulnerable” and “Hard-to-Reach” Populations

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# “Bioethical Trump Card”?

- “The concept of vulnerability appears to have been grandfathered into the lexicon, lore, and literature of research ethics without undergoing stringent certification. And yet the need for some such notion has long been appreciated.”

-Ken Kipnis, 2001

“Vulnerability in Research Subjects: A Bioethical Taxonomy”

# Definitions/Interpretations

- Vulnerable means “subject to exploitation”
- Unequal power relationships between potential subjects and investigators/sponsors create the potential for exploitation
- Exploitation is wrong, and therefore we want to prevent/avoid it in research

# Or... are we all at risk?

- We are all vulnerable although some may be more “predisposed” to additional harm than others
- Vulnerability is inevitable because people are interdependent
- One can be vulnerable w/o being harmed or wronged (and vice versa)

## 2 Ways of Looking at Vulnerability

- A characteristic inherent to an individual or group
- A characteristic inherent in a situation

# KEY RESEARCH ETHICS GUIDANCE DOCUMENTS

# Belmont Report

- A reaction to historical abuses perpetrated against certain groups in certain settings
- Principle of JUSTICE, fair selection of subjects
- Presumption: Certain categories of people are presumed more likely to be mistreated, misled, or otherwise taken advantage of
- Vulnerability generates a duty for “special protections” (for researchers, regulators, IRBs)

# Belmont Report

- Vulnerability results from
  - “dependent status and frequently compromised capacity for free consent”

combined with

- “ready availability in settings where research is conducted”



## CIOMS (2002)

- Vulnerable persons defined as “those who are relatively (or absolutely) incapable of protecting their own interests because they may have insufficient power, intelligence, education, resources, strength or other needed attributes to protect their own interests”

Kipnis

**“A MOTLEY COLLECTION OF  
VULNERABLE SUBPOPULATIONS”**

# Belmont Report (1979)

- racial minorities
- economically disadvantaged
- very sick
- institutionalized

# 45 CFR 46

“vulnerable category of subjects”

“special problems of research involving vulnerable populations”

“vulnerable to coercion or undue influence”

## ADD'L PROTECTIONS CODIFIED

- Pregnant women (Subpart B)
- Prisoners (Subpart C)
- Children (Subpart D)

## ADDITIONAL SAFEGUARDS?

- handicapped persons
- mentally disabled persons
- economically disadvantaged persons
- educationally disadvantaged persons

# OHRP Guidance (Website)

- “Vulnerable populations” has its own heading
  - Children
  - People with HIV/AIDS
  - Prisoners
  - Privacy protections/ Certificates of Confidentiality
  - A video that I could not bring myself to watch

# OHRP IRB Guidebook (2001)

- Cognitively impaired
- Traumatized
- Comatose
- Terminally ill
- Elderly/aged
- Minorities
- Students
- Employees
- “normal” volunteers
- Participants in international research (anyone not American?)

# CIOMS (2002)

- Residents of nursing homes
- People receiving welfare benefits & social assistance
- Unemployed
- Other poor people
- People in emergency rooms
- Homeless
- Nomads, refugees, displaced persons
- Prisoners
- Patients with incurable disease
- Individuals who are politically powerless
- Members of communities unfamiliar with modern medical concepts

# Does the concept help us protect participants?

- “So many groups are now considered to be vulnerable in the context of research, particularly international research, that the concept has lost force.” (Levine, et al)
- Obsession with adding groups to the list
- Little talk of appropriate protections
- Stereotyping versus actually protecting? (doesn't distinguish between individuals in a group)



**RECOMMENDED SAFEGUARDS,  
“EXTRA” & “SPECIAL” PROTECTIONS**

# Declaration of Helsinki (2013)

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

- All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

## 45 CFR 46.111(a)(3) - approval

- Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

## 45 CFR 46.111(7)(b)-approval

- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

# Types of Safeguards

- IRB membership/representation in ethics review
- Specific regulations
- Restrictions/limitations on participation prisoners (prisoners)
- “Add-ons” to or replacements for individual informed consent (children)
- Processes for community input (EFIC)

## 45 CFR 46.107a – IRB membership

- If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

# Specific Subparts

- 45 CFR 46
  - Subpart A) prisoners
  - Subpart B) children
  - Subpart C) pregnant women
- 21 CFR 50.24 (FDA)
  - Exception from informed consent requirements for emergency research

# Prisoners 46.304 (representation)

- (a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
- (b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.



# Restrictions on Participation: Prisoners

- Studies of causes/effects/processes of incarceration or of prisons as institutions that are ≤ minimal risk
- Research on conditions that particularly affect prisoners as a class
- Research with strong possibility of direct benefit

# Children (Subpart D) 46.408

- Parental consent
  - 1 or both parents – depends on risk, benefit, and reasonableness
  - Waivers of parental consent allowable provided “an appropriate mechanism for protected the children who will participate” is in place....
- Child assent
  - Rule of 7s
  - When to require assent/take dissent seriously
  - Always inform

# EFIC

- A different way of looking at vulnerability?
- Consultation
- Public disclosure
- Independent data monitoring
- LAR or contact within “therapeutic window” with a family member
- Inform subject as soon as possible

**“RECONNOITERING THE TERRAIN  
OF VULNERABILITY”**

# Kipnis (2001)

- Analyzed categories of vulnerability, not subpopulations
- Defined vulnerability as limit on ability to provide informed consent
- What characteristics are common among disparate groups?
- What should researchers do?

# Cognitive Vulnerability

- Does the individual have the capacity to deliberate about and decide whether or not to participate in the study?
  - Immaturity, dementia, mental illness, mental retardation
  - Education, language
  - Individuals in situations where there's not enough time
- Plain language forms, advance directives, supplementary education, surrogates/advocates

# Juridic Vulnerability

- Is the person liable to the authority of others who may have an independent interest in that participation?
- Formal authority relationships
  - Prison
  - Military
  - Children/parents
  - Students
  - Institutionalized
  - Women subjected to husbands' authority
- How to devise a consent procedure that adequately protects the individual from the hierarchical system

# Deferential Vulnerability

- Is the individual given to patterns of deferential behavior that may mask an underlying unwillingness to participate?
- Informal relationships (as opposed to juridic)
- IC process should eliminate pressure



# Medical Vulnerability

- Has the individual been selected, in part, because she has a serious health-related condition for which there are no satisfactory remedies?

# Allocational Vulnerability

- Is the person seriously lacking in important social goods that will be provided as a consequence of his or her participation in research?

# Infrastructural Vulnerability

- Does the political, organizational, economic, and social context of the research setting possess the integrity and resources to manage the study?

# Social Vulnerability

- Does the individual belong to a socially undervalued group?

# Kipnis' Conclusions

- Some individuals/populations will exhibit multiple vulnerabilities
- More attention to medical vulnerability
- Need to consider “fair entitlements of research subjects who are disadvantaged in economic and others ways”
- Need for more resources to help guide decision-making re: appropriate protections

# Criticisms of Kipnis (Levine et al)

- Leads to problematic inferences
  - Everyone who fits into any of these categories is vulnerable
  - Anyone who is capable of free consent is NOT
- More focus needed on
  - Features of the research
  - Institutional environment
  - Social/economic context
  - Timing of research
    - Women in labor, right after a natural disaster
  - Emotional factors
    - Disease that killed a loved one
  - Prior personal experience

# Are we all vulnerable?

- Benefits of research can never be guaranteed in advance
- Much clinical research is combined with care (i.e. participants are sick)
- If it applies to everyone, “every research protocol requires some type of special attention and IRBs have no guidance on where to concentrate their limited attention and resources” (Levine et al)

# “Special Scrutiny” (Levine et al)

- Translates new scientific advances to humans for the 1<sup>st</sup> time (especially when intervention is novel and/or irreversible)
- Known/credible risk of significant harm AND NO potential of direct medical benefit
- Raises ethical questions about research design or implementation for which there is no consensus



# Challenges to Traditional Conceptions of Vulnerability

- NIH policy on inclusion of women and minorities (1994, updated 2001)
- NIH policy on inclusion of children (1998)
- Increased funding for health disparities research, research on minority health

# Question for Discussion

- If the research is minimal risk, should extra/special protections, safeguards be required? Why or why not? Does your answer differ depending on the population?
- *“Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”*

DISCUSSION/BRAINSTORM

**WHAT ARE APPROPRIATE  
PROTECTIONS?**

- You've been funded to conduct a survey with LGBT teens on drug and alcohol use. You assumed you'd request a waiver of parental consent, but you've heard from others that your IRB doesn't like to waive parental consent.

- You're planning research at a health clinic that involves a survey, an intervention, a post-test, and an in-depth interview. You're told that the clinic has a policy that research involving their patients can only pay \$10 per research interaction. You expect the interviews to last an hour and have paid \$30 for other similar research. When you ask for an exception, the administration tells you that the subjects are vulnerable and that more than \$10 is coercive.

- A tornado touches down in the middle of Logan Square. Perfect timing for your dissertation! You want to study the effects of social networks on coping with natural disasters. Time is of the essence, and you really want your protocol to be approved the first time around.

# Category 2 Exemption

Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

- For patients with Alzheimer's disease, it's highly likely that their LAR is going to be a child – possibly someone with an increased risk (real or perceived) of developing the disease themselves. Does anyone else think these individuals should be prohibited from giving consent for parental participation in research that is greater than minimal risk?