Research with Vulnerable Subjects

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Readings

- Ethics Issues for Canadian HIV/AIDS Researchers in International Settings, especially pages 5-15: https://www.cahr-acrv.ca/wp-content/uploads/2012/10/cahrreportfinal.pdf
- Abdoler, Wendler. Journal of Empirical Research on Human Research Ethics 2012; 2:37–50.

Clinical Research

- Clinical research is critical to improving health and well-being.
- To ensure clinical research is ethical, it is necessary to protect subjects.
- This is especially challenging with respect to vulnerable subjects.

Focus

- IRBs should be aware of "the special problems of research involving vulnerable populations" and should consider whether additional requirements are needed to protect them.

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- Some regulations also mandate specific protections for vulnerable subjects.

US Regulations

- US regulations mandate additional protections for 3 groups: pregnant women/fetuses; prisoners; children.
- These regulations include risk limits, additions to IRB review, and modifications to the consent process.

Three Questions

- What is vulnerability?
- Who is vulnerable?
- What additional protections are needed for vulnerable subjects?

Vulnerability

Vulnerability

- Very generally, vulnerable individuals are ones who can be harmed or hurt.
- Merriam Webster: vulnerable individuals are those who are: capable of being wounded or harmed; open to damage

Everyone?

- All human beings can be wounded or harmed: they can experience disease, illness, loneliness, rejection, pain...
- This suggests all humans, hence, all human research subjects, are vulnerable.

Concern

- If all humans are vulnerable, how can we implement *additional* protections for vulnerable subjects.
- "If everyone is vulnerable, then the concept becomes too nebulous to be meaningful."

Levine et al. AJOB 2004;4:44-49

Pragmatic Account

- Need to distinguish between categorical and comparative claims.
- Categorical claims refer to the vulnerability of all individuals in a group.
- Comparative claims refer to the extra vulnerability of some individuals.

Categorical Claims

- The claim that all humans are vulnerable is a categorical claim.
- It highlights the need for regulations to protect all human research subjects (e.g. IRB/REC review).

Comparative Claims

- Claims that some individuals, such as children and employees, are vulnerable are comparative claims.
- These claims mean that children and employees are more vulnerable than average adult subjects.

Additional Protections

- The fact that some individuals are more vulnerable suggests that the safeguards for subjects in general (e.g. IRB review) may not be sufficient for them.
- They may need added protections.

Context Dependence

- Comparative claims of vulnerability tend to be context dependent.
- Some individuals may be more vulnerable in some settings, but not in others.

Employee Example

- Maki has worked in a lab at the NIH for 15 years.
- One day she sees an advertisement for a study and is interested in enrolling.
- Is Maki vulnerable? Does she need additional protections?

Two Possibilities

- If the primary researcher is her boss, she may be vulnerable to pressure or coercion.
- In other cases, her knowledge and experience may make her more informed and empowered. Hence, she may be *less* vulnerable than other subjects.

Needed Protections

- The fact that some group is more vulnerable does not reveal what added protections are needed.
- It depends on how they are more vulnerable.

Examples

- Employee: independent consent assessment
- Children: parental permission
- Different language: translation

Lesson

To assess comparative vulnerability claims:

- Are existing safeguards sufficient for the group given the nature of the study in question?
- If not, what are the increased concerns? How significant are they?
- If the concerns are significant, what added requirements might address them?

Lymph Node Biopsy Study

- HIV+ patients taking HAART were found to have undetectable virus.
- Was the virus eliminated from the body or was it hiding?
- Removal and examination of superficial lymph nodes from 10 patients who had undetectable virus after HAART.

Vulnerability

- The IRB expressed concern that HIV+ patients at vulnerable.
- They have a serious illness.
- They also are at greater risk of infection.

Not a Significant Concern?

- However, because of the use of sterile techniques, the chances of infection were extremely low.
- In addition, subjects would be very closely monitored and treated at the first sign of infection.

Less Vulnerable?

- The subjects were well educated, upper middle class white men.
- They were very informed about HIV.
- They considered themselves part of the HIV community and experienced greater benefits from contributing to the research.

Reminder

- Comparative claims of vulnerability are context dependent.
- A group may be more vulnerable in one setting, but less vulnerable in another.

Response

- Don't focus on the condition or label (e.g. HIV infected): consider whether there is a potential for greater harm given the specific study.
- To assess the extent of any concern: need expertise on condition, study, context, and existing regulations.

Subjects Who are Unable to Consent

Consent Capacity

- Informed consent is one of the most important research protections.
- Hence, concerns about vulnerability often focus on individuals who cannot give informed consent.

Adults

- Children often are not able to consent.
- What about adults who are unable to consent (in non-emergency settings)?

Ms. P

- Ms. P is a 70 year-old retired government worker.
- She is brought to the NIH by her husband for evaluation of her memory.

In-patient study

- The team is interested in enrolling Ms. P in a 3 week in-patient research study.
- The study involves head MRI, lumbar puncture, blood studies, psychological and behavioral testing.
- The test pose some risks and offer no potential for subject benefit.

Ms. P's response

- The study is explained to Ms. P.
- She says she wants to enroll: "because you have such nice pictures on the wall."
- Ms P's decision is voluntary. However, that is not sufficient protection in her case because she does not understand.

Understanding

- A number of instruments have been developed to evaluate whether potential subjects understand enough to give valid consent.

Wendler. Archives Intern Med 2004;164:2201-2204.

- Formal instruments, post-consent quizzes

SAMPLE EVALUATION

1. What will you be asked to do if you enroll?
2. What are the risks to you?
3. What would happen if you decided you did not want to be in the study?
4. What are the chances you will benefit personally?
5. What things could you do besides being in the study?
6. Why are you interested in enrolling in this study rather than [what you could do otherwise]?

Protect by Prohibiting

- Some guidelines prohibit research with individuals who cannot consent.
- The first principle of the Nuremberg Code states: subjects' informed consent is "absolutely essential" to ethical research.
- This approach offers strong protection.

Problems with Prohibition

- However, prohibition also blocks important research needed to improve clinical care for vulnerable subjects.
- Is it possible to institute safeguards to allow important research while still protecting adults who cannot consent?

#1 'Necessity' Requirement

- In general, individuals unable to consent should be enrolled only when the research cannot be conducted equally well with those who can give consent.
- NIH policy requires a compelling reason, approved by the IRB, for enrolling adults who cannot consent.

#2 Surrogate Decision Maker

- Individuals who are unable to consent should have a surrogate decision maker.
- Surrogates should be guided by decision-making standards for those who cannot consent: substituted judgement and best interests.

Decisional Standards

- Is there sufficient reason to think that the subject wants to be in the study: would the subject choose to enroll if they could decide for themselves?
- More convincing evidence is needed as the risk-benefit profile of the study becomes less favorable to the subjects.

#3 Assent/Dissent

- Adults who are unable to consent should be asked to assent (i.e. positive agreement).
- Subjects' dissent should be respected.

Black. Am J Geriatr Psychiatry 2010; 18:77-85

#4 Risk/Benefit

- Most agree that individuals who cannot consent may be enrolled in research that poses low risks, and research that offers subjects a compensating potential for clinical benefit.
- Riskier, non-beneficial research is either not permitted or requires special review.

Summary

- Research with vulnerable subjects raises important ethical concerns.
- Distinguish categorical and comparative claims.
- For comparative claims: assess the specific concern given the context and potential ways to address it.