

Research with Vulnerable Subjects

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Clinical Research

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

Regulations

- Regulations mandate additional protections for vulnerable subjects.
- US regulations: IRBs should be aware of “the special problems of research involving vulnerable populations” (46.111 a. 3/56.111 a. 3) and should consider whether additional requirements are needed to protect them.

Three Questions

- Which subjects are vulnerable?
- What concerns does the enrollment of vulnerable subjects raise?
- What additional protections are needed to address these concerns?

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; open to damage; assailable

Everyone?

- All human subjects are vulnerable to being harmed: to disease and illness, loneliness, rejection, pain, dying.
- Hence, this definition seems to suggest that all humans and, hence, all human research subjects are vulnerable.

CIOMS

medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, members of armed forces, police, the elderly, patients with incurable, serious, potentially disabling or life-threatening diseases, nursing home residents, people receiving welfare benefits, people receiving social assistance, poor people, the unemployed, patients in emergency rooms, some ethnic and racial minority groups, homeless, nomads, refugees, displaced persons, prisoners, politically powerless, those unfamiliar with modern medical concepts

Concern

- If all humans are vulnerable, it is not clear that it makes sense to 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

Two Types of Claims

Categorical: All the individuals in a group are vulnerable: All cars are at risk of being stolen

Comparative: Specific individuals within a group are especially vulnerable: Hondas are at increased risk of being stolen

Categorical Claims

- The claim that all human subjects are vulnerable is a categorical claim.
- It points to the need for research regulations to protect human subjects in general.

Categorical Example

“The new framework should accept broad subject vulnerability and then move forward with human research despite the uncertainty of risk assessment and informed consent, analogous to the way that the precautionary principle moves forward environmental action in the absence of scientific certainty.”

Grinnell AJOB 2004: 4: 72-74

Comparative Claims

- Claims that specific groups, such as children and prisoners, are vulnerable are comparative claims.
- They point to the need for additional safeguards beyond those that apply to all human subjects.

Kipnis

- “While I shall assume in what follows both that the existing guidelines are sufficient to deal ethically with the paradigmatic research subject, and, further, that all those standard protections are reliably in place, the vulnerable research subject nonetheless requires ethical consideration going beyond that baseline.”

Special Protections

- DOH: “Some research populations are particularly vulnerable and need special protection.
- CIOMS “Accordingly, special provision must be made for the protection of the rights and welfare of vulnerable persons”

Comparative Examples

- For example, US regulations for research with prisoners and children are additional to the regulations applied all human subjects research.
- These include stricter limits on the risks to which these subjects can be exposed

Context Dependence

- Comparative claims of vulnerability tend to be context dependent.
- Hondas are less vulnerable to theft in mining towns than trucks and SUVs.

Research Example

- Maki has worked in a lab at the NIH for 15 years.
- One day she sees an ad for a study and considers whether to enroll.

Is Maki a vulnerable subject?

Safeguards

- What protections are appropriate for vulnerable subjects depends on why the standard regulations are not sufficient for them.
- If the PI is her boss, the protections needed for Maki are different than the protections needed for infants.

Vulnerabilities and Safeguards

- Employee: independent assessment
- Children: parental permission
- Don't speak English: translator

Informed Consent

- Informed consent is one of the most common protections for research subjects.
- Hence, individuals who are unable to consent represent one of the most important examples of vulnerable research subjects (exception: when consent is not a requirement).

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, LP, blood studies, psych and behavioral testing.

Baseline Evaluation

- Ms. P is not oriented to time or place.
- Her MMSE is 11.

Study Explanation

- Ms. P is informed that she is being invited to participate in research.
- It is explained that many of the procedures are done to obtain information to help others, and will not benefit her.

Ms. P's response

- Ms. P is asked whether she is willing to be in the study: “Of course, since 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.

US Regulations

- US regulations have additional protections for pregnant women/fetuses/neonates; prisoners (may become a prisoner after enrolled!); and children.
- No additional regulations for research with adults who cannot consent (in non-emergency settings) beyond obtaining consent from a surrogate.

Task Specificity of Consent

- Valid consent requires individuals to consent to a particular study.
- Hence, standardized tests (e.g. I.Q.), and certain diagnoses (e.g. Alzheimer disease) do not determine whether an individual can provide valid consent.

Diminished Ability to Consent

- Individuals may be unable to consent because they cannot understand.
- Individuals also may be unable to consent because they cannot make a voluntary decision whether to enroll.

Timing

- Some individuals may be unable to provide valid consent for initial enrollment.
- Others may lose the ability to consent after they have been enrolled (e.g. high dose steroids).

Assessment

- Investigators should consider whether potential subjects understand and are giving voluntary initial consent.
- Formal evaluation should be pursued when concern is raised about specific individuals' ability to consent.

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

Voluntariness

- A voluntary decision requires that the participant has not been inappropriately influenced by others.
- Less work has focused on instruments for evaluating voluntariness of consent to research.

Assessing Voluntariness

- Why do you want to be in the study?
- What do you think would happen if you decided not to be in the study?
- Is anyone pressuring you to be in the study?
- What does your family/doctor think about your enrolling in the study?

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?

The Ethical Concern

- The primary ethical concern is that investigators might exploit individuals' incompetence to enroll them in research that conflicts with their preferences or values.
- The primary challenge then is to implement safeguards to protect individuals from “unwanted” enrollment.

Data

- What do the empirical data show about individuals' willingness to be enrolled in research if they become incapacitated?

Individuals at Risk for AD

- 98.8% willing to participate in a non-beneficial computer task study.
- 97.5% willing to participate in a non-beneficial study involving 2 X-rays.
- 79.8% willing to participate in a non-beneficial study involving an experimental medication.

Clinical Center Data (N= 2371)

- 13% *not* willing to participate in research should they become unable to consent.
- 49% willing to participate in research that would not help them, and is minimal risk.
- 9% willing to participate in research that would not help them, and is greater than minimal risk.

Survey Older Americans (N=1,515)

Subsample of 2006 US Health and Retirement Study (Ages 51 and older).

- 67.5% to 82.5% (depending on scenario) said society should allow family consent and 57.4% to 79.7% (depending on scenario) would be willing to participate.

Findings

- Many individuals endorse and are willing to be enrolled in research if incompetent; others do not want to be enrolled in the event of incapacity.
- Individuals' willingness decreases as the risks increase and the potential benefits decrease.

Which Safeguards?

- Enrollment decisions should be based on evidence regarding *this* individual's preferences and values.
- What safeguards can help to realize this protection?

NIH Regulations

- NIH has a policy (87-4) governing intramural research with adults who cannot consent.
- The policy attempts to implement the following safeguards.

#1 'Necessity' Requirement

- In general, individuals unable to consent should not be enrolled when the research can be conducted equally well with those who are able to give valid 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.

Standards for Decision Making

- Substituted Judgment: choose the option the individual would have chosen in the situation (option consistent with individual's preferences and values).
- Best Interests: If the participant's preferences are unknown, choose the option that best promotes her interests.

Substituted Judgment

- Clinical Center policy requires that the surrogate “has sufficient reason to believe participation in the study is consistent with the individual’s preferences and values.”

Implications of Task Specificity

- Patients not able to make *enrollment* decisions may be able to appoint a surrogate.
- 37.7% deemed incapable of consenting to a drug RCT were found capable of appointing a research surrogate.

Kim. Arch Gen Psychiatry 2011; 68:214-220

#3 Assent/Dissent

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

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

Challenge: Dissent

- Sometimes it is difficult to determine what constitutes dissent: pulling arm away; “I want to go home”
- At sign of dissent: stop, evaluate, address.

#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.

Importance

- To implement this safeguard, IRBs (and others) must evaluate the risks and benefits of individual studies.
- Challenge: develop a systematic framework to make these evaluations.

Quiz #1: Prospect Benefit

- Should those who cannot consent be excluded from potentially beneficial research that could be completed with adults who can consent?
- Should an adult who cannot consent be enrolled in a phase II study of a new treatment for type I diabetes?

Quiz #2: Risks v Consent

- Consider a study that can be done in incapacitated adults with very low risks, or in competent adults with much higher risk.

Who should be enrolled?

Quiz #3: Who?

- Must individuals who serve as research surrogates be assigned by the individual?
- Are individuals assigned as surrogates for clinical care appropriate for research?
- Next of kin surrogates?

Summary

- Research with vulnerable subjects raises important ethical concerns.
- Implementation of appropriate safeguards can protect vulnerable subjects while allowing valuable research that is needed to address the conditions that affect them.
- Some important challenges remain.