Research with Vulnerable Participants

The views expressed in this talk are my own. They do not represent the position or policy of the NIH, DHHS, or U.S. government.
‘Non-beneficial’ Interventions

Clinical research studies typically include interventions that expose participants to risks to collect information that might benefit future patients.

For example, participants undergo extra blood draws and biopsies to collect samples for basic lab studies.
Ethical Challenge

- As a result, all research participants need protection.

- National and international guidelines and regulations specify protections for research participants.
• Vulnerable Participants
• Most regulations also have additional requirements for vulnerable participants.

• For example, US regulations require additional protections for those participants who are “vulnerable to coercion or undue influence.”
Average Participants

Everyone is vulnerable to coercion and undue influence (e.g. being forcibly enrolled in research).

What is the point of citing the vulnerability of a subset of participants who need additional protection?
- Regulations as Policies

- Research regulations, like policies in general, cannot cover every possibility.

- Regulations are based on what is needed to protect the average participant (e.g. enrollment must be voluntary).

- Highlighting the vulnerable cites those who need extra protection beyond what is afforded by standard requirements.
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”
Who is Vulnerable?
Vulnerable participants, then, are individuals for whom standard regulations may not offer sufficient protection.

Given the importance of informed consent, vulnerable participants frequently are individuals who are unable to consent (e.g. unable to understand the study in question).
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.
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- **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 participants 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 participants understand enough to give valid consent.


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: participants’ 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.

Is it possible to institute safeguards to avoid these concerns 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.

Wendler D. Am J Psych 2002; 159:585-591
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 risk/benefit profile of the research becomes less favorable for participants.
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.
Challenge: 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?
Challenge: 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?
#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
Challenge: 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?
- #3 Assent/Dissent
- Adults who are unable to consent should be asked to give their assent or positive agreement.

- Participants’ sustained 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 participants 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.
Another Quiz

Is it preferable to enroll an individual who cannot consent in ‘non-beneficial’ research on a condition that affects them?

Is it inappropriate to enroll an individual who cannot consent in ‘non-beneficial’ research on a condition that does not affect them?
Summary

Research with vulnerable participants raises important ethical concerns.

Implementation of appropriate safeguards can protect vulnerable participants while allowing valuable research that is needed to address the conditions that affect them.

Some important challenges remain.