

# Vulnerable Subjects

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## I. Introduction

This outline will examine some issues involving vulnerable subjects in human subjects research.

Why do we worry about subjects in research? *Answer:* Past abuses of the rights of subjects. Lack of informed consent. Poor risk-benefit ratio. Coerced subjects. Unfair selection of subjects.

*Solution:* The Federal regulations governing research (45 Code of Federal Regulations (CFR) 46 and 21 CFR 50 (FDA regulations) which include at section 50.24 the emergency research rules) and the Belmont Report principals upon which the regulations are based.

*Issue:* Do the Belmont principals (respect for persons, beneficence, and distributive justice) and the regulations adequately define, cover and protect the universe of vulnerable subjects?

## II. History

A. *What makes a subject vulnerable?* The Current Regulatory rules (from 45 CFR 46):

1. 46.102 A “Human subject” is a living individual about whom an investigator obtains data through intervention or interaction with the individual or the individual’s identifiable private information.
2. 46.111 The Institutional Review Board (IRB) in approving research must assure that 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

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problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically disadvantaged persons.” 46.111 Informed consent will be sought from each prospective subject or the subject’s legally authorized representative.

3. Subpart B: Additional protections for research involving fetuses, pregnant women and in vitro fertilization. 46.201 et. seq. has been revised in 2001 with an effective date to be announced by HHS. (The new proposed regulations were discussed at the SAS seminar). See <http://www.access.gpo.gov/index.html> the Government Printing Office website.
  4. Subpart C: Additional protections for Prisoners. Since prisoners “may be” under constraints because of being in prison which could affect their ability to make “a truly voluntary and uncoerced decision whether or not to participate in research” special protections are required. Essentially the special protections include having a prisoner or prisoner representative on the IRB and limiting research to conditions particularly affecting prisoners as a class (for example hepatitis).
  5. Subpart D: Additional protections for children. This section has special rules restricting use of children in research to minimal risk research or to research greater than minimal risk but presenting the prospect of direct benefit. The regulations require parental consent and minor (if old/competent enough to comprehend) assent. Note that the FDA April 24, 2001 published an interim rule to amend its regulations by substantially adopting the existing 45 CFR 46 subpart D rules for research involving children. The interim rule is open for comment until July 23, 2001. See: [http://frwebgate.access.gpo.gov/cgi-bin/...bname=2001\\_register&docid=01-10008-filed](http://frwebgate.access.gpo.gov/cgi-bin/...bname=2001_register&docid=01-10008-filed). Meanwhile the OHRP National Human Research Advisory Committee (appointed in November of 2000) has a report finding the current regulations are sound and recommending some “clarifying memos”. See <http://ohrp.osophs.dhhs.gov/nhrpac/mtgs.htm> and look at the April meeting materials for the report.
- B. *Are there other “vulnerable subjects”?* In its Guidebook at chapter VI OHRP lists the following under “Special Classes of Subjects”:
1. Fetuses
  2. Human in vitro fertilization
  3. Women
  4. Children and minors
  5. Cognitively impaired persons
  6. Prisoners
  7. Traumatized and comatose patients
  8. Terminally ill patients
  9. Elderly and aged persons
  10. Minorities
  11. Students, employees and normal volunteers
  12. International research

So, it appears that young, generally healthy, competent patients are not special subjects, but almost everyone else is.

C. *Case Study:*

Ima Researcher, M.D. wants to conduct a study on 60-year-old patients with mildly elevated blood pressure. She proposes to do a randomized, double-blinded study to compare an FDA approved drug to a non-FDA-approved drug. All patients will be recruited from newspaper ads and she will not personally ask any of her patients to enroll. Payment is simply reimbursement for parking expenses. Are these vulnerable subjects?

What if the study is on 80 year olds?

What if the study is on patients with severe cardiac disease?

What if Ima does want to approach her patients directly?

What if she wants to include children or minorities or only women?

**III. Other Regulations**

- A. *Guideline on inclusion of children in research* (<http://grants.nih.gov/grants/guide/>) Sets forth the NIH policy (as of March 6, 1998) that children must be included in research. Why? Because many of the drugs used for children have never been tested in children. Note that NIH defines “children” as “individuals under the age of 21”.

The guideline says all research must comply with 45 CFR 46 but that researchers in their protocol must include a section entitled “Participation of Children” with a plan to include or an explanation for excluding children.

- B. *Guideline on the inclusion of women and minorities in research* (same URL). This guideline was effective March 18, 1994 and it requires researchers to include women of childbearing age and minorities in research. Again the rationale is that since research can lead to a change in the standard of care it must include all populations to see if the intervention or therapy being studied affects women or men or minorities differently. “Increased attention, therefore, must be given to gender, race, and ethnicity...”

- C. *Research involving individuals with impaired decision-making capacity* (<http://grants.nih.gov/grants/policy/questionablecapacity.htm>). Has a paper on the importance of research involving individuals with questionable capacity to consent. It asks that IRB review research involving vulnerable subjects and has as a member someone experienced with the proposed subject population. It requires an assessment of capacity to consent and suggests use of independent monitors and surrogate and waiting (reflection) periods before consent is final. The National Bioethics Advisory Commission (NBAC) has a comprehensive report entitled: Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity. It is found at <http://www.bioethics.gov>.

The NBAC report stresses care to avoid improper use of the mentally ill in research. Their report calls for independent monitors and an independent professional to assess competency prior to someone entering into research.

NBAC December 19, 2000 also issued a detailed report on Ethical and Policy Issues in Research Involving Human Participants (same Web site) calling for more specific protections for vulnerable subjects.

NBAC in May, 2001 released a report concerning international research stating recommendations for rules involving potentially vulnerable international subjects.

D. *Case study:*

Ima Researcher wants to study diabetes and its relation to schizophrenia. She wants to study homeless patients being treated by the County Mental Health Facility. She doesn't want to alarm the proposed subjects and she knows that many of them deny they have schizophrenia so she proposes a study entitled: "Eating habits in a homeless population". The study is a survey, blood draw and weight analysis on a monthly basis for 6 months. The subjects will be given a five-dollar Target coupon, which is not good for alcohol for each month they participate. They will not be told the study is about schizophrenia or diabetes. They will sign a consent allowing Ima to review their medical records.

Are they a vulnerable population? What protections are necessary? Can this research be approved by the IRB?

**IV. How can vulnerable subjects be protected?**

- A. Don't include them in research. *Problem:* The guidelines requiring inclusion.
- B. Include them only if the research is designed to study conditions particular to the subject population. *Problem:* Does this violate the justice principal?
- C. Monitor any study that contains vulnerable subjects. *Problem:* Who does the monitoring? How is the monitoring paid for?
- D. Be sure the IRB has members familiar with the issues of the target population. NBAC originally proposed 50% of IRB members be community or non-scientific members but the final report will instead propose that IRBs add more non-scientific and community members.
- E. IRB requires specific procedures to assess competency.
- F. Surrogates are used (with assent from subject where possible) and Advance Directives are used so people when competent can decide about research when they may not be competent.
- G. *Case:*

Mr. Ure OK, age 65, is diagnosed with early Alzheimer's. He is competent (understands the nature and consequences of his actions) and decides he wants to participate in research about his disease. He signs a durable power of attorney for health care that authorizes his son to act on his behalf and to consent to a specific set of research protocols described by his physician and "any other new research that seeks to discover more about or a cure for Alzheimer's".

Can he be enrolled in studies his son approves after he is no longer competent?

What if the study was never discussed with him and involves a brain biopsy?

H. Other ideas?

## V. Future Direction

- A. Currently the regulations want both to protect and to include vulnerable subjects. This will put more pressure on IRB's to be creative, to monitor enrollment and the consent process and to educate researchers on new ideas.
- B. NBAC in its reports is torn between protecting subjects and encouraging inclusion. It is likely that new rules will be proposed by NBAC this year.

## VI. Where to find out more.

- A. The ORI (<http://ori.dhhs.gov/>), OHRP (<http://ohrp.osoph.dhhs.gov/>); FDA (<http://www.fda.gov/>), and NBAC (<http://bioethics.gov/>) Web sites are good places to start.
- B. The Journal of Law, Medicine & Ethics Volume 28:4 Winter 2000 had a symposium on human subjects research.
- C. The newsletter IRB: A Review of Human Subjects Research has a number of articles on vulnerable subjects.
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- E. Mammel, K. and Kaplan, D., Research Consent by Adolescent Minors and Institutional Review Boards, Journal of Adolescent Health 1995; 17:323-330.
- F. Levine, R., Adolescents as Research Subjects without Permission of Their Parents or Guardians: Ethical Considerations, Journal of Adolescent Health 1995; 17:287-297.
- G. The Hastings Center Report symposium: A World of Research Subjects; volume 28 No. 6 (Nov-Dec. 1998).
- H. Journal of Law, Medicine & Ethics symposium on research with decisionally impaired subjects, Volume 25:2&3 Summer& Fall 1997.
- I. Journal of Law, Medicine & Ethics, Women and Clinical Trials, Volume 27:2 Summer 1999.
- J. Buring, J. , Women in Clinical Trials-A Portfolio for Success, NEJM 343:7, 505-6, August 17, 2000.
- K. Baird, K., The New NIH and FDA Medical Research Policies: Targeting Gender, Promoting Justice 24 J. Health Pol. Pol'y & Law 531 (June 1999).

## VII. Final Thought

April 25, 2001 the National Academy of Sciences issued an Institute of Medicine report urging researchers to study “sex differences from womb to tomb” because “Sex – that is, being male or female – is an important basic human variable.” It’s comforting to know that science and scientists understand that sex is important.