

The Limitations of "Vulnerability" as a Protection for Human Research Participants

Carol Levine, United Hospital Fund
 Ruth Faden, The Johns Hopkins University
 Christine Grady, National Institutes of Health
 Dale Hammerschmidt, University of Minnesota
 Lisa Eckenwiler, Old Dominion University
 Jeremy Sugarman, The Johns Hopkins University
 for The Consortium to Examine Clinical Research Ethics

Vulnerability is one of the least examined concepts in research ethics. Vulnerability was linked in the Belmont Report to questions of justice in the selection of subjects. Regulations and policy documents regarding the ethical conduct of research have focused on vulnerability in terms of limitations of the capacity to provide informed consent. Other interpretations of vulnerability have emphasized unequal power relationships between politically and economically disadvantaged groups and investigators or sponsors. So many groups are now considered to be vulnerable in the context of research, particularly international research, that the concept has lost force. In addition, classifying groups as vulnerable not only stereotypes them, but also may not reliably protect many individuals from harm. Certain individuals require ongoing protections of the kind already established in law and regulation, but attention must also be focused on characteristics of the research protocol and environment that present ethical challenges.

A fundamental assumption underlies modern clinical research ethics: certain categories of people are presumed to be more likely than others to be misled, mistreated, or otherwise taken advantage of as participants in research. These populations are deemed "vulnerable," a status that generates a duty for researchers, review committees, and regulators to provide special protections for them. While other basic tenets of research ethics—informed consent, for example—have been the topic of extensive discussion and debate, until recently the concept of vulnerability has been relatively unexamined. The most prevalent questions raised about vulnerability have been whether to add a particular group to the vulnerable category, with the answer usually being "yes" (Stone 2003; Hawana 2003), and to a lesser degree, what form the special protections should take.

After examining the concept of vulnerability in the context of current clinical research, we find it wanting. We recognize that certain individuals, who lack decisional capacity or who are in a dependent status, or both, require ongoing protections of

the kind already established in law and regulation. The concept of vulnerability, however, fails to address less settled situations arising from the context in which contemporary research is conducted.

The research enterprise has changed dramatically since the 1970s when the current approach to understanding the ethical issues was largely formulated. Unlike the research that set the context for the existing ethical framework, research today has many complicating features, including increasing privatization and globalization of research; a growing number of complex, multisite trials and office-based trials, with treating physicians as researchers; rapid development in the pipelines for novel agents, many based on genomic and proteomic discoveries; and, most recently, an elevated concern with public health threats such as bioterrorism and new or resurgent infectious diseases.

What Is Vulnerability?

Although concern about research in orphanages, mental institutions, and hospitals dates to at least

Keywords

vulnerability
 research ethics
 decisional capacity
 research involving children
 research involving prisoners
 international research

Open Peer Commentaries

Gail E. Henderson, Arlene M. Davis, and Nancy M.P. King, p. 50
 Jonathan D. Moreno, p. 52
 Mary Faith Marshall, p. 54
 Anita Silvers, p. 56
 Amy T. Campbell, p. 58
 Nancy S. Jecker, p. 60
 Alan B. Jorkowitz, p. 62
 David B. Resnik, p. 63
 Ari M. VanderWalde, p. 65
 Luis Justo, p. 67
 Stuart G. Finder, p. 68
 Kenneth Kipnis, p. 70
 Frederick Grinnell, p. 72
 Dorothy E. Vawter, Karen G. Gervais, and Thomas B. Freeman, p. 74
 Debra A. DeBruin, p. 76
 Chalmers C. Clark, p. 78
 Sandra Anderson Garcia, p. 81
 Joseph P. DeMarco, p. 82
 Tricha Shivas, p. 84

Author's Response

Carol Levine, Ruth Faden, Christine Grady, Dale Hammerschmidt, Lisa Eckenwiler, and Jeremy Sugarman, p. W32

the beginning of the twentieth century in the United States (Lederer 1995), the prominence of the concept of vulnerability and its staying power in research ethics undoubtedly derives from the specific political context in which Congress created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission) in 1974. Revulsion against the abuses of research on captive populations in World War II by the Nazis profoundly affected the development of international codes of research ethics (Katz 1972), but the National Commission was formed as a response to domestic research scandals. The revelations began in the United States in the 1960s, with Henry Beecher's famous article detailing what he considered to be ethically problematic research (Beecher 1966), including injecting cancer cells into unsuspecting elderly patients and deliberately exposing institutionalized retarded children to hepatitis. In the early 1970s the most influential revelations concerned the misleading and harmful use of poor African-American men in a "natural history" study of syphilis (Jones 1981).

These scandals created a regulatory climate in which the need for protection was paramount (Rothman 1991), and the National Commission was specifically charged with studying particular problems such as research with the human fetus, children, prisoners, and the "mentally infirm." It was also asked to explicate general ethical principles relevant to research with human subjects, which resulted in the Belmont Report (U.S. National Commission 1979). This report set out the moral foundations for the current federal regulations regarding the conduct of research with human subjects.

Although the Belmont Report linked the requirement to protect the autonomy of persons with diminished capacity to the ethical principle of respect for persons, it addressed vulnerability in the framework of the principle of justice, which calls for distributing the benefits and burdens of research. Vulnerable populations such as "racial minorities, the economically disadvantaged, the very sick, and the institutionalized" may continually be sought as research subjects because of their "ready availability in settings where research is conducted," the Report asserted. Yet they should not bear disproportionate burdens in research. If they do participate, they require special protections because of their "dependent status and frequently compromised capacity for free consent" (U.S. National Commission 1979, 8).

The U.S.-Code of Federal Regulations does not define vulnerability but provides special protections for "particularly vulnerable populations," specifically pregnant women, human fetuses, and neonates; prisoners; and children (45CFR46 Subparts B-D). Although used freely in the Institutional Review Board (IRB) Guidebook offered by the Office of Human Research Protections (OHRP 2001), the term vulnerability is not defined in its extensive glossary.

While the drafters of these guidelines and regulations were reacting to a series of specific historical events and groups of research subjects, the recent history of the use of vulnerability is more expansive, particularly in the international context. While in the U.S. regulatory system, vulnerability has been ascribed primarily to the absence of, or presumed diminished, capacity to consent or to dependence based on incarceration, in research in developing countries the principal focus has been on broader concerns about inequalities of power and resources. This opens the category of vulnerability to many more groups. The Council for International Organizations of Medical Sciences' (CIOMS) guidelines for biomedical research do define, if not vulnerability, then at least vulnerable persons: "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" (CIOMS 2002). Similarly, Zion, Gillan, and Loff define vulnerable people in political terms: "those who lack basic rights and liberties that make them particularly open to exploitation" (Zion 2002).

Beyond individuals or groups, Macklin suggests that whole communities or countries may be vulnerable to exploitation, particularly if "investigators or sponsors are from a powerful industrialized country or a giant pharmaceutical company and the research is conducted in a developing country" (Macklin 2003, 472). In arguing against "double standards" in research in multinational studies—permitting research in destitute countries that would not be approved in wealthy ones—Kottow (2003) distinguishes between vulnerability and susceptibility. Vulnerability, he says, applies to everyone; what really matters in research ethics is susceptibility, which means being poor, undernourished, and lacking in medical care and therefore predisposed to additional harm (Kottow 2003, 460).

In a paper commissioned by the National Bioethics Advisory Commission, Kipnis (2001)

analyzed the category of vulnerability not by subpopulations, but by types of vulnerability. He outlined a taxonomy of six types of vulnerability, which he defined as a limit on the ability to provide informed consent (Kipnis 2001). These are: (1) cognitive: the ability to understand information and make decisions; (2) juridic: being under the legal authority of someone such as a prison warden; (3) deferential: customary obedience to medical or other authority; (4) medical: having an illness for which there is no treatment; (5) allocational: poverty, educational deprivation; and (6) infrastructure: limits of the research setting to carry out the protocol. In a revised version of his forthcoming paper, Kipnis added a seventh type: social vulnerability, that is, belonging to a socially undervalued group. While this taxonomy offers useful distinctions, it leads to two inferences: that everyone who fits into any of these categories is vulnerable, and that everyone capable of unfettered consent is not.

Vulnerability: Too Broad and Too Narrow

As conventionally understood, even if not formally defined, the concept of vulnerability has three basic, related problems. First, so many categories of people are now considered vulnerable that virtually all potential human subjects are included. Consider how the labeling of groups as vulnerable has burgeoned. In U.S. regulations, for example, beyond the protected populations covered by special regulations, other "special classes of subjects" are highlighted in OHRP's guidebook for special consideration. These include cognitively impaired persons; traumatized and comatose patients; terminally ill patients; elderly/aged persons; minorities; students, employees, and normal volunteers; and participants in international research (U.S. Dept. of Health and Human Services 2001).

The most recent revision of the World Medical Association's Declaration of Helsinki, while not defining vulnerability, simply states: "Some research populations are vulnerable and need special protection" (World Medical Association 2002). The Declaration advises: "The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care."

With an even more specific list, the 2002 CIOMS guidelines include as vulnerable "junior or subordinate members of a hierarchical group," such as "medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police." Furthermore, the guidelines describe elderly people as "likely to acquire attributes that define them as vulnerable." Other categories include residents of nursing homes; people receiving welfare benefits or social assistance and other poor people and the unemployed; people in emergency rooms; some ethnic and racial minority groups; homeless persons, nomads, refugees, or displaced persons; prisoners; patients with incurable disease; individuals who are politically powerless; and members of communities unfamiliar with modern medical concepts.

Under one or another of these rubrics, nearly everyone is vulnerable, especially since the benefits of research can never be guaranteed in advance and since much clinical research, by definition, is combined with care. If everyone is vulnerable, then the concept becomes too nebulous to be meaningful. Presumably, the purpose of designating a group as vulnerable is to provide additional protections above those required for all human participants. For certain classes, these special protections are codified in regulations. For most vulnerable groups, however, the only additional protection is an exhortation to investigators and IRBs to pay "special attention" or to give "special consideration" to research in which these groups may be included. As more and more groups come to be so labeled, the result is that every research protocol requires some type of special attention and IRBs have no guidance on where to concentrate their limited attention and resources.

Second, if the concept of vulnerability is overbroad, it is also too narrow. An almost exclusive emphasis on group characteristics that ostensibly undermine or eliminate the capacity to give consent can divert attention from features of the research itself, the institutional environment, or the social and economic context that can put participants in harm's way. Much recent concern, for example, stems from the deaths of four research participants. Two of the three women who died were healthy volunteers affiliated with medical centers as student or employee; the third was a nurse. The problems that led to their deaths were not related to vulnerability as a status, but to serious flaws in protocol design and implementation and in inadequate oversight (Steinbrook 2002a; Steinbrook 2002b).

The other research fatality was a participant in a Phase I gene transfer experiment, who fell into the broad vulnerability category of a person with an incurable illness. But his genetic disease was not seriously debilitating, he was 18 years old and had the capacity to give consent, and his father was closely involved in his decision to participate. Questions about risk also played a central role in discussions of the aftermath of this case, as well as concerns that the investigators' financial interests may have affected decisions about enrollment and medical management. In these four deaths it appears that the participants' *capacity* to consent was not in question.

While consent is surely a serious concern, the root of the concept of vulnerability lies in the possibility of physical harm. The term derives from the Latin *vulnus* (wound). In ordinary language vulnerable means "capable of being attacked, harmed, or injured in some way" or, in psychological parlance, "susceptible of being emotionally damaged or offended." Goodin (1985) emphasizes that some vulnerabilities are "inherent and immutable"; vulnerability is inevitable in society because people are dependent on one another. However, he says, "In no case should [vulnerabilities] be so severe and asymmetrical that one party has exclusive, discretionary control over resources that the other needs to protect his vital interests" (Goodin 1985, 206). In contemporary bioethical discourse, one can be vulnerable to being harmed or being wronged. There is much that puts research participants at risk beyond their membership in a "vulnerable" group.

Third, the concept of vulnerability stereotypes whole categories of individuals, without distinguishing between individuals in the group who indeed might have special characteristics that need to be taken into account and those who do not. Particular concerns have been raised about considering all poor people, all pregnant women, all members of ethnic or racial minorities, and all people with terminal illness as inherently vulnerable (DeBruin 2001).

Inclusion in the category of vulnerable has been challenged in the past on similar grounds, that is, out of concern that not all members of a group are necessarily vulnerable. The National Commission considered at great length the use of prisoners as research subjects. Prisoners at Jackson State Prison in Michigan asserted that they wanted to have the opportunity to participate for benefits such as money, better living conditions, and relief from boredom (R. Levine 1986). Nevertheless, current federal

regulations concerning prisoners set very high barriers for research.

A more successful challenge came in the 1990s, as women's health advocates marshaled support for more representation of pregnant women and women of childbearing age among study populations. These groups had been excluded based on fears of harm to a real or potential fetus and liability to sponsors. In 1994 the Institute of Medicine (IOM) concluded, "volunteers for clinical studies should be offered the opportunity to participate without regard to gender, race, ethnicity, or age" (Mastroianni, Faden, and Federman 1994). The National Institutes of Health policy guidelines that followed the IOM report stated that women should not be excluded from research on the grounds that they were or might become pregnant (National Institutes of Health 2001). However, inclusion of pregnant women is governed by regulations in which the notion of vulnerability is embedded (45CFR46 Subpart B).

Furthermore, some people may be vulnerable in certain circumstances and not in others because of the timing of the research (e.g., pregnant women in labor, the first few hours after a natural or man-made disaster), the emotional impact of the research (e.g., a disease from which a loved one has recently died), prior experiences, or other personal factors. Thus, an individual's needs for special protections in the research context depend not solely on that person's inclusion in a group, but importantly on the particular features of the research project and the environment in which it is taking place.

Public policy is a blunt instrument and sometimes it is necessary to set cut-offs or designate whole groups for special treatment because individualized decision making is not feasible. For example, most jurisdictions in the U.S. designate nearly everyone under the age of 18 as a "child." But it is critical that designated groups be drawn as narrowly as possible and for only so long as special consideration is otherwise justifiable.

While we have argued that the strategy of relying on categorical vulnerability to guide investigators and IRBs is flawed, we believe that the existing regulations to protect children have been useful and should be preserved, although modifications might be made. In part because there are special regulations for research involving children, not all research protocols in this category present difficult decisions. Many, perhaps most, follow well-accepted and ethically acceptable patterns. Kipnis (2003) also created

a taxonomy of seven vulnerabilities for research with pediatric patients.

Furthermore, people with permanent cognitive impairments, such as severe mental retardation or advanced Alzheimer disease, will not attain or regain a state of cognitive capacity. While proposed regulations regarding this category have been mired in dissension for years, special protections for research involving such persons should be considered.

Nevertheless, merely identifying a research protocol as involving participants who come from particular groups or who might be vulnerable in particular ways is not the only way to determine which research protocols warrant more intensive review, in what particular areas, and then to determine how to strengthen protections. We suggest a broad discussion among researchers, sponsors, study coordinators, ethicists, IRB members, policy makers, and research participants to determine ways in which the concept of vulnerability is useful, but also how to provide more targeted forms of protection for participants in protocols where vulnerability misses the mark.

We offer one such scheme under the rubric "special scrutiny." Three criteria for special scrutiny—more focused review of certain kinds of protocols that present special ethical challenges—are: (1) the research involves initial experiences of translating new scientific advances into humans, especially when the intervention is novel and/or irreversible; (2) there is a known or credible risk of significant harm (death or serious disability being the clearest examples) *and* there is no potential of an offsetting direct medical benefit; or (3) the protocol raises ethical questions about research design or implementation for which there is no consensus. Special scrutiny is a mechanism that aims to provide appropriate protection of all research participants, not just those officially deemed vulnerable (C. Levine et al. 2004). ■

Received 5 November 2003; accepted 3 December 2003; posted for commentary 5 February 2004.

Acknowledgments

This paper is a project of the Consortium to Examine Clinical Research Ethics (CECRE), which is funded by the Doris Duke Charitable Foundation. Other members of CECRE who provided valuable contributions to this manuscript were Angela Bowen, M.D., Western IRB; Ezekiel Emanuel, M.D., Ph.D., National Institutes of

Health; Alan Fleischman, M.D., New York Academy of Medicine; and Kenneth Getz, CenterWatch. Kenneth Kipnis, Ph.D., provided useful unpublished materials and suggested important references.

Competing Interests Statement

The authors declare that they have no competing financial interests.

References

- Beecher, H. K. 1966. Ethics and clinical research. *New England Journal of Medicine* 274(24): 1354–1360.
- Council for International Organization of Medical Societies. 2002. *International Ethical Guidelines for Biomedical Research Involving Human Subjects, Commentary on Guideline 13*. Available from: www.cioms.ch
- DeBruin, D. 2001. Reflections on vulnerability. *Bioethics Examiner* 5(2): 1, 4.
- Goodin, R. E. 1985. *Protecting the vulnerable: A reanalysis of our social responsibilities*. Chicago: University of Chicago Press.
- Hawana, J. S. 2003. Vulnerable research subjects may exceed definition in clinical research. Washington, DC: Washington Fax. Available from: www.washingtonfax.com
- Jones, J. H. 1981. *Bad blood: The Tuskegee syphilis experiment*. New York: Free Press.
- Katz, J., ed. 1972. *Experimentation with human beings*. New York: Russell Sage Foundation.
- Kipnis, K. 2001. Vulnerability in research subjects: A bioethical taxonomy. In *Ethical and policy issues in research involving human research participants*. Bethesda, MD: National Bioethics Advisory Commission, G-1–G-13.
- . 2003. Seven vulnerabilities in the pediatric research subject. *Theoretical Medicine* 24:107–120.
- . n.d. Vulnerability in research subjects: An analytic approach. In *The variables of moral capacity*, ed. D. C. Thomasma and D. N. Weisstub. Dordrecht: Kluwer Academic Publishing. Forthcoming.
- Kottow, M. H. 2003. The vulnerable and the susceptible. *Bioethics* 17(5–6): 460–471.
- Lederer, S. E. 1995. *Subjected to science: Human experimentation in America before the second world war*. Baltimore: Johns Hopkins University Press.
- Levine, C., R. Faden, C. Grady, et al. 2004. "Special scrutiny": A targeted form of research protocol review. *Annals of Internal Medicine* 140:220–223.
- Levine, R. J. 1986. *Ethics and regulation of clinical research*. Baltimore: Urban and Schwarzenberg.

- Macklin, R. 2003. Bioethics, vulnerability, and protection. *Bioethics* 17(5-6): 472-486.
- Mastroianni, A. C., R. Faden, and D. Federman, eds. 1994. *Women and health research: Ethical and legal issues of including women in clinical studies*. Washington, DC: National Academy Press.
- Rothman, D. J. 1991. *Strangers at the bedside: A history of how law and bioethics transformed medical decision making*. New York: Basic Books.
- Steinbrook, R. 2002a. Protecting research subjects: The crisis at Johns Hopkins. *New England Journal of Medicine* 346:716-720.
- Steinbrook, R. 2002b. Improving protections for research subjects. *New England Journal of Medicine* 346:1425-1430.
- Stone, T. H. 2003. The invisible vulnerable: The economically and educationally disadvantaged subjects of clinical research. *Journal of Law, Medicine, & Ethics* 31(1): 149-153.
- National Institutes of Health, U.S. Department of Health and Human Services. Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects. Available from: <http://ohrp.osophs.dhhs.gov/polasur.htm>
- National Institutes of Health, U.S. Department of Health and Human Services. 2001. *NIH policy and guidelines on the inclusion of women and minorities as subjects in clinical research—Amended October 2001*. Available from: http://grants.nih.gov/grants/funding/women_min/guidelines.amended.10.2001.htm
- Office for Human Research Protections, U.S. Department of Health and Human Services. 2001. *Institutional Review Board Guidebook*. Available from: http://ohrp.osophs.dhhs.gov/irb/irb_guidebook.htm
- U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. *The Belmont report: Ethical guidelines for the protection of human subjects of research*. Washington DC: U.S. Government Printing Office.
- World Medical Association. 2002. *Declaration of Helsinki: Ethical principles for medical research involving human subjects*. Available from: <http://www.wma.net/e/policy/b3.htm>
- Zion, D., L. Gillan, and B. Loff. 2002. The Declaration of Helsinki, CIOMS and the ethics of research on vulnerable populations. *Nature Medicine* 6:615-617.