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

Carol Levine, Unites Hospital Fund
Ruth Faden, The Johns Hopkins University
Christine Grady, National Institutes of Health
Kate Hammermeckler, University of Minnesota
Lisa Eckenweiler, 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 term that generates a duty for researchers, review committees, and regulators to provide special protections for them. While other basic tenets of research ethics— informs 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 2005; Hawn 2005) or 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 obvious 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 ethics set the context for the existing ethical framework, research today has many complicating factors, 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, more recently, an elevated concern with public health threats such as bioterrorism and new or re-emergent infectious diseases.

What is Vulnerability? Although concern about research in orphanages, mental institutions, and hospitals dates to at least 1800-90.
the beginning of the twentieth century in the United States (Lurie 1995), the prominence of the concept of vulnerability and its varying 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 abuse 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 (Emanuel 1991), and the National Commission was tasked with examining similar problems such as research with the human fetus, children, prisoners, and the "mentally ill." It also asked to restate 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 described vulnerability in the framework of the principle of justice, which calls for distributing the burdens and benefits 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 "readily available, 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 "dependence 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 specific protections for "particularly vulnerable populations," specifically pregnant women, human fetuses, and neonates; prisoners; and children (45 CFR 46 Scopeware B-D). Although used directly in the Institutional Review Board (IRB) Guidebook offered by the Office of Human Research Protections (OHARP 2005), the term vulnerability is not defined in its extensive glossary.

While the drafters of these guidelines and regulations were reacting to a mood 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 identified primarily as 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, Gillon, and Liff 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 "investigator or patient power is from a non-powerful institutionalized country or drug pharmaceutical company and the research is conducted in a developing country." (Macklin 2001, 472). In arguing against "double standards" in research in developing countries that would not be approved in wealthy ones—Korosc (2003) distinguishes between vulnerability and susceptibility. Vulnerability, he says, applies to everyone; what really matters is a research ethics is acceptability, which requires being non-pathologized, and lacking in medical care (and therefore uncompensated) in additional harm. (Korosc 2003, 460).

In a paper commissioned by the National Bioethics Advocacy Commission, Kippins (2003)
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 factors limiting the "ability to provide informed consent" (Koplin 2002). 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) infrastructural: limits of the research setting to carry out the protocol. In a revised version of his forthcoming paper, Koplin added a seventh type: social vulnerability, that is, belonging to a socially underserved group. While this taxonomy offers useful distinctions, it leads to two inferences: the everyone who fits into any of these categories is vulnerable, and that everyone capable of uninformed 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. Dep't 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 staff; junior or 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 invitation 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 guide 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 minimize 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 investigator oversight (Steinbrook 2002a; Steinbook 2002b).
The other research feasibility was a participant in a Phase I gene transfer experiment, who died in 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 their 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 suavis (soft). 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 (values) be so severe as to minimize or encourage the 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, whose 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 (DeoBrun 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 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" (Masuraroni, Paden, and Ederman 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 (45 CFR 46 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 child one has recently died), prior experiences, or other personal factors. Thus, an individual's need for special protections in the research context depend not solely on this 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 age 18 as a "child." But it is crucial 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 investigations 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, all research protocols in this category present difficult decisions. Many, perhaps most, follow well-accepted and ethically acceptable patterns. Koger (2003) also noted...
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 modified in dimension for years, special protocols 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 ways, and then to determine how to strengthen protections. We suggest a broad discussion among researchers, sponsors, study coordinators, ethicists, ERB 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 exists.

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 unusual 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. 2004b).

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; Emekol 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


