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Introduction: Vulnerability in Biomedical Research

Ana S. Iltis

- Patients with chronic intractable pain will be enrolled in a study comparing the effects of a widely prescribed opioid taken with a new agent meant to improve the efficacy of the opioid versus the opioid taken with placebo.
- Individuals with advanced familial amyotropic lateral sclerosis (ALS) who have a confirmed superoxide dismutase (SOD1) mutation will be enrolled in a gene transfer trial to assess the safety of a vector that would be used to deliver a healthy SOD1 gene.
- Migrant farm workers in the United States suffer from parasitic infections at rates much higher than the U.S. average.[1] Investigators are studying a vaccine that would protect against ascariasis. People at high risk in the U.S. will be enrolled.

These hypothetical studies would examine different scientific questions using different types of participants. Yet all of these studies would likely enroll at least some individuals who might be deemed "vulnerable participants." During the late 1960s and early 1970s, revelations of research on persons who were exposed to significant risks without freely and voluntarily agreeing to participate emerged.[2] In some cases, such as the Tuskegee Syphilis Study sponsored by the United States Public Health Service, they did not know they were being used in research.[3] In other cases, most notably the Willowbrook State School hepatitis studies, it appeared that the subjects' parents had been strongly encouraged to enroll their children in a study in which they would be intentionally infected with hepatitis.[4] Public revelation of these cases, especially the 1972 *Washington Star* and *New York Times* articles exposing the Tuskegee Syphilis Study,[5] prompted congressional action and passage of the National Research Act in 1974.[6] Given this history, it is not surprising that concern over the participation of vulnerable individuals was prominent in research policy development and discussions of research ethics during the 1970s and early 1980s in the United States. For example, the National Commission for the Protection of Subjects of Biomedical and Behavioral Research called for special protections for vulnerable subjects in the Belmont Report and issued reports on research on special populations, including fetuses, prisoners, children, and the institutionalized and mentally ill.[7] The Common Rule, the portion of the Code of Federal Regulations that governs much of the human research conducted in the United States, reflects the National Commission's emphasis on the importance of protecting prisoners and children along with a concern for protecting pregnant women and fetuses who might be research subjects. Subparts B, C, and D of the Common Rule restrict the research that may be performed on members of these groups and require additional protections when enrolling them. The Common Rule notes that others may be vulnerable and requires IRBs to ensure that protocols include unspecified protections for those who might be vulnerable:

> When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or education-

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> ally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.[8]

What Is Vulnerability?

Vulnerability typically has been understood in terms of the ability to give or withhold informed consent and the likelihood of being "misled, mistreated, or otherwise taken advantage of" in research.[9] The Belmont Report, for example, refers to the capacity to give informed consent and the prospect of inappropriate over-inclusion of some potentially vulnerable groups in research in its discussion of subject selection:

> Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.[10]

The Council for International Organizations of Medical Sciences (CIOMS) guidelines on human research state that "[s]pecial justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied."[11] The commentary on this guideline suggests that CIOMS relies on a broader definition of vulnerability than one focused solely on consent. It defines vulnerable persons as "those who are relatively (or absolutely) incapable of protecting their own interests."[12]

The National Bioethics Advisory Commission's (NBAC) discussion of obtaining informed consent for research also addresses the issue of vulnerability in terms of voluntary participation: "Those who are not fully capable of resisting the request to become participants — such as prisoners or other institutionalized or otherwise vulnerable persons — should not be enrolled in studies merely because they are easily accessible or convenient."[13]

Despite the similarity between the NBAC discussion of vulnerability and other reflections on vulnerability that emphasized the ability to give or withhold consent and the likelihood of being over-used, the NBAC report and one of the papers commissioned by NBAC represented an important development in shaping our understanding of what it means to be vulnerable for the purposes of research participation and what investigators and institutional review boards, who are charged with appropriately protecting without unnecessarily categorically excluding vulnerable persons, should do to fulfill their obligations. Early discussions of vulnerability and the regulations governing human research focus on vulnerable populations, such as children and institutionalized persons. Kenneth Kipnis' work for the National Bioethics Advisory Commission in 2001 recommended that we move away from a populations approach.[14] Instead, we should focus on the specific factors or conditions that may render individuals vulnerable in the research setting, such as cognitive deficits, financial constraints, being in a deferential relationship toward an investigator, being under the authority of others who may want one to participate, having a serious illness for which no further known effective therapy is available, or being asked to participate in research that is conducted in a setting in which there are not appropriate resources for overseeing and conducting a study. The NBAC report on *Ethical and Policy Issues in Research Involving Human Participants* incorporates Kipnis' work and notes that:

> In general, persons are vulnerable in research either because they have difficulty providing voluntary, informed consent arising from limitations of decision-making capacity (as in the case of children) or situational circumstances (as in the case of prisoners), or because they are especially at risk for exploitation (as in the case of persons who

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> belong to under-valued groups in our society). An adequate characterization of vulnerability must attend to both types of concern.[15]

Protections offered to individual research participants should correspond to the specific sources of their vulnerability. The NBAC report reflects Kipnis' framework with slight modifications and recommends a factors-approach to vulnerability. Vulnerability should be evaluated by asking: what aspects of a person or the circumstances in which the research is being conducted might render this person less able to give free and voluntary informed consent or more likely to be exploited? One advantage to such an approach is that it may lead to better, more appropriate protections for those who need them and avoid unnecessary barriers to research participation, insulting restrictions, and stereotyping. The emphasis on the characteristics and circumstances that contribute to vulnerability can help bring greater attention to the kinds of protections that might correct the source of vulnerability or alleviate its effects.

The re-conceptualization of vulnerability from something that emerges primarily from membership in a specific population to a reality that emerges from characteristics of persons or the environment in which research is conducted also can inform our interpretation and application of the Common Rule. The Common Rule requires special protections for pregnant women, fetuses, neonates, children, and prisoners. It also requires special but undefined protections for any other participant who is "likely to be vulnerable to coercion or undue influence."[16] The Common Rule and Office for Human Research Protections (OHRP) are virtually silent on the question of who these other vulnerable persons might be and what protections investigators and IRBs should implement on their behalf.[17] Kipnis' and NBAC's recommendations offer a framework for identifying those persons who may require additional protections and the procedures that IRBs and investigators may use to determine which protections are appropriate.

Future Understandings and Applications of Vulnerability in Research

Recent discussions have sought to better understand the concept of vulnerability and the implications a re-conceptualization of vulnerability should have on the oversight and conduct of research. Some analyses have identified problems not only with the current regulatory approach to vulnerability but with the way the concept has been developed and expanded. Levine et al., for example, have argued that "so many categories of people are now considered vulnerable that virtually all potential human subjects are included."[18] Not only are virtually all potential human subjects vulnerable, Levine and her co-authors argue, but "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."[19] A third major criticism of the way vulnerability has been used is that there has been "[a]n almost exclusive emphasis on group characteristics that ostensibly undermine or eliminate the capacity to give consent," and this emphasis "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."[20]

Many other commentators have focused on specific types of persons who may be vulnerable and the protections that might be appropriate when enrolling them in research. These include discussions of research on the homeless, patients receiving palliative care and terminally ill patients, persons with untreated addictions, minorities, and cancer patients enrolled in phase 1 oncology studies.[21] Two of the most thorough examinations of specific factors that may contribute to vulnerability and the protections that might be offered to participants who experience those sources of vulnerability include the NBAC reports on trials conducted in resource poor settings and research involving people who have mental disorders that may affect their decision-making capacity.[22]

This symposium contributes further to the understanding of vulnerability in research by advancing the conversation on who may be vulnerable in research, why they may be vulnerable, and to what they may be vulnerable. It also informs the discussion of what kinds of protections are appropriate as well as the types of practices and policies that may diminish vulnerability or mitigate the effects of vulnerability.

Carl Coleman argues that the current regulatory approach to vulnerability is inappropriate because it uses one term, vulnerability, to describe disparate situations that do not all involve the same policy and practical concerns. He argues that to understand concerns about vulnerability and vulnerable research subjects, we should turn our attention to the "basic 'deal' that underlies society's regulation of human subject research, as reflected in both regulatory standards and internationally agreed-upon ethics guidelines."[23] Three of the conditions that must be met for it to be permissible to use humans in research are that: (1) the anticipated benefits of a study exceed the risks and the risks are reasonable relative to those benefits; (2) a study's risks have been minimized insofar as possible; and (3) the free and voluntary informed consent of subjects will be sought. Vulnerability can be understood in terms of these requirements: "a vulnerable person can be seen as someone who is at risk of being enrolled in research in violation of one or more of the deal's basic premises."[24] For example, some may be vulnerable because study participation is riskier for them than for others. Coleman illustrates the three types of vulnerability and demonstrates that sometimes, but not always, vulnerabilities can be remedied. It is through this lens of vulnerability, Coleman argues, that IRBs should evaluate protocols and potential subject populations to determine whether protections can and should be put into place to alleviate vulnerabilities.

Christine Grady examines the common assertion that persons who are economically or socially disadvantaged are especially vulnerable in the research setting and require special protections.[25] Typically, the concern is that such persons may not be able to make a free and voluntary decision to participate because they do not understand the information or they may be exploited, coerced, or unduly influenced. As a result, sometimes it is held that persons who are resource-poor should not be enrolled in certain studies. Grady argues that to categorically restrict research participation of persons who have limited financial or social resources may violate important ethical obligations, such as ensuring fair subject selection, may wrongly deny some people the potential benefits of research participation, and may render research results less generalizable. No one who is coerced, unduly influenced, or exploited should participate in research. No one who misunderstands study information should consent to research participation on his own behalf. But, unless there is a valid justification for holding that persons with limited resources necessarily suffer from impaired decision making or are being exploited, coerced, or unduly influenced, they should not as a group be barred from participation. Investigators and IRBs should ensure that all participants understand study information, that benefits offered are fair and appropriate, and that participants are free to enroll or not.

Dan Bustillos examines ethical, legal, and scientific factors related to the inclusion and exclusion of persons with limited English proficiency (LEP) in clinical trials.[26] Bustillos summarizes the current state of clinical research in the United States, in which persons with LEP are underrepresented and often categorically excluded from participation. He contrasts this state of affairs with the legal and public policy initiatives, including Title VI of the Civil Rights Act of 1964 and the 1994 NIH Revitalization Act, that are incompatible with the widespread categorical exclusion of persons with LEP from most clinical research. If followed strictly, such policies also would lead to greater availability of translation services for research participants throughout the research process. He identifies the legal, ethical, and scientific concerns that arise when persons with LEP are routinely excluded from clinical research and argues that significant efforts ought to be undertaken to ensure that persons with LEP are included appropriately in clinical research.

This symposium contributes further to the understanding of vulnerability in research by advancing the conversation on who may be vulnerable in research, why they may be vulnerable, and to what they may be vulnerable. It also informs the discussion of what kinds of protections are appropriate as well as the types of practices and policies that may diminish vulnerability or mitigate the effects of vulnerability.

Rebecca Dresser argues that the current emphasis on translational research is likely to lead to an increase in the number of first-in-human (FIH) trials in healthy volunteers, seriously ill patients, and stable patients.[27] She identifies a number of ethical issues that must be considered in designing and reviewing FIH studies. Dresser recommends practices that could improve not only the level of protection offered to participants in FIH trials, but also could increase the scientific and social value of such studies.

Jerry Menikoff explores ethical issues surrounding the inclusion of persons who are medically vulnerable in research, i.e., of persons who are seriously ill and especially those for whom there are no known effective therapies.[28] One concern is that such persons' decision-making capacity may be compromised because of their illness and the psycho-social consequences of being seriously ill. Even if such persons' decisional capacity is in tact, Menikoff argues, other factors may contribute to their vulnerability in the research setting. Individuals who are seriously ill and for whom no known effective therapies exist have a strong enrollment incentive. Interventions available in a study — and often only in a study — may be their "only chance." As a result, Menikoff argues, investigators may be able to reduce the anticipated benefits to participants and/or increase the risks to participants and still be able to enroll a sufficient number of people. Whereas other people might refuse to participate unless risks where decreased and/or there were greater potential direct benefits to them for participating, sick people who have no other treatment options might still enroll. While one might think that the regulations governing research would prohibit such cases, Menikoff demonstrates that such studies can be designed in ways that fulfill the regulatory obligation to ensure that overall benefits of a study (benefits to subjects plus benefits to society) exceed risks, that risks are appropriate relative to anticipated benefits, and that risks are minimized according to the requirements of the Common Rule. The willingness to participate in such studies because they offer persons their "only chance" contributes to the vulnerability of patients who have been labeled medically vulnerable. Menikoff identifies some of the factors IRBs should consider in reviewing studies that propose to enroll seriously ill persons for whom there are no known effective treatments.

The concept of vulnerability figures prominently in the research ethics literature, and the regulations governing human research in the U.S. call on IRBs and investigators to provide special protections to vulnerable participants. Yet questions concerning who is vulnerable and what protections may be effective in reducing or eliminating the source or effects of their vulnerabilities remain unanswered. This symposium advances discussion of both questions.

Raymond Tait identifies some of the ways in which persons experiencing chronic pain may be vulnerable in the research environment.[29] Vulnerability can be the result not only of the circumstance of being in pain with no satisfactory relief in sight (e.g., cognitive and affective co-morbidities common in chronic pain patients), but also from situational factors related to the clinical and research environments, including the relationship a potential research subject has with an investigator, the investigator's relationship to a study sponsor, and a failure by persons overseeing research (IRB members) to appreciate the possible psychiatric co-morbidities potential subjects with chronic pain may experience. Tait argues that attention must be given to different factors that contribute to vulnerability before, during, and after a trial, noting that poor management of pain prior to and following trial participation can raise significant ethical concerns for research involving persons with chronic pain.

Paul Ford argues that patients who are candidates for neurosurgical procedures that are unproven, whether they are offered clinically as innovative interventions or through formal research studies, may experience a number of vulnerabilities that should be mitigated.[30] He identifies the nature of those vulnerabilities and mechanisms that should be implemented to address them. In neurosurgery in particular, he argues, the line between research and innovation often is blurred. Our focus should not be on the question of whether an IRB should oversee such procedures and what protections should be offered to patients who are in formal neurosurgical research, but on the circumstances that render a category of patients who have significant vulnerabilities in common regardless of whether they are enrolled in a study or merely receiving an innovative intervention in the clinical setting. Neurosurgeons have an obligation to mitigate those vulnerabilities whether they approach a patient as a clinical investigator or an innovative clinician.

The concept of vulnerability figures prominently in the research ethics literature, and the regulations governing human research in the U.S. call on IRBs and investigators to provide special protections to vulnerable participants. Yet questions concerning who is vulnerable and what protections may be effective in reducing or eliminating the source or effects of their vulnerabilities remain unanswered. This symposium advances discussion of both questions.

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