Federal Interpretation and Enforcement of Protections for Vulnerable Participants in Human Research

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ABSTRACT: Regulations and policies governing research, codes of ethics, and the research ethics literature reflect the need to provide special protections to vulnerable research participants. Nevertheless, there is disagreement about who is vulnerable and why, what protections are appropriate, and when to disallow research involving vulnerable persons. The Common Rule (CR) governs much of the human research conducted in the United States and the Office for Human Research Protections (OHRP) oversees much of this research. The CR requires special protections for pregnant women, fetuses, neonates (subpart B), prisoners (subpart C), and children (subpart D). The CR requires that information given to persons with limited English proficiency (LEP) be “given to the subject or the representative . . . in language understandable to [them]” (DHHS, 45 CFR 46.116) and allows RECs to approve alterations in the consent process to accommodate LEP (DHHS, 45 CFR 46.117.b). The CR states, “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 educationally disadvantaged persons, additional safeguards [should be] included in the study to protect the rights and welfare of these subjects” (DHHS, 45 CFR 46.111.b). The CR offers no specific guidance on who requires these “additional safeguards” or what constitutes appropriate additional safeguards.

As part of his work for the National Bioethics Advisory Commission (NBAC), Kenneth Kipnis argued that protection of vulnerable subjects should focus on the characteristics or circumstances that render persons vulnerable (2001). He identified six types of vulnerability: cognitive, juridic, deferential, medical, allocational, and infrastructural. Infrastructural vulnerability differs from the others in that it concerns the research environment, while the others refer to subject characteristics. Infrastructural concerns can render any participant vulnerable because they reflect failures to follow proper processes in conducting or overseeing research, such as the failure to conduct substantive independent reviews, have appropriately trained staff or REC members, and adhere to protocols. NBAC (2001) adopted a framework similar to Kipnis’s. NBAC eliminates the infrastructural category and includes “social” vulnerability, which refers to persons who “belong to undervalued social groups” (2001, p. 90). Neither of the alternative frameworks for understanding vulnerability is formally recognized by OHRP, although the frameworks have
received attention in the literature (Quest & Marco, 2003; Levine et al., 2004; Kopelman, 2004).

While the CR and OHRP guidance documents provide little explication regarding protections for vulnerable persons not covered by subparts B, C, and D, it is possible that guidance about specific requirements has been developed within the OHRP letters of determination. OHRP’s letters of determination are directed to institutions following for-cause investigations and compliance audits, and they clarify OHRP’s expectations for all institutions and investigators under their purview. Information in these letters is not easily searchable and there are only two published studies that systematically examine them (Borror et al., 2003; Burris & Welsh, 2007). Neither study focused on vulnerability. In this study, we systematically categorized OHRP findings and recommendations regarding vulnerabilities in letters of determination issued over a 6.5-year period.

Methods and Results

All authors contributed to the development of the methodology. All letters of determination issued by OHRP between July 1, 2000 and December 31, 2006 (N = 636) were extracted. Follow-up letters that referred to a previous letter were combined, for a total of 402 cases. AI, AW, JL, and ER developed standards for categorizing the findings and recommendations. AI and AW each examined 201 cases and independently examined 195 cases in common to estimate reliability (Kappa coefficient for chance-adjusted agreement). “Findings” referred to failures cited by OHRP, “recommendations” referred to suggested improvements, and “items” referred to both findings and recommendations. Each item was categorized according to type of vulnerability. Although Kipnis and NBAC treat cognitive and communicative issues together and include LEP under “cognitive vulnerability,” we treated LEP separately, which is consistent with the CR. Infrastructural vulnerability referred to practices, policies, or procedures that OHRP requires to be in place in the research environment to ensure adequate protection of human subjects. The emphasis on infrastructural issues, particularly matters that might not significantly affect subjects’ rights or safety, is consistent with previous criticisms of OHRP (Burris & Welsh, 2007; Fost & Levine, 2007).

Discussion

We found that OHRP letters of determination yielded little significant guidance regarding protections for persons with subject-based vulnerabilities who are not covered by subparts B, C, or D of the CR. There are at least four possible explanations for this:

1. Limited amounts of research are conducted on these populations, such that few problems emerge. (2) RECs and investigators regularly provide adequate protections for all vulnerable participants, including those not covered by subparts B, C, or D.

Both of these explanations are unsatisfactory. Considering only the amount of research with elderly, cognitively impaired, and severely medically-ill persons, it is clear that significant numbers of vulnerable people not covered under the CR subparts participate in research. Moreover, given the lack of guidance on vulnerability, it is unlikely that RECs and investigators have
developed and implemented systems to ensure adequate protections for persons not covered by the CR subparts. (3) OHRP, as a regulatory body, has refrained from imposing a particular interpretation given the ambiguity over vulnerability and the lack of clear evidence for appropriate protections. (4) In its general audits or focused investigations, OHRP may fail to look for evidence of appropriate protections in research records because monitors have no method for determining whether studies involve vulnerable groups.

The third and fourth explanations are more useful because they acknowledge the lack of understanding of subject-based vulnerabilities. This is consistent with the disagreements in the research ethics literature over which subjects are vulnerable, how they should be protected, and the extent to which “vulnerability” is a useful concept (Levine et al, 2004; Berry, 2004; Hawryluck, 2004; Kishore, 2006; Leavitt, 2006; Sieber, 2008). Infrastructure vulnerabilities, on the other hand, are comparatively easy to define, identify, and cite. However, some of these citations may not address vulnerability because they refer to procedural matters that are unlikely to affect research participants (e.g., recording vote counts of RECs).

With respect to limitations of this study, we had access only to letters posted on the OHRP website, and we found a small number of letters for which the links did not work. We also found letters that referred to previous letters or that were probably referred to in future correspondence, but we were unable to locate the past or future letters. These instances were sufficiently rare that there is no reason to believe that the inaccessible letters would have changed the results significantly. In addition, the alternative frameworks for understanding vulnerability we relied on have not been adopted by OHRP and it is possible that a radically different understanding informs OHRP’s interpretation of vulnerability.

Despite these limitations, our results suggest that there is no substantive guidance available through OHRP about how to understand vulnerability, determine whether a study includes vulnerable persons, or how to protect vulnerable persons. This lack of guidance and enforcement might mean that appropriate protections for some potentially vulnerable persons are not in place and that institutions might not be cited for such failures. This suggests that institutions and investigators must assume responsibility for developing and executing practices to fulfill their obligation to protect vulnerable subjects. Potential mechanisms for addressing this obligation at the institutional level are considered below.

Best Practices

Given the lack of guidance on protections for vulnerable persons, institutions and investigators might improve protection of vulnerable persons by developing and implementing practices informed by the research ethics literature. For example, institutions might adopt an alternative framework for understanding vulnerability, such as the one described by Kipnis (2001) or NBAC (2001), and require investigators to address potential participant and study context vulnerabilities and their efforts to reduce those vulnerabilities. Example queries might include: “Are any potential subjects likely to feel social pressure to defer to others (deferential vulnerability)? If so, what are the expected effects of this pressure? What means will you use to eliminate or mitigate the effects of this pressure?” Similar questions could be developed for each vulnerability type. RECs could then evaluate whether investigators’ responses and plans were satisfactory. The success of such a system would depend on investigators’ and REC members’ understanding and appreciation of vulnerability, as well as honest dialogue between RECs and investigators regarding particular protocols.

Adopting a vulnerability framework such as Kipnis’s (2001) or NBAC’s (2001) has several advantages. The focus on aspects of persons and circumstances that contribute to vulnerability, rather than on membership in a population, allows investigators and RECs to recognize individual differences among persons and to acknowledge that a person may be vulnerable under some circumstances and not others. A system that focuses on why a person is vulnerable directs investigators and RECs to addressable features of persons and circumstances, including safeguards for vulnerabilities that cannot be eliminated. For example, Kipnis (2001) examines the vulnerability of patients who have life-threatening conditions for which no effective treatment is available and who are eligible for phase 1 studies. The main concern with such potential participants is the evidence that many of them enroll in studies because they believe research offers a “last chance” for effective therapy. However, most phase 1 studies pose virtually no prospect of direct therapeutic benefit. One approach to decreasing vulnerability, which Kipnis (2001) defends, is to increase the potential therapeutic benefit of such studies by allowing subjects enrolled in early phases to enter later phases.

Another advantage of adopting this type of vulnerability framework is that vulnerability determination is flexible, thereby helping to avoid unnecessary safeguards that may embarrass subjects or pose barriers to
participation. For example, a person who has a diagnosis of bipolar disorder might at times have compromised decisional capacity, but be capable of making some research participation decisions. Such a person would not be required to have a legally authorized representative in the absence of compromised capacity (see NBAC, 1998, Recommendation 6). In contrast, a population-based approach could lead to blanket “protections” for individuals with particular conditions (e.g., pregnant women), which may not be necessary with specific situations/individuals.

Research Agenda

There are four principal difficulties with the proposed approach to vulnerability which could be partially resolved through research and education. (1) Given the lack of regulatory enforcement in the U.S. of the additional safeguards requirement, successful implementation of this system would require that institutions and investigators self-regulate in the absence of significant external motivation. (2) The objective identification of all significant vulnerabilities awaits further empirical research. This is an area where further research is needed. (3) Currently, there is limited information about the types of protections that are effective for specific populations (DuBois, unpublished; Alzheimer's Association, 1997; Sachs, 2002). Effective implementation of such an approach requires empirical research. (4) The success of such an approach depends on a significant commitment by institutions to education, implementation, and enforcement.

Educational Implications

There is evidence that REC members may not recognize potential vulnerabilities, including under-estimation of the potential for psychiatric comorbidities among medically-ill research subjects to compromise decisional capacity (Luebbert et al., 2008). This suggests that attempts to implement protections for the various types of vulnerable persons will require significant education of REC members and investigators.

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