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# Vulnerability as a Regulatory Category in Human Subject Research

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The concept of vulnerability has long played a central role in discussions of research ethics. In addition to its rhetorical use, vulnerability has become a term of art in U.S. and international research regulations and guidelines, many of which contain specific provisions applicable to research with vulnerable subjects. Yet, despite the frequency with which the term vulnerability is used, little consensus exists on what it actually means in the context of human subject protection — or, more importantly, on how a finding of vulnerability should affect the process of research ethics review.<sup>1</sup>

## **Vulnerability in Existing Regulations and Guidelines**

The Common Rule, the centerpiece of the U.S. human subject protection regulations, uses the word “vulnerable” three times. First, it provides that institutional review boards (IRBs) that regularly review research involving “a vulnerable category of subjects” should “consider” including one or more individuals “who are knowledgeable about and experienced in working with these subjects.”<sup>2</sup> Second, in the section on equitable selection of subjects, the regulations direct IRBs to be “particularly cognizant of the special problems of research involving vulnerable populations.”<sup>3</sup> Third, “when some or all of the subjects are likely to be vulnerable to coercion or undue influence,” the regulations require “additional safeguards” to protect these subjects’ rights and welfare.<sup>4</sup>

The regulations do not define vulnerability, but each time the word is used, it is accompanied by the phrase “such as children, prisoners, pregnant women, or handicapped or mentally disabled persons”<sup>5</sup> and, in two of the three sections, “economically or educationally disadvantaged persons.”<sup>6</sup> The words “such as” suggest that these groups are simply examples of vulnerable populations, rather than an exhaustive list, but the diversity of the examples makes it difficult to identify what characteristics a group must have to be considered vulnerable. For example, some of the groups could be considered vulnerable because they lack the capacity to provide informed consent to research (e.g., children and mentally disabled persons), or because they are unusually susceptible to coercion (e.g., prisoners), but with other groups (e.g., pregnant women), it is not clear why any special issues related to capacity or coercion would necessarily arise.

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In addition to lacking a clear definition of vulnerability, the regulations offer little guidance on how IRBs should respond to proposed research protocols involving subjects who have been determined to be vulnerable. The instruction to be “particularly cognizant of the special problems of research involving vulnerable populations”<sup>7</sup> is not especially helpful, given that the regulations never explain what any of these special problems are. Similarly, while the regulations call on IRBs to adopt “additional safeguards” to protect subjects who are vulnerable to coercion or undue influence,<sup>8</sup> they do not offer any suggestions on the nature of such safeguards, nor do they indicate whether certain types of vulnerability should ever preclude participation in research. Some of these ambiguities are addressed in the separate subparts of the regulations applicable to pregnant women (subpart B), prisoners (subpart C), and children (subpart D),<sup>9</sup> but these subparts do not address all of the groups listed as examples of vulnerable populations. In addition, the subparts have not been adopted by all federal agencies.<sup>10</sup>

If it is hard to discern a coherent approach to vulnerability in the federal regulations, then it becomes even more difficult when other international guid-

For the Council of International Organizations of Medical Sciences (CIOMS), vulnerable persons are “those who are relatively (or absolutely) incapable of protecting their own interests” as a result of “insufficient power, intelligence, education, resources, strength, or other needed attributes.”<sup>12</sup> CIOMS’s list of examples of vulnerable persons is lengthy: in addition to many of the expected categories, it includes such groups as “patients with incurable disease, individuals who are politically powerless, and members of communities unfamiliar with modern medical concepts.”<sup>13</sup> The “central problem” in research involving these groups, the Guidelines explain, is the danger that there will be “an inequitable distribution of the burdens and benefits of research participation.”<sup>14</sup>

The International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice also contain an expansive list of vulnerable populations, ranging from “employees of the pharmaceutical industry” to “unemployed or impoverished persons” and “nomads.”<sup>15</sup> The ICH guidelines equate vulnerability with situations in which an individual’s “willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory

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ance documents are also considered. For example, the introduction to the Declaration of Helsinki states that “[s]ome research populations are vulnerable and need special protection,” and specifically mentions “the economically and medically disadvantaged,” “those who cannot give or refuse consent for themselves,” “those who may be subject to giving consent under duress,” “those who will not benefit personally from the research,” and “those for whom the research is combined with care.”<sup>11</sup> This list is so broad that almost any research subject could be fit into it — particularly one of the last two categories, which together encompass virtually the entire universe of individuals who participate in medical research. Moreover, the Declaration, like the federal regulations, does not clearly specify the type of “special protections” it has in mind.

response from senior members of a hierarchy in the case of refusal to participate.”<sup>16</sup> Unlike the CIOMS guidelines, which focus on equity-related considerations about the distribution of benefits and burdens, the ICH guidelines seem more concerned with whether the subjects’ agreement to participate reflects a genuinely voluntary choice.

One theme that runs through all of these documents is the idea that vulnerability stems primarily from belonging to particular “populations” (e.g., prisoners or persons with mental disabilities) — the implication being that individuals who are members of these populations are inherently vulnerable in all research settings. Criticizing this approach, the National Bioethics Advisory Commission (NBAC) observed that “vulnerability is sensitive to context,

and individuals may be vulnerable in one situation but not in another.”<sup>17</sup> Rather than focusing on vulnerable populations, NBAC proposed to define vulnerability in terms of “situations in which individuals might be considered vulnerable.”<sup>18</sup> For example, the problem of “deferential vulnerability” arises when the prospective subjects “have the cognitive capacity to consent but are subject to the authority of others who might have independent interests in whether prospective participants agree to enroll in the research study.”<sup>19</sup>

Although NBAC identified six different types of vulnerability-inducing situations, it suggested that all of these situations boil down to two basic concerns. First, some subjects “have difficulty providing vol-

ulnerability actually means, calls for “protecting the vulnerable” seem to have an intuitive ethical appeal, and are therefore likely to continue.

From a regulatory perspective, however, using a single term to describe disparate situations is problematic, particularly when the situations do not raise identical policy concerns. Rather than simply instructing IRBs to identify “vulnerable subjects” and implement unspecified “protections,”<sup>22</sup> it would be more useful if the regulations (and/or accompanying guidance documents) were to break the concept of vulnerability down into more nuanced categories, and indicate exactly how these different categories should be taken into account in the process of ethics review.

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untary, informed consent arising from limitations in decision-making capacity (as in the case of children) or situational circumstances (as in the case of prisoners).”<sup>20</sup> Like the ICH guidelines, NBAC took a broad view of the type of circumstances that can compromise voluntariness. For example, it suggested that seriously ill individuals in “dire circumstances” may be unduly influenced by the expectation of medical benefits, or that poor people might enroll in research “against their better judgment” if they are offered payment or access to free health care. In addition to consent-related vulnerability, NBAC concluded that some subjects are vulnerable because they “are especially at risk for exploitation (as in the case of persons who belong to undervalued groups in our society).”<sup>21</sup> However, NBAC did not define what it meant by “exploitation,” and it did not explore whether the two different types of vulnerability it identified might call for different regulatory responses.

### **Specifying Vulnerability**

The concept of vulnerability has been used so extensively, and so inconsistently, that it is tempting to conclude that it is incapable of providing any meaningful ethical guidance. As a practical matter, however, it is unlikely that vulnerability language will disappear any time soon. Even if there is no consensus on what

The first step in developing a coherent regulatory approach to vulnerability is recognizing that vulnerability is not a stand-alone concept. Rather, a person must be vulnerable *to* something. The potential objects of vulnerability are extensive, ranging from physical harm to temptation to criticism to ridicule. Regulatory references to subjects who are simply “vulnerable” in the abstract — such as two of the three references to vulnerability in the Common Rule — are therefore inherently nonsensical. Few people are simply “vulnerable” in every possible sense of the word.

Thus, the central question is determining the nature of the human subject’s vulnerability — i.e., what are vulnerable human subjects actually vulnerable *to*? Commentators have offered differing answers to this question. Carol Levine and colleagues, for example, argue that “the root of the concept of vulnerability lies in the possibility of physical harm.”<sup>23</sup> This implies that human subjects are vulnerable when they are prone to a heightened risk of injury. Frank Leavitt, by contrast, suggests that, when we say that research subjects are vulnerable, we mean that they are open to “an assault” on their “respect, health, or rights,” which extends the focus well beyond concerns about physical harm.<sup>24</sup> For Samia Hurst, being vulnerable means being at a heightened risk of experiencing a *wrong*, a concept that is broader than harm. Thus, she argues,

vulnerable research subjects are those who are at a heightened risk of any type of research-related impropriety, ranging from physical harm to breach of confidentiality to not “getting fair consideration in resource allocation.”<sup>25</sup>

One way to think about this question is to link the concept of vulnerability to the basic “deal” that underlies society’s regulation of human subject research, as reflected in regulatory standards and internationally agreed-upon ethics guidelines. According to this deal, we will permit researchers to invite individuals to participate as subjects in experiments — even experiments that will expose those individuals to risks without any compensating medical benefits — but only if certain conditions are satisfied. These conditions include, among other things, the IRB’s determination that the risks of the study are reasonable in relation to its total anticipated benefits (both direct benefits to subjects and potential long-term benefits to society), that the risks have been minimized to the extent reasonably possible, and that the subjects will be able to provide voluntary, informed consent. Importantly, none of these conditions requires the IRB to determine that participating in the study would be a “good choice” for the participants. Rather, as long as the IRB finds that the conditions described above have been satisfied, it is up to the individual subjects to determine whether they personally desire to participate in the research. In making this individual-level determination, subjects are free to take into account a broad range of potential benefits the IRB is not supposed to consider in its overall risk-benefit assessment, such as the psychological rewards of acting altruistically or the material benefits of participating in a study that offers payments or access to medical attention.

This division of authority between IRBs and research subjects reflects a middle ground between two theoretically possible systems. At one extreme, we could let competent adults participate in any type of research, regardless of the study’s objective risk-benefit ratio, on the theory that autonomous individuals have the right to take whatever risks they find personally acceptable. We do not have such a system: if the study does not offer a net social benefit, then the IRB is not supposed to approve it, even if a fully informed subject would be willing to participate. At the other extreme, we could require IRBs to determine that participating in research would be in the individual best interests of all the subjects in a study. But we do not do this either. Even if the risks clearly outweigh the potential benefits from the individual subjects’ perspective (as

with, for example, a Phase I study of a new drug, in which subjects will be exposed to risk without any real possibility of direct medical benefits), the IRB may approve the study if the potential societal benefits are sufficiently great. The deal, in short, is that we defer to individuals’ choices to take research-related risks for idiosyncratic reasons — but only if they are genuinely capable of acting autonomously, and only if the risks are “worth it” from a societal point of view.

Within this framework, 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. This risk can arise from different sources. First, some vulnerabilities can create or exacerbate barriers to obtaining informed consent to research (“consent-based vulnerabilities”), potentially violating the deal’s condition that research risks be voluntary. Second, some vulnerabilities may enhance the level of risks associated with subjects’ participation in a study (“risk-based vulnerabilities”), thereby calling into question the study’s underlying risk-benefit ratio. Finally, some vulnerabilities can raise concerns about the distribution of the benefits and burdens of the research (“justice-based vulnerabilities”), and these distributional concerns may also be relevant to the risk-benefit analysis.<sup>26</sup>

Consent-based vulnerabilities challenge the deal’s basic premise that subjects have provided their voluntary, informed agreement to assume the risks of research. These vulnerabilities can be either remediable or irremediable. An example of a remediable

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consent-based vulnerability would be a study involving students or employees of the investigator, in which the prospective subjects may not be in a position to exercise genuinely voluntary choice. In these situations, the IRB can impose requirements to safeguard the voluntariness of the consent process, either by prohibiting the recruitment of students or employees or ensuring that a decision not to participate will have no academic or job-related consequences. Assuming the IRB can mitigate the potential impact of the vulnerability-inducing factor, the study can then be evaluated according to the usual standards governing research ethics review.

Irremediable consent-based vulnerabilities, by contrast, are barriers to informed consent that can never be eliminated. For example, no matter what additional safeguards or protections are added to a protocol, it will never be possible to conduct a study involving 3-year-old children (or 90-year-old advanced Alzheimer's patients) with the subjects' voluntary and informed agreement. In these situations, additional safeguards can be developed to protect the subjects' rights and welfare, including requiring parental or surrogate consent in place of the subject's. However, these additional safeguards do not change the fact that one of the key terms of the deal — individual informed consent — has still not been satisfied. Accordingly, these vulnerabilities make it impossible to justify research according to the usual arrangement, and an entirely different justification will be needed if the study is to be approved.<sup>27</sup>

A second condition of the deal is that the risks to subjects must be reasonable in relation to the total anticipated benefits of the study. This condition may be jeopardized if some subjects are at risk of greater-than-usual harms from participating in research. For

as long as the expected benefits of the study outweigh the study's overall risks.

The final type of vulnerability, justice-based, can best be illustrated by some types of research in developing countries. Many existing guidance documents recognize impoverished residents of developing countries as vulnerable populations,<sup>28</sup> but the basis of this characterization is not always clear. In some cases, the implication seems to be that such individuals are inherently incapable of acting autonomously or protecting their own interests. However, even if individuals living in low-income countries have fewer alternatives to research than most residents of wealthy countries, the majority of them nonetheless retain the capacity to make autonomous choices.<sup>29</sup> Similarly, while developing country research may involve heightened risks due to differences in resources, legal protections, or cultural practices, many of those risks can be reduced to minimal levels, and those that cannot may be justified by the potential societal gain. Rather than being primarily an issue of consent or risk, the chief vulnerability in developing country research stems from the danger that the societal benefits anticipated from

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example, in a study in which the primary risk is the potential disclosure of confidential medical records, subjects can be considered vulnerable if their records contain particularly sensitive information, such as a history of treatment for serious mental illness. The IRB can address this vulnerability by requiring heightened safeguards to protect the subjects' privacy, including perhaps a requirement that the subjects' identities not be recorded.

As with consent-based vulnerabilities, risk-based vulnerabilities can be either remediable or irremediable. Where a risk-based vulnerability cannot be eliminated through the use of additional safeguards, it should be treated like any other risk in the study and factored into the overall risk-benefit assessment. Thus, an irremediable risk-based vulnerability need not be an absolute barrier to proceeding with research,

the research will not be practically available in the host country, despite the fact that host country residents will be exposed to the risks. This violates what might be seen as one of the deal's implicit premises: that, even if the individuals in a study do not stand to receive direct benefits from participation, the study is expected to benefit the society of which the individual subjects are a part.

Justice-based vulnerabilities are at least theoretically remediable, by ensuring that the benefits of the study do, in fact, extend to the population from which the subjects will be recruited. The problem is determining the type of benefits to host countries that should count as legitimate trade-offs for research-related risks.<sup>30</sup> For some commentators, any type of benefits important to the community can be factored into the analysis, including, for example, general contributions to

building the country's health care infrastructure.<sup>31</sup> For others, the only relevant benefits are those that will be derived from the knowledge expected to be generated from the study itself.<sup>32</sup> In addition, disagreements can arise over the appropriateness of various risk-benefit trade-offs. For example, at one point CIOMS took the position that Phase I studies should not be conducted in developing countries, because those countries would not receive any of the benefits from the research. After developing countries criticized this position, CIOMS withdrew it.<sup>33</sup> Presumably, the developing countries believed that, even if Phase I studies offer no prospect of direct benefit to the individual subjects, they provide sufficient overall benefits to the host countries to justify asking residents of such countries to undertake the risk.

would be a violation of the principle of respect for personhood" — i.e., it would be paternalistic.<sup>35</sup> Limiting research on vulnerability grounds is paternalistic only when such limitations reflect the idea that individuals are incapable of making their own decisions. With risk-based and justice-based vulnerabilities, however, the point is that *even if* individual subjects are fully capable of acting autonomously, society may have an interest in limiting some studies to which competent individuals might voluntarily consent.

The distinction between consent-based and justice-based vulnerabilities is also a departure from CIOMS's approach, which defines vulnerability in terms of the subject's inability to protect his or her interests. In light of this definition, CIOMS's effort to limit Phase I studies to wealthy country residents implied that developing country residents were incapable of protecting themselves, an implication that understandably came across as paternalistic. If CIOMS had framed its concerns in terms of international justice, rather than subjects' diminished capacity for self-protection, then its proposal might have met with a better response.

Ultimately, recognizing the distinction between consent-based and other types of vulnerabilities gives IRBs a way to respond to concerns about exploitation without having to look at all vulnerability-related considerations through the lens of coercion or undue inducement. In so doing, it avoids the stigmatizing implication that vulnerable subjects are necessarily incapable of making decisions for themselves.

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#### References

1. For differing approaches to these questions, see, e.g., S. A. Hurst, "Vulnerability in Research and Health Care: Describing the Elephant in the Room?" *Bioethics* 22, no. 4 (2008): 191-202; B. C. Vladeck, "How Useful Is 'Vulnerable' as a Concept?" *Health Affairs* 26, no. 5 (2007): 1231-1234, F. J. Leavitt, "Is Any Research Population Not Vulnerable?" *Cambridge Quarterly of Healthcare Ethics* 15, no. 7 (2006): 81-88; C. Levine, "The Limitations of 'Vulnerability' as a Protection for Human Research Participants," *American Journal of Bioethics* 4, no. 3 (2004): 44-49; K. Kipnis, "Vulnerability in Research Subjects: A Bioethical Taxonomy," *Ethical and Policy Issues in Research Involving Human Participants*, Vol. II, 2001, at G1-G13.
2. 45 CFR 46.107(a).
3. 45 CFR 46.111(a)(4).
4. 45 CFR 46.111(b).
5. 45 CFR 46.107(a).
6. 45 CFR 46.111(a)(4) and (b).
7. 45 CFR 46.111(a)(4).

## Distinguishing among the three different types of vulnerabilities reveals that the relationship between vulnerability and consent is not the same in all situations.

### Conclusion

Looking at vulnerability as three distinct phenomena — consent-based, risk-based, and justice-based — has several implications. First, it suggests that it would be a mistake to characterize vulnerability as either an entirely individual or an entirely group-based phenomenon. Consent- and risk-based vulnerabilities make more sense conceptualized as individual issues, but justice-based vulnerabilities are hard to understand as anything other than a population-based concern.

Second, distinguishing among the three different types of vulnerabilities reveals that the relationship between vulnerability and consent is not the same in all situations. With consent-based vulnerabilities, it will often be possible to remedy the vulnerability by eliminating barriers to voluntariness or improving comprehension.<sup>34</sup> But these measures, no matter how effective, are not a sufficient response to risk-based or justice-based vulnerabilities. Even if all the individual participants are making voluntary and informed choices, their willingness to participate does not eliminate the risk- or justice-based concerns.

This point is important because it responds to NBAC's concern that excluding vulnerable subjects from research should be avoided because it would "treat them as though they are not autonomous agents, which

8. *Id.*
9. 45 CFR 46.201 (subpart b), 45 CFR 46.301 (subpart c), 45 CFR 46.401 (subpart d), respectively.
10. National Bioethics Advisory Committee (NBAC), "Federal Agency Survey on Policies and Procedures for the Protection of Human Subjects in Research," *Ethical and Policy Issues in Research Involving Human Participants*, Vol. II: Commissioned Papers and Staff Analysis, Bethesda, Maryland, 2001, at J-14.
11. World Medical Association, *Declaration of Helsinki*, WMA General Assembly, 1964, as amended through 2004, at A(8).
12. Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Geneva, 2002, at Guideline 13, commentary.
13. *Id.*
14. *Id.*
15. International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline, *Guideline for Good Clinical Practice*, 1996, at 1.16.
16. *Id.*
17. National Bioethics Advisory Commission (NBAC), "Assessing Risks and Potential Benefits and Evaluating Vulnerability," *Ethical and Policy Issues in Research Involving Human Participants*, Vol. I: Reports and Recommendations, Bethesda, Maryland, 2001, at 87.
18. *Id.*, at 88.
19. *Id.*, at 89.
20. See NBAC, *supra* note 17, at 85.
21. *Id.*
22. See *supra* note 6.
23. See Levine, *supra* note 1.
24. *Id.*
25. See Hurst, *supra* note 1.
26. The justice-based dimensions of vulnerability were explicitly recognized in the Belmont Report. See The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report*, 1979.
27. For an attempt at such a justification in connection with decisionally impaired adults, see C. H. Coleman, "Research with Decisionally Incapacitated Human Subjects: An Argument for a Systemic Approach to Risk-Benefit Assessment," *Indiana Law Journal* 83, no. 3 (2008): 743-789. For proposed justifications for research with children, see, e.g., D. L. Coleman, "The Legal Ethics of Pediatric Research," *Duke Law Journal* 57, no. 3 (2007): 517-624, and P. Litton, "Non-Beneficial Pediatric Research and the Best Interests Standard: A Legal and Ethical Reconciliation," *Yale Journal of Health Policy, Law and Ethics* 8 (2008): 359-420.
28. See CIOMS, *supra* note 12; NBAC "Guidelines," *supra* note 17, respectively.
29. Cf. C.C. Denny and C. Grady, "Clinical Research with Economically Disadvantaged Populations," *Journal of Medical Ethics* 33, no. 7 (2007): 382-385.
30. See Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, "Moral Standards for Research in Developing Countries: From 'Reasonable Availability' to 'Fair Benefits,'" *Hastings Center Report* 34, no. 3 (2004): 17-27; J. Arras, "Fair Benefits in International Medical Research," *Hastings Center Report* 34, no. 3 (2004): 3; S. Gbadegesin and D. Wendler, "Protecting Communities in Health Research from Exploitation," *Bioethics* 20, no. 5 (2006): 248-253.
31. The "mutually advantageous exploitation" model is critiqued by A. Ballantyne, "Fair Benefits Accounts of Exploitation Require a Normative Principle of Fairness: Response to Gbadegesin and Wendler, and Emanuel et al.," *Bioethics* 22, no. 4 (2008): 239-244.
32. A. J. London and J. Kimmelman, "Justice in Translation: From Bench to Bedside in the Developing World," *The Lancet* 372, no. 9632 (2008): 82-85.
33. R. Macklin, "Bioethics, Vulnerability, and Protection," *Bioethics* 17, nos. 5-6 (2003): 472-486, at 480.
34. For an example of how persons who initially appear to lack decision-making capacity can be rendered capable through education, see J. Stephenson, "Probing Informed Consent in Schizophrenia Research," *JAMA* 281, no. 24 (1999): 2273-2274.
35. See NBAC, *supra* note 17, at 92.