Exploring the Concept of Vulnerability in the Work of the US Presidential Commission for the Study of Bioethical Issues*

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Abstract

Established in 2009, the US Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) advises the President on complex topics in bioethics that arise from advances in medicine, science and technology. The Bioethics Commission repeatedly addresses certain core ethical issues in its analyses, such as the concept of vulnerability and appropriate protections for potentially vulnerable research participants. The Bioethics Commission has addressed vulnerability in several contexts, including paediatric research, multinational research and neuroscience research. In this article, we summarise the Bioethics Commission's analyses and recommendations concerning vulnerability and identify some ethical commonalities across contexts. Through its work on the concept of vulnerability, the Bioethics Commission has sought to clarify long-standing ethical dilemmas and move the conversation forward in support of ethical and scientific progress.

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* The findings and conclusions presented here are those of the authors and do not necessarily represent the official position of the Presidential Commission for the Study of Bioethical Issues, National Institutes of Health, or the Department of Health and Human Services.

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Established in 2009, the US Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) advises the President on complex topics in bioethics arising from advances in medicine, science and technology. It is the most recent in a long line of US bioethics advisory bodies that began with the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) in 1974, which penned the seminal *Belmont Report*.[1]

The Bioethics Commission has been prolific, authoring nine reports in fewer than five years since its first meeting. These reports address wide-ranging topics, from synthetic biology, to the US Public Health Service-supported STD studies in Guatemala in the late 1940s, to privacy and whole genome sequencing. Despite the reports' varied subject matter, the Bioethics Commission repeatedly addresses certain core ethical issues in its analyse, such as the concept of vulnerability and appropriate protections for potentially vulnerable research participants.

Vulnerability often describes individuals or groups at greater risk of being harmed, mistreated, misled or exploited—that is, unfairly taken advantage of—in research.[2] Sometimes groups (such as children) are categorically defined as vulnerable. Vulnerability can also depend on context. The National Bioethics Advisory Commission (NBAC; another predecessor US bioethics advisory body), for example, identified six types of vulnerability, including: cognitive or communicative vulnerability; institutional vulnerability; deferential vulnerability; medical vulnerability; economic vulnerability; and social vulnerability.[3] The concept of vulnerability sits at the centre of ongoing scholarly debate—a debate that the Bioethics Commission has entered through its work.

The Bioethics Commission has addressed vulnerability in several contexts, including paediatric research, multinational research and neuroscience research.[4] In this article, we summarise the Bioethics Commission's analyses and recommendations concerning vulnerability, and identify some ethical commonalities across contexts. We focus, in particular, on the Bioethics Commission's report, *Safeguarding Children: Pediatric Medical Countermeasure Research* (*Safeguarding Children*).[5] In that report, the Bioethics Commission sought to reconcile the fundamental tension between protecting children from undue risk in research, and protecting children (to the extent possible) through the fruits of research—a tension that often describes research with vulnerable participants more broadly.[6]

Research with Children

Background

Governments and international organisations consistently recognise children as vulnerable in research.[7] Children cannot legally or ethically consent to participate in research and therefore require additional protections. US regulations governing Department of Health and Human Services (HHS)-supported research specify these protections in Subpart D[8] and the Common Rule (regulations adopted by 18 US agencies, including HHS, that govern federally supported research with human participants).[9] They include requirements for parental permission and meaningful child assent, as well as limits on the amount of research risk to which paediatric participants may be exposed. These regulations derive directly from the National Commission's 1977 recommendations for protecting children in research.[10]

Subpart D reflects a central tenet of ethical paediatric research: generally, research with children is only permissible when it exposes children to no more than minimal risk, unless the research offers a prospect of direct benefit to participants or the benefit of vital generalisable knowledge about participants' condition.[11] "Minimal risk" is a level of risk no greater than that ordinarily encountered in daily life or during routine physical or psychological examinations or tests.[12] Scholarly debate surrounds the question of whether this definition reflects a subjective or objective standard. The Bioethics Commission and other national advisory bodies in the United States agree that it should be interpreted as the "degree of risk encountered in the daily life of a healthy child living in a safe environment or the risk to which a healthy child is exposed during a routine examination."[13]

Under extraordinary circumstances, greater-than-minimal-risk research that offers no prospect of direct benefit to healthy participants can proceed ethically. The National Commission recognised this exception to the general rule decades ago, noting: "[e]xceptional situations may arise in which considerable dangers to children or to the community at large might be avoided or prevented by exposing children to research attended by more than minimal risk."[14] It is now codified at Section 407 of Subpart D.

According to US regulations, research under these exceptional circumstances can proceed only if the Secretary of HHS, upon consultation with a panel of experts and after having provided the opportunity for public comment, determines that: (i) the research presents a reasonable opportunity to address a serious problem; (ii) the research will be conducted in accordance with sound

ethical principles; and (iii) provisions are made for parental permission and meaningful child assent.[15] Such national-level review stands in stark contrast to the local-level review typical of other research (including paediatric research that is minimal risk, that which provides the prospect of direct benefit, and that which is likely to produce generalisable knowledge about participants' condition), which is conducted by institutional review boards (IRBs).

Safeguarding Children

In early 2011, the US government conducted "Dark Zephyr", an exercise simulating federal, state and local response to a large-scale anthrax attack. Officials quickly realised that, although the government had plans in place to treat adults in such an event, no evidence supported a clear course of action for children. After a scientific and technical assessment by the US National Biodefense Science Board, the US Secretary of HHS sought an ethical review to inform future decision-making.[16]

Thus, in January 2012, the US Secretary of HHS asked the Bioethics Commission to review a particularly complex type of paediatric research: paediatric medical countermeasure (MCM) research. For its analysis, the Bioethics Commission defined MCMs as clinical products and interventions (i.e. drugs, devices or biologics) used in response to chemical, biological, radiological and nuclear terror attacks. Catalysed by the lack of data on the paediatric safety and effectiveness of MCMs, the Secretary asked the Bioethics Commission to "conduct a thorough review of the ethical considerations of conducting clinical trials of medical countermeasures in children."[17]

The Bioethics Commission recognised that the ethical landscape depends on whether such research occurs before a terror attack ("pre-event" research) or after ("post-event" research). In pre-event research, a terror attack has not occurred and thus no one is sick. Pre-event research necessarily involves healthy participants who do not stand to directly benefit from it. Indeed, the likelihood that the results of such research will ever be needed to benefit future children is unknown because the likelihood of a terror event occurring is unknown or unknowable.[18]

By contrast, in post-event research, an attack has already occurred and children have been exposed to the agent or pathogen that an MCM is intended to combat. Under such circumstances, paediatric MCM research might benefit participants directly or yield generalisable knowledge about their condition. Such research might also pose only minimal risk to participants; for example, if children have already received the MCM outside of research (i.e. because it is

made available in an emergency) and only observational research occurs.[19] There are limits to what research would be scientifically and logistically feasible post-event, however, because of the predictable fear and confusion that will ensue.

The Bioethics Commission also recognised the ethical complexity inherent in all paediatric research. Accepting that children are vulnerable in research because they cannot ethically or legally consent to participate, the Bioethics Commission also acknowledged that children's vulnerability can derive from multiple sources, including "expectations of deference to adult authority, lack of independent resources for autonomous decision making, and longstanding institutionalised relationships of adult authority and power."[20] It further highlighted a "commitment to repudiating exploitation" in paediatric research protections, grounded in foundational principles of respect for persons, non-maleficence, and justice.[21] The Secretary's charge required the Bioethics Commission to navigate the intricate ethical contours of both MCM research and paediatric research in its report.

Pre-event Research

The Bioethics Commission's recommendations in *Safeguarding Children* reflect the central tenet of paediatric research ethics discussed above. More specifically, the Bioethics Commission concluded that pre-event paediatric MCM research should pose no more than minimal risk except under extraordinary circumstances. In other words, pre-event MCM research generally cannot proceed unless it is minimal risk.

The Bioethics Commission carefully described a research design through which such minimal risk research might be possible.[22] Before beginning pre-event research with children, modelling, animal studies and research with the youngest adults should be completed. Research with young adults might support an inference that research with the oldest children is minimal risk. Similarly, research with the oldest children might then support an inference that research with the next oldest cohort is also minimal risk. Minimal risk pre-event paediatric MCM research could thus be designed using careful age de-escalation to support similar inferences from one group of children to the next. Not only does this age de-escalation design begin with research with the oldest children for scientifically sound reasons and for risk titration, but it also begins with the group of children who are best able to understand the research and give their meaningful assent.

Nonetheless, it will sometimes be impossible to design minimal risk pre-event research; for instance, if inferring risk levels between groups of children in

different developmental stages proves impossible or if there is not enough time to conduct full age de-escalation.[23] In such cases, national-level review is required. The Bioethics Commission recommended a framework for such review grounded in the requirements of Section 407 (Figure 1). In this framework, it clarified when research presents a "reasonable opportunity" to address a "serious problem", specified what constitutes accordance with "sound ethical principles", and reiterated the importance of parental permission and meaningful child assent.

1. Does the research present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem that could affect the health or welfare of children?

A. Serious problem, as judged by:
   i. Consequences of exposure
   ii. Likelihood (or threat) of exposure
   iii. "Vital importance"
B. Reasonable opportunity

2. Will the research be conducted in accordance with sound ethical principles?

A. Ethical threshold of acceptable risk and adequate protection from harm
B. Ethical research design
   i. Scientific necessity
   ii. Research plan
      a. Scientific validity
      b. Small trials and age de-escalation
      c. Appropriate monitoring
      d. Proper planning for post-event research
   iii. Prior adult testing to minimize risk to children
   iv. Sufficient benefit over alternatives
   v. Fair subject selection
C. Post-trial requirements to ensure ethical treatment of children and their families
   i. Distribution protocol for all children tested or assured
   ii. Compensation for research-related injury
D. Community engagement in pre-event research
E. Transparency and accountability

3. Are adequate provisions made for soliciting the permission of parents or guardians and the meaningful assent of children?

Figure 1. Bioethics Commission's Ethical Framework to Guide National-Level Review of Paediatric MCM Research under Section 407[24]

Although Section 407 introduces the term "sound ethical principles", it does not define what these principles are, nor what it means to be in accord with them. The bulk of the Bioethics Commission's ethical framework focuses on how to understand and implement this language. Accordingly, the Bioethics Commission specified rigorous conditions for conducting research in accordance with sound ethical principles. These conditions fall into five general categories: ethical threshold of acceptable risk; ethical research design; post-trial requirements; community engagement; and transparency and accountability. The Bioethics Commission discussed these conditions in detail in *Safeguarding Children*. Here, we focus on one particularly thorny category: limits on research risk.

Section 407 does not explicitly limit the amount of risk to which children may be exposed in research that falls under its purview (e.g. greater-than-minimal-risk pre-event MCM research with healthy participants who do not stand to directly benefit from it). This lack of a risk ceiling is particularly noteworthy because limitations on risk are a central protection for paediatric research participants.[25] Unlike adult participants, children cannot legally or ethically consent to undertake risk for the benefit of others. Generally, only minimal risk research is permitted, unless there is a prospect of direct benefit. Even when research will likely yield vital generalisable knowledge about participants' condition, only a minor increase over minimal risk is permitted.[26]

The Bioethics Commission concluded that, in the context of pre-event paediatric MCM research, a risk ceiling is ethically required despite Section 407's silence on this point. "[R]esearch protections," it explained, "can be summarized as adequately protecting children from harm in light of the expected results of the research—that is, whether the research is of possible direct benefit to individual participants, of potential benefit to an identifiable class of children with a disorder or condition, or of potential benefit to all children as a class."[27] Because the likelihood of a terror attack is unknown, it is unclear whether the results of paediatric MCM research will ever be needed to benefit future children. For this critical reason—the uncertainty of the research, even if successful, ever benefitting any children—a risk ceiling is necessary for such research to be in accord with sound ethical principles.

For the most part, the Bioethics Commission's ethical framework can provide guidance for research reviewable under Section 407 beyond the context of MCM research. That is not the case, however, for its conclusion regarding risk limitations. The Bioethics Commission's reasoning, grounded firmly in the uncertainty of a future terror attack, is not necessarily generalisable beyond the specific case of pre-event paediatric MCM research.

Post-event Research

The question whether to conduct pre-event research at all is ethically fraught and must be carefully navigated. By contrast, when untested or minimally tested MCMs are given to children in response to an attack in an effort to save lives, post-event research is ethically required by principles of beneficence—to benefit children who are exposed to an agent or pathogen—and justice—to secure the well-being of some of our most vulnerable citizens.

Mindful of the extraordinarily stressful and confusing circumstances under which any post-event study would take place, the Bioethics Commission recommended that post-event paediatric MCM research be planned in advance, with attention to the likely exigencies of a post-event situation. Although ethically clearer than pre-event research, post-event paediatric MCM research presents enormous scientific and logistical challenges.[28] For example, a post-event study would necessarily include uncontrolled variables that could lead to limited data. In addition, parents and children might not be at the same place at the same time when an attack occurs or an MCM is administered. Moreover, research might take place in the midst of a rapid emergency response, in which communication about and comprehension of the situation will be difficult. Victims of a terror attack will likely be fearful and vulnerable and therefore are also potentially deserving of special protections.

As part of this advance planning, the Bioethics Commission called for IRBs to ensure adequate processes for informed parental permission and meaningful child assent, scientifically sound research design and participant access to the best available care. In addition, plans should be in place for treatment or compensation for research-related injury, and provisions should be made for community engagement.[29]

In *Safeguarding Children*, the Bioethics Commission declared an "unwavering commitment to safeguard all children *from* unacceptable risks in research and *through* research that promotes their health and well-being."[30] It sought to promote an ethical path forward to accomplish both goals. Because the Bioethics Commission is an advisory body that neither funds nor regulates research, it is incumbent on others in the research community to adopt and implement its recommendations. Though still relatively recent, *Safeguarding Children* has been positively received. The American Academy of Pediatrics, for example, favourably discussed the Bioethics Commission's age de-escalation recommendation for designing pre-event paediatric MCM studies in 2014 guidance concerning clinical management of paediatric anthrax.[31]

Research with Other Potentially Vulnerable Participants

Under US law, when research participants "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" must be included in the study to protect their rights and welfare.[32] Such protections arguably are clearer for paediatric research participants than for other potentially vulnerable groups. For the most part, children are vulnerable for the same reasons, and thus, appropriate additional protections are more easily generalisable to children as a group (e.g. through a set of regulations in Subpart D). The Bioethics Commission has addressed issues of vulnerability in at least two other, less straightforward contexts: research with participants in low- and middle-income countries and research with participants with potentially impaired consent capacity.

Multinational Research: Avoiding Exploitation

Catalysed by the revelation of highly unethical US Public Health Service-funded research in Guatemala in the late 1940s, President Obama asked the Bioethics Commission to review current standards for protecting research participants.[33] After conducting a thorough review, the Bioethics Commission concluded that the current system generally protects people from avoidable harm or unethical treatment in research and offered 14 recommendations for improvement in *Moral Science: Protecting Participants in Human Subjects Research* (*Moral Science*).[34] These recommendations targeted various aspects of human subjects research, including compensation for research-related injury, transparency and accountability, community engagement and—most relevant for this discussion—research site selection.

The US Public Health Service studies in Guatemala in the 1940s enrolled subjects outside the United States including prisoners, psychiatric patients and conscripted soldiers, exposed them to sexually transmitted diseases without their informed consent, and often left them untreated.[35] Against this historical backdrop in which researchers chose sites based in part on the ease with which they could enrol potential research subjects, the Bioethics Commission considered the ethics of research site selection in *Moral Science*.

The Bioethics Commission recognised that certain settings raise heightened concerns about possible exploitation of research participants.[36] Research in low-income countries, for example, "raises particular concern that communities with limited access to needed healthcare will accept the risks of research but derive

benefits that are disproportionately low in relation to the risks involved—or that they will be enrolled in research to answer questions that will only benefit those in richer countries."[37] Ensuring that a study is responsive to the needs and priorities of the local community is one strategy for minimising the potential for exploitation. Ensuring adequate local infrastructure and ethical oversight is another.

With these strategies in mind, the Bioethics Commission recommended careful examination of site selection to ensure the protection of participants. Research sites should have the capacity—or be able to achieve the capacity—to support their protection.[38] Moreover, researchers should thoughtfully consider how responsive the research is to the health needs of the community. The Bioethics Commission cautioned, however, that the perfect (i.e. approving only research that serves the highest health priorities of a poor community) should not be the enemy of the good (i.e. approving research that serves a worthy health need). It recognised the complexity in the concept of responsiveness, and recommended further research and analysis to inform some of the challenging questions that responsiveness can raise.[39]

Neuroscience Research: Research with Participants with Potentially Impaired Consent Capacity

In 2015, the Bioethics Commission revisited the concept of vulnerability in its report, *Gray Matters: Topics at the Intersection of Neuroscience, Ethics, and Society* (*Gray Matters*, vol. 2)—the second instalment in a two-volume report responding to President Obama's request to consider ethical issues related to advances in neuroscience and technology.[40]

Many of the disorders and conditions studied in contemporary neuroscience research are associated with impaired, fluctuating or diminishing decision-making capacities. Questions surrounding how to conduct ethical research with individuals with potentially impaired consent capacity were thus central to the Bioethics Commission's analysis. It emphasised that such individuals must be adequately protected in research, and also responsibly included in research so that research benefits can inure to them and others with similar conditions.

In *Gray Matters*, vol. 2, the Bioethics Commission described the concept of vulnerability:

> Research ethics often invokes the concept of vulnerability to highlight the unique needs of certain populations who participate in research. Importantly, this framework of vulnerability highlights the ethical goal of providing special protections to those participants who might be more susceptible to exploitation or harm than others as a result of research participation. The

> concept of vulnerability in research ethics is longstanding and complicated. … Nevertheless, invoking the concept of vulnerability does serve a vital practical and ethical function—it calls our attention to research with human participants that warrants special scrutiny.[41]

When a potential participant lacks capacity to consent to research, he is vulnerable in a very fundamental sense. Informed consent helps to protect potential research participants from exploitation by providing them with information and offering them a choice. When informed consent cannot serve this protective function—for example, when participants lack consent capacity—alternative or additional protections can serve the same protective purpose.[42]

The Bioethics Commission carefully examined several such protections in *Gray Matters*, vol. 2—such as assent and dissent, independent monitors and research advance directives—and noted that appropriate additional protections will vary based on the proposed research project.[43] The Bioethics Commission also recognised gaps in our understanding of vulnerability and consent capacity, and called for continued research to better understand these concepts to improve research protections.[44]

In addition, the Bioethics Commission cautioned against labelling all members of a particular group—for example, all persons with a particular mental illness—as vulnerable or lacking capacity to consent. Such generalisations can have unintended, stigmatising effects.[45] As the Bioethics Commission explained, "[a]lthough certain conditions might be associated with impaired consent capacity, different individuals with the same diagnosed condition can exhibit varying capacities."[46] Rather than making assumptions about potential participants' capacity to consent, researchers should rely on robust capacity assessment before research begins (and, when indicated, during research) to help ensure that participants with potentially impaired consent capacity are adequately protected.[47] Neuroscience researchers can further help to mitigate stigma through their research, for example, by providing a more accurate picture of human abilities that might undermine common assumptions about individuals with stigmatised conditions.[48]

Ethical Themes across Contexts

Protections for Vulnerable Participants are Context-Dependent

Throughout its work on vulnerability, the Bioethics Commission has consistently rejected "one-size-fits-all" approaches. For example, it warned against assuming that all persons with certain diagnoses lack capacity to consent to research, in

favour of individualised assessments and tailored protections. Furthermore, when considering multinational research, the Bioethics Commission stressed that the ethical acceptability of a research site depends on site-specific factors, including whether the proposed site has the capacity to protect research participants.

In paediatric MCM research, the Bioethics Commission recognised that participant protections differ based on the situation, and more specifically, whether a terror attack has occurred. The ethical protections that should be in place for greater-than-minimal-risk pre-event paediatric MCM research differ meaningfully from those that should be in place for post-event research that might be minimal risk, or in which paediatric participants might benefit directly. In both situations, adequate protections must be in place for research to proceed ethically, but the content of the protections differs with context.

Community Engagement Can Help Address Concerns about Vulnerability

The Bioethics Commission has also stressed the importance of community engagement both to educate the public about proposed research and to educate researchers about community-specific concerns. Community engagement can provide protection against the potential for exploitation. As the Bioethics Commission explained, "community engagement can help improve informed consent processes, build relationships and trust, and increase the likelihood that research findings are relevant for affected communities."[49] A Bioethics Commission subcommittee similarly emphasised that "[c]ommunity engagement can be especially important to … close the gap in power differentials between those conducting or sponsoring the research and the community."[50]

Moreover, community engagement can help mitigate stigma that might be associated with a label of vulnerability. In *Gray Matters*, vol. 2, the Bioethics Commission specifically recommended that funders and neuroscience researchers engage with stakeholders and communities to build understanding of consent capacity and associated diagnoses.[51] Better understanding of conditions that might lead to impaired consent capacity can undermine stereotypes about particular groups and provide insight in crafting additional protections to safeguard participants with impaired consent capacity.

Responsible Inclusion Ensures Progress

Finally, the Bioethics Commission has always considered vulnerability in light of scientific progress. The opportunity for progress does not trump the ethical

imperative to protect those at risk of exploitation in research. Rather, it counsels in favour of charting an ethically appropriate path forward to ensure a just distribution of research's benefits and burdens. A well-described "pendulum" between under- and overprotection in human subjects research exists.[52] Policies developed in reaction to abuses and unethical research practices often focus on exclusion of potentially vulnerable research participants in order to minimise risk, and can lean towards overprotection. In response, other policies focus on maximising inclusion and the benefits of research, and sometimes risk under-protection. The Bioethics Commission has recommended travelling the path between both extremes.[53]

In *Safeguarding Children*, for instance, the Bioethics Commission did not call for a halt to paediatric MCM research; nor did it support such research moving ahead unchecked. Rather, it recognised the ethical duty to prepare for an emergency to the extent possible and recommended an ethically thoughtful and responsible course to proceed. Similarly, the Bioethics Commission recognised the potential cost of overprotection to participants with impaired consent capacity and, again, recommended a reasoned middle-ground approach.

Scholars, regulators and researchers often cite "vulnerability" as a justification for excluding participants from research. The Bioethics Commission has recognised, however, the need for information about certain vulnerable groups—obtainable through research—to better their health and condition. An approach of responsible inclusion enables such research to proceed, ensuring progress through research *and* adequately protecting those involved.

This approach to ethics—treating ethics not as a "stop sign" but rather as a necessary partner to scientifically sound research—is consistent throughout the Bioethics Commission's work. From its first recommendations for "prudent vigilance" in the emerging field of synthetic biology, to its more recent recommendations to integrate ethics and science early and throughout research, the Bioethics Commission has made clear that good science is ethical science.[54] It has advocated for research that protects potentially vulnerable participants both by ensuring that they are not unfairly taken advantage of and that they benefit from the promise of research.

Conclusion

The Bioethics Commission has analysed varied and complex topics in its reports, including many foundational topics in research ethics. Through its work on the concept of vulnerability, the Bioethics Commission has sought to clarify long-standing ethical dilemmas and move the conversation forward in support of

ethical and scientific progress. It has maintained a consistent message over the course of several reports—a message that constitutes a thoughtful addition to bioethics scholarship and policy.

Notes

1. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (DHEW Publication OS 78-0012) (Washington, DC: Department of Health, Education, and Welfare, 1978).
2. C. Levine et al., "The Limitations of 'Vulnerability' as a Protection for Human Research Participants", *The American Journal of Bioethics* 4, 3 (2004): 44–9; Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (*CIOMS Guidelines*) (Geneva: CIOMS, 2002), Guideline 13.
3. National Bioethics Advisory Commission (NBAC), *Ethical and Policy Issues in Research involving Human Participants* (Bethesda, MD: NBAC, 2001), pp. 88–90.
4. The Bioethics Commission has also released educational materials on the topic of vulnerability. These materials are free and available for download at http://bioethics.gov/education.
5. Presidential Commission for the Study of Bioethical Issues (PCSBI), *Safeguarding Children: Pediatric Medical Countermeasure Research* (*Safeguarding Children*) (Washington, DC: PCSBI, 2013).
6. See, for example, A.D. Lyerly, M.O. Little and R. Faden, "The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research", *International Journal of Feminist Approaches to Bioethics* 1, 2 (2008): 5–22.
7. *CIOMS Guidelines*, Guidelines 13 and 14; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *International Conference on Harmonisation Harmonized Tripartite Guideline: Clinical Investigation of Medicinal Products in the Pediatric Population*, 2000, E11; 45 C.F.R. Part 46, Subpart D.
8. 45 C.F.R. Part 46, Subpart D. The US Food and Drug Administration has adopted similar regulations. 21 C.F.R. Part 50, Subpart D. For ease of reference, we discuss and cite the regulations that comprise Subpart D in this article.
9. 45 C.F.R. Part 46, Subpart A.
10. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research involving Children* (DHEW Publication OS 77-0004) (Washington, DC: Department of Health, Education, and Welfare, 1977).
11. *Safeguarding Children*, p. 24; 45 C.F.R. §§ 46.404–6.
12. 45 C.F.R. § 46.102(i).
13. *Safeguarding Children*, p. 40. Minimal risk includes risks of conditions such as redness or moderate soreness at an injection site and risks of procedures such as drawing blood. Ibid., p. 68.
14. *Research involving Children*, p. 140.
15. 45 C.F.R. § 46.407.

16. *Safeguarding Children*, pp. 15–7.
17. Letter from Secretary Kathleen Sebelius, Health and Human Services, to Amy Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues, 6 January 2012. Available at http://bioethics.gov/sites/default/files/news/Pediatric%20Countermeasures%20Letter%20from%20the%20Secretary.pdf. The Secretary also asked the Bioethics Commission to review specifically the ethical considerations of testing the anthrax vaccine as post-exposure prophylaxis with children. We focus on the first (and more general) part of the Secretary's charge here.
18. *Safeguarding Children*, p. 51.
19. Ibid., pp. 91, 91n220.
20. Ibid., p. 26.
21. Ibid., p. 36.
22. Ibid., pp. 52–6.
23. Ibid., p. 60.
24. Ibid., p. 138.
25. See *Safeguarding Children*, p. 28: "The imposition of a rigorous risk ceiling ensures that, no matter how great the potential benefit, child research participants are not exposed to a disrespectful and exploitative level of risk for the interests of others in society."
26. 45 C.F.R. § 46.406. A minor increase over minimal risk includes risks of conditions such as missing a few days of school due to temporary fever or malaise and risks of procedures such as a skin biopsy or chest x-ray. *Safeguarding Children*, p. 68.
27. *Safeguarding Children*, p. 68.
28. Ibid., pp. 93–5.
29. Ibid., p. 97.
30. Ibid,. p. 105.
31. J.S. Bradley et al., "Pediatric Anthrax Clinical Management", *Pediatrics* 133, 5 (2014): e1411–36.
32. 45 C.F.R. § 46.111(b).
33. Letter from President Barack Obama to Amy Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues, 24 November 2010. Available at http://bioethics.gov/sites/default/files/Charge%20Letter%20FN7.pdf.
34. Presidential Commission for the Study of Bioethical Issues (PCSBI), *Moral Science: Protecting Participants in Human Subjects Research* (*Moral Science*) (Washington, DC: PCSBI, 2011).
35. PCSBI, *'Ethically Impossible': STD Research in Guatemala from 1946 to 1948* (Washington, DC: PCSBI, 2011).
36. *Moral Science*, p. 82. The Bioethics Commission further recognised that such settings could be either domestic or international.
37. Ibid., p. 85.
38. Ibid., p. 87.
39. Ibid., p. 88.
40. PCSBI, *Gray Matters: Topics at the Intersection of Neuroscience, Ethics, and Society* (*Gray Matters*, vol. 2) (Washington, DC: PCSBI, 2015).
41. Ibid., p. 59.

42. Ibid.
43. Ibid., pp. 65–74.
44. Ibid., pp. 79–80.
45. Ibid., pp. 60–1.
46. Ibid.
47. Ibid., p. 66.
48. Ibid., p. 61.
49. Ibid., p. 74. See also *Safeguarding Children*, p. 79: "Engaging marginalized communities along with the general public and other relevant stakeholders in the planning and conduct of … research will help to ensure ethical study design, implementation, and access to benefits should the need arise"; *Moral Science*, p. 78: "Effective community engagement provides an additional layer of safeguard by providing the community with opportunities to more thoroughly weigh and accept or reject the risks and benefits of research activities, discover possible implications of research that might have unintended consequences to host communities, and independently evaluate the effectiveness of research protections."
50. PCSBI, *Research across Borders: Proceedings of the International Research Panel of the Presidential Commission for the Study of Bioethical Issues* (Washington, DC: PCSBI, 2011), p. 7.
51. *Gray Matters*, vol. 2, p. 80.
52. A. Mastroianni and J. Kahn, "Swinging on the Pendulum: Shifting Views of Justice in Human Subjects Research", *Hastings Center Report* 31, 3 (2001): 21–8.
53. *Gray Matters*, vol. 2, pp. 59–60.
54. PCSBI, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies* (Washington, DC: PCSBI, 2010); PCSBI, *Gray Matters: Integrative Approaches for Neuroscience, Ethics, and Society* (Washington, DC: PCSBI, 2014).