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Reopening Old Divisions

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In seeking to “expand the debate” about minimal risk, Jeremy Snyder, Cari Miller, and Glenda Gray (2011) have actually reopened old divisions concerning the risks that children may be exposed to in research. Protections for pediatric research subjects, found in 45 CFR 46, Subpart D, emerged from a debate that took place more than 30 years ago (Freedman et al. 1993; Jonsen 2006). In the mid-1970s, the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research considered whether investigators should be allowed to enroll children in studies that are not likely to benefit them medically. Theologian Paul Ramsey argued that children should not take risks for the good of society (Ramsey 1970). Although adults can make an informed choice to participate in non-beneficial research, children cannot. In making a proxy decision for a child, one must act in the child’s best interests and protect him or her from harm or exploitation. Richard McCormick, another theologian, countered Ramsey’s position by arguing that the child’s interests not need be limited to the child’s own well-being, and may include an interest in making a contribution to society. Children can play a key role in helping to advance biomedical research and should be allowed to take some risks to benefit others (McCormick 1974). As long as these risks are minimal, children will be adequately protected from harm and exploitation. After much discussion, the National Commission sided with McCormick, and the language in 45 CFR 46.404 largely reflects his viewpoint (Jonsen 2006).

During the 1990s, it became apparent to many that the definition of minimal risk in the federal regulations—“the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” (45 CFR 46.102i)—is vague and subject to different interpretations (Kopelman 2000). Risks ordinarily encountered in daily life may refer to the risks encountered by the research subjects (a relativistic interpretation) or to the risks encountered by a normal member of the population (an absolutist interpretation). Many have objected to the relativistic interpretation on the grounds that this could be used to impose greater risks on populations that already face increased risks in their daily life, which would be unjust and potentially exploitative (Kopelman 2000). Also, sponsors and investigators would be encouraged to shop for high-risk environments, such as the inner city or a developing nation, to conduct non-beneficial pediatric research. Justice requires that similar cases be treated similarly. It would be unjust, therefore, to treat groups of children differently: If an experiment is too risky to be performed on suburban children living in the United States, it should also be too risky to be performed on inner-city children in the United States or children in a developing nation. Children living in different environments deserve equal protection from research risks (Resnik 2005).

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Snyder, Miller, and Gray make a strong case for including adolescents in HIV vaccine trials in South Africa, since these studies could offer important benefits to the population by reducing the rate of new HIV infections. To date, most HIV vaccine trials have only included adults. As Merck's failed HIV vaccine trial, named STEP, has demonstrated, the risks of participating in a vaccine trial can be significant. The vaccine was not effective at preventing HIV infection and several subgroups of participants had an increased risk of contracting HIV, compared to placebo groups. Uncircumcised males receiving the vaccine had a new HIV infection rate of 5.2% per year, compared to 1.4% of uncircumcised males receiving the placebo. The vaccine was an adenovirus vector carrying HIV antigens, designed to induce cellular immunity. While the vaccine was not the source of the infection, it may have increased some of the participants' vulnerability to infection (Buchbinder et al 2008). Participants in HIV vaccine trials may also increase their engagement in risky behaviors, such as sexual activity or intravenous drug use, under the mistaken belief that the vaccine will offer them additional protection (Chesney, Chambers, and Kahn 1997). Education in HIV prevention and blinding the participants (so they don't know if they are receiving the vaccine or a placebo) can reduce this risk.

Since an increased risk of HIV infection would be considered by most to be more than a minor increase over minimal risk and the participants are not likely to receive direct benefits, the proposed study discussed by Snyder, Miller, and Gray would not be approvable under 45 CFR 46.404 ("Research not involving greater than minimal risk"), 45 CFR 405 ("Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects"), or 45 CFR 46.406 ("Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition"). However, it might be approvable under 45 CFR 46.407 ("Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children"). (This commentary only considers U.S. regulations, which were the main focus of Snyder, Miller, and Gray's analysis.)

To make the case for including adolescents in HIV vaccine trials in South Africa, Snyder, Miller, and Gray argue that a relativistic standard of minimal risk should be applied to this study. If this standard is used, then the study may present only a minor increase over minimal risk in this population, given the risks that these adolescents already face in their environment, such as infectious diseases, malnutrition, and violence. The authors rely on Wendler's (2004) analysis of minimal risk to support their position. They argue that ethical review committees can use a relative standard of minimal risk to evaluate pediatric research, provided that a proposed study (A) is relevant to the needs of the host community; (B) is scientifically necessary; (C) is expected to benefit the host community; and (D) will not make participants prospectively worse off than if they had not been in the study. Snyder, Miller, and Gray claim that the HIV prevention trial in South Africa meets all of these conditions, and therefore use of relative standard of minimal risk is ethically acceptable.

There is little doubt that this proposed study would meet conditions A, B, and C. What is at issue is whether the study would make the participants prospectively worse off, and whether this potential outcome is ethically justifiable. One could argue that a study with an increased risk of HIV infection would make some participants prospectively worse off, if by "prospectively" one means worse off in the long run. A study that imposes temporary pain or discomfort on subjects would not make them prospectively worse off, but one that leads to permanent disability, chronic disease, or death would. Since HIV is a chronic infection that is often fatal, a study that increases the risks of HIV infection would leave some participants prospectively worse off. Snyder, Miller, and Gray could argue that many of these participants would have developed HIV even if they had not participated in the study,

so that they wouldn't be prospectively worse off, but this point is debatable. We could argue all day about whether the proposed study presents a "minor increase over minimal risk" in this population, or whether it makes some participants prospectively worse off, but a key question is whether these risks are ethically justifiable. Is it ethical to expose children to an increased risk of HIV infection in order to develop a vaccine that may benefit other children? That is what the evaluation of the proposed study boils down to.

If we view the matter as primarily a question about justifying the imposition of risks on pediatric research subjects, then we can see how this detour through the concept of minimal risk has taken us back into the middle of an old debate. Snyder, Miller, and Gray claim that the risks are justifiable, because the study is not exploitative or unjust. While this proposed study would benefit the population, these adolescents would be participating in research that would probably not be regarded as ethical (or approvable) in a population that faces lower daily life risks. Thus, a strong case could still be made that this would be unfair treatment, because these subjects would face higher research-related risks than other adolescent populations. Given these concerns, I argue that adolescents should not be included in HIV vaccine studies until we have a better understanding of the risks related to this research. Clinical trials should only include adults until we can be sure that participation does not significantly increase the risks of HIV infection.

References

- Buchbinder S, Mehrotra D, Duerr A, Fitzgerald D, Mogg R, Li D, Gilbert P, Lama J, Marmor M, del Rio C, McElrath M, Casimiro D, Gottesdiener K, Chodakewitz J, Corey L, Robertson M. and the Step Study Protocol Team. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): A double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet*. 2008; 372:1881–1893. [PubMed: 19012954]
- Chesney M, Chambers D, Kahn J. Risk behavior for HIV infection in participants in preventive HIV vaccine trials: A cautionary note. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 1997; 16:266–271. [PubMed: 9402073]
- Freedman B, Fuks A, Weijer C. In loco parentis. Minimal risk as an ethical threshold for research upon children. *Hastings Center Report*. 1993; 23:13–19. [PubMed: 8463083]
- Jonsen A. Nontherapeutic research with children: The Ramsey versus McCormick debate. *The Journal of Pediatrics*. 2006; 149:S12–S14. [PubMed: 16829235]
- Kopelman L. Children as research subjects: A dilemma. *Journal Medicine Philosophy*. 2000; 25:745–764.
- McCormick R. Proxy consent in the experimental situation. *Perspectives in Biology and Medicine*. 1974; 18(1):2–20. [PubMed: 4438051]
- Ramsey, P. *The patient as person*. New Haven, CT: Yale University Press; 1970.
- Resnik D. Eliminating the daily life risks standard of minimal risk. *Journal of Medical Ethics*. 2005; 31:35–38. [PubMed: 15634751]
- Snyder J, Miller C, Gray G. Relative versus absolute standards for everyday risk in adolescent HIV prevention trials: Expanding the debate. *American Journal of Bioethics*. 2011; 11(6):5–13. [PubMed: 21678205]
- Wendler D. Risk standards for pediatric research. *Kennedy Institute of Ethics Journal*. 2004; 14:187–198. [PubMed: 15281189]