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Response to Open Peer Commentaries on “Relative Versus Absolute Standards for Everyday Risk in Adolescent HIV Prevention Trials: Expanding the Debate”

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The aim of our target article, as implied in the title, was to expand the debate over use of a relative standard of risk for adolescent involvement in HIV vaccine trials. Given the number and calibre of responses, we have clearly succeeded in our primary aim. We sincerely thank all of the commentators for their insightful and illuminating responses.

Our argument in favor of the use of a relative standard of risk was motivated in part by an observed absence of adolescents in HIV research generally and HIV vaccine research particularly, despite their situational importance within the global pandemic. Several of the authors (Binik, Weijer, and Sheehan 2011; Nelson 2011; Philpott 2011; Shah 2011; Slack 2011) argue that participation in an HIV vaccine trial, following demonstration of efficacy among adults, does hold out the prospect for direct benefit to trial participants. If so, research guidelines allow for exposure to greater than minimal risk among adolescent trial participants, they argue, obviating the need for a relative standard of risk. Proposed HIV vaccine efficacy trials are designed so that they are monitored closely for harm, futility, or benefit. Currently, the most common adaptive design used in HIV vaccine trials is the group sequential monitoring design that allows for premature stopping of a trial due to safety, futility, or efficacy. It is unlikely that adolescents would be involved in the early stages of an HIV efficacy study. Thus, currently, adolescent inclusion would only occur after adult analyses demonstrated no harm or futility. Hence, our argument was to facilitate the immediate inclusion of adolescents in HIV vaccine trials prior to finding efficacy among adults for the important reasons outlined by Slack (2007) and others (Alonsa et al. 2005; Moorthy et al. 2004) who argue for the need for adolescent participation to delineate differences between adults and adolescents with respect to consenting processes, immunogenicity, adolescent HIV risk, sexual and reproductive health, and importantly to proactively engaging adolescents in HIV prevention.

Even if adequate levels of adolescent participation in HIV vaccine trials are achievable under the current application of ethical standards, it is worthwhile to consider whether a relative standard of risk is ethically justifiable and applicable in other circumstances. To put the question another way, given the importance of trial participation by adolescents, is there any ethical justification, based on an interest in protecting adolescents from exploitation and unjust treatment, to use the more stringent, absolute standard of risk? Binik and colleagues (2011) argue that the various formulations of a relative standard of risk in the literature are well justified and their individual rationales have not been refuted. Our defense of a relative standard received several objections in the other commentaries, however, and we use the remainder of this space to respond to them.

Janet Malek (2011) raises the concern that the use of a relative standard of risk may expose populations to exploitation. Worries about exploitation are common in human subject research, and have been leveled against studies that (1) use placebos when effective treatments are available elsewhere and (2) produce limited benefit for the study participants and host communities (Hawkins and Emanuel 2008). While Malek refers to Wertheimer’s (1996) account of mutually beneficial exploitation as a form of unfairness, more recently he has addressed the issue of exploitation in human subject research directly (Wertheimer 2008). Malek gives an example of a research trial conducted on population B, whose members face greater risks in their everyday lives.

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lives than persons in population A. If population A would benefit from the study conducted on population B while not taking on any of the risks of trial participation, Malek argues, then “the researchers are taking unfair advantage of the fact that community B is a riskier place to live” (23). We find this conclusion unconvincing on two grounds. First, Malek does not specify a baseline for measuring fairness, so it is unclear in what sense the trial takes unfair advantage of population B. There are many baselines for fair interactions, including Wertheimer’s hypothetical fair market standard, a just institutional standard, and others, all of which can produce different, conflicting accounts of exploitation (Snyder in press). Second, if unfairness is produced whenever one community takes advantage of generalizable knowledge produced via human subject trials without taking on any of the risk of participating in the research, then all research must be exploitative. As trial participation is limited but generalizable knowledge and its benefits are widespread, human subject research will never result in globally shared benefits and burdens. While we might be particularly concerned with burdens being placed on an already vulnerable population like population B, Wendler’s third, sufficient benefit criterion is intended to protect against exploitation in these cases.

Seema Shah (2011) takes issue with the relative standard by arguing that “daily life risks must be ethically acceptable before we can use them to normalize research risks” (22). We feel that this requirement is too stringent, given the benefits of increased trial participation. The conditions that we impose on the use of a relative standard of risk are meant to ensure that the research trial is responsive to the increased, and often unjust, risks faced by some communities while ensuring that research participants do not face more than a minimal increase over these risks. If the relative standard were being used simply to take advantage of these elevated risks, then we agree that a relative standard would be ethically unjustifiable. But our use of this standard both recognizes these elevated risks and requires the administration of benefits that would ameliorate them. Shah is right to note that community benefits should not be used as a justification for the exploitation of individuals. The requirement that adolescents not face risks greater than those relative to their everyday lives, and the other protections for adolescent trial participants, we argue, ensure that these individuals are not being exploited for the purpose of research. In this paper, we had in mind geographical communities where the risks of exposure and benefits of research were aligned to become primary beneficiaries of the research. While a relative standard may expose adolescents to more risk than compared to an absolute standard, it would not necessarily do so when compared to the relative risks in their everyday lives. Our argument is that, when balanced by benefits that meet the needs of the host community, these risks are justifiable and nonexploitative.

As should be clear from these commentaries, more discussion is needed as to how best to understand the concepts of minimal risk and direct benefits, among others. We feel that while consensus on the defensibility of a relative standard of risk is lacking, there is a strong case for its use in order to expand trial participation by adolescents in cases where trials may not extend direct benefits to their participants. We hope that our target article, the open peer commentaries it produced, and this response contribute to expanding the debate on adolescent participation in HIV vaccine trials. Collectively we must consider whether the current guidelines that have thus far protected adolescents from the risks of HIV vaccine trial participation are ultimately excluding critical biological, social, and environmental information that will only be clarified with their involvement. We must also ask whether we are justified in their exclusion, given the potential delay this may cause for effective vaccine delivery to adolescents and the potential that we are missing an important opportunity to harness the revolutionary energy that adolescents have to change their environments and circumstances when fully engaged.

REFERENCES


