

# Anticipating IRB Review of Inclusion of Adolescents in HIV Vaccine Trials in the United States

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## Background: Toward Adolescent HIV Vaccine Trials in the US

Although there are over thirty different HIV vaccine trials currently in clinical trials worldwide, no trial presently includes a cohort of adolescents. Two Phase I clinical trials of HIV vaccines in neonates in the US were initiated over ten years ago, but some believe that clinical trials involving adolescents in the US involve regulatory issues that may be too difficult to resolve. There is new interest in addressing adolescent participation in HIV vaccine trials. In May 2006, the FDA published Guidance on FDA consideration of a preventive HIV vaccine for pediatric populations, and in April 2007, the NIAID published a preliminary paper addressing adolescent trials. Most importantly, perhaps, there are currently discussions about a Phase I trial with adolescents in South Africa using a Merck Ad5 HIV vaccine candidate. This trial would require approval of the South African Medicines Control Council.

## Description of the Program and Evaluation Method

AVAC consulted with a multidisciplinary group of bio-ethics experts to consider the potential regulatory pathway for IRB approval of testing of an HIV vaccine in US adolescents in Phase I or Phase II trials. In particular, we asked these experts if there are circumstances under which on HIV vaccines in adolescents could be approved as "presenting the prospect of direct benefit" under DHHS §46.405?

Alternatively, we asked whether such a trial would have to be approved under the more onerous requirements of DHHS §46.407 requiring appointment of a special committee, public comment and approval by the Secretary of Health and Human Services.

In exploring these issues, AVAC also reviewed the literature on risks posed by HIV vaccine trial participation by adolescents, including the prospect of disinhibition and vaccine induced seropositivity. The purpose of this review was to develop practical strategies for implementing ethical oversight over HIV vaccine testing in adolescents. We did not explore whether adolescents could be enrolled in Phase IIB or III efficacy trials.

## Results

The experts surveyed identified a number of risks for adolescents which could frame an IRB decision on whether to approve the testing in Phase I and II safety and immunogenicity trials. The risk of adverse events appeared low to these experts. The current HIV vaccine candidates have a safety profile in adults that supports the view that they would be of low risk to adolescents. Favorable safety data in adults was thought to be an critical precursor to consideration of an adolescent trial.



The possibility of disinhibition to risky sexual behavior was identified as a significant risk to adolescents. The potential for societal harm from vaccine induced HIV seropositivity was the most significant risk that experts identified. Experts were not always convinced that adolescents would be able to limit HIV testing in ways that could avoid false positive results. Finally, the vulnerability of testing upon vulnerable adolescents at risk of HIV, who might not have a strong support system, was identified as a significant ethical issue.

These risks were balanced against the benefits of participation. The sole benefit that experts identified was the potential benefit of an HIV vaccine should the vaccine be determined to be effective in Phase III trials and licensed.

## Conclusions

Most of those surveyed believed that there are grounds under which HIV vaccine trials with adolescents could be approved as "presenting the prospect of direct benefit" under DHHS §46.405. The likelihood of such approval by an IRB would depend in the opinion of those surveyed on measures taken to reduce risk to adolescents, and on the age and vulnerability of the adolescent cohort selected for the study.

Some measures identified for reducing risk include:

- counseling to reduce the risk of disinhibition;
- improved testing procedures to reduce the risk of vaccine induced seropositivity;
- limiting the aged of adolescents in the study to 14 years of age and older;
- institution of consent monitoring procedures; and
- exclusion of adolescents with low parental involvement and support.

Most of those surveyed saw some limited benefit to trial participation for those adolescents at even remote risk of HIV infection. For one expert, the potential for vaccine induced seropositivity posed too great a barrier to approval of the trial under DHHS §46.405. Absent some or all of these measures to reduce risk, some experts believed the trials could be approved only through the committee approval process under DHHS §46.407.