

Ethical and Regulatory Considerations for the Inclusion of Adolescents in HIV Biomedical Prevention Research

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Abstract: Adolescents should be enrolled in ethically appropriate and scientifically rigorous HIV biomedical prevention research involving vaccines, pre-exposure prophylaxis, or microbicides. There is general agreement that children should only be enrolled in a clinical trial if the scientific objectives cannot be met either through enrolling adult subjects who can provide informed consent personally or through conducting research using animal models. In addition, the risks to which children are exposed in a clinical trial without the possibility of direct therapeutic benefit must be low. Children also should not be placed at a disadvantage after being enrolled in a clinical trial by, for example, being exposed to an unnecessarily risky intervention or by failing to receive a comparable treatment that would prevent significant morbidity or mortality. In light of this shared framework, we discuss the timing of enrolling adolescents in HIV prevention trials; some general study design considerations that may be necessary for adequate labeling of products for an adolescent indication; the use of data obtained from international studies for licensure applications in the United States; the role of parental permission and adolescent assent to research participation; and the inclusion of pregnant adolescents in HIV biomedical prevention research.

Key Words: adolescent, clinical trials, control group, ethics, HIV, informed consent, microbicides, placebo, pre-exposure prophylaxis, pregnancy, vaccines

(*J Acquir Immune Defic Syndr* 2010;54:S18–S24)

INTRODUCTION

The starting point for a discussion of the ethical and regulatory issues surrounding enrollment of adolescents in HIV biomedical prevention research is a fundamental commitment to

improve the access of children and adolescents worldwide to safe and effective medicines. Yet, to acquire data on the use of new medicines in children requires addressing the fact that children are considered to be vulnerable persons who, as research participants, are in need of additional or special protections beyond those afforded to competent adults.^{1–3}

Over the past 15 years, we have shifted from the view that children should be protected from participation in research to the realization that children should be protected from unsafe therapies through the information gained from ethically appropriate and scientifically rigorous research. Clinical trials are increasingly being conducted on a global scale, presenting opportunities and challenges in ensuring that children are adequately protected and represented as we seek to achieve the goal of improved access to essential pediatric medicines and HIV prevention strategies.

This article will first discuss the basic ethical framework that serves as the foundation for the design and conduct of pediatric clinical trials in countries around the world. We will then specifically consider the timing of enrolling adolescents in HIV prevention trials, and some general study design considerations for studies of particular prevention modalities that may be necessary for adequate labeling of products for an adolescent indication (eg, data necessary for expeditious licensure, choice of control group, etc). As most HIV prevention trials will be conducted outside of the United States, we will discuss the use of data obtained from international studies for licensure applications in the United States. Finally, we will discuss the role of parental permission and adolescent assent to research participation.

GENERAL ETHICAL CONSIDERATIONS

There seems to be general agreement on the basic ethical and regulatory framework governing pediatric clinical trials. First, children should only be enrolled in a clinical trial if the scientific objectives cannot be met either through enrolling adult subjects who can provide informed consent personally or through conducting research using animal models.^{2–5} Second, if the children who are enrolled in a clinical trial would not have the possibility of direct therapeutic benefit (ie., nondirect benefit research), the risks to which those children would be exposed by being in the trial must be low.^{2,5} Third, children should not be placed at a disadvantage after being enrolled in a clinical trial by, for example, being exposed to an unnecessarily risky intervention or by failing to receive a comparable treatment that would prevent significant morbidity or mortality.¹

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Sources of support: None.

Disclaimer: The opinions and information in this review article are those of the authors, and do not represent the views and/or policies of the US Food and Drug Administration.

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There are, however, some differences in how this general framework is articulated by different countries. First, there are differences in how the level of permissible nondirect benefit risk exposure is categorized. Second, the terms used to describe the permissible level of nondirect benefit risk exposure may vary. Third, there are differences in how these terms are defined, even if the same term is used. These differences will be discussed below. It should be noted that some countries seem not to permit nondirect benefit research involving children (Marta Fracapani, unpublished data, August 7, 2009). Other regulations seem to discourage nondirect benefit research involving children (unpublished data). Finally, there are regulations which permit nondirect benefit research by using the phrase “direct benefit to the group” (rather than to the individual) to counter arguments that pediatric research should only be done when there is “direct benefit” for the enrolled children.²

Interpretations of “Low” Risk

The permissible level of risk exposure for children enrolled in nondirect benefit research may be classified using either 1 or 2 risk categories. Many countries use 1 category of permissible pediatric nondirect benefit risk exposure (Hans Stoetter, unpublished data, July 30, 2009),^{3,4,6,7} whereas a minority uses 2 categories of permissible nondirect benefit risk exposure.^{8,9} For example, the United States divides permissible nondirect benefit risk exposure into 2 categories, “minimal risk” and a “minor increase over minimal risk,” with the latter category restricted to children with a disorder or condition.⁸ This same approach is adopted by the Council of International Organizations of Medical Specialties in Guideline 9.¹⁰ Other countries follow the International Conference on Harmonization (ICH) Good Clinical Practice guidelines by limiting enrollment in “low” risk nondirect benefit research to children with a disorder or condition.^{5,11}

Different terms are used to describe the permissible level of nondirect benefit risk exposure, such as “easily tolerated,” “minimal,” “minor increase over minimal,” “low,” “minimal risk and minimal burden,” “lower,” or “minimal or negligible.”^{4,5,6-9,12} In addition, the same term, when defined, may have more than one definition, and the definition may not specify the reference population. For example, the United States defines minimal risk as that risk which is “ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”⁸ Only one standard of the two (daily life or routine examinations) must be met for a risk to be considered minimal. Although the US National Commission (1978) recommended that minimal risk refer to the daily life or routine examinations of healthy children, the phrase “of healthy children” was omitted from the eventual regulation.¹³ The Canadian Tri-Council policy defines minimal risk as that risk which is “encountered by the participant in those aspects of his or her everyday life that relate to the research.”^{3,4} This definition seems similar to the US “daily life” standard, yet specifically defines the reference population as those persons who are participating in the research. Alternatively, Mexico defines minimal risk as the risk of those “common procedures and physical examinations or psychological diagnoses or routine treatment.”⁹ This

definition is similar to the US “routine examinations” standard. Although there is well-documented variability in the application of the category of minimal risk to specific interventions and procedures, it is unclear whether any of this variability would be reduced by the adoption of a common term and shared definition. Even although functioning under a common set of regulations, there seems to be wide variability in the assessment of minimal risk and minor increase over minimal risk within the United States.¹⁴

Restrictive definitions and/or interpretations of “minimal risk” may render certain nondirect benefit pediatric studies more difficult to conduct absent the availability of other categories such as “minor increase over minimal risk” or “low” risk. For example, adolescents who are “at risk” for HIV infection (ie, have a condition) could be enrolled in some nondirect benefit HIV trials that exceed minimal risk, such as a single-dose pharmacokinetic (PK) study of a drug with a documented safety record, provided that the risk was considered “low”⁵ or no more than a “minor increase over minimal risk.”⁸ The alternative approach of adopting a more liberal definition of minimal risk would be problematic as children who face a greater “everyday” risk may then be enrolled in riskier yet still minimal risk research unrelated to their disorder or condition. It is for this reason that the restriction of “low” risk research to individuals with a disorder or condition is important; otherwise, healthy children could be enrolled in nondirect benefit research involving the administration of an experimental drug.⁵ Adolescents who are currently healthy but “at risk” for HIV infection are considered to have a condition.¹⁵

Apart from these concerns, it is important to note that there are no data to suggest that these differences in terms and definitions result in substantive differences in regulatory and/or ethical approval of protocols within those countries that allow nondirect benefit research involving children.

Fallacy of the Package Deal

Research protocols often combine nondirect benefit interventions that may present more than minimal risk (ie, “high risk”) with other interventions that either (1) offer (as a research intervention) a prospect of direct benefit to the enrolled child; or (2) would be considered part of necessary health care for that child. It is possible that such “therapeutic” protocols which contain “high-risk” nondirect benefit interventions are being approved based on the presence of other interventions, research or otherwise, that offer the prospect of direct benefit. The evaluation of a research protocol needs to separate “research only” interventions from the interventions that offer the prospect of direct benefit. The risks of the “research only” interventions should not be justified by the prospect of direct benefit from other interventions included in the protocol. Rather the risks of an experimental intervention must be offset by the prospect of direct benefit from that specific intervention, or absent any prospect of direct benefit, be limited to the acceptable risk for a nondirect benefit intervention (whether characterized as minimal, minor increase over minimal, or low). Otherwise one could bundle “high-risk” nondirect benefit interventions with necessary health care to justify the nondirect benefit research risk. This mistake has been called the “fallacy of the package deal” and

can be prevented only by a careful “component analysis” of the research protocol.^{1,4,15} The one exception to this approach may be when a “research only” procedure is scientifically necessary to evaluate the effect of another research intervention that offers a prospect of direct benefit. Here, the risks of the “research only” procedure may be justified by the potential benefits of the “direct benefit” research intervention.

The Timing of Adolescent Clinical Trials

An experimental intervention that presents “*more than*” a minor increase over minimal risk or more than low risk must provide a sufficient prospect of direct benefit to the enrolled child to justify those risks. In other words, when the experimental intervention exceeds the risks that would be acceptable for a nondirect benefit intervention, there must be sufficient data (from nonclinical animal models or, more commonly, from adult human trials) to establish that the prospect of direct benefit is sufficient to justify the risks. Whether or not the data on possible direct benefit are sufficient is a complex quantitative and qualitative judgment. Factors that will impact on this judgment may include the importance of the direct benefit to subjects; the possibility of avoiding greater harm from the disease; the disease severity such as the degree of disability or risk of death; and the availability of alternative treatments. As such, the threshold for initiating an adolescent trial, either as a separate trial or as part of an adult trial, may vary between products and may shift based on the results of past experience for that same therapeutic product or class.

In addition, the evidence supporting a prospect of direct benefit for an adolescent trial may be less robust than evidence that would be required to demonstrate efficacy. Otherwise, the answer to the research question would have to be known before doing the research. The evidence for prospect of direct benefit may be based on a surrogate endpoint if there is sufficient evidence linking the chosen surrogate to clinical efficacy. For example, in HIV treatment trials, measurement of HIV-1 RNA and achieving an undetectable level represents a validated surrogate endpoint. Absent an adult human disease correlate, one may be able to establish a sufficient “proof of concept” in an appropriate animal model.

The appropriate timing of enrolling adolescents in a clinical trial can be illustrated using the example of a vaccine to prevent HIV infection. Expressing concern that any delay in the licensing of an HIV vaccine for adolescents would prove detrimental to the public health, some have argued that adolescents should be included in HIV vaccine trials when there is “sufficient promise” to undertake an efficacy trial in adults.¹⁶ However, the simple initiation of an adult trial with an efficacy endpoint does not establish a sufficient prospect of direct benefit that would allow for enrolling children. Rather, there must be data in support of the judgment that there is a prospect of direct benefit for children. Absent an immune correlate for protection from HIV infection, demonstrating an immune response alone would not establish a sufficient prospect of direct benefit to offset the risks of the experimental product. Thus, one would need preliminary efficacy data from adults before enrolling adolescents.¹⁷ Without this proof-of-concept or evidence of potential efficacy of a candidate HIV vaccine, an adolescent assumes all the risk associated with the

intervention without reasonable prospect of direct benefit. In the case of an oral agent for pre-exposure prophylaxis (PrEP) that is already approved for HIV treatment, the known antiviral efficacy in disease treatment and the accumulated safety database may allow a more favorable risk/benefit assessment for the enrollment of adolescents.

Development of vaginal microbicides in adolescents should take into consideration the prevalence of HIV among adolescents, the likelihood of adolescent usage of a product after approval and differences in vaginal mucosa between adolescence and adulthood. Once approved, a microbicide may be used by individuals younger than 18 absent a well-characterized safety profile. In this scenario, conducting trials in an adolescent population before approval will provide useful safety data. One approach can be initiation of the first adolescent trial before drug approval if review of interim safety data from phase 3 adult trials indicates favorable findings. Additionally, enrollment of older adolescents between ages 16 and 18 years in the initial adolescent trial followed by evaluation of younger adolescent groups may be preferred because older adolescents will likely reflect the target adolescent population.

Given the risks of HIV infection in an “at-risk” adolescent population, one could tolerate greater uncertainty in the context of a serious and/or life-threatening condition. Thus, one approach to determining when an intervention shows “sufficient promise” to initiate a pediatric trial in the context of a serious and/or life-threatening condition would be to accept a trend in favor of the experimental intervention in adults at the interim efficacy analysis as evidence of such promise. This approach may also allow such a protocol to be classified as having the prospect of direct benefit in countries where research regulations do not allow nondirect benefit research involving children.

Concurrent Licensure

Concern may be raised that the need to demonstrate a sufficient prospect of direct benefit in adults to justify the risks of moving into adolescents will create a delay, which may render concurrent licensure for an adolescent and adult indication difficult if not impossible. The answer to this question partially depends on what data are needed for an adolescent indication. Food and Drug Administration (FDA) uses the principle of extrapolation to determine whether additional efficacy studies in children are necessary to adequately label a product for pediatric use. Extrapolation, as defined in the US regulations, is possible when “the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients.”¹⁸ When data exist to support this scientific judgment, “pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as PK studies.”¹⁸ This approach has been structured into an algorithm (Fig. 1) for determining the need for pediatric studies in support of labeling.¹ If it is not reasonable to assume that children, when compared with adults, would have a similar disease progression and response to intervention, one must conduct a full portfolio of studies in support of appropriate dosing, safety, and efficacy in children.

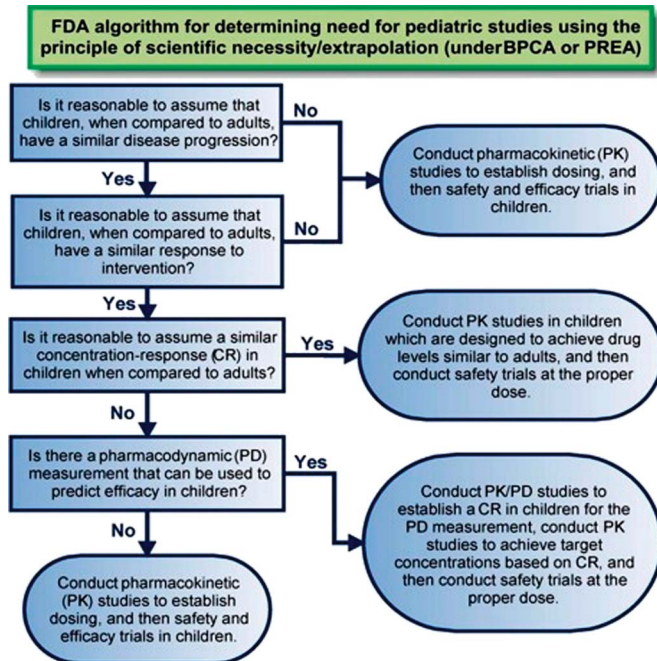


FIGURE 1. FDA algorithm for determining need for pediatric studies using the principle of scientific necessity/extrapolation (under Best Pharmaceuticals for Children Act of 2007 [BPCA] or Pediatric Research Equity Act of 2007 [PREA]).²¹

If one can assume that children have a similar disease progression and response to intervention when compared with adults, it may not be necessary to do separate efficacy trials in children. If adult studies have established a correlation between drug concentration and clinical response, one may be able to perform PK studies in children that are designed to achieve drug levels similar to adults. This principle has been used routinely to extrapolate efficacy in pediatric HIV treatment trials because the pathophysiology of HIV infection is similar in all age groups and the response to treatment is related to drug exposure and virus susceptibility, both of which can be measured. For example, the indication for Kaletra (lopinavir/ritonavir) was extended to adolescents based on documentation that the studied dose was safe and provided similar drug exposure to that shown to be both safe and effective in adult clinical trials. A similar scenario may be applicable to PrEP. In the absence of a correlation between drug concentration and clinical response, one may be able to use a pharmacodynamic measurement to predict efficacy, if such exists. However, in the absence of an established drug concentration–response or pharmacodynamic measurement, one may need to do an efficacy trial in children. The extrapolation of efficacy requires an understanding of disease pathophysiology and the mechanism of therapeutic response for the investigational product. The ability to extrapolate efficacy for a microbicide based on concentration–response or pharmacodynamic measurement needs further exploration. Microbicides may not be systemically absorbed, therefore, a PK extrapolation is challenging. Also, measurement of drug concentrations in genital secretions needs further investigation and validation. For an HIV vaccine, bridging studies using

humoral or cellular immune response or reduction in viral load may be required to support extrapolation. Thus, whether or not concurrent licensure is a realistic goal when the enrollment of adolescents is delayed until one has a sufficient prospect of direct benefit from adult studies to justify the risk will depend upon the results of the studies themselves.

If a concentration–response or a pharmacodynamic measure is established that correlates with adult efficacy, a sufficient adolescent sample size to make an independent determination of efficacy in the adolescent population may not be needed; that is, extrapolation of efficacy from larger adult trials can be used to justify approval. Regardless, a sufficient adolescent sample will be necessary to assess the safety of the experimental product. The selection of an appropriate dose (ie, drug exposure) and the assessment of pediatric-specific safety should never be extrapolated.

Choice of Control Group—Use of Placebo

There is general agreement that children should not be placed at a disadvantage by failing to get necessary health care after being enrolled in a clinical trial. There is also general agreement that research that will not produce scientifically valid results is unethical. At times, these 2 principles may be in tension, such as when the scientific choice of the comparator used in the control group (eg, placebo, or a low or ineffective dose) would involve withholding proven effective treatment.

The concept of “equipose” is often cited in support of the view that proven effective treatment should never be withheld. There are, however, two meanings of the concept “equipose” that should be distinguished: scientific uncertainty and the appropriate balance of risk and potential benefit. Equipose is often used to refer to the principle that there must be a sufficient uncertainty concerning the answer to the scientific question being addressed by the protocol for the research to be justified. It may also be used to argue that research participants should not be placed at a disadvantage by failing to get necessary health care after being enrolled in a clinical trial.¹

These two meanings have important implications for the debate over the appropriate choice of control group in a clinical trial. Equipose as scientific uncertainty can be cited in support of the position that there may be a valid scientific reason for withholding proven effective treatment if there is a limited risk exposure. Equipose could also be cited in support of the view that research participants should not be placed at a disadvantage by failing to get necessary health care after being enrolled in a clinical trial regardless of the risk involved. Although the first position may support a placebo control, the latter position demands an active control.

Although there continues to be debate about the appropriate use of placebo controls, the 2008 revision of the Declaration of Helsinki and the ICH E-10 document on Choice of Control Group seem to have the same standard for the upper limit of allowable risk exposure from withholding proven effective treatment. The Declaration of Helsinki (2008) permits a placebo control if it is scientifically “necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm.”¹⁹ ICH E-10 states that “effective treatment” may be withheld as long as

this would not result in “serious harm, such as death or irreversible morbidity.”²⁰ However, there seems to be a subtle difference in emphasis. The Declaration of Helsinki stipulates that one must use the “best current proven intervention” (instead of placebo) although ICH E-10 seems more permissive if the use of placebo does not present an unacceptable risk (even if current proven interventions exist).

The fact that the revised Declaration of Helsinki (2008) allows for the limited use of a placebo control has not been without controversy. For example, the Brazilian National Health Council passed a resolution opposing a prior version of this revision (2000).⁷ The draft Canadian guidelines (2008) seem similar to the revised Declaration of Helsinki: “a placebo control is ethically acceptable ... if its use is scientifically and methodologically sound to establish the efficacy or safety of the ... intervention, and, it does not compromise the safety or well being of participants.”³ Other national guidelines seem similar to the ICH E-10 standard. Australia, for example, considers a placebo control unacceptable if there is “known risk of significant harm in the absence of effective treatment.”⁶

The European Medicines Agency (2008) guidance document discusses the use of placebo controls in pediatrics. The pediatric use of a placebo control may be “needed for scientific reasons” but use of a placebo in children should be more restrictive than in adults.²¹ Although the European Medicines Agency document suggests that avoiding “irreversible harm” should be the upper limit to allowable risk exposure when using a placebo control in pediatrics, this question is not explicitly addressed. Using the ethical framework discussed above, placebo administration does not offer a prospect of direct benefit in the context of a clinical trial (setting aside any alleged “placebo effect”). Also, the risk of administering a placebo product is generally “minimal” (if appropriately chosen). Thus, the risk of being randomized to a placebo control group generally is related to the risk of harm from not receiving “proven” or “effective” treatment. The risk, then, of receiving a placebo in lieu of proven effective treatment must be no more than the permissible level of nondirect benefit risk, whether minimal or low.

In the case of HIV prevention trials to date, no biomedical intervention has been proven to be safe and effective and, consequently, a study using an active control is not possible. Unfortunately, a single-arm open-label study fails to provide a comparator by which to assess important safety and/or efficacy parameters. The use of condoms has been shown to decrease transmission of HIV and is considered the “standard of care” in prevention in sexually active individuals. Therefore, all HIV prevention trials conducted in adults or adolescents must include safe-sex counseling and provision of condoms to participants. In effect, the experimental HIV prevention product is added to this standard of care (ie, an “add on” trial) with the control group receiving a corresponding placebo along with the standard of care to maintain blinding.

Applicability of Foreign Data for US Licensure

The global burden of HIV/AIDS has driven a tremendous international treatment and prevention research agenda.

The heterogeneous US HIV epidemic, particularly the staggering incidence rates among racial, ethnic, and cultural minorities, compels the drive for more research to identify efficacious prevention interventions that can be relevant to at-risk US populations.²² However, the nature of the heterogeneous youth epidemic in the United States with “hot pockets” where high-risk adolescents congregate makes the conduct of some biomedical prevention studies difficult if not impossible. As an alternative, the conduct of large-scale multinational efficacy studies of a given biomedical prevention modality in an area with homogeneously high HIV seroincidence, such as that of sub-Saharan Africa where high-risk youth are not as “hidden”, can afford the possibility of obtaining important data on a vulnerable population that may be applicable to youth globally, including those in the United States.

The FDA has no authority over studies conducted entirely outside the United States that have not been submitted as part of an Investigational New Drug application. There is no requirement for such a study to be submitted to the FDA before being performed if it is not going to be submitted for approval in the United States.²³ If it has been submitted, FDA exercises its authority over Investigational New Drug studies regardless of study location. Thus, proposed clinical investigations are evaluated for scientific and ethical merit according to a single standard regardless of where it will be conducted.

Many studies of new products, including HIV biomedical prevention products, are conducted multinationally, involving both US and foreign sites. If so, there must be sufficient US data to establish that the results are applicable to the US population and US medical practice. However, if an application is based solely on foreign clinical data, it still may be approved if the foreign data are applicable to the US population and US medical practice.²³ For approval in the United States, foreign data may be acceptable provided the data can be inspected and verified by FDA. Safety data from adolescents in the United States are desired to provide local data applicable to the US population. HIV treatment trials have frequently included multinational sites, and HIV experts generally agree that these studies support that the course of disease and response to treatment are similar across widely diverse populations. Participation in multinational HIV treatment trials provides a basis for sites in areas of high prevalence to participate in HIV prevention trials.

Adolescent Consent

Parental permission (ie, informed consent) is recognized worldwide as an important protection for children who are being considered for enrollment in a research protocol. However, the feasibility of obtaining parental permission may be a problem in some areas, for example, due to great distances, lack of communication infrastructure, social dislocation, or high parental mortality. US research regulations governing Health and Human Services (HHS)-funded research allow for a waiver of the requirement for parental or guardian permission if a research ethics committee determines that such a requirement is not reasonable. Advocates in support of the application of this waiver to adolescent HIV research cite evidence of the capacity of a mature adolescent to make decisions concerning their own interests in a manner comparable to adult decision-making.

Additionally, there is concern that without a waiver, vital research involving mature adolescents may not be conducted. An example that is often cited is the experience with HIV-infected adolescents in the late 1980s and early 1990s. These adolescents might have been denied access to potentially life-prolonging interventions available within clinical trials if parental permission were required. Others argue that the waiver of parental permission should be limited to circumstances where there is a reasonable argument that informing the parent may result in harm to the child or that the parent is unable to act in the child's best interest. Here the emphasis is on parental disqualification rather than on adolescent capacity. This latter position is more consistent with the views of the US National Commission in recommending the waiver.¹³

The US National Commission viewed the legal ability of an adolescent to provide consent for a treatment or procedure involved in a clinical trial under the applicable law of the location where the research is being conducted as excluding them from the purview of the additional protections for children in research.¹³ As such, parental permission would not be required. Accordingly, US regulations define children as persons who have not attained the legal age for consent to treatments or procedures involved in a clinical study under the law of the local jurisdiction.⁸ For example, all states in the United States allow an adolescent to consent for treatment for sexually transmitted diseases without parental permission. Parental permission may also not be required for an adolescent to be enrolled in a study of an investigational product for a sexually transmitted disease, depending on the interpretation by responsible legal counsel at the local site. Thus, the fact that the FDA regulations governing pediatric research do not include the same waiver of parental permission is of limited significance. If the laws of the local jurisdiction would allow for an adolescent to consent for HIV treatment, contraception, and treatment for sexually transmitted diseases, the adolescent would not be considered a child for the purposes of applying the additional protections. As such, parental permission would not be required.

The use of local judicial or legal procedures to either appoint a guardian or establish that an adolescent is emancipated is more defensible as a policy than relying on the idiosyncratic adoption and interpretation of the parental permission waiver by individual research ethics committees. The use of established, transparent, and fair judicial procedures to establish the right of an adolescent to consent to research participation under the applicable laws of the appropriate jurisdiction could respect the differing moral and legal views of local communities although affirming a liberty interest of parents to raise their children as they see fit.

Inclusion of Adolescents Who Become Pregnant

To date, many trials exclude pregnant women, regardless of age, from enrollment and discontinue women who become pregnant during the trial to protect the fetus from research-related risks. High pregnancy rates in recent microbicide trials for the prevention of HIV infection were observed and have a major impact on the conduct and interpretation of the trials. The FDA's current thinking regarding the evaluation of women

who become pregnant while participating in trials of microbicides is evolving. Importantly, upon approval of a product for prevention of HIV acquisition, pregnant women may either opt to use a microbicide despite a lack of data in this special population or may not use an efficacious microbicide because the effects during pregnancy and to the fetus are unknown. Therefore, lack of data in pregnant women at the time of a New Drug Application (NDA) submission is not optimal. Systematic collection of data in a prospective controlled clinical trial before approval is preferred.

The decision to allow use of the product in women who become pregnant while participating in clinical trials of microbicides or PrEP trials depends on the safety profile of the product in nonclinical studies and early clinical trials. Decisions are made on a case-by-case basis and include knowledge of nonclinical studies and human trials. Data including but not limited to the following are important factors in determining whether or not women who become pregnant are permitted to continue in a trial: completed reproductive toxicology studies (segment I, II, and III), genotoxicity studies, chronic toxicity studies in at least 2 species, and data on systemic absorption of the microbicide in nonpregnant female subjects. Additionally, trial designs need to include provisions for women who become pregnant such as re-consent and additional safety monitoring to ensure adequate precautions are taken to protect both mother and fetus. As with adult microbicide trials, on-site contraception counseling should be provided to adolescent subjects because limited data suggest that it may help reduce the number of pregnancies in clinical trials.

Early phase clinical studies of the safety and immunogenicity of HIV vaccine candidates have been conducted with HIV-positive pregnant women to explore the role of active immunization in preventing maternal-to-infant HIV transmission.²⁴ Pregnant women have also been enrolled in vaccine immunogenicity and prevention studies for diseases such as influenza that have an increased risk of serious illness and hospitalization among this population.^{25,26} The timing of enrollment of HIV-negative pregnant women in a vaccine prevention trial to obtain needed safety and immunogenicity data before licensure may depend on safety and at least preliminary efficacy data from nonpregnant adults and the availability of immune correlates for preventing HIV infection.

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