Considerations for HIV Vaccine Clinical Trials in Adolescents

Vaccine Clinical Research Branch
Vaccine Research Program
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health

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Abbreviations and acronyms used in the text

AAP ..... American Academy of Pediatrics
AAPS ..... Association of American Physicians and Surgeons, Inc.
ACIP ..... Advisory Committee on Immunization Practices
Ad ..... Adenovirus
AIDS ..... Acquired Immune Deficiency Syndrome
AIS ..... Cervical Adenocarcinoma *In Situ*
ATN ..... Adolescent Trials Network or Adolescent Medicine Trials Network
AVAC ..... AIDS Vaccine Advocacy Coalition
BLA ..... Biologics License Application
BPCA ..... Best Pharmaceuticals for Children Act
CAB ..... Community Advisory Board
CDC ..... U.S. Centers for Disease Control and Prevention
CER ..... Community Educators/Recruiters
CFR ..... U.S. Code of Federal Regulations
CIN ..... Cervical Intraepithelial Neoplasia
DAIDS ..... Division of AIDS (United States)
DHHS ..... Department of Health and Human Services
DOH ..... Department of Health (South Africa)
ECGMO ..... Executive Council of Genetically Modified Organisms (South Africa)
FDA ..... Food and Drug Administration (United States)
FDAMA ..... FDA Modernization Act
FR ..... Federal Register
GCP ..... Good Clinical Practice
GSK ..... Glaxo Smith Kline Biologicals
HIV ..... Human Immunodeficiency Virus
HPV ..... Human Papilloma Virus
HSV ..... Herpes Simplex Virus
ICH ..... International Conference on Harmonization
IND ..... Investigational New Drug
IOM ..... Institute of Medicine
IRB ..... Institutional Review Board
LD ..... Lyme Disease
MCC ..... Medicines Control Council (South Africa)

Merck.....Merck & Co., Inc.
MMWR ..... Morbidity and Mortality Weekly Reports
MRC .....Medical Research Council (South Africa)
MTCT.....Mother to Child Transmission
NCHS ..... National Center for Health Statistics
NCI .....National Cancer Institute
NIAID..... National Institute of Allergy and Infectious Diseases (United States)
NICHD ..... National Institute for Child Health and Human Development (United States)
NIH.....National Institutes of Health (United States)
NHREC .....National Health Research Ethics Council (South Africa)
OHRP .....Office for Human Research Protection (United States)
PACTG..... Pediatric AIDS Clinical Trials Group
PREA.....Pediatric Research Equity Act
REC .....Research Ethics Committee
RSA .....Republic of South Africa
STI..... Sexually Transmitted Infection
UNAIDS.....Joint United Nations Programme on HIV/AIDS
VaIN ..... Vaginal Intraepithelial Neoplasia
VIN.....Vulvar Intraepithelial Neoplasia
VRBPAC .....Vaccines and Related Biological Products Advisory Committee
VRP .....Vaccine Research Program

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Introduction

This document provides a summary of the current thinking of the Vaccine Research Program (VRP) of the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health on the scientific, ethical and logistical issues surrounding the initiation of clinical trials of HIV vaccine candidates in adolescents. The document was written in accordance with the *NIH policy and guidelines on the inclusion of children as participants in research involving human subjects* (NIH, 1998). This document discusses issues specific to prophylactic (preventive) vaccines and does not cover issues related to the study of vaccines for therapeutic indications. The document provides considerations for why, when and where such studies should be conducted; summarizes the major challenges of conducting these studies; outlines the major issues for implementing feasibility studies; discusses examples from the development of other vaccines, particularly for other sexually-transmitted infections (STIs); and provides a brief summary of the regulations relevant to the conduct of such trials.

Definitions: adolescents and children

The terms "adolescents" and "children" are defined somewhat differently in the medical, psychosocial, legal, and regulatory contexts. Adolescents are a heterogeneous group that includes individuals of different life experiences, levels of vulnerability and needs. It is therefore worthwhile summarizing the similarities and differences, particularly in the regulatory setting in the U.S. and internationally, e.g., International Conference on Harmonization (ICH).

Adolescents

The National Center for Health Statistics (NCHS) defines adolescence as "*the period of life from puberty to maturity."*

The U.S. Food and Drug Administration (FDA) defines adolescence as "*ages 12 to 15 years (up to 16 years)"* in 21 CFR 201.57 (f) (9) (i) and in the specific requirements on content and format of labeling for human prescription drugs: Revision of "Pediatric Use" subsection in the labeling; Final Rule (FDA, 1994).

The ICH guidelines define adolescents as "*those of age 12 to 16 or 18*" (ICH, 2000).

Children

The term "child" is generally used broadly to refer to individuals age 0 to 19 or to cover all individuals below the age at which a person can provide legal informed consent (18 in the U.S. in most states[1]).

The definition of children provided by the FDA is "*2 to 11 years (up to 12 years)*"; see 21 CFR 201.57 (f) (9) (i) and (FDA, 1994). The ICH guidelines provide the same definition. Further, the FDA provides a definition of children in 21 CFR 50.3 (o) based on legal rights instead of age ranges, as follows: "*Persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.*" This latter definition encompasses together

[1] The age for legal informed consent is 19 in Alabama (Code of Ala. § 26-1-1) and Nebraska (Nebr. Rev. Stat. Ann. § 43-2101); and 21 in Mississippi (Miss. Code Ann. § 1-3-27[a]).

the age ranges previously defined as "children" and "adolescent." Thus, it becomes somewhat unclear how the FDA views those who are 16 and 17 years old, who are in all states below the age to legally provide informed consent for research but above the age ranges specified for adolescence. Still, they would seem to be considered "pediatric," though they fall above the specified age range for that definition in the regulations governing drug labeling.

The NIH/Department of Health and Human Services defines children in 45 CFR 46.402 (a) (see Appendix 3) based on legal rights, as "*persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted."* This definition does not specify age ranges that encompass the ages of "children" or "adolescents."

In other countries these definitions may vary; for example, in South Africa (Republic of South Africa) where adolescent trials may start in the near future, children are defined as "*someone younger than 18 years.*"[2]

Why is it necessary to study HIV vaccine candidates in adolescents?

1. Adolescents are severely affected by the epidemic.

The HIV epidemic affects adolescents and young adults disproportionately. Globally, 50 percent of new HIV infections are in the 15-24 age group (UNAIDS, 2006).

a. United States

In the U.S., HIV/AIDS among adolescents and young adults continues to contribute substantially to the epidemic. The transmission modality in adolescents and young adults is mainly sexual. Male adolescents are most often infected through sex with men. Female adolescents are most often exposed through heterosexual contact. HIV infection is the ninth leading cause of death for those aged 15 through 24 and the sixth leading cause of death for those aged 25 to 44 (CDC, 2006). Since the time from HIV infection to the development of AIDS averages 10 years, most adults who develop AIDS in their early twenties were likely infected with HIV while they were adolescents. Statistics and surveillance data available for AIDS or HIV/AIDS by age are available from CDC (CDC, 2007). The most recent CDC data show that 1.2 percent of the estimated number of AIDS cases in 2005 alone occurred in adolescents (ages 13-19). Most adolescents infected recently will not be diagnosed until their twenties. Therefore, it is noteworthy that the statistics for the estimated number of HIV/AIDS cases - including those infected but not yet diagnosed - more truly reflects the involvement of adolescents: they represent 3.3 percent of all U.S. HIV infections.

b. International

While HIV infection in U.S. adolescents is recognized as a serious problem, the magnitude of infection among adolescents in some low and middle income countries is significantly greater. For example, the prevalence of HIV infection in adolescents in South Africa is 4.7 percent in 10-14 year-olds and 5 percent in 15-18 year-olds (Brookes, 2004). There is also a disproportionately greater prevalence of HIV infection in females. For example, in South Africa, the prevalence of HIV infection among 15-17 year-olds is 4-6 percent in girls and 2-3

[2] Constitution of the Republic of South Africa, Act No. 108 of 1996 and Child Care Act, No. 74 of 1983.

percent in boys (Pettifor, 2005). HIV incidence among 15-21 year-olds has ranged from 1.2 to 8.3 percent (Gouws, 2002; Rollins; 2002; Bekker; 2005-A).

In low and middle income countries, the existing high prevalence of HIV infection, relatively early age of sexual debut, concomitant diseases, and poverty all likely contribute to earlier acquisition. In addition, high rates of cross-generational sex, some of which may constitute child abuse and rape, likely contribute to the high incidence of HIV infection in adolescent girls.

2. Consideration must be given to equity of subject selection, per ethical guidelines.

Consideration must be given to whether subject selection for clinical investigations is equitable. As will be discussed later, the U.S. Congress passed legislation requiring clinical investigations to be conducted for children (FDA, 2003). Further, it is the U.S. NIH's policy that children be included in health research when they would benefit from that research, with only some exceptions (NIH, 1998). Relevant international ethical principles should be applied. The appropriateness of the research should include assessment of the research purpose, the setting in which the research will be conducted, and the special problems of research involving vulnerable populations like children. Inclusion of children in research must be justified; exclusion of children from research from which they could potentially benefit is likely unjustified.

3. Vaccine responses may differ in different age groups.

There are a number of physiological differences between adolescents and adults, including, for example, the extensive changes in hormonal levels experienced by adolescents at puberty (Verthelyi, 2001). In addition, there are data that indicate that sex hormones may have direct or indirect effects on immune cells or immune responses, suggesting that responses to vaccination with HIV vaccine candidates may not be equivalent in adults and adolescents. In February 2006 *AIDS* published an in-depth review written by Heather Jaspan et al summarizing the steps involved in the progressive physiological maturation of the immune system in infancy and adolescence (Jaspan, 2006-A).

It is important to note that for several experimental and licensed vaccines, children and adolescents have responses to the vaccine that are the same or better than responses in older individuals. In a study comparing an experimental hepatitis B vaccine to a licensed vaccine across age groups, adolescents and pre-teens achieved the same response with half the dose of that given to subjects 20 to 30 years of age (Martins, 2004). Other studies of hepatitis B vaccine products demonstrated that a 2-dose series produced excellent immune response in teens, whereas adults and young adults required 3 doses to develop adequate hepatitis B responses (Heron, 2002; Levie, 2002). For influenza vaccine, a study showed better immunity and better protection in children compared to adults 2.5 years after vaccination (Foy, 1981). Better immune responses, measured as higher antibody titers, were recently demonstrated in adolescents compared to young adults in a human papilloma virus (HPV) vaccine study conducted by Merck (Nolan, 2005).

4. Adolescence is the right time for vaccination against sexually transmitted infections (STIs).

The vaccination of adolescents or pre-adolescents before they become sexually active could have a profound effect on the epidemic. It has been shown that girls in the United States are reaching sexual maturity at younger ages than in the past (Kaplowitz, 2001). It is thus possible that the age of sexual debut will decline. Therefore, it is reasonable to accelerate the study of promising HIV vaccine candidates in adolescents in areas where incidence of HIV infection is high.

When during vaccine development is it reasonable to initiate trials in adolescents?

While adolescents are at risk of HIV infection, they are also a vulnerable population in other ways. Adolescent participation in HIV vaccine trials is fraught with numerous ethical, cultural, social, religious and legal considerations. Adolescents participating in Phase I and Phase II trials would likely not expect personal benefit from the vaccine. Yet, in countries and communities where adolescents are at highest risk for HIV infection, it is highly likely that they would benefit from a safe and effective vaccine. Therefore, a plan that compresses the typical time frame of sequential trials – completed first in adults and later begun in adolescents – in order to ensure simultaneous licensure or registration of a successful, safe and effective vaccine for both adult and adolescent indications could save many lives.

As discussed in detail below, the control of hepatitis B transmission in the U.S. was delayed nearly a decade after licensure of hepatitis B vaccines. Not until adolescents and younger children were specifically included in the public health recommendations for vaccine receipt did national incidence begin to decline substantially. Recently, similar considerations by the pharmaceutical industry have influenced the planning of vaccine trials against non-HIV STIs (e.g., human papilloma virus – HPV, herpes simplex virus type 2 – HSV-2) for which vaccination of adolescents would most likely have a significant effect on control of these diseases.

Even under the optimistic scenario of solid efficacy in Phase IIb and Phase III trials of an HIV vaccine in adults, a validated correlate of immunity/protection may not be readily available to assist in reliable "bridging" for licensure for adolescents based on small immunogenicity studies. Therefore, in order to accelerate licensure for adolescents, trials in adolescents in any particular country or region should begin based on the safety observed in adults in that region and on immunogenicity against the prevalent clade(s) circulating in that region without necessarily awaiting completion of adult efficacy trials. Performing studies in adolescents only after efficacy studies in adults are completed would preclude timely availability of vaccine for adolescents by many years, as exemplified by the experience with hepatitis B vaccine in the U.S. The precedent of investigating vaccines in adolescents before completion of adult efficacy trials has been established for other indications (HPV and HSV-2) where immunogenicity and safety trials were initiated in adolescents well before efficacy trials in adults were completed.

Given the challenges of preparing sites in which cohorts of adolescents could be enrolled in trials, determination of the feasibility of conducting such trials should begin before sufficient data from adults warrants commencement of trials in adolescents.

Decision-making about the conduct of trials in adolescents needs to be closely tied to the data from the studies of the vaccine candidate in adults. Since adolescents will be among the highest priority target population for a licensed HIV vaccine to prevent sexual transmission, trials in adolescents should routinely be initiated as soon as possible after the safety and immunogenicity profiles in adults are solidly established and the vaccine is considered to be sufficiently promising to enter efficacy trials. It should be noted that exactly how early these studies can commence may also be determined by the class of products to which the candidate vaccine belongs (e.g., viral vector, bacterial vector, etc.); available safety data obtained through trials of other vaccine candidates based on the same vector or similar vectors (e.g., in other fields of research) may accelerate initiation of studies in adolescent populations.

For vaccine candidates with significant safety data in adults and no biological reason to expect safety issues unique to adolescents, trials that progressively step down from 17 to 12 year-olds to establish safety should usually be initiated once efficacy evaluation in adults is under way. Review of the safety and immunogenicity data may allow for inclusion of individuals in the older adolescent age range into the efficacy evaluation. The strategy proposed in Figure 1 (page 11) provides one example of how older adolescents may be included in HIV vaccine efficacy trials. Once the safety database from early Phase I and Phase II trials is substantially increased in the early part of Phase IIb trials, enrollment of older (16-17 year old) adolescents would be justified. Safety and immunogenicity data from the sub-cohort obtained during the "run-in" phase of this trial would trigger the enrollment of younger adolescents in safety and immunogenicity trials. Initially this group of younger adolescents would include 12-15 year-olds. Consideration would eventually need to be given to including children as young as 9-11 years old to insure that ages younger than most potential ages of sexual debut are captured in the study, as an ideal target age for vaccination is prior to sexual debut and thus risk of exposure. Pivotal Phase III trials would then be inclusive of individuals down to the lowest age for which safety data have been obtained, considering the legal and/or cultural barriers to enrollment of younger adolescents.

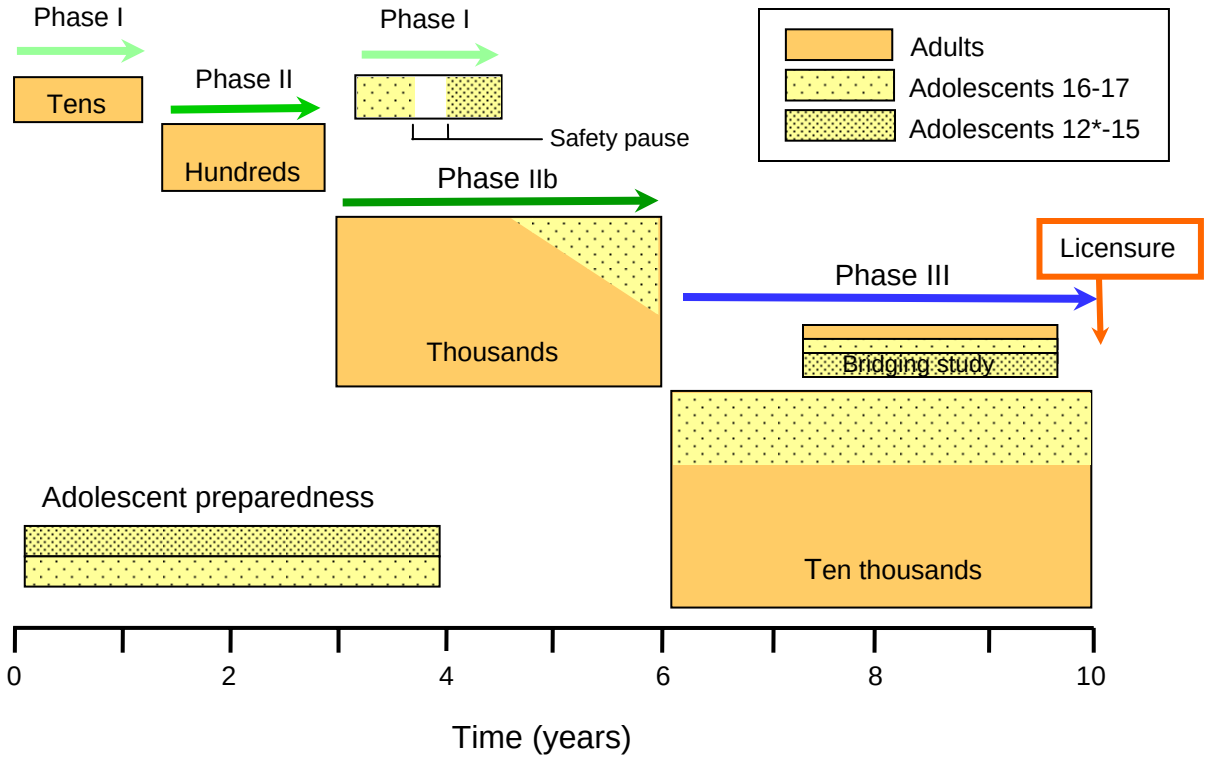

Figure 1. HIV vaccine development program in adolescents relative to adults

* This could include younger ages

Where should these studies be conducted?

Careful consideration should be given to the choice sites for the first HIV vaccine trials in adolescents.

United States

In the U.S., NIH-funded organizations are currently developing strategies for enrollment of adolescents in vaccine clinical trials, cohort studies and behavioral studies. The International Maternal Pediatric Adolescent AIDS Clinical Trials group (IMPAACT)[3], a joint effort of the NIAID and the National Institute for Child Health and Human Development (NICHD), currently sponsors a pilot Family Mapping Project that employs peer recruitment of adolescents, led by HIV-positive youth, into a vaccine preparedness cohort. This cohort will be evaluated on its knowledge of HIV and vaccine trials as well as its willingness to participate in future trials.

The NIH-funded Adolescents Trials Network (ATN) focuses on community intervention and aims to establish a primary prevention infrastructure based on epidemiologic intelligence, community partnerships, and capacity building. Its six-year *Connect to Protect*® program intervenes at the structural level to change community attitudes, policies, and programs in order

[3] Formerly known as the Pediatric AIDS Clinical Trials Group (PACTG).

to improve health and decrease HIV risk for community youth. Enrollment in HIV vaccine trials will be one of the prevention research opportunities offered to the participating communities.

Phase I and Phase II trials that enroll adolescent volunteers at low risk of HIV infection may be feasible in the U.S., but considerably more justifiable in higher risk adolescents. Phase IIb and Phase III trials of vaccine efficacy necessitate enrolling larger number of volunteers at higher risk. Higher risk populations in the U.S. likely have an annual HIV incidence rate of 1-2 percent, in spite of other prevention efforts; therefore, a Phase III trial would require many thousands of volunteers to have the statistical power to demonstrate efficacy.

International

Because adolescents are disproportionately affected by the epidemic in many regions of the world, the necessity for implementing potentially useful prevention strategies is high. In addition, defining low- versus high-risk adolescents for inclusion in trials may also vary by locale or region. Several elements must be considered for studies in the adolescent population outside the U.S.: the availability of reliable estimates of current HIV incidence; expected trends in incidence and transmission dynamics of the epidemic in that country; experience in the conduct of HIV or other STI vaccine trials in adults; existence of adequate infrastructure for recruitment and follow-up of adolescents; existence of structured panels of experts for ethical review of HIV vaccine research protocols involving adolescents; and existence of regulatory authorities with experience in review of HIV vaccine/prevention trials and pediatric research.

Investigators in South Africa are currently engaging in HIV vaccine trial preparedness studies with adolescents and stakeholders. Investigators are following cohorts of adolescent subjects in vaccine preparedness programs to study HIV incidence, risk factors for HIV acquisition, and willingness to participate in future HIV vaccine trials (Jaspan, 2006-B). Other issues such as adolescent support systems, parental consent and access to confidential information are also being explored. Focus group discussions with teachers, parents, community stakeholders, and Institutional Review Board (IRB)/Research Ethics Committee (REC) members are also taking place.

Lessons from licensed or pending vaccines

1. Adolescents in trials of STI vaccines

   a. Human Papilloma Virus (HPV) Vaccines

   It may be useful to examine the development process of vaccines for HPV infection, as several characteristics are relevant to the study of HIV vaccines in adolescents.

   Vaccines against HPV have been studied by the NIH's National Cancer Institute (NCI), GlaxoSmithKline, Inc. (GSK), and Merck & Co Inc. (Merck). Merck's experience is summarized below, because Merck's tetravalent vaccine, Gardasil®, is the most advanced vaccine developed to date, and the vaccine is currently licensed for use in the U.S., countries of the European Union, Mexico, Canada, Australia, New Zealand, Brazil, Croatia, Serbia, and Malaysia. Merck's Gardasil® includes serotypes 16 and 18 to prevent cervical cancer in females, and serotypes 6 and 11 to prevent genital warts in males and females.

   On November 28-29, 2001, the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened to review issues surrounding efficacy trial endpoints for

vaccines for the prevention of infection by human papilloma viruses. The VRBPAC recommended gathering immunogenicity data, and most importantly, cytopathology data to support licensure of the vaccine (FDA Advisory Committee transcripts, 2001).

Merck has conducted studies with Gardasil® in different age groups (Figure 2).[4] One Phase II dose ranging study was conducted in 277 women aged 16 to 23 (Villa, 2005). A large Phase III efficacy trial was conducted internationally (U.S., South America, and Europe) in 17,800 participants 16 to 26 years old. It is important to stress that Merck was able to initiate this Phase III efficacy trial in young adult women and a bridging study in pre-adolescents and adolescents concomitantly, because several thousand young adult women received both the monovalent and tetravalent versions of the vaccine in Phase I and Phase II studies.

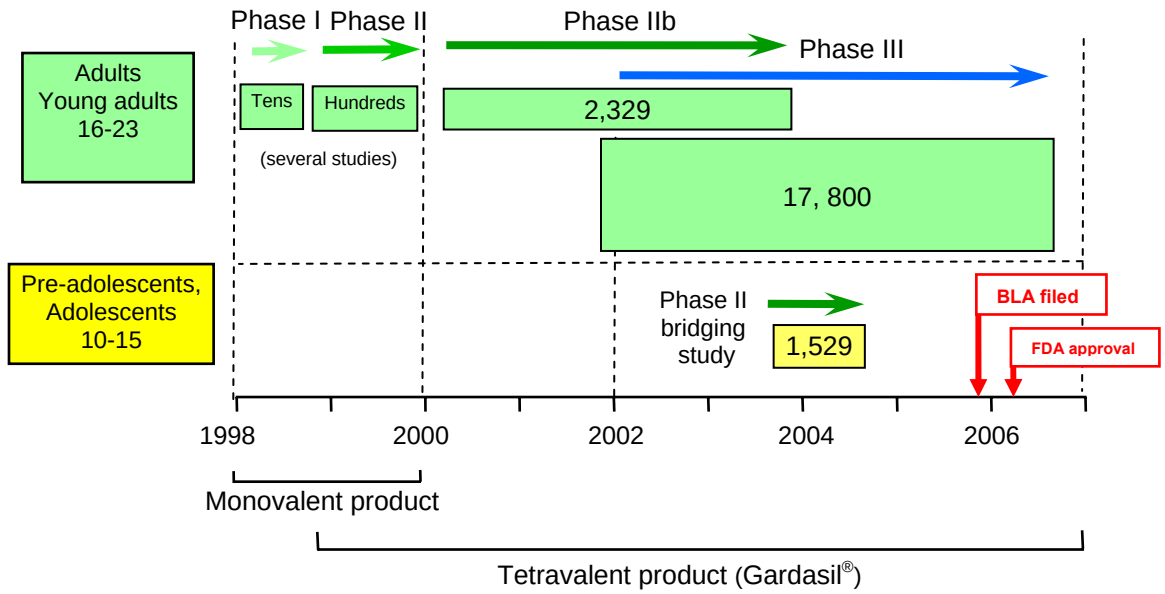

Figure 2. Merck's HPV vaccine development

In mid-May 2005 at the Annual Meeting of the European Society for Paediatric Infectious Diseases in Valencia, Spain, Merck scientists presented the results of a Phase II bridging study conducted in pre-adolescents and adolescents with the tetravalent HPV vaccine (Nolan, 2005). The study objective was to demonstrate comparable HPV type-specific immunogenicity in young adolescent boys and girls versus young women. The study included 1,529 participants divided into three groups (see table below). Group C was included in the study to allow for bridging the data of this study in adolescents with the data obtained from the pivotal Phase III study conducted in young women.

[4] Figure 2 includes studies conducted by Merck to bring the product to licensure in the U.S. The company is now conducting additional studies to expand the label indications in the U.S. and to support licensure of the vaccine in other countries; these studies are not included in Figure 2 nor discussed in this document.

The Phase II bridging study showed that over 99 percent of participants developed antibodies to all four HPV serotypes by month 7, and the tolerability of the vaccine was similar in all three groups. Compared to adult women, adolescents had higher antibody titer, between 1.67- and 2.7-fold higher depending on serotype.

Group	# of participants	Sex	Age	Percent of seroconversion at month 7	Ratio of serum Ab titer Relative to group C
A	510	♂	10-15	100% serotype 6, 11,15, 18	1.82 – 2.70
B	513	♀	10-15	100% serotype 6, 11,15 99.8% serotype 18	1.67 – 2.03
C	506	♀	16-23	100% serotype 6,11,15 99.1% serotype 18	--

Comparison of Gardasil® in male and female adolescents versus young adult women

Although participants in the Phase III trial were followed until the end of 2006, conclusive data from this study was available at the end of 2005. Merck filed a biologics License Application (BLA) for the approval of Gardasil® with the FDA in December 2005.

The FDA reviewed the licensing application submitted by Merck under FDA's priority review process and convened the VRBPAC on May 19, 2006 for final evaluation of the safety and effectiveness data collected by Merck. The VRBPAC unanimously recommended the approval of Gardasil® for the vaccination of females 9-26 years of age for the prevention of the these conditions:

Cervical cancer
Genital warts (condyloma acuminata) and the following precancerous or dysplastic lesions:
- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1

The FDA issued a letter of Licensing Action on June 8, 2006 (FDA, 2006-A). Merck has agreed to conduct several studies following licensure, including additional studies to further evaluate general safety and long-term effectiveness. Also, Merck has an ongoing study to evaluate the safety and effectiveness of Gardasil® in males for prevention of anal cancer and genital warts.

The above approach could serve as a model option to consider for accelerating the development of a vaccine for adolescents. However, the general lack of knowledge of immune correlates for HIV protection imposes significant limitations. Given the similarities between acquisition of infection for HIV and HPV, it should be noted that important lessons

could be gained from the now opened program for the deployment of the HPV vaccine around the world (AVAC, 2006).

b. Hepatitis B Virus (HBV) Vaccines

Like HIV, hepatitis B is transmitted by sexual contact and through contaminated blood. Hence, also like HIV, hepatitis B is not only an STI but also a threat to the blood supply in some countries and a risk to healthcare workers. Hepatitis B was the first sexually transmitted infection for which an effective vaccine was licensed by the U.S. FDA. In addition, HBV infection, like HPV and HIV infections, is associated with serious long-term complications; most notably, hepatic cirrhosis and hepatocellular carcinoma. The U.S. Centers for Disease Control and Prevention (CDC) has recognized hepatitis B vaccine as the first anti-cancer vaccine, because it can prevent primary liver cancer (Chang, 1997). The Merck HBV vaccine was the first to be licensed in 1981. Merck's and other companies' recombinant HBV vaccines are now available internationally.

In spite of the widespread availability of HBV vaccines in the U.S. and other high income countries since the early 1980s, the contributions of HBV vaccines to the overall prevention of hepatitis B in the U.S. was significantly limited for many years by the initial decision to target only high-risk adults for vaccination. Despite the introduction of vaccine, HBV incidence rose by 37 percent in the subsequent decade (CDC, 2004).

Consequently, both the CDC Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases recommended including infants and adolescents in the vaccination program (Committee on Infectious Diseases, 1997). These landmark recommendations led to a dramatic decline in the incidence of hepatitis B infection. The total number of infections in 2003 was 7,526 - a 64 percent decrease compared to the 21,102 cases reported for 1990. Rates among adolescents aged 12 to 19 years have declined by 90 percent since 1990 (MMWR, 2005).

c. Herpes Simplex Virus (HSV) Vaccine

GlaxoSmithKline Biologicals (GSK) has completed two Phase III studies of a vaccine directed against HSV-2, the agent that causes acute and recurrent genital herpes. Over 2,700 people aged 18 to 45 have participated in studies that evaluated the ability of the vaccine to prevent disease in individuals with herpes-infected sexual partners. The vaccine showed a trend toward being effective in women but did not protect men from HSV infection, and the trials were underpowered to demonstrate efficacy in only a sub-group, i.e., women. Therefore, GSK is continuing to study the vaccine in collaboration with the NIH. One ongoing study is being conducted in adolescent girls aged 12 to 17, also establishing precedence for how to perform trials in adolescent girls for vaccines for which there is reasonable safety data but no established correlate of protection. This study may inform planning for HIV vaccine trials by providing insights into cohort development, enrollment, follow-up, and ethical, legal and social issues.

2. Adolescents in trials of non-STI vaccines

Lyme Disease (LD) Vaccine

Lyme Disease (LD) is an anthropozoonotic disease transmitted to humans by the bite of ticks of the *Ixodes ricinus* complex that feed both on humans and on infected non-human obligate

mammalian host of the disease. The disease affects both adults and children, but the highest reported rates occur in children less than 15 years of age and in adults 30 to 59 years of age (CDC, 2003). GSK developed a vaccine for the prevention of LD was developed by GSK; the vaccine consisted of a recombinant lipoprotein, OspA, which is a surface antigen of *Borrelia burgdorferi*, the agent that causes the disease. Initially shown to be immunogenic and protective in animal models, the vaccine was subsequently licensed for 15-70 year-olds in the U.S. under the trade name LYMErix® in 1998.

After a small Phase I study, an initial safety profile of the vaccine was established in a Phase II double-blind, placebo-controlled dose range study conducted in 350 healthy adult residents of New England sites where LD is highly endemic (Telford, 1995). In 1995, the sponsor initiated a pivotal trial which included adults and adolescents. This was a Phase III multi-center, double-blind, randomized, placebo-controlled trial to evaluate the efficacy, safety and immunogenicity of the vaccine. A total of 10,936 subjects aged 15 to 70 years old who lived in ten states where LD is endemic were enrolled in the study.

Of note in the LD vaccine development program is the fact that a large Phase III study involving adolescents living in a high risk region was initiated without experience in adolescents from the preceding Phase II studies.

3. Vaccine recommendations for adolescents

Considerable experience has been gained in testing and deploying vaccines in adolescents. The U.S. CDC and ACIP currently recommend that the following be administered to adolescents: quadrivalent meningococcal conjugate, HPV, hepatitis B and booster tetanus/diphtheria/acellular pertussis, mumps, measles, rubella, and varicella vaccines based on clinical studies (CDC, 2005; CDC, 2006-B). In the future this list may be expanded to include respiratory syncytial virus, herpes simplex virus type 2, and chlamydia and group B streptococcus vaccines (Grabenstein, 2005) depending on research results.

Collectively, the above examples show that adolescents have been involved in numerous vaccine trials, several of which have also included children, sometimes before efficacy data in adults was collected. When adolescents are affected by a disease, it is imperative to design the vaccine development program so that adolescents are included well before licensure of the vaccine. However, in order to initiate studies in adolescents, safety data need to be established in at least an adequate number of adult participants.

Challenges for studies in adolescents

Issues that may prove challenging in adult trials may be amplified in an adolescent population (Mills, 2004). Some issues are relevant only to adolescents and may differ substantially across different cultures and jurisdictions. Many of the ethical and legal complexities of adolescent trials stem from the evolving autonomy of adolescents and their limited legal capacity in both international law and domestic legal systems. In order to successfully conduct clinical trials in adolescents, these challenges must be identified and addressed early, not only in the U.S. but also in other countries where trials will occur.

Identification of appropriate populations

Finding appropriate populations for the conduct of safety and efficacy studies is a challenge. The appropriate population for a trial in adolescents depends on several factors, including a rational and scientifically defensible trial, supportive attitude of the community, and supportive regulatory environment. In addition, risk of HIV infection varies by gender and locality. In most places in the world, girls are at higher risk than boys, but risk differences vary by locale. Willingness to participate in clinical trials is also of crucial importance in the identification of populations for vaccine studies. A survey conducted in adolescents in South Africa found that 53 percent of the individuals interviewed said they would definitely participate in an HIV vaccine study (Bekker, 2005-B; Jaspan, 2006-B).

Risk of sexual disinhibition of adolescent participants

Sexual disinhibition due to misconceptions of experimental vaccine efficacy could result in changes in a participant's risk behavior. Studies in adult volunteers in preventive HIV vaccine trials have shown no change or slightly lower risk-taking behavior overall (Chesney, 1997), because extensive risk reduction counseling is an integral part of the conduct of HIV vaccine trials. As there have been no HIV vaccine clinical trials that enrolled adolescents, and thus no prospective controlled trials assessing risk-taking in this context, clear information as to whether risk behavior will change in this population is unavailable. However, data from any relevant studies with adolescents (or adult trials), including other prevention modalities like microbicides, contraceptive diaphragms, and male circumcision, should be obtained in order to assist stakeholders like REC to deliberate on the probability and magnitude of this specific risk. In addition, protocols should specify what measures they will put in place to assess and reduce the risk.

Legal barriers

The legal implications related to disclosure of HIV testing and HIV status results could be accentuated for adolescents participating in HIV clinical trials. In addition, legally reportable findings such as illicit drug use, incest and child abuse, prostitution, and infection with other reportable STIs could also have significant implications for adolescent participants. Crucial to the inclusion of younger adolescents in efficacy trials would be the laws concerning rape and related reporting requirements. Such laws create substantial barriers to investigators asking adolescents to enroll or parents giving consent or permission for their adolescent to participate in an efficacy trial in which sexual transmission is the risk factor for endpoints and when such sexual activity, whether consensual or not, could be considered statutory rape. Researchers are obliged to operate within the law.

Additionally, laws governing emancipated minors would be relevant to consider to determine what legal rights are or are not conveyed to such adolescents. Finally, in many countries children may fall under the guardianship of individuals, related to the child or not, who are not recognized as legal guardians. The implications for obtaining informed consent from the adult responsible for the adolescent's welfare need to be considered, and mechanisms for ensuring ethical consent and assent in such circumstance sought. In many places it simply may not be legally or ethically feasible to enroll into HIV vaccine clinical trials all adolescents who stand to benefit from HIV vaccine research.

Confidentiality

In addition to standard confidentiality issues, adolescents and children may have unique or compelling concerns associated with disclosure of information on HIV status or risk, including, for instance, information on underage sexual activity, pregnancy, child abuse or rape, or illegal activities (e.g., illicit drug use or commercial sex work) to parents/guardians, friends or associates. Consideration will also need to be given to who has the right to privacy or right to confidentiality when the legal right is ascribed to the person giving informed consent (i.e. the parent(s) or legal guardian). Ethically, the adolescent's right to privacy, even from disclosure to the parents, must also be assured when legally feasible. The means to accomplish this must be considered carefully. The parent(s) should also be informed during the consent process about what information would or would not be disclosed to them and what medical or other services the adolescent would be provided without further parental permission.

In the U.S., the National Institutes of Health (NIH) and other DHHS agencies issue Certificates of Confidentiality to protect identifiable research information from forced or compelled disclosure. These certificates are issued at the request of any investigator conducting research that collects identifiable personal information of a sensitive nature from participants. "They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to participants." (NIH, 2002; OHRP, 2003)

Issues of consent/autonomy

Only a few jurisdictions in the U.S. address the participation of children or adolescents in research, and these state laws mostly pertain to mental health research. In general, the Code of Federal Regulations, which governs federally funded research in the U.S., requires parental permission[5] for the enrollment of children and adolescents in research in conjunction with the minor's assent[6] to participate in the study (45 CFR 46 Subpart D). In most other jurisdictions, children below the age of majority ordinarily would not have capacity for independent consent to research. Legislation providing that children may consent independently to medical treatment does not necessarily extend to research. It is unlikely that incarcerated adolescents would be able to participate in HIV vaccine clinical trials. Adolescents in foster care may be eligible to participate depending on the circumstances. The laws governing these specific classifications of adolescents should be surveyed and considered, as relevant at the particular trial site, before considering enrolling such adolescents.

In each jurisdiction, it would have to be established whether legislation governing research exists and whether such legislation sets an age of consent. For example, in South Africa, the impending National Health Act (s71 of 2005) requires consent from a parent or legal guardian (not other caregivers) for health research until minority status ends and the consent of the child if

[5] Decision made by a parent(s) or guardian with legal authority to allow a child to participate in research.
[6] Assent is a child's affirmative agreement to participate in research.

the child is capable of understanding. If there is no dedicated legislation outlining the age for independent consent to research, it should be assumed that children below the age of majority do not have this capacity. In addition, adolescents who have lost their parents, a reality in countries with a high prevalence of AIDS, need their guardian's permission, if guardianship exists. Where legally recognized guardians do not exist, it may not be possible to enroll these adolescents unless legal guardianship is formally transferred to the primary caregiver. In such cases, it must be established how trial sites can assist caregivers to become legal guardians. If it were possible to identify a mechanism for ensuring the legal and ethical rights of the adolescent in the care of guardians not legally recognized as such, consideration could be given to enrolling them. Further, in those jurisdictions that permit other caregivers to consent for research even if they are not legally recognized as guardians, considerations must be given to how to involve such persons. Laws governing emancipated minors will be relevant to consider, as some jurisdictions may allow adolescents who have married to give independent consent for research participation. Finally, involving two or more parties in the decision-making process poses a challenge, as the information needs of the parents/guardians and adolescent volunteers must be managed carefully. These complex consent processes require careful planning.

Compensation for participation in clinical trials

Offering compensation, especially monetary forms, to adolescents participating in clinical trials is a complex ethical issue. Compensation models for adolescent trials should be debated in all jurisdictions where trials are being planned. Possible models include reimbursement for out-of-pocket expenses, payment for time and inconvenience, payment as an incentive to increase enrollment, or a token of appreciation (Wendler, 2002). Every effort should be made to employ sound consent procedures and ensure the following: 1) payment does not distort decision-making by the parent or guardian giving consent or by the adolescent assenting to the research, and 2) payment does not lead to enrollment in research that contravenes participants' interests. Sound ethical review to establish that the risks posed to adolescent participants are indeed reasonable must be emphasized.

Social environment/cultural issues

Fear of stigma, isolation and discrimination, a tangible issue in adult trials, could have an even greater effect on the welfare of adolescent participants. Also, family, friends and work relationships may be negatively affected by participation in trials. Distrust of clinical research may be more pronounced in adolescents than in older individuals. The struggle for adolescents to confide in their peers about their participation may lead to inadvertent disclosure and social harms. This struggle may be more pronounced in adolescents than in adults. Furthermore, many low and middle income countries may not have adequate legal protections that prohibit unfair discrimination based on an individual's real or perceived HIV status.

In areas where sex with an HIV-negative female is believed to "cleanse" a man of HIV, or where incest or rape of children is common, discovery of a female's participation in an HIV clinical trial may inflame an attacker, causing him to be more violent (Wood, 1998).

Data from prior relevant studies should be obtained in order to allow RECs to make a rational assessment of this potential social harm. Investigators should plan and present to RECs the measures they will undertake during the trial to identify, assess, and resolve the social impact of participating in vaccine trials. This is particularly important for more vulnerable groups, for

example, adolescent girls, particularly in communities in which females do not have the same socio-legal rights and social standing as males.

HIV seropositivity resulting from HIV vaccination

Adolescent populations may be more vulnerable than adult populations to the consequences of testing seropositive, even though uninfected with HIV, in routine diagnostic tests as a result of the vaccination. For example, many more adolescents than adults may not yet have established their own health insurance coverage, and seropositivity resulting from the vaccination may impair their ability to obtain insurance. Unless access to tests that detect true infection is provided, false positive results could also impact current or future educational, employment and travel opportunities for adolescent volunteers. Plans to provide support to mitigate such risks, including tests to distinguish vaccination from infection, even after the trial is completed and until the trial volunteer reverts to seronegativity, should be considered in the design of the clinical trial protocol.

Compliance and retention

Clinical trials with investigational vaccines are demanding because of multiple scheduled visits, blood draws, and injections. In addition, the necessary follow-up period is long. Retaining populations, including adolescents, that lack support or resources will likely be a challenge. Although retention rates for adolescents in some less demanding studies have been remarkably high and the lessons learned from that research will be applied to the vaccine effort (Stanford, 2003), it is difficult to anticipate what the retention rate will be in HIV vaccine studies. Some insight on retention also comes from the Birth to Twenty cohort study in South Africa; that study has demonstrated that a relatively high retention rate in studies in children in low and middle income countries can be achieved across as much as 15 years of follow-up (Richter, 2004).

Venues for trial activities will need to be adapted in design, location, staff practices and operating schedules, in order to facilitate adolescent involvement. Successful recruitment and retention of adolescents in clinical trials will require that their needs be thoroughly addressed.

What could improve the feasibility of HIV vaccine studies in adolescents?

Prepare communities

It is essential to create an environment that supports HIV vaccine trials and allows community partners to participate meaningfully in trial planning and implementation. A supportive environment can be achieved through appropriate community education, media campaigns and community leadership; engendering a sense of trial ownership; and political advocacy and structures to facilitate community participation, like Community Advisory Boards (CABs) that include adolescent members. Adolescents could also serve as community educators/recruiters (CER). Community education strategies that teach adolescents and their parents about the disease, trial participation, and risk behavior modification must be developed and carefully evaluated. Community leaders also need to be educated about the importance of including adolescents in HIV vaccine trials and the ethical-legal protections that exist to ensure that the rights and welfare of adolescent trial participants are promoted. Other forms of effective adolescent participation should be explored.

Provide benefits

One way to enhance study feasibility would be to offer a service or product in the context of the clinical trial that is beneficial to the individual trial participant and/or the community from which trial participants will be recruited. For example, offering hepatitis B, HPV or the quadrivalent meningococcal conjugate vaccination free of charge to research participants or to the broader community could increase acceptability of the trial to Institutional Review Boards (IRB) or Research Ethic Committees (REC) in countries or communities where the hepatitis B, HPV, or quadrivalent meningococcal conjugate vaccine are not yet widely available. This practice could also serve to operationalize ethical requirements to actively promote the welfare of trial participants and benefit host communities.

Other general ways to increase the benefit of the study include providing services for adolescents that would not be widely available to the community. Training of health care providers in the community, providing supportive psychological intervention, and providing non-vaccine related prevention services for STIs are possible examples. In consultation with community members, consideration must be given to which additional trial benefits would be considered appropriate.

Consider study design

One approach that might make the conduct of studies in adolescents more acceptable to the IRB/REC and/or regulatory authorities is to implement a study design that will initially accrue older adolescents, e.g., 16-17 years of age, then proceed to progressively younger groups, e.g., 14-15 years of age, 12-14 years of age, once post-vaccination safety is ascertained in the older group. Other study design approaches should be considered as more information becomes available.

What needs to be done?

Identification of cohorts and assessment of feasibility

Investigators conducting cohort studies in adolescents at higher risk of HIV exposure need to be identified. Once potential communities and trial sites are identified, in-depth studies of HIV prevalence and incidence in adolescents should be performed. Other studies should evaluate willingness to participate in vaccine trials, understanding for informed consent, compliance with study requirements and ability to retain adolescents.

Importance of community involvement

Local community support is integral to a clinical trial's success. Community partnerships should be formed and these partners meaningfully engaged. This is especially true in low or middle income countries, where information is often spread through local leaders and by word of mouth.

"Community" includes all people who are affected by the trial, not just trial participants. Local leaders are part of this group. Their ability to influence popular ideas must not be underestimated, and local leaders should be involved as early as possible in trial communications. In general, the community should participate in trial planning and conduct to ensure that the community's needs and concerns are addressed. Community members, typically through a CAB, can act as liaisons between the community and protocol teams. Sincere community involvement can engender support early and facilitate trial conduct.

Community education

Education of the community in which the trial will be conducted facilitates community engagement and support. Culturally and linguistically sensitive educational strategies need to be developed. If the larger community understands HIV vaccine research, trial-associated misconceptions and stigma will be minimized. This is especially important for trials involving challenging populations, such as adolescents.

Communication plan / media plan

Design and implementation of an education plan directed to media professionals will help ensure timely, unbiased, and accurate reporting of adolescent trials. Consideration must be given to the potential negative effect of media reporting on the conduct of HIV vaccine clinical trials in adolescents. Specifically, the media's reaction to adverse events and coverage of breakthrough infections, even if they are predicted, could hinder a study. It will thus be imperative to design and implement a strong media education plan to insure accurate reporting and minimize sensationalism by "normalizing" adolescent trials (i.e., HIV vaccine trials in adolescents are not unusual). This media education plan could be a component of the broader community engagement plan.

Social impact evaluation

Strategies to identify, assess, mitigate, and resolve the social impact of participating in vaccine trials should also be implemented. This is particularly important for more vulnerable groups, e.g., adolescent girls, particularly in communities in which females do not have the same socio-legal rights and social standing as males. Planning of such strategies should take into account the fact that support may need to continue after the trial is completed, particularly in regard to vaccine-induced seropositivity.

Harness expertise in pediatric and adolescent medicine

Recruitment and training of personnel with expertise in pediatric and adolescent medicine, including personnel capable of providing appropriate social and psychological support, at the sites where the trials will take place is of primary importance for the conduct of HIV vaccine trials. Sensitivity training focused on adolescence and gender should also be undertaken for trial site staff at all levels. Also, efforts should be made by the local investigators to advocate for the inclusion of members with this expertise on the site's IRB/REC.

International cooperation

International cooperation is of paramount importance to set the foundation for the conduct of HIV vaccine studies in adolescent populations. An audit of the ethical-legal framework should be undertaken to identify protections and gaps in protection for volunteers. In March 2006, the World Health Organization and the Ethics, Law, and Human Rights Working Group of the African AIDS Vaccine Programme held a consultation in Gaborone, Botswana on "inclusion of adolescents in HIV vaccine trials" in follow-up to an earlier consultation on gender, age, and race in the context of HIV vaccine trials. This consultation focused on the issues relevant to including adolescents in HIV vaccine trials to be conducted in low and middle income countries, particularly in Sub-Saharan Africa. An outcome of this consultation was the drafting of a Position Paper for the WHO. At this time, the document remains in draft form and is not yet publicly available; however, it considers and makes recommendations for ethical, social, legal, community, scientific, and clinical trial design issues relevant to inclusion of adolescents in HIV vaccine clinical trials that are discussed herein.

Regulatory environment

United States

The U.S. Congress, the U.S. Food and Drug Administration and the U.S. National Institutes of Health are committed to the thorough study of drugs and biologicals in all populations for whom these agents may be beneficial, including children when applicable. Historically, many drugs and biologicals were licensed without specific assessment of safety and efficacy in sub-populations including children, women and ethnic minorities. By necessity, the use of these agents in these populations beyond the labeling claims is called "off label" use. As an example, 75 percent of the prescription drugs on the market in the U.S. in 2002 did not have pediatric use information but were used off label in pediatric patients (AAP Committee on Drugs, 2002).

The growing sophistication in the understanding of the heterogeneity of the pediatric population and the realization that, because of the extent of off label use of drugs and biologics, a much larger number of children have been exposed to treatment risks in the interest of avoiding research risk, have shifted the paradigm toward inclusion of pediatric populations in clinical studies. Consequently, over the last decade, Congress has passed legislation followed by FDA rule-making to ensure adequate assessment of new and existing drugs and biologics in pediatric populations (Goldkind, 2005).

In 1997 Congress passed the FDA Modernization Act (FDAMA) Exclusivity Provision. This legislation granted six months exclusivity to sponsors that voluntarily agreed to conduct studies in pediatric populations. In 1998 the FDA issued the "pediatric rule"[7] under which manufacturers are required to directly assess the safety and effectiveness of drugs and biological products in the pediatric population (Federal Register, 1998). However, the FDA's statutory authority to mandate research in pediatric populations was challenged by the Association of American Physicians and Surgeons, Inc. (AAPS), a non-governmental organization. The U.S. District Court for the District of Columbia ruled against the FDA in October 2002. To fill the gap created by this ruling, Congress, which has the necessary statutory authority, enacted the Pediatric Research Equity Act (PREA) in 2003 (FDA, 2003). The Act amends the Federal Food, Drug and Cosmetic Act and authorizes the FDA to mandate certain research into drugs used in pediatric populations. The FDA has issued a *Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act* (FDA, 2005). The guidance provides recommendations on how to interpret the pediatric study requirements of PREA.

The FDA has issued a guidance for industry document entitled *Development of Preventive HIV Vaccines for Use in Pediatric Populations* (FDA, 2006-B). This document specifically focuses on adolescent populations and summarizes the current regulatory requirements for conducting studies in this age group. Among other issues discussed, the FDA recommends enrolling adolescents in HIV clinical trials in a stepwise fashion, from oldest to youngest, and to carefully design the trials to address safety concerns, including social harm derived from possible increases in risky sexual behavior and the impact of false positive HIV test results. Additionally, the guidance discusses options for licensure of an application for a pediatric indication using either adult efficacy data and extrapolation (bridging) to adolescents or pediatric efficacy data

[7] Contained in: "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biologic Products in Pediatric Patients."

with clinical outcomes, such as documented HIV infection. While the document states that bridging would be facilitated by "identification of an immune response that is predictive of protection," it does not state this would be required.

A table outlining the major milestones in U.S. laws and FDA regulations affecting the conduct of clinical trials in children is contained in Appendix 1.

Human subject protection regulations

U.S. federal regulations provide additional safeguards to protect the rights and welfare of subjects when some or all of the subjects, such as children, are likely to be vulnerable to coercion or undue inducement. These regulations acknowledge the need to abide by state or local laws or regulations, as well as any non-U.S. laws or regulations that might otherwise be applicable in international research, which provide additional protection for human subjects.

Once these local and international regulations have been applied, the current FDA and OHRP regulations[8] pertaining specifically to safety of clinical studies in children and adolescents apply. These regulations, found in 21 CFR 50 Subpart D[9] (Code of Federal Regulations, 2004 reproduced in Appendix 2) and 45 CFR 46 Subpart D (Appendix 3) are summarized below:

21 CFR 50 Subpart D contains FDA regulations regarding conduct of clinical trials in children. 21 CFR 50 Subpart D was published with comments explaining why it was issued in the Federal Register on April 24, 2001 (Federal Register, 2001).

CFR Title 21 Part 50: *Protection of Human Subjects.* Subpart D: *Additional Safeguards for Children in Clinical Investigations.* The regulation classifies permissible research into four categories requiring increasing levels of scrutiny (50.51 – 50.54) based on degree of risk and prospect of benefit. The regulation describes the role of ethical review committees, referred to in the regulations as IRBs, to determine whether the conduct of research with healthy children should be limited to that which involves no more than minimal risk of harm.[10] Research in children who have some disorder or condition is restricted to no more than a minor increase over minimal risk, unless potential benefit is anticipated to offset the potential harms to the participants.

There are three categories of research that can be conducted in children approvable at the IRB level, defined in 21 CFR. 21 CFR 50.51 covers what is discussed above on clinical investigations (21 CFR) involving not greater than minimal risk. 21 CFR 50.52 covers

[8] Regulations are interpretation of the laws provided by the federal agency responsible for a given sector (in this case the FDA and OHRP.) Regulations are binding like laws.

[9] The Code of Federal Regulations (CFR) is the codification of the rules published in the Federal Register by the executive departments and agencies of the Federal Government. It is divided into 50 titles that represent broad areas subject to Federal regulation. Title 21 of the Code of Federal Regulations contains the regulations set forth by the Food and Drug Administration. Title 45 contains the regulations set forth by the Department of Health and Human Services and the National Institutes of Health.

[10] Federal regulations define the term "minimal risk" as meaning "*that 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 46.102 (i); 21 CFR 50.3 (k)

clinical investigations that involve greater than minimal risk but present the prospect of direct benefit to the individual research subjects. Finally, 21 CFR 50.53 applies to clinical investigations involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about a subject's disorder or condition.

Thus, it is possible that an HIV vaccine trial in adolescents, in which more than minimal risk is possible, may need to be conducted following FDA regulation 21 CFR 50.54.

Two aspects of 21 CFR 50.54 must be considered. First, in 21 CFR 50.54 (a), IRBs/RECs play a central role in deciding if the research is appropriate.[11] The research may be considered appropriate if the IRB/REC finds that the clinical investigation or research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the welfare of children even though the research may involve greater than minimal risk and does not present the prospect of direct benefit to the individual subject nor yield generalizable knowledge about a subject's disorder or condition. Second, 21 CFR 50.54 (b) stipulates that a proposed trial should undergo review by a panel of experts[12] before implementation.

CFR Title 45 contains regulations set forth by the DHHS Office of Human Research Protection (OHRP). OHRP has jurisdiction on clinical trials research funded by U.S. federal agencies (45 CFR 46. 401). The OHRP regulations that apply to trials in adolescents are contained in 45 CFR 46 Subpart D.

Title 45 of the Code of Federal Regulations, Part 46, Subpart D: *Additional Protections for Children Involved as Subjects in Research.* This subpart describes the terms under which children, including infants, could be included in research. The stipulations are consistent with 21 CFR 50, Subpart B.

OHRP regulation 45 CFR 46 asserts that OHRP has jurisdiction regarding trials funded or conducted by the federal agencies of the Department of Health and Human Services (DHHS or HHS). Section 407 may apply to vaccine studies in adolescents. Section 407 is very similar to 21 CFR 50.54 in that it stipulates the requirement for an independent review by a panel of experts. When a study is conducted under U.S. Investigational New Drug Application (IND), OHRP will defer the need for independent review by a panel of experts to the FDA advisory panel. Essentially, when both 21 CFR 50 and 45 CFR 46 are relevant, the more stringent of the regulations applies.

It should be noted that the regulations protecting children could be subject to change in the future. In passing the Best Pharmaceuticals for Children Act in 2003, Congress charged the Institute of Medicine (IOM) to provide a comprehensive report on issues related to pediatric research. The report was published in 2004 under the title "Ethical Conduct of Clinical Research Involving Children"[13] (The National Academies Press, 2004).

[11] FDA may require that the minutes of the IRB deliberation on this issue be made available to them.

[12] In the case of vaccine research, this may entail review by the FDA's Vaccines and Related Biological Products Advisory Committee. It should be noted that all sessions of the FDA's Advisory Committees are open to the public and that the FDA encourages participation from all public stakeholders in its decision-making processes.

[13] The IOM recommended that the interpretation of "minimal risk" should be revised and that what constitutes a "condition" should be clarified and expanded in the regulations. The panel of experts also recommended focusing

The recommendations contained in the report are not for immediate implementation but will be considered by the FDA in future revision of 21 CFR. It is also important to emphasize that the IOM report explicitly states that the report recommendations apply only to research conducted in the U.S.[14]

International

Three main regulatory scenarios should be considered:

A) If a study is to be conducted at international sites, including U.S. sites, the study will need to be conducted under U.S. FDA and local regulations. An Investigational New Drug (IND) application will need to be filed and the regulations contained in 21 CFR 50 will apply. If the study is funded by the NIH or other component agency of the DHHS, then 45 CFR 46 will also apply.

B) If a study funded by the NIH or other component agency of the DHHS is to be conducted exclusively outside the U.S. with a vaccine candidate not manufactured in the U.S. and not intended for licensure in the U.S. (e.g., a vaccine for a clade C candidate to be studied in Africa), then the regulations in 21 CFR 50 would not apply. However, in addition to the rules set forth by the country in which the study is to be implemented and applicable regulations from the country of manufacture, the investigation must follow the regulations contained in 45 CFR 46 Subpart D.

   The DHHS Office of Human Research Protection (OHRP) has recently issued guidance for the correct interpretation of 45 CFR 46 Subpart D (OHRP, 2005-A). When conditions for 407 review have been met and FDA regulations do not apply, as in the case of a study with no sites in the U.S. and not conducted under U.S. IND, OHRP, once notified of the intent to conduct such a study, will identify a panel of experts in pertinent disciplines and relevant child advocates to review the protocol.

C) If a study funded by the NIH or other U.S. government agency is to be conducted exclusively outside the U.S. with a vaccine candidate manufactured in the U.S., the regulations in 21 CFR 50 may not apply[15] but 45 CFR 46 Subpart D will apply. FDA, however, has jurisdiction on the exportation of unapproved human drugs, biologics and devices as stipulated in the Food Drug and Cosmetic Act section 802 (U.S. Code on line, 2001) as amended by the Export Reform and Enhancement Act of 1996. Under those provisions an unapproved human drug, biologic or device can be exported directly to a list of several countries[16] but will require notification to the FDA for unlisted countries. The

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attention on the process of requesting parents' permission and children's assent to research participation, and to structure the process for requesting assent from the minor. Other recommendations included the addition of experts in pediatric medicine to IRBs.

[14] "*The committee did not consider in depth other important questions, including financial and other conflict of interest, standards for pediatric research in developing countries, priorities for pediatric research, scientific methods, scientific misconduct and appropriate review of low-risk social science research.*" (Page 31 of the IOM report)

[15] If the data obtained from the study is intended to support licensure of the vaccine in the U.S. or for use by U.S. citizens while traveling abroad, then the sponsor should file an IND and 21 CFR 50 will apply.

[16] Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, the European Union, and the countries of the European Economic Area.

> notification's primary purpose is to provide the FDA with documentation that the country receiving the unapproved product has statutory or regulatory requirements that will ensure review by government officials of the product for Good Manufacturing Practices (GMP), safety and effectiveness, reporting of adverse events, et cetera. Such studies, however, may be conducted under U.S. IND, in which case, 21 CFR 50 would apply.

A useful tool to access information about the laws, regulations, and guidelines of over 50 countries was developed by the Office for Human Research Protection. The compilation provides direct web links to each country's key organizations and laws, where available. The compilation can be accessed through the OHRP web site (OHRP, 2005-B).

Republic of South Africa

The Republic of South Africa is one of the low and middle income countries where all the proposed conditions necessary for conducting studies in adolescents, as outlined above,[17] may be met. Additionally, RSA is listed among the countries the FDA recognizes as having the regulatory capacity to review investigational products and to which a product from the U.S. could be exported without FDA notification.

a. Ethical framework

Current ethical guidelines establish the conditions under which adolescents or their parents/guardians may consent to participate in research, including the level of research-related risk to which adolescents may be exposed. However, these ethical guidelines pose challenges to those planning and reviewing trials, as inconsistency between guidelines has been reported (Strode, 2005).

The current South African Medical Research Council (MRC) guidelines on medical ethics, *General Principles* (MRC, 2001), appear to limit parental consent for research classified as "non-therapeutic" to "observational" research with risk levels that are "negligible." HIV vaccine trials are likely to be classified as non-therapeutic, as the guidelines provide by definition that healthy volunteers will participate in non-therapeutic research. However, HIV vaccine trials are likely to involve interventions with risks that may exceed negligible or everyday risk (Appendix 4).

The other set of widely used guidelines for clinical trials are the Department of Health's (DOH) *Good Clinical Practice Guidelines* (GCP) (DOH, 2000). These appear not to preclude adolescent participation in HIV vaccine trials; they do not restrict parental consent to certain kinds of study designs. They also seem to allow a more flexible risk level. Specifically, they assert that generally (there are exceptions) adolescents should be exposed to research risk commensurate with daily life or routine tests. However, research involving a greater than everyday risk could be allowed. If the research does not hold direct benefit, a minor increase in risk could be justified by contribution to generalizable knowledge. If the research holds the prospect of direct benefit, the increased risk could be justified by this direct benefit.

The MRC has released guidelines specifically on research ethics for HIV preventive vaccine trials (MRC, 2004) (see Appendix 5). These guidelines state that adolescents are eligible for enrollment in clinical trials provided the risks of interventions that do not provide direct benefit (e.g., additional blood draws for lab tests) confer no more than a slight increase over everyday

[17] "Where should these studies be conducted?"

life risk and can be justified by a positive knowledge-risk ratio. Examples of direct benefit include counseling on HIV prevention and provision of health care.

Ethical guidelines also adopt differing views regarding the persons with authority to consent for children. On the one hand, the RSA DOH GCP guidelines provide for consent from a child's "parents or legal guardians" for clinical trials. If HIV vaccine trials are classified as more than minimal risk (everyday risk) with no direct benefit, permission from *both* parents may be required. Trials classified as more than minimal risk but likely of direct benefit would require the permission of *one* parent.

On the other hand, the MRC's guidelines on research ethics for HIV preventive vaccine trials allow that 'a parent' or guardian may give consent and a child may give assent to preventive HIV vaccine trials if trials are classified as "non-therapeutic"; if classified as "therapeutic," then a child of 14 and older may consent independently, although parental consent is desirable. These guidelines will likely supersede MRC Book 1 because they are more recent and endorsed by the National Health Research Ethics Council (NHREC). The new NHREC guidelines adopt the same approach as DOH GCP (DOH, 2000). The 2004 NHREC guidelines on children are provided in Appendix 6.

b. Legal framework

The primary legislation dealing with the protection and care of children is the Child Care Act (RSA, 1983). The Act provides for some of a child's health rights, including the circumstances in which children may consent to medical treatment, but it does not deal with research. The primary health legislation that deals briefly with research with human subjects including research with child participants is the National Health Act (RSA, 2004). The pertinent part of the Act has not as yet been operationalized, and it is uncertain when it will become binding. The regulations accompanying the Act, which may contain additional norms and standards for research with human subjects including children, are still being developed.

A further complexity is that the Children's Act (RSA, 2006) also exists. While it has been signed by the President, Parliament has not at the time of this writing decided on a date for implementing the Act. It will consolidate all legislation dealing with children into a single Act. On the other hand, the Children's Bill (RSA, 2003) deals with many of a child's health rights, but it does not describe the rights of child research participants. The Children's Bill will supplant the existing Child Care Act.

In summary, for research involving children, even with the above mentioned uncertainties, there are a number of procedural and substantive requirements that seem to apply. For research designated "non-therapeutic," these appear to include:

A) When the National Health Act is implemented, children will not be able to consent independently to research and will require parental or legal guardian consent until the age of 21. However if the Children's Bill becomes law, children will be able to consent independently to all forms of medical research from the age of 18.

B) When section 71 of the National Health Act is implemented, children will be required to consent formally along with their parents or legal guardians to participation if they have "understanding."

C) When the National Health Act is implemented, authorization will have to be obtained from the Minister of Health (or designee) for "non-therapeutic" research. The details thereof are anticipated to be outlined in the accompanying regulations.

D) The clinical trial must have ethical approval from an REC, scientific approval from the Medicines Control Council, and if the candidate vaccine includes genetically modified components, authorization from the Executive Council of Genetically Modified Organisms (ECGMO) (MCC, 2003).

Given that the South African legal framework for child research is evolving, careful consideration must be given to both current and future legal requirements.

Conclusions

Making an effective vaccine available for vaccination of both adults and adolescents will be necessary to control the AIDS epidemic. As the examples above illustrate, ideal public health use of vaccines requires the design of a vaccine development program to permit concomitant filing for licensure for both adults and adolescents. Overall incidence of HIV may decrease only after implementation of a vaccination program for both adults and children, as illustrated by the hepatitis B vaccination experience in the U.S. Without a validated correlate of protective immunity, it is unclear whether or how FDA and other national regulatory authorities will accept a "bridging study" to extend the indication for HIV vaccine to adolescents based on successful Phase III trial(s) in adults. This will hopefully be clarified early in product development. Alternatively, the schematic development program represented in Figure 1 would shorten the overall time to evaluation and appropriate licensure and public health usage of a successful HIV vaccine for adolescents. The Division of AIDS is committed to the timely evaluation of promising vaccines in the adolescent population as proposed in this document.

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Appendices

Appendix 1: U.S. laws and FDA regulations affecting the conduct of clinical trials in children

YEAR	PRECIPITATING EVENT	LEGISLATION (Congress)	REGULATION (FDA)	COMMENTS
1902	13 children died of tetanus after receiving contaminated diphtheria antitoxin.	**Biologics Control Act**		Established the Federal government's regulatory power over antitoxin and vaccine development.
1906	Unsanitary practices in the meat-packing industry.	**Pure Food & Drug Act**		Prohibited mislabeling and **ADULTERATION** of drugs.
1938	A poisonous component used for preparation of elixir of sulfanilamide killed 107 people, 100 of them children.	**Food, Drug & Cosmetic Act**		Required that new drugs be **SAFE** as well as pure.
1962	Thalidomide, introduced in Europe in 1957-58, was found to have caused birth defects in thousands of babies born in western Europe.	**Kefauver-Harris Amendment to the Food, Drug & Cosmetic Act**		Established guidelines for reporting information about adverse reactions, clinical testing and advertising of new drugs. Required **PROOF OF EFFECTIVENESS** in addition to safety for new drugs and for drugs released since 1938.
1979				FDA added a Pediatric Use subsection to drug labels.
1986		**National Childhood Vaccine Injury Act**		Requires patient information on vaccines, gives FDA authority to recall biologics, and authorizes civil penalties.
1991			**Common Rule**	Several federal entities involved in human subject research adopted the 1981 FDA and DHHS policy for protection of human subjects in research. The Common Rule requires researchers to obtain and document informed consent; secures special protection for children, women, and prisoners; elaborates on required procedures for Institutional Review Boards; and ensures that research institutions comply with the regulations.
1994			**Specific content and format requirements for human prescription drug labeling: revision of "pediatric use"** subsection in the labeling: Final Rule (21 CFR 201). Federal Register 1994 95: 314-7.	Sponsors should review pediatric data to determine its adequacy to support pediatric labeling.

	PRECIPITATING EVENT	LEGISLATION (Congress)	REGULATION (FDA)	COMMENTS
1997	The formal study of drugs in children was declared a moral imperative by the American Academy of Pediatrics Committee on Drugs in 1995.	**FDA Modernization Act** (*FDAMA*) Public Law 105-115 105th Congress (Nov 21, 1997)		Established the pediatric exclusivity incentives: 6 months of marketed protection (on the entire moiety) is granted for the sponsor's **VOLUNTARY** conduct of trials in children.
1998			**Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biologic Products in Pediatric Patients "*Pediatric Rule*"** Final Rule. Fed. Reg. 1998 63 (231) 66632-72.	The Pediatric Rule took effect in April 1999.
2000		**Children's Health Act** Public Law 106-310, Title 27 2701 106th Congress (Oct 17, 2000)		All research in children conducted, supported or regulated by HHS must comply with 45 CFR 46 Subpart D.
2002		**Best Pharmaceuticals for Children Act** (*BPCA*)		Reauthorized FDAMA's pediatric exclusivity. Established the Office of Pediatric Therapeutics at the FDA. Established a collaboration between FDA and NIH for the study of off patent drugs in children. Mandated the dissemination of findings from studies in children.
2003	A challenge filed by the Alliance for Human Research Protection resulted in a 2002 Federal District Court decision striking down the Pediatric Rule.	**Pediatric Research Equity Act** (*PREA*) Public Law 108-155		Reinstated the Pediatric Rule: research in children is now **MANDATED** under defined circumstances. Broadened the role of the Pediatric Advisory Committee.
2005			Draft Guidance for Industry **How to Comply with the Pediatric Research Equity Act**	Interprets PREA legislation.
2006	The Elizabeth Glaser Pediatric AIDS Foundation solicited Congress to urge FDA to issue guidance for HIV vaccine studies in pediatric populations.	Congressional reports for **Agricultural, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act**, 2006, Public Law No. 109-97 (enacted November 10, 2005) House Report 109-102 at 80-81 (2005). See also Senate Report 109-92 at 153-154 (2005).	Guidance for Industry **Development of Preventive HIV Vaccines for Use in Pediatric Populations**	These Congressional reports urged the FDA to issue guidance addressing the minimum requirements for obtaining FDA approval for both HIV vaccine testing in pediatric populations and HIV vaccine licensure for pediatric indication. The FDA Industry Guidance primarily addresses clinical trials conduct in adolescents, and discusses options for vaccine licensure for pediatric indication using adult efficacy data with 'bridging' or pediatric efficacy data.

Appendix 2: U.S. Code of Federal Regulations Title 21 Part 50 Subpart D: Additional Safeguards for Children in Clinical Investigations

50.50 IRB duties.

In addition to other responsibilities assigned to IRBs under this part and part 56 of this chapter, each IRB must review clinical investigations involving children as subjects covered by this subpart D and approve only those clinical investigations that satisfy the criteria described in §50.51, §50.52, or §50.53 and the conditions of all other applicable sections of this subpart D.

50.51 Clinical investigations not involving greater than minimal risk.

Any clinical investigation within the scope described in §§50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in §50.55.

50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation within the scope described in §§50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds and documents that: (a) The risk is justified by the anticipated benefit to the subjects; (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in §50.55.

50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

Any clinical investigation within the scope described in §§50.1 and56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds and documents that: (a) The risk represents a minor increase over minimal risk; (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and (d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in §50.55.

50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If an IRB does not believe that a clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of §50.51, § 50.52, or § 50.53, the clinical investigation may proceed only if: (a) The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and (b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either: (1) That the clinical investigation in fact satisfies the conditions of § 50.51, § 50.52, or § 50.53, as applicable, or (2) That the following conditions are met: (i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) The clinical investigation will be conducted in accordance with sound ethical principles; and (iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in § 50.55.

50.55 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent. (b) In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate. (c) The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines: (1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or (2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation. (d) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that: (1) The clinical investigation involves no more than minimal risk to the subjects; (2) The waiver will not adversely affect the rights and welfare of the subjects; (3) The clinical investigation could not practicably be carried out without the waiver; and (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation. (e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that the permission of each child's parents or guardian is granted. (1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient, if consistent with State law, for clinical investigations to be conducted under §50.51 or §50.52. (2) Where clinical investigations are covered by §50.53 or §50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child if consistent with State law. (f) Permission by parents or guardians must be documented in accordance with and to the extent required by §50.27. (g) When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

50.56 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations approved under §50.53 or §50.54 only if such clinical investigations are: (1) Related to their status as wards; or (2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. (b) If the clinical investigation is approved under paragraph (a) of this section, the IRB must require appointment of an advocate for each child who is a ward. (1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis. (2) One individual may serve as advocate for more than one child. (3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation. (4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.

Appendix 3: U.S. Code of Federal Regulations Title 45 Part 46 Subpart D: Additional Protections for Children Involved as Subjects in Research

46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services. (1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint. (2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of §46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type. (b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed. (c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of Subpart A are applicable to this subpart.

46.402 Definitions.

The definitions in §46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart: (a) *Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. (b) *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. (c) *Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in research. (d) *Parent* means a child's biological or adoptive parent. (e) *Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

46.404 Research not involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that: (a) The risk is justified by the anticipated benefit to the subjects; (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

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.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that: (a) The risk represents a minor increase over minimal risk; (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental,

psychological, social, or educational situations; (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and (d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of § 46.404, § 46.405, or § 46.406 only if: (a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and (b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either: (1) That the research in fact satisfies the conditions of § 46.404, § 46.405, or § 46.406, as applicable, or (2) The following: (i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) The research will be conducted in accordance with sound ethical principles; (iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408.

Appendix 4: Guidelines for Good Practice in the Conduct of Clinical Trials in South Africa, Book 1. *Section 2.3.1* (South Africa)

2.3.1 Children and Adolescents

Research in children should only be approved if:

- The research does not place the child/minor at no greater than minimal risk.
- The research involves more than minimal risk but provides direct benefit for the child/minor. The risk must however be justified by the potential benefit.
- The research involves greater than minimal risk with no prospect of direct benefit to the child/adolescent, but there is a high probability that it will provide "generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition." (IRB, 1996:11) In addition the risks must represent only a minor increase over minimal risk and the intervention or procedure "presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or education settings." (IRB, 1996:11)
- In all cases, assent from both child and permission from their parents or legal guardians must be sought. No other caregiver can provide consent on behalf of a child to participate.
- Child Assent:[5] The Ethics committee must ensure that adequate steps are outlined in the protocol to obtain the child's assent, when in the judgment of the Ethics Committee the child is capable of providing such assent. When the Ethics Committee decides that assent is required, it must also state if and how assent must be documented.
- Parental Permission: Where the research does not involve greater than minimal risk to the child, or involves greater than minimal risk but presents a likely direct benefit to the child, the Ethics Committee may find that the permission of one parent is sufficient. Permission from both parents is necessary where the research involves greater than minimal risk, no direct benefit to the child but is likely to produce generalizable knowledge about the subject's condition. "Exceptions would include: 1) one parent is deceased, unknown, incompetent, or not reasonably available, or 2) when one parent has legal responsibility of the care and custody of the child." (IRB Policy and Procedure Manual 1997:4).

[Footnote 5 to 2.3.1] Worth noting is the following discussion provided by the IRB Guidebook on gaining the assent of children to participate in a trial. "While children may be legally incapable of giving informed consent, they nevertheless may possess the ability to assent to or dissent from participation. Out of respect for children as developing person, children should be asked whether or not they wish to participate in the research, particularly if the research: (1) does not involve interventions likely to be of benefit to the subjects; and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others. The [Ethics Committee] must determine for each protocol – depending on such factors as the nature of the research and the age, status and condition of the proposed subjects – whether all or some of the children are capable of assenting to participation. Where appropriate the [Ethics Committee] may choose to review on a case-by-case basis whether assent should be sought from given individual subjects. Assent should be sought when, in the judgment of the [Ethics Committee], the children are capable of providing their assent. [Ethics Committees] are to take into account the ages, maturity and psychological state of the children involved" (IRB, 1996:12)

Appendix 5: Guidelines on Ethics for Medical Research: HIV Preventative Vaccine Research, Book 5. *Section 18* (South Africa)

As children should be recipients of future HIV preventive vaccines, children should be included in clinical trials in order to verify safety, immunogenicity and efficacy from their standpoint. The development of HIV vaccines for children in South Africa must address specific scientific, ethical, and legal considerations relevant to children, so that their welfare is safeguarded and promoted.

18.1 The Constitution defines a child as someone younger than 18 years.

18.2 Children, including infants and adolescents in many communities throughout South Africa, are at high risk of HIV infection. Infants born to HIV-infected mothers may be at risk of becoming infected during birth or during the postpartum period through breast-feeding. Adolescents are also at high risk of infection because of sexual activity, and/or lack of access to HIV prevention means.

18.2.1 As children are at risk of HIV infection, children stand to benefit from the development of HIV preventive vaccines. Therefore, children should be included in clinical trials in order to verify safety, immunogenicity and efficacy from their standpoint.

18.2.2 The participation of children in research also honours their right to equal consideration by enabling their access to safe and efficacious products.

18.3 Before undertaking research in children, investigators must satisfy research ethics committees of the points detailed below.

18.4 **The research could not be carried out equally well with less vulnerable participants:** Ethical justification of the involvement of children in research requires that the research would not be equally informative if carried out on less vulnerable participants, and there is a specific need to perform the research on children (see Book 1, 7.1.3.2). According to this reasoning, the participation of children in HIV vaccine research should be considered only if their participation is indispensable to establish safety, immunogenicity and efficacy data relevant to children.

18.5 **The purpose of the research is to obtain knowledge relevant to the health needs of children:** Ethical justification for the involvement of children in research requires that the purpose of the research is to obtain knowledge relevant to the health needs of children. That is, the research is intended to obtain knowledge that will lead to the improved prevention or treatment of diseases or health problems characteristic of children, either to actual child participants or children as a class.

18.6 **The risks presented by research interventions are reasonable and justifiable in relation to expected benefits:**

18.6.1 The risk from research interventions and procedures that *do not* hold out the prospect of direct health-related benefits for the individual participant should be no more likely and no greater than the risk attached to routine medical or psychological examination of children, or the risk that is normally encountered in the daily lives of people in a stable society (see Book 1, 5.3.1.2.1 and 9.12.4.3.1).

18.6.1.1 Slight increases above such risk may be permitted when there is an over-riding scientific or medical rationale. The research should be designed to be responsive to the disease affecting the prospective participants or to conditions to which they are particularly susceptible, and the objective of the research must be sufficiently important to justify exposure of the participants to the increased risk.

18.6.2 The risks of research interventions or procedures that *do* hold out the prospect of direct health-related benefits should be justified by the anticipated benefit to participants.

18.6.3 In making these determinations, research ethics committees should consult with experts, including persons with expertise in paediatric and child health.

18.7 **Legal and ethical requirements for informed consent will be met:**

18.7.1 In South Africa, the Constitution states that no person shall be subject to experimentation without informed consent. Persons above the age of 18 years, who are of sound mind, are generally considered capable of giving

independent informed consent for participation in research (see Point 12.7). When persons below the age of 18 are to be involved in research, proxy consent from a parent or legal guardian must be obtained.

18.7.1.1 Therefore, the enrollment of children in HIV vaccine research in South Africa requires informed consent from a parent or legal guardian, and assent from the child, according to his or her evolving capabilities.

18.7.2 Because the Child Care Act specifies that South African children who are 14 years and older may give consent to medical treatment of themselves (see Book 1, 5.3.1.2.1), such children are considered (by implication) able to give consent to "therapeutic research."

18.7.2.1 If a research ethics committee classifies an entire HIV vaccine trial protocol as "therapeutic research," it is possible that independent consent for participation could be secured from children who are 14 years and older. However, the permission of the parents or legal guardian is still highly desirable. The participation of children who are under 14 years would require parental consent as well as assent from the child according to his or her evolving capabilities.

18.7.3 If a research ethics committee classifies an entire HIV vaccine trial protocol as "non-therapeutic research," parents must provide proxy consent for participation and the child must assent (according to his or her evolving capabilities), provided that the risks are no more likely and no greater than the risk attached to routine medical or psychological examination of children, or the risk that is normally encountered in the daily lives of people in a stable society (see Point 18.6.1). Where there is an over-riding medical or scientific rationale, such risks may be slightly increased (see Point 18.6.1.1).

Appendix 6: Ethics in Health Research: Principles, Structures and Processes: *Section 5.1, 5.2 and 5.3* (South Africa)

5.1 Research involving minors

Minors[19] should participate in research only where their participation is indispensable to the research and where participation is not contrary to the individual minor's best interests. The research should investigate a problem of relevance to children. Where research involving minors is proposed, a research ethics committee should determine whether the research might be equally informative if carried out with consenting adults. If so, the research ethics committee should require strong justification for the inclusion of minors. Note that all types of **clinical research on minors** should be scrutinized carefully.

For purposes of these guidelines,

- 'Child' means a person who has not yet reached puberty;
- 'Adolescent' means a person who has reached puberty;
- 'Therapeutic' means interventions that may hold out the prospect of direct health-related benefit for the participant;
- 'Non-therapeutic' means interventions that will not hold out the prospect of direct health-related benefit for the participant but results may be produced that significantly contribute to generalizable knowledge about the participant's condition.

5.2 Research involving a child

Research involving a child should be approved only if:

- The research, including observational research,[20] places the child at no more than minimal risk (that is, the risk commensurate with daily life or routine medical or psychological examinations – referred to as 'negligible risk' in some guidelines); or
- The research involves more than minimal risk but provides possible benefit for the child participant. The degree of risk must be justified by the potential benefit; or
- The research, including observational research,[21] involves greater than minimal risk, with no prospect of direct benefit to the child participant, but has a high probability of providing significantly generalizable knowledge; that is the risk should be justified by the risk-knowledge ratio. The risks must represent no more than a minor increase over minimal risk.

Consent for minors to participate in research must be obtained from:

- The parents or legal guardian in all but exceptional circumstances (such as emergencies); and
- The minor where s/he is competent to make the decision; and
- Any organization or person required by law, e.g. the National Health Act 61 of 2003.
- Where the minor is not competent, assent from the child (where appropriate) and permission from the parent(s) or legal guardian must be sought. No other caregiver can act on behalf of a child in providing consent to participate.
- A minor's refusal to participate in research must be respected, i.e. such refusal settles the matter.
- In all cases, the protocol must provide sufficient information to justify clearly why children should be included as participants.

[19] Section 6 of the Children's Bill stipulates various factors that must be considered when applying the best interest of child standard. Research ethics committees should familiarize themselves with these factors.
[20] Of a non-invasive nature that involves no interference with the bodily or psychological integrity of the child.

[21] Of an invasive nature that may involve interference with the bodily or psychological integrity of the child, e.g. questions about sensitive matters that could cause emotional upset for the child. The consequences of reporting obligations on health care workers in cases of suspected abuse must be taken into consideration too.

5.2.1 Child assent

The research ethics committee must ensure that adequate steps are outlined in the protocol to obtain the child's assent when, in the judgment of the research ethics committee, the child is capable of providing such assent. When the research ethics committee decides that assent is required, it must also indicate whether and how such assent must be documented.

5.2.2 Parental permission

Where the research does not involve greater than minimal risk to the child, or involves greater than minimal risk but presents the likelihood of direct benefit to the child, the research ethics committee may find that the permission of one parent is sufficient. Permission from both parents is necessary where the research involves greater than minimal risk, is of no direct benefit to the child but is likely to produce generalizable knowledge. Where only one parent is available for reasons including the death, incompetence or disappearance of the other, or where a court has placed the child in the sole custody of one parent, then the permission of that one parent is sufficient for participation in the latter type of research. In the event of conflicting views between the parents, the child's best interest settles the matter. [22]

5.3 Adolescents

In terms of section 39(4) of the Child Care Act 74 of 1983 and in the absence of specific legislative provisions to the contrary, adolescents who have attained the age of 14 years are legally capable of consenting to medical treatment of themselves and their children. Adolescents who have attained the age of 18 years are legally capable of consenting to surgical operations upon themselves provided in all cases the adolescent is competent, i.e. sane and sober. Conversely, the consent of a parent or legal guardian is required for medical treatment or an operation if the adolescent is under the age of 14 or 18 years respectively. Note, however, that an unmarried mother who is herself a minor may not consent to the participation of her child in research investigations. Her guardians (usually her parents) are also the guardians of her child[23] and must thus consent to the child's participation as set out above.

The Children's Bill will repeal the Child Care Act, amongst other legislation. The Children's Bill makes no provision for age categories and consent to treatment. Instead it states that '[e]very child capable of participating meaningfully in any matter concerning that child has the right to participate in those proceedings in an appropriate way and views expressed by the child must be given due consideration'.[24] The National Health Act does not distinguish between minors who are children and minors who are adolescents and requires the consent process to be the same for both groups, subject to the distinction between 'therapeutic' and 'non-therapeutic' research. As discussed above, research is not the same as medical treatment. It is rarely arguable that participation in medical research is necessary.

It is arguable, however, that adolescents may be capable of consenting themselves to certain types of research participation and that, for particular types of research, it may be desirable that they do so unassisted.

5.3.1 Research involving **adolescents who may consent unassisted** should be approved only if:

- The research, including observational research,[25] places the adolescent at no more than minimal risk; **and**
- The nature of the research is such that, in the opinion of the research ethics committee, the parents or legal guardians or community at large are unlikely to object to the adolescent consenting him or herself to participation in the investigation. The opinion of the research ethics committee must be informed by information gathered from the community concerned and by contributions from the lay members of the committee.
- In all cases, the protocol must provide sufficient information to justify clearly why adolescents should be included as participants.
- In all cases, the protocol must justify clearly why the adolescent participants should consent unassisted.

[22] See n 3.

[23] In terms of the Guardianship Act 192 of 1993.

[24] Section 10 of the Children's Bill. Section 17 of the Bill stipulates the age of majority as 18 years.

[25] Of a non-invasive nature that involves no interference with the bodily or psychological integrity of the adolescent.

5.3.2 Research involving adolescents who assent assisted by parents or legal guardians should be approved only if:

- The research involves more than minimal risk but provides possible direct benefit for the adolescent participant. The degree of risk must be justified by the potential benefit; or
- The research, including observational research,[26] involves greater than minimal risk, with no prospect of direct benefit to the adolescent participant, but has a high probability of contributing to generalizable knowledge. In addition the risk must represent no more than minor increase over minimal risk. (See 5.2).
- In all cases the protocol must provide sufficient information to justify clearly why adolescents should be included as participants.
- In all cases, assent from the adolescent and permission from the parent(s) or legal guardian must be sought. No other caregiver can act on behalf of an adolescent in providing consent to participate.

5.3.3 Adolescent assent

The research ethics committee must ensure that adequate steps are outlined in the protocol to obtain the adolescent's assent when, in the judgment of the research ethics committee, the adolescent is capable of providing such assent. When the research ethics committee decides that assent is required, it must also indicate whether and how such assent must be documented.

5.3.4 Parental permission

Where, in the judgment of the research ethics committee, the adolescent should not consent unassisted, or where the research involves greater than minimal risk but presents the likelihood of direct benefit to the adolescent, the research ethics committee may find that the permission of one parent is sufficient. Permission from both parents is necessary where the research involves greater than minimal risk, is of no direct benefit to the adolescent but is likely to produce generalizable knowledge about the adolescent's condition. Exceptions would include situations as set out in 5.2.2.

[26] Of an invasive nature that may involve interference with the bodily or psychological integrity of the adolescent, e.g., questions about sensitive matters that could cause emotional upset for the adolescent. The consequences of the reporting obligations on health care workers in cases of suspected abuse must be taken into consideration too.