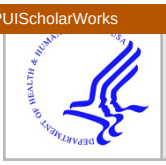

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Inclusion of Adolescents in STI/HIV Biomedical Prevention Trials: Autonomy, Decision Making, and Parental Involvement

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INTRODUCTION

In order to develop new methods for prevention and treatment of sexually transmitted infection (STI) and human immunodeficiency virus (HIV), clinical trials must be conducted in relevant populations. In the U.S., half of all STI incident infections are among 15-24 year olds (Satterwhite et al., 2013), making healthy adolescents a highly relevant population. The inclusion of adolescents in STD/HIV prevention research is critical for developing appropriate strategies to promote adolescent sexual health. Results from adult studies may not generalize to adolescents, given their biological and psychosocial developmental status (Hwang et al., 2009). In order to understand the extent to which these differences are applicable to safety, efficacy, and acceptability, the products must be tested in minors. Enrolling adolescents who have not reached the legal age of majority in sexual health research, though, poses legal and ethical challenges. Investigators have been described as facing moral conflict between their responsibility to protect the scientific rigor of the study and the well-being of the participants (Merritt, 2005). Institutional Review Boards (IRBs) must balance the interests of minors, their parents, and the institution (Knopf et al., 2016). Data suggest that adolescents are under-represented in biomedical trials of HIV and STD prevention (Tolley et al., 2014; Hoffman et al., 2016). We propose that the inclusion of these adolescents in sexual health research is not only ethically permissible but is ethically required. Relevant research and specific recommendations for inclusion is presented below.

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The Department of Health and Human Services (HHS) characterizes children as a vulnerable population in need of special protections. They define children as those "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" (HHS, 2009). As such, adolescents under the age of 18 generally meet the definition of children. Federal regulations require additional protections for research involving children (45CFR46 subpart D). These regulations limit the amount of risk that children may be exposed to without the prospect of direct benefit and delineate the extent of the requirement to obtain consent from a parent or guardian before enrolling a child in research. Unfortunately, in some cases these additional requirements may impede the ability to conduct valuable and ethically sound research with minors, particularly in the area of adolescent sexual health (Fisher et al., 2013).

Based on the three principles of the Belmont report, it is unethical to exclude adolescents (in particular those 15 through 17 years) from biomedical sexual health research. Given that the inclusion of adolescents in HIV and STI biomedical prevention research poses challenges, pediatric psychologists can play an important role in collaborating with investigators and IRB's to develop strategies to support this inclusion. Although we draw on relevant ethical principles and legal guidelines, we are neither ethicists nor lawyers. We also make the assumption that all clinical trials use best practices, and standards in most circumstances should not be higher for minors.

APPLICATION OF THE BELMONT REPORT

The Belmont Report serves as a guiding principle for research ethics and has three main elements; Justice, Respect for Persons and Beneficence (HHS, 1979).

Justice

The principle of *Justice* requires fair distribution of the risks and benefits of research participation. Adherence to the principle of justice ensures that research burdens are not disproportionately borne by a vulnerable population, or by a population that will not benefit from the knowledge gained from the research. As discussed above, it is in the best interest of adolescents to better understand sexual health promotion. In addition, research participation may come with direct benefits, such as access to potentially enhanced care through regular health contacts built into the clinical trial, and indirect benefits, such as participation for altruistic reasons (Chávez et al., 2016) and/or knowledge gained through the process (Castillo, Jandorf, Thelemaque, King, & Duhamel 2012). Thus, it is clear that inclusion of minors in STI/HIV prevention research is consistent with the ethical principle of justice.

Respect for Persons

The *Respect for Persons* principle requires that investigators respect the decision-making capabilities of autonomous agents. Further, it states that those with diminished autonomy are entitled to protection. U.S. research regulations generally do not consider children capable of making autonomous decisions about research participation (HHS, 2009). However, regulations require that assent be sought before enrolling children in research in appropriate

situations, recognizing that children are entitled to contribute to the decision (45CFR46 subpart D). As children grow into adolescents and young adults, they are entitled to an increasing share in this decision-making process. Brain maturation is a process that continues well into young adulthood, and different aspects of cognition develop at different ages (Steinberg et al., 2008). Decision-making capacity continues to develop into the young adult years (McCabe, 1996). As a result, minors may have adult-like capacities in some domains and not in others, and those of legal age may not have fully reached cognitive maturity in decision-making. The challenge is to determine when minors need special protection and when they can function autonomously.

At least four factors should be considered when determining the extent to which an adolescent can make an autonomous decision about research participation. First, the evaluation of the adolescent's autonomy should not be based on if he/she makes what we believe is the "right decision" (McCabe, 1996). Second, the adolescent's experiences with the topics being studied and the extent to which they need to make a decision in emotionally-charged situations should be considered (Casey, Jones, & Hare, 2008). Third, if they have diminished autonomy, then one must determine who is able to act in their best interests. In general, it is assumed that parents will act in their child's best interests; however, this may not always be the case. If an adolescent's parents do not know his/her sexual orientation and/or gender identity, they may not be able to help with the decision to participate in a study enrolling lesbian, gay, bisexual, and transgender (LGBT) youth. If an adolescent is homeless, parents simply may be unavailable. Fourth, parental permission for research participation is not required when the adolescent has been declared to be an emancipated minor. Further, if an adolescent does not meet the definition of "child" for the purposes of research, parental permission is not required (HHS, 2009). For example, based on mature minor statutes, adolescents may typically obtain contraception or treatment for a STI without the permission of their parents (Center for Adolescent Health and the Law [CAHL], 2014; English, 2007). When the research is limited to interventions for which the adolescent would be considered an adult in the clinical context, it is possible for the IRB to determine that, for purposes of the research, these adolescents do *not* meet the definition of a child.

Even when an adolescent does meet the definition of a child, there are situations in which an IRB may permit a waiver of parental consent (§46.116 of subpart A). Broadly speaking, the requirement for parental permission may be waived when the research poses no more than minimal risk, or when it is believed that parental permission is not a reasonable requirement to protect the subject (Santelli et al., 2003). Finally, the cultural context of decision-making is relevant. This is not unique to minors, but serves as a reminder that autonomy also includes the right to involve others in decision-making.

Beneficence and Nonmaleficence

The principles of *Beneficence and Nonmaleficence* require that researchers act to maximize benefits and minimize risks and costs. IRBs must weigh the risks against the potential benefit to the participant and importance of the knowledge to be gained. When considering enrolling adolescents in HIV/STI prevention clinical trials, we are assuming that the

requirements of beneficence and nonmaleficence have been met for inclusion of adults in the study. We must then ask whether the risks or benefits are different for adolescents than they would be for adults. Possible sources of additional risk include physiologic differences between adults and adolescents (e.g., potential bone loss due to oral pre-exposure prophylaxis medication), psychosocial harm caused by study participation, and loss of confidentiality. The issue of whether physiologic differences impact the risk/benefit analysis is clearly best handled by medical experts on the research team and on the IRB.

Some IRBs and investigators express concern about asking adolescents very specific questions about sexuality (Flicker & Guta, 2008; Irvine, 2012), suggesting that exposing adolescents to these questions poses more than minimal risk. However, no more than minimal risk is a regulatory category defined as “those (risks) ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” (45 CFR 46 subpart D). Querying adolescents about sexual behaviors is consistent with recommended routine health care (Elster & Kuznets, 1994) and thus, should be classified as “no more than minimal risk.” The fact that even detailed questions about sexual behaviors are part of primary health care may not be known by the broader medical community or public.

Adolescents may be particularly sensitive to the possibility of loss of confidentiality, as their parents may be unaware of their sexual activity or orientation. In some cases, simple parental awareness that their adolescent is participating in a particular study may alert them to information that the adolescent wishes to keep confidential. IRBs need to determine the level of risk posed by participation which could occur based on inclusion/exclusion criteria or evaluations conducted during the study. If a study involves any interventions that may be billed to the participant’s insurance, another avenue for a breach of confidentiality arises. Investigators and IRBs should be aware of these concerns and should inform eligible subjects of the risks, as well as any processes in place to mitigate the risks.

However, IRBs may over-estimate the risk of research that involves sexual behavior. It has been argued that this over-estimation of risk impedes conduct of research designed to benefit the community of LGBT youth (Fisher & Mustanski, 2014). Researchers and IRBs should be encouraged to consult with pediatric psychologists if there is concern that study procedures may be excessively troubling or otherwise pose risk to adolescent subjects.

Even if an adolescent is enrolled in a study without parental consent, study participation may threaten the adolescent’s right to privacy. A breach of confidentiality could occur when reminder phone calls for study visits or test results need to be made. Investigators should discuss with the adolescent participant how best to contact them in order to protect their privacy. When study participation includes laboratory tests or administration of medications, arrangements should be made in advance to avoid inadvertent disclosure through health insurance notices sent to parents. These issues have been successfully managed in the clinical care of adolescents, and recommendations have been made for managing pregnancy testing in the context of clinical trials (Morris & Rosenthal, 2017).

Despite the fact that cognitive maturation continues into the adult years, there is no evidence that minors do not have the cognitive capacity to understand the risks associated with participation in order to consent. In a reanalysis of data from a study examining predictors of 16 to19-year-old adolescents' willingness to participate in a simulated phase 3 HIV vaccine clinical trial, (Lally et al., 2014) the minors (16 and 17 year olds; n=58) did not differ significantly from those of legal age (18 and 19 year olds; n=62) on knowledge of the clinical trial, subjective numeracy, health literacy, impulsive decision-making, and willingness to participate (see Table 1). A qualitative study with a subset of these participants confirmed that they actively processed information provided to them, made use of the interviewer by asking clarifying questions, and corrected misunderstandings when provided with new information (Ott, Alexander, Lally, Steever, & Zimet, 2013). It is possible, however, that decision-making with respect to a hypothetical clinical trial scenario may place significantly less cognitive demands on adolescents than decision-making related to enrollment in a real clinical trial.

CLINICAL CARE VERSUS RESEARCH

Although laws differ from state to state (CAHL, 2014), in general, minors can consent to STI/HIV clinical care. With treatment research, then, they may be considered "adults" rather than "children" since they have "attained the legal age for consent to treatments or procedures involved in the research" (45 CFR 46 subpart D). However, research differs from clinical care, in part because research should have equipoise (i.e., genuine uncertainty) about the value of different interventions. Prevention-focused biomedical research adds additional complexity, as healthy adolescents are exposed to medications, such as microbicides. However, research participation often brings with it additional access to care, and sometimes better access to the current standard of care. Historically, the approach has been to require investigators to justify why research should be considered similar to clinical care. Perhaps it is time to adopt a different perspective, that is, to require justification as to why research is not similar to clinical care.

PRACTICAL CONSIDERATIONS

Despite the ethical clarity that minors should be offered participation in STI/HIV research, there are still practical considerations that investigators must take into account when working with young people. Below, we provide advice based on the literature and experience related to working with IRBs, managing parental involvement, managing special populations, enhancing adherence, and developing future research.

Working with IRBs

When determining whether it is appropriate to waive the requirement for parental permission for research participation, IRBs are charged with determining whether parental permission is a "reasonable requirement to protect the subjects." (45 CFR46.408(c)) The expertise of pediatric psychologists is directly applicable to this determination. Pediatric psychologists can play a key role in developing training tools for investigators and for IRB members about adolescent development, independent of the review of specific studies. Further, the knowledge and experience of pediatric psychologists should inform institutional policies

about research with minors. Pediatric psychologists can also serve as valuable consultants to IRBs reviewing challenging protocols. Investigators can be encouraged to provide the IRB with advance notice of controversial adolescent issues, as was done by those seeking to enroll high-risk minors with adolescent self-consent for a pre-exposure prophylaxis (PrEP) trial (Gilbert et al., 2015). Providing the actual guidelines for the content of adolescent well-child visits (Fisher & Mustanski 2014; Hagan 2007) may help IRB members understand what is routine care.

Enhancing understanding

Complex trial designs may be difficult for adults and adolescents to understand (Kodish et al., 2004; Susman, Dorn, & Fletcher, 1992), and a lack of health literacy has been linked to numerous barriers to research participation (Simonds, Garroutte, & Buchwald, 2017). Psychologists' understanding of cognitive functioning and how to help individuals understand complex information could be better employed to help develop new and innovative strategies. For the adolescent population, this may include the use of adolescent-friendly tools such as apps and other digital multimedia (Tait, Voepel-Lewis, & Levine, 2015) to engage them in understanding the research process.

Parental Involvement

There is no doubt that parents play an important role in protecting and supporting adolescents, but the provision of legal consent by parents does not necessarily equate to active involvement. Even if a parent does provide consent for an adolescent to participate in a research study, the parent may not necessarily remain involved throughout the course of the research. In a study of females ages 14 to 21 years related to vaginal microbicide acceptability, there were no differences between those under 18 (whose parents provided consent) and those over 18 (who consented on their own accord) in terms of whether the adolescent reported discussing the study with her parent (Sunder, Ramos, Short, & Rosenthal, 2006).

Little is known about parents' and adolescents' perspectives on parental involvement in research, and this is an area for which psychological research is critical. However, one study of parent-adolescent dyads suggests that there is an expectation of some parental involvement in the research process and, not surprisingly, parents expect greater involvement than adolescents (Rosenthal et al., 2016). Older adolescents and sexually experienced adolescents expected less parental involvement than younger and non-sexually experienced adolescents. Females wanted less parental involvement in learning about STI testing and pregnancy evaluations than males; perhaps because sexuality is often viewed differently for males than for females. Psychologists can help the investigator delineate clearly how the process of involving parents will work and how confidentiality will be managed.

Special populations

The inclusion of younger adolescents in HIV/STI research poses particular challenges. State laws that permit minors to access confidential health care related to STIs and pregnancy recognize that in many cases a 12-year-old should be treated differently from a 17-year-old. From a regulatory standpoint, parental permission ought not to be waived if research poses

more than minimal risk and the research intervention would not be permitted without parental consent in a clinical context. IRBs should consider consulting with a pediatric psychologist when enrollment of young adolescents in HIV/STI research is considered. Waiving the requirement for parental permission may also be problematic for adolescents with chronic medical conditions. A parent who remains responsible for an adolescent's health care should be informed of any study medications or interventions that may impact his or her chronic medical condition or the treatments for that condition. This could be problematic if the adolescent chooses not to disclose the relevant information to the parent. On the other hand, it is possible that an adolescent with a chronic medical condition may have more experience with making medical decisions, and therefore, the adolescent possibly may be more skilled and/or more comfortable with asking questions of medical staff.

Adherence to Study Demands

Minors may or may not have unique difficulties adhering to study expectations. In a vaginal microbicide trial undertaken in South Africa, there were no differences in adherence to study protocols between 16-17 year olds and 18-19 year olds (Schenk et al., 2014). However, in an open-label PrEP trial, only 21.6% of 15-17 year olds adequately adhered to the study drug at 48 weeks (Hosek et al., in press), compared to 34% of 18-22 year olds, which, admittedly was also poor (Hosek et al., 2017). Regardless of trial adherence, there is a particular duty to protect vulnerable populations and psychologists may be in a unique position to identify trial adherence challenges faced by minors and work to develop strategies for addressing them. As in clinical care, the strategies to enhance adherence may be difficult to employ when an adolescent lives at home but wants to participate without parental knowledge. For example, cell phones and text messaging do not always keep messages private. The location of the study also may impact the adolescent's adherence to study visits. On the one hand, study locations in which the adolescents are already present may make it easier and more comfortable for them; on the other hand, there may be a risk of accidental disclosure of research participation. Attendance at research visits could interfere with school attendance, and transportation may be difficult for the adolescent (Magazi et al., 2014). If research participation requires using medications (e.g., PrEP) or devices (e.g., vaginal rings), adherence may be improved by having a convenient yet confidential place to store the product. Understanding barriers to study adherence is crucial. For adolescents, this process should include a focus on unintentional loss of confidentiality and the ability to be independent in adhering to expectations.

Research opportunities

More research is needed to identify and address barriers to adolescent research participation, particularly from the perspective of adolescents who are eligible to participate in biomedical HIV/STI prevention research as well as from their parents. Psychologists and clinical investigators conducting HIV/STI research have an opportunity to gather data to inform a best-practices approach to the involvement of these adolescents in research. The breadth of possible research approaches is vast but should include assessing the attitudes of adolescents who opt to not participate in relevant clinical trials.

CONCLUSIONS

It is crucial that adolescents in the U.S. be offered the opportunity to participate in HIV/STI research in a safe manner in order to ensure that we develop products that are safe, effective and acceptable in this population. Pediatric psychologists are in a unique position to develop guidelines to support IRBs and investigators in determining which strategy is most appropriate for any given study. Specifically, we believe that the principles of biomedical ethics discussed in the Belmont Report and elsewhere indicate that biomedical HIV or STI prevention studies should be designed to include rather than to exclude adolescent participants. Academic medical institutions should consult with pediatric psychologists to develop guidelines to maximize benefits and minimize risks to adolescent participants. As investigators and IRBs address these questions, the answers and solutions should be informed by the psychological literature and empirical evidence and not by personal experience. Psychologists also need to continue to enhance the empirical evidence about adolescent research decision-making and parental involvement to develop more sophisticated approaches to involving minors in research.

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Table 1

Comparisons between 16-17 years olds and18-19 year olds in a simulated phase III HIV vaccine clinical trial

Measures*	**16-17 year olds (n=58) Mean (SD)****	**18-19 year olds (n=62) Mean (SD)**
Impulsive Decision-Making (12 items) Scale of 1 to 5 (5 = always impulsive)	2.39 (.68)	2.26 (.63)
Health Literacy (REALM-SF) (7 items) Asked to read health words	5.22 (1.82)	5.73 (1.10)
Subjective Numeracy (8 items) Scale of 1 to 6 (6 = comfortable with numeracy)	3.85 (.91)	4.00 (.96)
Clinical Trials Knowledge Score (10 items) Scale of 1 to 5 (5 = strongly agree with true statement)	3.92 (.44)	4.03 (.50)
Willingness to Participate (3 items) Scale of 1 to 5 (5 = definitely participate)	3.33 (.81)	3.27 (1.08)

*More information on measures in Lally et al., 2014

**No significant differences between 16-17 years olds and 18-19 year olds