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Moral conflict and competing duties in the initiation of a biomedical HIV prevention trial with minor adolescents

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Abstract

Background—Biomedical HIV prevention research with minors is complicated by the requirement of parental consent, which may disclose sensitive information to parents. We examine the experience of principal investigators (PIs) and study personnel who faced this complicated

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ethical issue in the first biomedical HIV prevention study that allowed minors to self-consent for enrollment.

Methods—We conducted in-depth interviews with PIs and study personnel from 13 medical trial sites in cities across the U.S. Data were analyzed using a conventional content analysis.

Results—Participants experienced moral conflict as they struggled to fulfill conflicting duties in this trial involving minor adolescents with multiple vulnerabilities. Our participants experienced conflict between the two types of duties—protective and scientific—previously identified by Merritt. Protective duties were owed to the child, the parents, and the institution, and participants expressed tension between the actions that would protect these subgroups and the actions necessary to fulfill their scientific duties.

Conclusions—Moral conflict was resolved in a variety of ways, including: reflecting on the protocol's alignment with Federal regulations, modifying consent language, considering each individual for enrollment carefully, and accepting institutional review board (IRB) decisions. Potential solutions for future studies are discussed, and include flexible protocol consent procedures and centralized IRB reviews.

Keywords

adolescents; HIV; moral conflict; clinical trial; pre-exposure prophylaxis; parental consent

Background

An estimated 26% of all new HIV infections in the United States occur in youth aged 13–24. Young men who have sex with men (YMSM) are at especially high risk, accounting for 72% of all incident HIV infections among American youth (CDC 2014). Among adults, new biomedical HIV prevention approaches have dramatically decreased the risk of infection. One such approach is pre-exposure prophylaxis (PrEP), which involves prescribing an HIV treatment medication (tenofovir-emtricitabine [TDF-FTC]) to individuals at risk of HIV acquisition. Randomized controlled clinical trials of PrEP in different high-risk populations have demonstrated a combined 53% reduction in the relative risk of HIV acquisition in treatment groups compared to placebo groups (Jiang et al. 2014). However, post-hoc analyses reveal efficacy is closer to 95% in adherent PrEP users (Anderson et al. 2014; Baeten et al. 2012). PrEP may be a useful prevention tool for American adolescents, including YMSM, but it has only been tested in adult populations.

Adolescents differ from adults in ways that may affect the risks and benefits of taking PrEP. First, there are biologic differences, which include puberty and the associated physical and mental maturation processes, which may impact drug safety (Pace et al. 2013). Second, the structure of adolescent sexual partnerships differs from adults' (Grigsby et al. 2010). Compared to adults, adolescents have shorter sexual partnerships and less time between partnerships, which makes them more vulnerable to sexually transmitted infections, including HIV (Foulkes et al. 2009; Foxman et al. 2006). Finally, minor adolescents living with parents or other adult caregivers have different privacy concerns than adults living independently.

The biologic and social differences between adolescents and adults warrant investigation of PrEP's feasibility and safety for adolescents at risk of HIV infection. However, there is pervasive reluctance to enroll minor adolescents in biomedical HIV prevention trials, presumably because doing so is burdensome for investigators and their Institutional Review Boards (IRBs) (Chavez 2015; MacQueen and Karim 2007). Minors are a protected class of research subjects whose vulnerability demands additional protections beyond those afforded to adult human subjects (Nelson et al. 2010; 45 CFR 46). One such protection is the requirement for a parent's or guardian's consent for the minor's participation in research.

Parental consent for HIV prevention trials can be problematic because of the risk of disclosing to the parent sensitive information about the adolescent. Risk of disclosure is especially relevant in HIV research with minors because HIV in the U.S. is inextricably linked to stigmatized behaviors including same-sex sexual behavior and substance use. Among American adolescents and young adults, the most common mode of HIV transmission is male-to-male sexual contact (CDC 2015). Although popular opinion on same-sex relationships is rapidly changing (Pew Research Center 2015), disclosing same-sex sexual partnerships poses significant risks to adolescents, especially those living in families or communities that hold unfavorable views of same-sex relationships (Ryan et al. 2009). Therefore, consenting minors for HIV research creates ethical tension between age-related vulnerabilities (Kipnis 2003), such as inexperience or biological differences that could affect drug safety, and disclosure-related vulnerabilities, such as the risk of social harm that may befall an adolescent who is "outed" by the consent process (Ott 2014).

These multiple vulnerabilities, and their concomitant ethical complexities, may contribute to reluctance to involve adolescents in biomedical HIV prevention trials. However there are limited empiric data on investigators' experiences engaging minor adolescents in such trials (Short et al. 2010; Schenk et al. 2014). In this study, we describe the ethical challenges principal investigators (PIs) and study personnel faced as they prepared to initiate a biomedical HIV prevention study (Project PrEPare) with minor adolescents. Specifically, we focus on the ethical challenges that arose during the IRB review process, from preparation for review to its conclusion.

Project PrEPare was a multi-site open label feasibility and safety study of the antiretroviral medication TDF-FTC as PrEP for 15–17 year old YMSM. The protocol is described in detail elsewhere (Gilbert et al. 2015). Briefly, the primary study aims were to: 1) provide safety data regarding TDF-FTC use among HIV-uninfected YMSM, 2) examine acceptability, patterns of use, and drug adherence among YMSM, and 3) examine patterns of risk behavior reported by YMSM who are provided with a behavioral intervention as well as TDF-FTC for daily use. A secondary aim, and the focus of this manuscript, was to examine the process of ethics review and protocol initiation to inform the design of future biomedical trials with minor adolescents.

This secondary aim was important because Project PrEPare was the first U.S. biomedical HIV prevention study that allowed minor adolescents to consent to enrollment without parental knowledge or permission. During the design phase of this study, Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) investigators were concerned

that high-risk YMSM most appropriate for this study would not enroll if parental permission were required, and FDA regulations do not permit the application of a waiver of parental permission for participation in investigational drug studies (21 CFR 50). Many states allow mature minors to access medical care for sexually transmitted infections (STIs), including HIV, without parental permission (Culp and Caucci 2013). After consultation with relevant regulatory bodies, including the FDA, the ATN and its ethics advisory panel concluded that these legal provisions may entitle adolescents to consent for their own participation in research studies about HIV and STI, as long as local IRBs agree this approach is consistent with local laws and regulations (Gilbert et al. 2015). This approach is consistent with the opinions of Nelson et al. of the U.S. FDA, who concluded that from a regulatory standpoint adolescent self-consent could be considered sufficient for minor adolescent enrollment in FDA-regulated HIV biomedical prevention studies (Nelson et al. 2010).

Although parental permission was not solicited or required, YMSM could choose to discuss the trial with a parent or guardian if they wished. However, parents did not directly participate in the recruitment, consent, and documentation procedures that are typically mandatory in clinical trials with minor participants. Since this was the first biomedical HIV prevention study in the U.S. to allow minor self-consent, the process of ethics review and protocol initiation was of great interest to the ATN. Thus, each of the 13 ATN medical trials units (AMTUs) documented and later discussed with a member of our team the process of initiating ethics review and the concerns it raised (Gilbert et al. 2015).

Methods

Methodological Approach

We used qualitative descriptive methods as described by Sandelowski (2000). Qualitative descriptive methods rely on purposive sampling, moderately structured interviews, and analytic methods that closely follow the data. We selected qualitative descriptive methods for this study because little is known about the topic, and these methods facilitate the construction of a comprehensive summary of an event or issue, in everyday language.

Study Population and Setting

The study population included ATN site PIs and study personnel (participants, henceforth) at all 13 of the AMTUs that intended to participate in Project PrEPare. All sites agreed to participate. Our sampling goal was to interview the person(s) responsible for each site's IRB submission. We originally invited each site's PI, however, as we reached out to PIs, we discovered that some felt their study coordinators or project managers were more familiar with the issues raised by IRB review and elected to have these study personnel also participate in the site's interview. Research activities took place between May 2013 and November 2013. This study was exempted from full review by the Indiana University IRB.

Study Procedures

A single interview was completed for each site. All participants received a study information sheet explaining the study's purpose, aims, and procedures. It included exemplar interview questions so participants could anticipate the types of questions they would be asked. The

study information sheet also described provisions for protecting confidentiality during data analysis and reports from this work, which included limiting access to the data to only the first and second authors (who are not affiliated with the ATN) and protecting identities in reports. To that end, we have randomly assigned each site a letter to represent it and the participants associated with it. Each interview began with confirmation that the participants had received and read the study information sheet, and time to clarify any questions the participant had about it.

Data Collection Procedures

Data were elicited from semi-structured interviews with participants. The second author conducted the interviews via telephone, soon after participants knew whether or not they would be able to enroll subjects in Project PrEPare. The interview guide covered the following topics: participants' experience working with local IRB on prior studies, prior experience conducting biomedical research that permitted minor self-consent, participants' own concerns about the study protocol, IRB members' concerns about the study protocol, confidence in the outcome of IRB review, and lessons learned. Some exemplar questions from the interview are:

- "Was there anything about the study protocol that personally gave you pause?"
- "How confident are you that the best possible decision was reached by your IRB?"
- "What practical lessons have you learned during the IRB approval process?"

Data Management and Analysis

Interviews were digitally recorded and transcribed verbatim. The first and second authors compared the transcripts to the audio-recordings, making corrections as needed. Data were uploaded to a cloud-based qualitative data analysis program (Dedoose, Hermosa Beach, CA, USA).

We used conventional content analytic methods, as described by Hsieh and Shannon (2005). During the analytic phase of the process evaluation, the transcripts were read by the first and second authors, and discussed in weekly meetings. Initial themes were identified and then a case-ordered meta-matrix was used to organize, code, and summarize the data. During this process we identified a recurring theme of competing duties and related moral conflict. The first author reread all the transcripts and extracted data that reflected competing duties and moral conflict. These data were reviewed and discussed by several members of the authorship team. We interpreted the data in light of Merritt's analysis of moral conflict in clinical trials (Merritt 2005).

Merritt's (2005) conceptual analysis serves as the theoretical framework for the findings presented below. Briefly, Merritt contends investigators inevitably face moral conflict in the conduct of clinical trials. The conflict arises when there are moral duties that seem equally important but cannot be fulfilled in all instances. Investigators have two moral duties—the *scientific duty* to ensure the trial is carried out with sufficient rigor to produce scientifically

valid results in a reasonable amount of time, and the *protective duty* to safeguard the well-being of participants in light of medical burdens and risks of participation (Merritt 2005).

We use the site as the unit of analysis rather than the person, and report by site because each site participated in a single interview. Some sites elected to have more than one person participate in the phone interview; in these cases, participants were interviewed simultaneously. We note that each individual did not always answer each question separately, and the participants frequently discussed the question during the interview in an effort to come to consensus.

Data credibility and rigor was assessed the following ways: (1) Data from the interviews were assessed for consistency with data from IRB applications, IRB memos, and emails (published separately, see Gilbert 2015); (2) Primary data were coded by two authors, with disagreements resolved by discussion; and (3) Data were presented back to ATN investigators involved with Project PrEPare for their review and comment. There were no discrepancies noted between data from IRB applications, memos, and emails. ATN investigators, many of whom were participants in this study, did not request any changes to the data interpretation when the preliminary findings were presented at a national meeting in April, 2015.

Results

All thirteen sites participated in the study. Four sites elected to have two participants participate in the interview together, resulting in a total of 17 participants—12 principal investigators, 3 study coordinators, 1 regulatory coordinator, and 1 project manager. A majority of these participants were female (N=12), white (N=14) and non-Hispanic (N=14). Their mean age was 48, and time with ATN ranged from less than 1 year to more than 10 years. Sites were located in the following states: California, Colorado, Florida, Illinois, Louisiana, Maryland, Massachusetts, Michigan, Pennsylvania, Tennessee, and Texas. Seven sites received IRB approval to enroll subjects in Project PrEPare, three were denied approval, and three had no formal IRB disposition. Of the three sites without formal IRB disposition, one was asked to withdraw its IRB application due to funding constraints at the ATN, and two did not formally submit the protocol to their IRBs because informal conversations and/or legal consultations made it clear the protocol would not be approved.

Articulation of Moral Conflict

Participants from seven sites expressed considerable conflict over the protocol:

> “I really struggled because I felt like the kids who’re going to be on this study really do have potential for more harm than risk, and they’re minors and [we] just don’t know that a 16- or 17-year-old understands this well enough to be able to consent for it. And I also felt like…if they’re a couple years older that’s not going to make a huge difference in their bone density but it does, I think, make a difference in terms of their analytic feedback, ability to consent. So I’ve always struggled with it…”(Site M)

Participants from these sites discussed a variety of concerns, including uncertainty about the legality of the protocol, apprehension about the possibility of adverse events, feeling torn when they placed themselves in the participants' parents' shoes, and doubt about high-risk adolescents' ability to comply with a demanding protocol. Most of their concerns were framed within the context of the participants' young age. For example, the Site K staff created a hypothetical scenario in which a study participant developed an adverse reaction to the study drug, to illustrate the difficulties in minors consenting for themselves:

> "And then the side effects came to the attention of parents who then found out the medication was given as part of a research study on their minor child—we were questioning the ethics and the morality of that from a research standpoint at our own site." (Site K)

Participants from six sites expressed low- or no-conflict. For example, participants at two sites mentioned aspects of the protocol that gave them pause, but did not use strong emotional language to describe them. They primarily reflected on what made this protocol different from others, namely, the need to be mindful of age restrictions when recruiting minors through social media sites, and the interpretation of state law as permissive of minors' self-consent for prevention of an STI rather than its treatment. Participants at the other four sites did not express personal conflict with the protocol. Of note, five of the six low- or no-conflict sites were granted IRB approval to implement the study, compared to just two of the high-conflict sites. The major source of conflict was tension between competing duties—scientific and protective. Data from participants at all sites contribute to a broad understanding of their felt sense of duty to different stakeholders. This is discussed in depth, below.

Protective Duties

Duty to the Child—Participants at all sites had significant experience conducting research with minor adolescents. However, none of the sites had experience conducting an investigational new drug study for which minors would self-consent. The lack of requirement for parental permission distinguished this study from others the participants had conducted. An additional distinguishing factor was the study's focus on prevention, in other words the administration of a study drug to healthy, albeit at-risk, adolescents. These two features of the study rendered it "*fundamentally different than anything we've done before*" (Site M), resulting in elevated concerns about risks to study participants.

Participants from multiple sites acknowledged grappling with the distinction between administering the study drug in a clinical setting to HIV-infected adolescents and administering it in a research setting to uninfected adolescents. Some (N=3 sites) were concerned that the risks, primarily of side effects of the study drug, could outweigh the benefits in the research setting. Others (N=2 sites) expressed worry that the study's intensive monitoring schedule could result in the enrollment of behaviorally low-risk adolescents rather than behaviorally high-risk adolescents, which would tip the balance toward risk rather than benefit. Participants from five sites discussed concern about whether minor adolescents have the capacity to provide informed consent to participate in a complex drug study:

> "I do know that a lot of our young kids are not the most savvy…they don't necessarily understand all the intricacies, even though you sit down and spend the hour on the consent." (Site I)

A specific duty to provide PrEP to at-risk adolescents also emerged. Participants at three sites that received IRB approval to implement the protocol expressed excitement about being able to offer PrEP to YMSM. Two participants from sites that were not approved referred to their experiences treating new cases of HIV infection among adolescents, or their general awareness of the prevalence among YMSM, as an impetus to do more to prevent infection in this population. One of these, Site H, decided it would offer PrEP to minors seen in clinic, when PrEP was clinically appropriate. Participants from these sites felt that offering PrEP, whether through Project PrEPare or routine clinical practice, was part of their duty to the adolescents in their communities:

> "…Morally and ethically, it was impossible not to allow these young people to participate in the study." (Site D)

Duty to Parents—Participants from three sites articulated a tension between their duties to minor adolescents who might benefit from participation in Project PrEPare, and their sense of duty to those adolescents' parents. For example, the PI at Site M described feeling relieved when the IRB denied approval, because:

> "As the provider I'm always accountable to those parents because they're really trying to do what's in the best interest for their kids. I feel like I'm accountable to them." (Site M)

Participants at the three sites were particularly concerned about adolescents' potential for experiencing side effects of TDF-FTC, and having the parents find out about the study as a result. They reflected on this by putting themselves in the parents' shoes:

> "When people personalize it in terms of what happens if … you got called to the ER because a 15 year old was in renal failure? When we brought it to that level, instead of processing how we want to prove things…you can see how torn people were with the protocol." (Site I)

One site (W) had already begun enrolling YMSM in Project PrEPare by the time of the interview. The participants from that site noted that many adolescents chose to informally involve their parents in their decision making process. In some cases, a parent's or family member's negative opinion of the study dissuaded a potential participant from enrolling:

> "One mom said she didn't want her [son] to do it and he wants to listen to what she says, so he's not going to go ahead. But we've encouraged [her that] if she has any questions to please give us a call. I think we've spoken to all of their aunties or grandmothers at some point." (Site W)

In contrast, a participant from a non-approved site reflected on the opposite experience with parents, noting it was parents who first heard about and advocated for their minor sons' inclusion in PrEP studies. These experiences led participants to conclude that some YMSM would be willing to include parents in the decision making process, and some parents would want their sons to participate.

Participants at three non-approved sites wished for a hybrid approach to study consent that would allow the adolescent participant to decide if he wanted his parents formally involved in the decision making process. They thought their IRBs might have approved a protocol with a more flexible approach to the consent process:

> "…We had some back and forth [with the IRB, which asked] 'Could there be a parental consent for those 15–17 year-olds that might choose to include their parents?' But we knew from ATN communications that this was an FDA edict and that there was no possibility for parental participation…there was no consent form for parents to be included…we were sort of perplexed why the FDA would exclude parental permission if it could be provided." (Site K)

A participant from another site echoed this sentiment, and wondered why some sites could not have tried a middle-ground approach, such as submitting the protocol with allowance for parental permission.

Duty to the Institution—Participants from 11 sites talked about the value they placed on their relationships to the IRB. They discussed various ways they reached out to IRB leadership and members to give "lots of warning" (Site X) that a potentially controversial protocol would be submitted for review. Participants framed these "heads up" conversations as part of an effort to maintain effective working relationships with their IRB, whose members face a difficult and time-consuming task. For example, Site M's PI said:

> "It's a great relationship, I really prize that and value that and work hard to maintain that. So I called our IRB Chair and I said, 'you know, I have this protocol that I think is going to be contentious, and I just want to run it by you first.'" (Site M)

Participants did not want their IRB members to be caught off guard, or left to review a controversial protocol without having all the information they might need to reach a decision, as the Site W PI notes:

> "I was worried about the legality and I didn't want to drag my institution through something that was not right…we spent time with the right people to make sure that everything they thought they needed to be answered upfront was answered." (Site W)

Like Site W, the Site I PI was aware of the potential for harm to the institution in the event of adverse study outcomes:

> "I think the lawyers took a look at [the protocol] and said 'There is no way.' [Our institution] had some issues in the past, and they're very aware of the community's feelings about and concern about being guinea pigs and I think they put all that together…that this can't happen." (Site I)

Scientific Duty

Participants' commitment to HIV prevention science and its advancement manifested in their sites' advocacy for the project. They undertook significant efforts to educate their institutional communities about PrEP and its importance to HIV prevention for YMSM. For

example, Site Y's PI noted that the institution's providers preferred educational prevention approaches that emphasized condoms, and were reluctant to prescribe medication for adolescents. Therefore, Site Y invited several physicians who had experience studying or prescribing PrEP to deliver lectures at the institution "because there's something about doctors talking to doctors" (Site Y). Additionally, the PI's Division Chief sent out a statement to encourage providers to refer youth to the study. Site L took a similar approach, noting:

> "It took some educating on how [TDF-FTC has] been used, how the medications have been used in HIV infection for a long time, and that there's been lots of monitoring. So, we know what to expect in terms of side effects and they can be easily managed." (Site L)

Participants from other sites leveraged laws and regulations as advocacy tools. For example, Site W was initially advised against submitting the protocol to the IRB, but when the FDA approved TDF-FTC for use in at-risk adults, the team presented the approval to its IRB as new evidence of support for PrEP. The Site W PI noted the importance of "not taking no for an answer. As circumstances change…reconsider or have others reconsider their previous decisions" (Site W). Six sites enlisted attorneys to help interpret local laws and their implications for the protocol. Site B found it particularly helpful and important to secure counsel independent of the institution, because:

> "He has, I think, a lot more objectivity than somebody who might be institutionally based; in other words he wasn't as focused on protecting [the institution's] interests because he's an employee." (Site B)

Participants from other sites (N=3) interpreted the laws on their own, and ensured IRB reviewers were familiar with them. For example, the PI at Site R met with a research ethics committee, and brought along the results from a clinical trial of PrEP for MSM, as well as copies of the state law that says minors can consent to HIV care and prevention. The ethics committee issued a document in support of the study, and it was ultimately approved and implemented at the site.

Commitment to scientific duty was also manifest in participants' reflection on their own experiences with diagnosing and treating adolescents with HIV infection, or with the high interest among, and successful enrollment of, YMSM in the Project PrEPare study for older (aged 18–24) youth (ATN protocol 110). These sentiments were clearly articulated by one the PI of Site B, who expressed no reservations about the protocol:

> "We see lots of new infections and infections among youth…So for us, the whole reason to do [this] kind of work is to make [PrEP] available to populations who might benefit most…Enrolling them in studies, importantly, we'll get useful information…it's just important to get these kind of data." (Site B)

Yet the PI of Site I had many reservations about it:

> "I have had 11- and 12-year-olds coming in newly infected with HIV. I think we do need to help prevent what is happening, particularly in [this city]…we really

wanted the study to be able to go forward. Because we know what is happening [here].” (Site I)

Resolution

During the interviews, participants from eight sites mentioned the processes by which conflict over the protocol was resolved. For instance, participants from two sites felt more comfortable with the protocol once they read documentation provided by the ATN that reflected its alignment with the policies of federal regulatory bodies (Gilbert et al. 2015). Those sites that were primarily concerned about adolescents’ capacity to consent (N=2) mitigated concerns by committing to a cautious approach to enrollment:

”Although I had pause, I think we could have been very careful in who we allowed to consent to be sure they were mature enough to understand what they were doing. I think we could have followed them closely enough that I would have felt that what we were doing was ethical and important.” (Site H)

Site B made modifications to the consent template that eased concerns about age-related capacity and about potential for social harm. They enlisted the help of a consultant to discuss the language that investigators would use when verbally describing the protocol during the consent process. Then they revised the study consent forms considerably, “to make it understandable and in language that was relatable [to adolescents]” (Site B), and to offer staff support to adolescents who might want to disclose participation to important adults in their lives. Finally, participants from three sites mentioned the actions and decisions of their respective IRBs as bringing resolution to their concerns. For example, after describing the team’s moral conflict about the lack of requirement for parental consent the participant from Site K said:

“But we didn’t have to make that decision, because our IRB is taking that decision away.”

Discussion

HIV prevention research with minor adolescent subjects is structured by ethical challenges resulting from potentially conflicting ethical duties: protective duties to the child, the parent, and the institution, and the broader duty to science. As HIV biomedical prevention advances, there is a scientific and ethical imperative to expand research to at-risk adolescents. Several lessons from Project PrEPare provide direction for future HIV prevention trials with minor adolescent participants who are at substantial risk of acquiring HIV infection.

During the process of initiating the Project PrEPare protocol, participants experienced moral conflict as they tried to fulfill protective and scientific duties. These duties were in direct conflict in this particular trial, which involved minor adolescents with multiple vulnerabilities. Participants were concerned about age-related vulnerabilities and the need to protect participants, parents, and institutions from harms if those vulnerabilities were left unaddressed. Broadly, there was concern over whether minor adolescents could understand the study sufficiently to consent to enrollment, whether it was ethical to prescribe an investigational new drug to a healthy minor adolescent without his parent’s consent or

awareness, and whether institutions would suffer untoward consequences if there were adverse events during the study. On the other hand, participants expressed a clear commitment to science, and saw this protocol as part of advancing the science of HIV prevention for YMSM. They accepted the ATN decision to require adolescent self-consent, and recognized that several external regulatory bodies agreed. This perspective is aligned with emerging data that indicate adolescents understand study information, appreciate how their own circumstances would be affected by study participation, and reason about risks and benefits (Nelson et al., 2016).

Allowing adolescents to consent on their own for trial enrollment prioritizes protection from disclosure-related vulnerabilities over those related to age. Moral conflict manifested when participants faced protective duties that would have mandated a different course of action. For example, if allowed to consider the duty to the parent in isolation from that owed to the child, the institution, or science, the balance of vulnerability tips toward age. Conversely, consideration of the duty to science tips the balance toward protecting privacy at the expense of age related vulnerabilities.

Although there was neither a required nor a formal role for parental involvement in the consent process, there was no prohibition against parental involvement if a minor adolescent wanted a parent present. However, the allowance for parental involvement, where desired, did not assuage the concerns of some of our participants or their respective IRB members. They wondered if there could have been a “middle ground” approach to consent. Some options might be for sites to enroll only those YMSM who felt comfortable seeking parental permission for participation, or to formalize the role for parents when YMSM wanted them present for the consent process. Such hybrid approaches to consent have been used successfully. In their vaginal microbicide trial, Schenk and colleagues (2014) allowed 16- and 17 year-old South African girls to self-consent for participation but gave them the option to request non-binding parental permission if they preferred to involve their parents. This may be a useful approach to the consent process in future studies with minor adolescents, in jurisdictions in which minor adolescents have the legal authority to consent for enrollment.

Many HIV prevention trials are organized by research consortiums with sites in multiple states or countries. Multiple sites are often required in order to accrue a sufficiently large number of study participants to demonstrate an effect on HIV incidence. Multi-site studies typically involve multiple IRB reviews, which complicates, delays, and sometimes inhibits the research process (Barchi et al. 2014). In this particular case, the ATN designed the protocol, including the consent process, but deferred to AMTU’s local IRBs to approve it. Thirteen AMTUs intended to implement the study, and IRB concerns prevented five from doing so (the sixth site lost ATN funding, and therefore its IRB did not provide a final decision on the protocol). This resulted in an unequal distribution of both the benefits and burdens of research across the network, and left out youth in states with high rates of HIV diagnoses among 13–19 year olds. Other research consortiums have established various mechanisms for IRB collaboration, such as streamlined, centralized review for domestic, multi-site studies. Centralized reviews are recommended by the U.S. Department of Health and Human Services, as they may expedite the research process and ensure members equal access to trial participation (Barchi et al. 2014). Research consortiums like the ATN can look

to these models for new approaches to IRB review of HIV prevention protocols, especially those that are likely to be controversial.

This study has several limitations. Readers should bear in mind that we interviewed participants after they received feedback or formal disposition from their respective IRBs. The IRB responses may have influenced participants' answers to the question about whether anything in the protocol gave them pause. For instance, a favorable IRB review may have assuaged participants' early concerns, and therefore they did not have any to discuss at the time of the interview. Likewise, a negative IRB response may have heightened participants' concerns. We used semi-structured interviews to collect the data presented here, which did not allow for anonymity. We tried to minimize the possibility for social desirability bias by assuring participants that their identities would not be revealed in publications and presentations, and we note a variety of opinions and perspectives in the data, which suggest participants felt comfortable during the interviews.

Advances in adolescent health lag behind those seen in younger children, and this global pattern is evident in HIV infection (Sawyer et al. 2012). Adolescent HIV infection rates have not declined at the same rate as early childhood and adult infections, underscoring the need to involve adolescents in HIV prevention studies (Ott 2014). Few biomedical trials have involved minor adolescents, because it is ethically challenging to do so. Investigators have a moral imperative to address and support adolescents' vulnerabilities, rather than using them as an exclusion criterion (MacQueen and Karim 2007). Practically, this is difficult because investigator roles include multiple, conflicting duties. They may best be supported through flexible consent procedures and collaborative IRB reviews that account for adolescents' multiple vulnerabilities rather than privileging one of them over the others.

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