testing the efficacy of Safe South Africa, an intervention to prevent HIV risk behavior and sexual violence among adolescent boys

NCT to be assigned

Study Protocol and Statistical Analysis Plan

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Principal investigators: Catherine Mathews[1]; Caroline Kuo[2],
Co-investigators: Lindsay Orchowski[3]; Yandisa Sikweyiya[4]; Abigail Harrison[5]; Tao Liu[5]
Consultants: Alan Berkowitz[6]

Affiliations

1. Health Systems Research Unit, South African Medical Research Council, Cape Town, South Africa; email: catherine.mathews@mrc.ac.za
2. American University and Brown University; email: ckuo@brown.edu
3. Rhode Island Hospital and Alpert Medical School Brown University; email: Lindsay_orchowski@brown.edu
4. Gender and Health Research Unit, South African Medical Research Council, Pretoria, South Africa; email: Yandisa.sikweyiya@mrc.ac.za
5. Brown University School of Public Health; email: Abigail_harrison@brown.edu and tao_liu@brown.edu
6. Independent consultant; California, USA; email: alan@snowcrest.net

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Introduction

Background and rationale

While much progress has been made against the global HIV pandemic, HIV continues to be a pressing public health concern, especially in the African region. Nearly 40% (approximately 500,000) of global infections occurred in Eastern and Southern Africa, highlighting regional disparities in South Africa and surrounding countries. Intimate partner violence (IPV) including sexual violence, can reinforce the HIV epidemic in several ways. There are causal links between sexual violence and HIV acquisition where sexual violence can increase tissue trauma associated with increased infection risk. There are also behavioral links, with literature showing an association between those who perpetrate IPV and HIV infection via pathways such as increased risk behaviors (such as multiple sexual partners, decreased condom use, substance use, and presence of other sexually transmitted infections or STIs). The interplay between HIV risk behaviors and IPV necessitates comprehensive intervention strategies that address both issues concurrently.

South Africa is the ideal geographic site to develop prevention science for these synergistic epidemics. South Africa has one of the largest HIV epidemics in the world. Adolescents are one of the sub-populations most at risk for HIV infection. National data in South Africa shows that adolescent boys are engaging in HIV risk behavior at higher rates than girls: 67.7% of boys reported condomless last sex compared to 49.8% for girls, and 25.5% of boys reported two or more sexual partners compared to 9% among girls. South Africa also has a high global burden of IPV. Globally, the sub-Saharan African region, including South Africa, has the highest prevalence of both intimate partner and non-partner sexual and/or physical violence at 65.6% (95% CI: 53.6-77.7%) and 21% (95% CI: 4.5-37.5%) respectively. Although all genders perpetrate violence, the vast majority of sexual violence is perpetrated by boys and men in South Africa, with a survey in South Africa reporting that 1 in 3 men (31.9%) reported rape perpetration. Adolescence is the ideal period to address these synergistic epidemics of HIV and violence. HIV transmission risk is primarily driven by sex. In South Africa, large longitudinal studies show that the median age of penetrative sexual debut among boys in South Africa is 15 years, with 38.2% of boys engaged in penetrative debut at this age. Developing interventions to address these issues in early adolescence would benefit boys and their current and future partners over their lifetimes.

There is limited evidence for interventions that address both HIV risk and sexual violence for this age group in this high-priority geographic site. In a systematic review that identified interventions

specifically targeting both HIV and IPV interventions for adolescents in sub-Saharan Africa, only six interventions had been tested using randomized or quasi-randomized trial designs. A review of these interventions showed that none used a theoretical approach focused on changing social norms. Yet, addressing social norms around violence and sexual behavior as it relates to HIV acquisition may be a promising intervention approach ideally suited for adolescence, an age when social norms – especially from young people's social circles (families, peers, teachers) – are incredibly influential for forming long-term ideas around relationships and healthy. Schools are ideal environment for a social norms-based intervention since adolescents spend a large majority of their time in schools, and this environment is full of social interactions with peers and other important people in adolescents' lives that help shape their behaviors relating to HIV and sexual violence. Changing social norms has been shown as a promising prevention strategy for addressing violence, especially when combined with behavioral change strategies.

Our team developed a behavioral intervention – Safe South Africa – specifically tailored to the South African context and the developmental and gender needs of boys. The Safe South Africa intervention integrates HIV and IPV prevention within the South African context.

Objectives

The primary aim of this randomized controlled trial is to investigate the efficacy of an integrated approach for preventing or reducing risk behavior related to the acquisition of human immunodeficiency virus (HIV) and perpetration of intimate partner violence (IPV) among adolescents in South Africa using a behavioral intervention that is gender and developmentally tailored for teenage boys in South Africa and delivered in the school setting. Participants are followed for twelve months after delivery of the intervention session. Our working hypothesis is that for adolescent boys randomized to Safe South Africa, a behavioral intervention will show (a) a lower incidence of STIs (gonorrhea and/or chlamydia and/or HIV) and (b) reductions in IPV perpetration frequency and decreased endorsement of IPV supportive attitudes compared with boys in the control arm.

Trial design

The study employs a randomized controlled trial (RCT) design using a parallel design. N=836 participants will be randomly assigned to either the intervention group or the control group with

an allocation ratio of 1:1. Randomization is conducted individually, since the outcomes that we are looking at, occur at the level of individual behavior change (e.g. adolescent boys' HIV and STI outcomes along with IPV behaviors). We will be examining the superiority of the intervention in comparison to the control. Any significant changes to methods after the trial commencement, such as adjustments to eligibility criteria, will be documented along with the reasons for these changes.

Methods: Participants, interventions and outcomes

Study setting

Recruitment will occur in up to five public high schools in South Africa in order to meet recruitment numbers. We have completed permission to work at these school sites by working through first HREC/IRB clearance, and then applying for and securing permission in a process defined by the South African Department of Education and meetings held with school administrators.

Eligibility criteria

Eligible participants include: 1) identification as boys; 2) ages 15-17 years; 3) enrolled at public high schools in South Africa situated in communities with high rates of HIV and violence. Participants also must be willing and able to provide informed written assent (following parental consent). Participants are not excluded based on sexual debut, STI or HIV status, or prior experience of violence since this intervention can function as primary and secondary prevention. Data collection and procedures occur on school grounds, with the Department of Education's permission and school administrators' permission. Permission to work in schools by the Department of Education and school administrators does not override the process of parental consent and adolescent participant assent.

Who will take informed consent?

All researchers who have contact with participants undergo a rigorous training process with pre-defined metrics needed to have any contact with participants or participant data, as well as re-training for researchers who have contact with participants regularly. Our trained team conducts all consent and assent procedures. The study starts with parental (or legal guardian) consent. We have arranged with each school to do study introduction sessions on days when many parents

are present on school grounds, such as required registration/enrollment of children into the school, parent-teacher meeting days, etc. After explaining the study, we describe its eligibility requirements. We offer blank parental consent forms to interested parents of potentially eligible boys. The parental consent form is designed to provide parents with a summary of the nature of the research, seeking their signed permission to approach their child to discuss the child's decision to participate. We clearly show parents that we seek their written consent, which is voluntary. If they do not provide written consent, we will not approach their child to seek child assent. In that case, all study procedures will not go further. Should they decide to provide written consent for us to approach their child for the assent procedures, the child will ultimately be able to decide whether to participate as captured in the assent form and process. The consent form emphasizes the limits of confidentiality, including mandatory reporting (suspected or actual child abuse, intentions to harm self or others, underage sex under certain circumstances as defined by South African law, and perpetration of violence with a named victim) and the steps we take to avoid mandatory reporting (survey done on tablets using audio-computer assisted self-interviewing, no collection of identifiable data along with the survey data and points of danger for mandatory reporting including the interactive intervention session for boys randomized to that session and the verbal reminders and steps taken in the intervention sessions themselves to remind boys of mandatory reporting). We also emphasize that participation is voluntary, no one can be coerced to participate, and decisions to participate (or not) cannot impact school services or any other social services. Parents do not need to sign the consent form that day. We give an extended period (1+ weeks) to ensure parents have our contact details if they have questions. For parents, we share the study team's specific contact details on the consent form so we can answer questions. We provide a method for them to easily request that we call them at no cost to them, commonly known as a free "please call me" method common for these sorts of studies in South Africa. We respond immediately to all requests for us to call parents. We purposively introduce a multi-day delay between (1) introducing the study when consent and assent forms are given out for review and (2) when we gather signed consent and assent forms. The delayed period ensures additional time for parents and minors to fully digest the form, including asking questions and considering all aspects of the study, including limits of confidentiality, study testing, disclosure procedures, etc. We also provide parents who sign consent forms with copies of child assent forms for their review, where they write down the name of their potentially eligible child. If the child wants to find out more, we provide them with the assent form to bring back to school. For parents who have provided written voluntary consent for us to approach their child for the assent process,

parents will specify the name of their potentially eligible child to us. We take note of that potentially eligible child's name.

Not all parents attend registration/enrollment days, parent-teacher meetings, or school meetings. In consultation with the schools, we have developed a process for gaining parental consent consistent with standard practice for schools in South Africa to send home written communication with students for parents. We considered visiting homes in the informal settlement community where we work. Still, most of these homes do not have addresses or street names/numbers, and parents often leave for work early and return home late, so visits are not feasible in person for every student's parents. In this process, our trained study staff will first visit all classrooms of potentially age-eligible participants for the survey (we anticipate this to be grades 9, 10, and 11). We briefly explain the purpose of the clinical trial. Then, we hand out the parental consent forms and child assent forms. The consent form emphasizes the limits of confidentiality, including mandatory reporting and the steps we take to avoid mandatory reporting (survey done on tablets using audio-computer assisted self-interviewing, no collection of personally identifiable data along with the survey data and points of danger for mandatory reporting including the interactive intervention session for boys randomized to that session and the verbal reminders and steps taken in the intervention sessions themselves to remind boys of mandatory reporting). We also emphasize that participation is voluntary, no one can be coerced to participate, and decisions to participate (or not) cannot impact school services or any other social services. Then we ask children to bring home forms to parents, and we will return them in a week to collect parental consent forms. We describe what parental consent means (that it allows our team to approach children for the assent process, but children ultimately have the right to decide to participate even if their parents have given consent). For parents, we share the study team's specific contact details on the consent form so we can answer questions. We provide a method for them to easily request that we call them at no cost to them, commonly known as a free "please call me" method common for these sorts of studies in South Africa. We respond immediately to all requests for us to call parents. We purposively introduce a multi-day delay between (1) introducing the study when consent and assent forms are given out for review and (2) when we gather signed consent and assent forms. The delayed period ensures additional time for parents and minors to fully digest the form, including asking questions and considering all aspects of the study, including limits of confidentiality.

Students who return signed parental consent forms can engage in the assent process. Again, we emphasize that children can refuse participation even if parents have signed consent forms. Our

team will then visit the schools to make contact with potential participants. After explaining the study, we re-describe its eligibility requirements. Then we ask potentially eligible children for whom we have secured parent's signed consent forms and who are interested in engaging in a further in-depth discussion to do so with us. We begin the session by emphasizing that children can refuse participation even if parents have signed consent forms. We screen for eligibility. For eligible potential participants, assent forms are verbally read aloud to students if their parents have provided written consent for us to approach them to complete the assent process. After reading aloud from the assent form by our team, we have a period to answer questions. Then, to ensure further understanding of the form following this more standard question period, we conduct an in-depth discussion to ascertain a meaningful sense of the assent form. Specifically, we use a “pros of joining the study/cons of joining the study” exercise to increase awareness of trial participation decisions. This includes an explicit discussion of mandatory reporting requirements as defined by South African law, including what circumstances require mandatory reporting (perpetration with a named victim, child abuse, homicidal intent, suicidal intent, specific age gaps for underage consensual sex and or underage sex with those under 12 years), who information is reported to, and potential consequences. We also make clear that mandatory reporting is highly unlikely in the survey and biological data collection process, given that no identifiers (date of birth, name, etc.) are collected with the survey data. Notable is that the only way that legal reporting would occur is if individuals come to the study team to "confess" reportable behaviors (for example, in the hallway of schools where we work, after the survey and biological sample data collection is completed, etc.). We describe where mandatory reporting is more likely - during the intervention session. We also describe the processes we take to remind boys of the circumstances where mandatory were to arise in the intervention session and the other steps we take to protect against inadvertent disclosure of mandatory reporting requirements. This also includes an in-depth discussion of HIV and STI testing, at what timepoints this biological testing is done in the study, and a description of the methods used for testing. We also describe in detail that children have a right under South African law (via the specific law laid out under The Children's Act) to be tested for HIV and STIs and to seek treatment and care for these conditions independently from the age of 12. This means that we would not disclose positive HIV and/or STI test results to parents; however, we would encourage children to disclose a positive finding to safe and trusted adults for support, including, for example, their parents. We describe the process of referring children who have tested positive to clinics and specifically lay out that we cannot disclose their positive test information to clinics without their permission. We describe the clinical liaisons that would receive them for care at the clinic and the cost (free treatment via South Africa's

public health care service but support from our study for transport costs), and we explain the treatment that positive participants would be offered. We have found this pros/cons discussion to be vital for participants to refine their understanding of the study with us because we hear their explanation and understanding of the study procedures in their words – and then we can offer further clarification.

We also focus on meaningful reminders of consent throughout the trial. For example, before the start of the eligibility screening, survey at baseline/4 months/12 months, session satisfaction surveys at the 1st and 2nd intervention session, and qualitative interviews, we remind participants that the only way we would be required to have any mandatory reporting is outside the context of normal study procedures. Specifically, an individual would need to come to the study team to "confess" reportable behaviors and give the specifics required for mandatory reporting. During the intervention, we purposively avoid eliciting discussion that could result in mandatory reporting - for example, we keep the debate quite broad, avoiding prompts for individual, real-life scenarios. We remind intervention participants of the mandatory reporting scenarios. Suppose an individual starts to disclose scenario details during the intervention discussion that might involve mandatory reporting. In that case, we will remind them of the mandatory reporting requirements. We would avoid these scenarios by stopping them and telling them not to share names.

Additional consent provisions for collection and use of participant data and biological specimens

Not applicable. We seek consent and assent to gather biological specimens for HIV and STI testing during the course of the consent and assent process for the trial.

Interventions

Explanation for the choice of comparators

There are no existing integrated intervention of HIV and violence prevention for this age group that are efficacious and in school settings in South Africa, so the control condition of usual care received nothing. We considered comparing the intervention arm to a more stringent control, but no efficacious interventions exist tailored for boy adolescents in South Africa.

Intervention description

The Safe South Africa intervention is gender- and developmentally-tailored, and designed to reduce actual or intended HIV risk behaviors relating to acquisition of STIs (gonorrhea and/or chlamydia and/or HIV) and reductions in IPV perpetration frequency and decreased endorsement of IPV supportive attitudes. The intervention is based on two individual behavior change theories: (a) the HIV risk prevention components were based on the Information-Motivation-Behavioral (IMB) theory; (b) the IPV perpetration prevention components were based on a conceptual model that places correcting misperceived social norms as a theoretical pathway to behavior change, called the Integrated Model of Sexual Assault and Acquaintance Rape described below.58,59

The intervention preparation begins with gathering social norms data from the target population's social environment (peers within the school that 15-17 year old boys attend). This data guides selection of data to populate content in the Safe South Africa intervention. These updates are critical because we need to have the data on HIV and violence behavior, as well as related (mis)perceived norms that reflect boys current peers and environment. The believability of the data from their peers and schools is what makes the intervention work. This data is generated from an ecological survey with all adolescents in the school that captures individual behaviors and norms data relating to IPV and HIV prevention needs within the boy's current school social ecology as well as perceived peer behaviors and norms data. This survey data is then slotted into Safe South Africa intervention content.

The theory driven components of the Safe South Africa intervention are as follows. Safe South Africa's HIV risk prevention components are based on Information-Motivation-Behavioral (IMB) theory. The change strategy of the intervention's HIV components include: (1) increasing HIV knowledge around protective behaviors (i.e., information), (2) encouraging adolescents to implement protective behaviors and tying HIV behaviors to future goals (i.e., motivation), and (3) building self-efficacy for prevention behaviors including condom use and negotiation and healthy sexual relationships (i.e., behavior). Safe South Africa's IPV prevention components are based on the Integrated Model of Sexual Assault and Acquaintance Rape. This conceptual model, originally proposed by Dr. Alan Berkowitz, suggests that interventions to prevent IPV and interpersonal violence are most salient when targeting risk and protective factors across the social ecology (i.e., individual-, peer-, and community-level risk factors) with correcting misperceived social norms as a vital change path in this ecology.

Our HIV theoretical model (IMB) is aligned with the violence prevention model, e.g., the Integrated Model of Sexual Assault and Acquaintance Rape Model. According to the violence prevention model, at the individual level, adolescent males must consider their own potential for IPV and

interpersonal violence including sexual violence (i.e., attitudes, beliefs and socialization experiences) and take a stand against violence perpetrated by others. In this intervention, we focus on changing personal attitudes and beliefs regarding both HIV risk and IPV, aligning the individual-level aspect of the violence prevention model with the "I- information" component of our HIV prevention theoretical model. For example, we educate adolescents on situational characteristics, including "triggers," that may lead to misperception of sexual interest.64 Triggers might include: a pre-existing relationship between victim and perpetrator that may increase the likelihood that a young man feels justified to use coercive or aggressive behavior in order to obtain sex;65 misinterpretation of a variety of behaviors and situations, such as friendliness, the wearing of revealing clothing, and female attractiveness, as seductive and indicative of sexual interest, even when stimuli are subtle or ambiguous; and assumptions that when a partner says "no" to sexual activity, they really mean "yes" (i.e., token resistance).69 We explore and challenge males' attitudes and beliefs, including stereotypical rape myths and adversarial views towards girls and women, as well as intimate partner and interpersonal violence behaviors.

We also address peer-level factors using bystander intervention techniques, thus aligning the peer-level of the violence prevention model with the "M-motivation" component of the HIV prevention theoretical model.79-83 For example, positive peer pressure, as exerted through prosocial bystander action, can prevent IPV in others. Importantly, bystander behaviors can also reinforce the bystander's own prevention behaviors. The bystander approach has promise in correcting misperceptions about IPV and decreasing personal engagement in IPV, interpersonal violence, and aggression. Bystander actions involve social learning where peer reinforcement results in self- and social-rewards for positive behaviors. Finally, we build self-efficacy and behavioral skills by, for example, practice in assertive bystander communication (e.g., what to say, how to say it) and behavioral action (e.g., confronting and halting peer IPV behavior, knowing who to contact for reporting and help in the case of suspected or actual IPV, linking peers and potential victims to appropriate services). This aspect of the violence prevention model is aligned with the "B-Behavior" component of the HIV prevention theoretical model.

The final tier of the social-ecological violence prevention model includes community-level factors. To address community-level factors, we use a survey with both boys and girls to evaluate the social ecology of the community that adolescents are in – in this case, peers within the school. Data from the survey are used to correct misperceived social norms using real data from current peers in the school environment, with this data integrated throughout the behavioral intervention with male adolescents. Our discussion of misperceived social norms with male adolescents helps

them to interrogate their specific social ecology of risk that can serve to inhibit or encourage problem behavior. Social norms contribute to sexual violence in two ways. First, data suggest perpetrators are acting in ways that they (mis)perceive to be appropriate and accepted by their community. For example, men who perpetrate violence are apt to believe that other men ascribe to stereotypical gender role beliefs and support violence against women. Men who believe their friends are using coercive behavior to obtain sex are more likely to engage in sexually coercive behaviors themselves. Taken together, misperception of community norms regarding sexual activity, in tandem with pressure to "fit" a (mis)perceived hyper-masculine ideal, fosters an environment where sexual activity—even if coerced or forced—is falsely believed to be normative and associated with increased status and acceptance. Social norms contribute to sexual violence by creating a false perception of high rates of sexual violence existing in a community. Even non-perpetrators believe that peers harbor more rape myths than they actually do. People also underestimate the extent to which their peers feel uncomfortable with sexist or degrading language/actions towards women. These misperceptions about how many community members accept violence or how few would stand up against it perpetuate violence by decreasing the likelihood that healthy community members stand up against the expression of inappropriate behavior in their community. Second, men who perpetrate acts of sexual aggression report feeling pressure to engage in sexually aggressive behavior in order to demonstrate masculinity and avoid humiliation from peers. Over-estimations of peer sexual activity contribute to high intentions to initiate early adolescent intercourse (especially relevant to our HIV prevention aims); pressure to be sexually active is a salient correlate of sexual assault perpetration. Accordingly, our social norms messaging corrects misperceived norms as a community-level prevention strategy for both HIV and IPV in boys' school environment by recognizing that: 1) community norms influence behavior; 2) community norms are often misperceived (i.e., they are over- or under-estimated); 3) these misperceptions encourage individuals to adjust their attitudes and behaviors to confirm to what they incorrectly perceive to be true; and 4) correcting misperceptions allows individuals in a community to act in accordance with their actual beliefs, which are most often positive and health promoting. Social norms theory proposes that when the actual norm of the peer group is revealed, individuals feel less pressure to engage in negative behaviors (sexual coercion, risky sex, etc.) and are more willing to intervene when witnessing inappropriate behavior. Following the acknowledgement that to be effective, prevention efforts must be positive, inclusive and empowering, correcting misperceived social norms approach also emphasizes the importance of championing "positive behavior" rather than focusing on ameliorating "negative behavior." The Integrated Model of Sexual Aggression suggests that prevention approaches can reduce proclivity

for sexual aggression by providing opportunity to share discomfort with aspects of the traditional male gender role script, combined with discussion of more positive alternatives. The change strategies of the IPV prevention components of the intervention include: (1) understanding conditions of sexual consent; (2) increasing male empathy regarding the effects of IPV, interpersonal violence, and sexual aggression; (3) correcting misperceptions regarding IPV and interpersonal violence prevalence as well as prevalence of sex, and consequences of these misperceptions; (4) increasing use of bystander strategies; and (5) increasing awareness of risk for IPV, interpersonal violence, and aggressive behavior and links to HIV transmission.

Hallmarks of the Safe South Africa intervention approach include the following: The first hallmark of Safe South Africa is our gender-tailored approach. For HIV prevention, sensitive topics such as puberty, first relationships, and sexual negotiation are easier to discuss in gender-tailored groups (in this case, boys). For example, medical male circumcision, an important biomedical HIV prevention strategy for this age group, is also an important cultural marker of manhood among Xhosa males in South Africa. Boys join circumcision school with includes rites of passage, and a male-specific space during which gender roles are discussed, topics such as sex and health are discussed, as well as conceptions of masculinity; male circumcision is denoted as a topic that should only be discussed by men and boys. For IPV perpetration prevention, gender separation decreases defensiveness among participants and promotes salience of program content. Fears of embarrassment make it difficult for boys/men to openly discuss boys/men's attitudes around topics relating to IPV and HIV prevention when girls/women are present. The single-gender format of our intervention will allow boys to more effectively unearth and challenge misperceptions of social norms. Facilitators take a "non-expert" stance in order to avoid inciting defensiveness among participants. A second hallmark of the Safe South Africa Intervention is our age- and developmentally-tailored approach. Adolescence marks a life transition with developmental hallmarks that naturally increase HIV and IPV risk. For example, adolescence is marked by increases in impulsivity, risk taking, and exploration of sexual identities leading to naturally elevated sexual risk for HIV. Although developmental hallmarks create elevated risk for HIV and IPV, our approach uses other developmental hallmarks as prevention opportunities including: peer influence, habituation of behaviors, and identity formation including desire for recognition, leadership, and independence. This age is when formative first experiences in sexual behavior, sexual relationships, and peer relationships occur. We capitalize on formative experiences to habituate prevention behaviors for HIV and IPV. This age is when peer norms have a strong influence so we tap into positive peer norms for larger prevention gains. For example, our bystander prevention leverages positive peer pressure by positioning boys as allies in violence

prevention. Given the vast majority of boys are not sexually aggressive and desire mutually respectful relationships, engaging this majority as allies in prevention is vital to promoting cultural norms that thwart the behavior of the minority of coercive and aggressive boys and men, and engage the majority as proactive bystanders to intervene with peers and support victims. This age is when identity development occurs, and a preventive intervention can reinforce healthy male identity formation and gender norms. We build on the natural trajectory of identity development formation to instill healthy notions of manhood and gender relationship norms to facilitate long-term life-course prevention.

Core components of the Safe South Africa intervention include the following:

Theory driven, best-evidence intervention approaches for adolescent HIV prevention: In our pilot testing of Safe South Africa, we integrated rigorous evidence in efficacious interventions for adolescent HIV prevention to create Safe South Africa. Our choice of adolescent HIV prevention components to integrate was guided by 4 global and South African specific systematic reviews and/or meta-analyses. We combined the latest evidence from these reviews – which were aligned with our IMB theory (described above) - with our own experience of adapting empirically supported interventions to the South African context for the final intervention approach.

Linkages between HIV and IPV: The intervention increases understanding of linkages between HIV and IPV including for example, risk behaviors related to both HIV transmission and IPV perpetration including condom use, number of partners, substance use, and existing STI infection, norms around sex and sexual relationships. The theory of behavior change is interwoven into this component, presenting information (“I” of IMB) on how HIV, IPV, and STIs impact this particular age group paired with substantive behavioral practice (“B” of IMB) around protective behaviors such as partner negotiation, correcting using condoms using condoms and lifelike penis and vagina models.) The intervention also addresses interpersonal violence and aggression, both linked to IPV and critical to addressing prevention for this age group because this can affect healthy interactions such as negotiation of protective behaviors by providing information (“I”) as well as motivation (“M”) on correcting misperceived norms and detailing the long-term health impacts for those who perpetrate and survive violence.

Victim Empathy: The intervention increases understanding of the impact of IPV by providing local and national statistics, discussing perceptions of false accusations, and debunking rape myths.

Healthy Norms Regarding Masculinity: Peer violence and delinquent behaviors are strongly associated with IPV. The intervention addresses this by correcting misperceived unhealthy social norms in order to create more healthy norms regarding masculinity and encourage development of positive peer groups relevant to HIV-IPV prevention. The intervention involves interactive discussion of misperceptions of social norms, critiquing traditional male socialization as it relates to violence and sexual intimacy. Participants are encouraged to share discomfort with aspects of traditional male gender roles and share positive alternatives. This component specifically builds upon the Integrated Model of Sexual Assault and Rape Prevention by showing how individual behavior, including decisions around behaviors, are shaped by the social ecology. In these portions of the intervention, we use real data around boys' individual behaviors, and the behaviors and norms of their peers, to challenge and correct misperceived social norms. By providing correct information, we motivate boys to adopt healthy behaviors and norms ("I" and "M").

Bystander Intervention Skills: Based on the bystander intervention approach, participants are encouraged to intervene when they witness other individuals (regardless of gender) engaging in inappropriate dating behavior, including engaging in intimate behaviors without consent. Our bystander approach supports individual level behavior change by making clear that coercive behavior is not acceptable. Since a relatively small group commit the majority of assaults,120 it is particularly important to engage all adolescents as proactive bystanders in changing the community norms that foster violence including risky sex and sexual violence. Participants will brainstorm responses to inappropriate behavior in a small group exercise and report responses back to the group. Misperceptions regarding males' discomfort with the inappropriate behavior and language of other young men serve as barriers to intervening with other boys and men's behavior. Thus, misperceptions are deconstructed through accurate data and an experiential group exercise that reveals the norm of intolerance. Bystander approaches have both theoretical and empirical promise in perpetration prevention.

The Safe South Africa intervention is a manualized behavioral intervention. In this trial, it is delivered by two trained facilitators (one lead and one co-facilitator) to participants in a group format in-person on school grounds but after school or during non-lesson times. Group sizes range from 20-30 boys; although the intervention is delivered in a group, the behavioral change strategies focus on individual behavior change. The sessions run for 1.5 to 2 hours each, and run once a week for two consecutive intervention sessions over two weeks. The intervention uses actual data from boys and their peers from their school in the intervention content to correct

misperceived social norms relating to the prevention of HIV, STIs, and violence and to enforce positive norms and behaviors relating to the prevention of HIV, STIs, and violence. Each session also involves take home activities to deepen behavioral practice and change. The intervention is guided by a manual to facilitate consistent and quality delivery. The intervention session topics are described below.

Session 1:

Module 1 - Welcome, Introduction, Hopes and Dreams: Orientation to the intervention, group norms

Module 2 - Core Values & Caring Relationships: Defining hopes and dreams, and discussing values as aligned with choice of peer and romantic partners and how one interacts to facilitate peer and romantic partners

Module 3 - Understanding Violence & What Other Guys Think: Sexual assault statistics and norms/behaviors in the school, types of coercive sexual behaviors, sexual pressure

Module 4 - Living healthy lives: Assertive communication towards peers and romantic partners including in sexual situations

Module 5 – Consent: Elements of on consent in relationships

Session 2:

Module 1- Gender Role & Healthy Relationships: Gender roles and expectations, connections to healthy behaviors in relationships and sexual decision making, triggers and problem solving

Module 2 - Myths/Facts About Sexual Violence: Deeper exploration of elements of consent including practice of getting consent, false accusations

Module 3 - Condom Practice & HIV and AIDS – Male and female condom use and motivation for use, information on HIV and STI prevention and treatment

Module 3 - Active Bystander Intervention – Type of active bystander strategies and practice

Criteria for discontinuing or modifying allocated interventions

The trial does not have any set protocol for discontinuing the intervention. We do have a Data Safety and Monitoring Board who has the purview to guide us on stopping the intervention due to safety concerns.

Strategies to improve adherence to interventions

The intervention is guided by a manualized protocol to ensure consistent and high quality delivery. Fidelity is monitored by a neutral observer and regular feedback sessions are given to the intervention facilitators by the investigative team to support adherence.

Relevant concomitant care permitted or prohibited during the trial

The trial provides linkage to care for HIV and STI treatment for those who test positive at any timepoint. We monitor for exposure to any additional interventions relating to behavioral HIV/STI and violence prevention but do not bar participants from engaging in these interventions.

Provisions for post-trial care

The trial provides linkage to care for HIV and STI treatment for those who test positive at any timepoint and this treatment is provided for free in the public health sector in South Africa.

Outcomes

Outcome assessments evaluate changes between the intervention and control groups at baseline compared to 4- and 12-months post-intervention. There are two primary aims of the study that focus on answering the questions: (1) Do adolescent boys report lower incidence of HIV and/or STI acquisition? and (2) Do adolescent boys report fewer experiences of completed and/or attempted sexual violence perpetration? Do adolescent boys report lower endorsement of IPV-supportive attitudes? The primary aim is defined as biologically verified Chlamydia trachomatis and/or Neisseria gonorrhoeae and/or HIV. These biological tests are done at baseline and twelve

months post-intervention. Primary aim two is captured using self-reported data on completed acts of forced touching, oral sex, anal sex, and vaginal sex, as well as attempted acts of forced oral, anal, and vaginal sex. Primary aim two is also captured using self-reported data on rape myth acceptance. Sensitive self-reported outcomes use audio-computer-assisted self-interviewing software (ACASI) to limit social desirability bias. For our secondary outcomes, we will examine mediators, moderators, and mechanisms for how behavior change occurs in primary outcomes.

Sample size

We use data from two prior studies conducted by our team members with a comparable study population (restricted to males ages 15-16 from a cohort of 14-16 year-old adolescent boys and girls) and other relevant secondary sources.9,11 To formulate a realistic range of necessary assumptions for sample size and power considerations for primary outcomes. We estimate that a total sample size of N=836 adolescent boys, or 418 adolescent boys per arm, will be required to power our study adequately. For HIV/STI acquisition, we power the study based on the outcome of any HIV/STI infection (which we expect to be primarily driven by chlamydia) based on a prior study examining the efficacy of an intervention to prevent HIV and STI acquisition. We hypothesize that at the 12-month visit, the prevalence of any STI (including HIV) will range from 12.5-20% in the control arm, and prevalence in the intervention arm will be reduced by at least Δ=7.5% and range in prevalence from 5-12.5%. With these effect sizes, the study has a power of at least 0.80 to demonstrate the difference between intervention and control. Individuals with STIs at baseline will be treated at that time, so it can be reasonably assumed that STI prevalence at twelve months represents incident cases only. We do not exclude individuals with HIV at baseline from the 12-month power calculations because these individuals can still contribute to incident STIs; in addition, HIV prevalence at baseline is expected to be extremely low, around 1%. For IPV frequency, we power the study based on the outcome of any sexual violence perpetration (oral, vaginal, or anal) between 4-months and 12-months follow-up (measured at the 12-month visit). We hypothesize that at the 12-month visit, the prevalence of sexual violence perpetration since the 4-month visit will be 25-35% in the control arm; the prevalence in the intervention arm will be at least 10% lower and range from 15-25%. With these effect sizes, the study has a power of at least 0.85 to demonstrate the difference between intervention and control. For IPV attitudes, we power the study based on the proportion of individuals who will lower their Rape Myth Acceptance (RMA) score between baseline and twelve months. We hypothesize that at the 12-month visit, 35-45% of those in the control arm will have a lower RMA score than baseline. We

expect this proportion in the intervention arm will be at least 15% higher and range from 60-70%. With these effect sizes, the study has a power of at least 0.98 to demonstrate the difference between intervention and control.

All sample size calculations were carried out using a power calculation for two proportions with the exact sample sizes in PASS 2021 (version v21.0.2), with a two-sided significance level of 0.05 and a conservative estimate of 10% loss-to-follow-up (given a 97% study retention rate in our pilot R34). Our power calculations assume that study subjects will be enrolled in four schools and randomized equally to two intervention groups within each school. The following table shows the powers for three intra-cluster/school correlations (ICC) of 0, 0.1, and 0.2. We expect the ICC to be around 0.1-0.2; a higher ICC would lead to a higher analysis power. All power calculations were carried out using the test statistics for the intervention effect regression coefficient from mixed-effect logistic regression models, with schools as random intercepts to account for the clustering effect from a social aspect of the intervention. Including data from all study visits and adjusting for baseline covariates will increase the study's power to detect the difference between the intervention and control.

Recruitment

Based on the estimated number of male students at each school, we have determined that we need to recruit at least 72% of the boys in 10th and 11th grades at each site to meet our target sample size. In previous studies, where we engaged with three of the five schools involved in this study, we successfully recruited 75-80% of eligible participants. Therefore, we plan to implement similar recruitment strategies for this project. These strategies include generating interest by providing a detailed study overview and explanation to both students and staff prior to recruitment, as well as ensuring that all eligible participants are reached using our structured data tracking systems.

Assignment of interventions: allocation

Sequence generation

In this randomized controlled trial, participants are prospectively assigned to intervention or control (standard usual care). We will randomize based on permuted block randomization in block sizes of 4 and 6. Randomization occurs after the baseline assessment is completed.

Concealment mechanism

The allocation is concealed from participants and researchers. A computer is pre-programmed with the allocation sequence, and participant assignment is determined by this pre-programmed sequence.

Implementation

The random allocation sequence for this trial will be generated using computer-based random number generation software to ensure objectivity and eliminate potential human bias. This pre-programmed by the study biostatistician and the data programming team. Then this pre-programmed sequence will be used by the trained team to allocate participants.

Assignment of interventions: Blinding

Who will be blinded

This will be a single-blind study. Intervention participants and facilitators will not be blinded to their condition. Study staff (e.g., the outcome assessment team) who assess outcomes after the experimental intervention has been delivered will be blinded to the condition participants have been assigned to.

Procedure for unblinding if needed

We do not allow for unblinding in this trial.

Data collection and management

Plans for assessment and collection of outcomes

Study outcomes are gathered using electronic survey issued on a tablet to capture the primary self-reported outcomes of the study (prevention of violence and HIV/STIs, behavioral and norms data related to these outcomes, along with demographics and other descriptive data relevant to interpreting outcomes) at baseline, 4 and 12 months. The survey options include audio-computer-assisted self-interviewing to address interviewer bias over sensitive questions. This audio-assisted self-interviewing involves a procedure where boys can hear question and answer options to sensitive questions via individual private headphones and reply without interacting with an interviewer face-to-face. Once the survey is complete, the data is synchronized via double encryption to our central database for data checking and processing by our team.

Biological samples for HIV and STI incidence for two curable STIs (gonorrhea and chlamydia) are gathered at baseline and twelve months. Biological samples are taken by trained staff on our team to meet the standards of South Africa's governmental body - the National Institute for Communicable Diseases Division of National Health Laboratory Services. These samples are labeled with research participant identifiers (randomly generated numerical sequences) and a corresponding barcode. Then, these samples are transported by a specialized carrier for laboratory tests. Laboratory tests will be conducted by the National Institute for Communicable Diseases in South Africa, which is responsible for microbiology, virology, epidemiology, surveillance, and public health research to support the government's response to communicable diseases. We have chosen dried blood spot HIV testing because this is minimally invasive (compared to venous blood samples using blood draw). Further, we only need dried blood spots for a five-spot dried blood spot card to test for HIV status, which is on the lower side of dried blood spot cards. We use a finger prick method that is less painful than venous blood samples and takes less blood than the dried blood spot cards in clinics, which might need more blood/dried blood spots to test for HIV status in addition to HIV treatment drug on board, etc. In this process, a sterile single-person pricking tool is used to create a blood spot (usually from the 3rd or 4th finger), and then the blood is collected on blotting paper. We use 4th generation assays (Biorad Genscreen ULTRA HIV Ag-Ab assay) from the National Institute for Communicable Diseases Division of National Health Laboratory Services. If the result between the Screen and confirmatory test is discrepant (i.e., Screen (+ve) and Confirm(–ve)), they will repeat the algorithm. If the results are still discrepant, they will be reported as Discrepant. Another specimen will be collected two weeks later (after a viral load has developed further) after the first specimen. For the urine sample for gonorrhea and chlamydia, if they find a positive result from the sample on the first sample assay using their in-house assay (Discharge Multiplex PCR with capabilities for testing our target STIs N.gonorrhoeae and C. trachomatis along with T. vaginalis M. genitalium which we do not

test for), they use a commercial assay with higher precision for confirmatory testing. If the results are still discrepant, they will be reported as Discrepant. Another specimen will be collected two weeks later (after a viral load has developed further) after the first specimen.

Results are communicated back to our study team via encrypted email, and our trained team members give boys results with experience in post-testing counseling for HIV and STIs. All participants, including those with positive HIV/STI cases will receive post-test counseling by our trained team members. Those who are positive for HIV and/or STIs will be referred for treatment in the free point-of-care public health clinic. We use trained research team members to gather HIV/STI biological data and to counsel and conduct referrals for confirmatory testing and treatment sensitively and privately. For participants with clinically significant biological test results (indicating they have HIV and/or an STI), we will refer the participant to a public health clinic and offer support to the participant to link him to treatment and care, including the offer from our research team members of accompanying him to the clinic. We will also support the participant if he wishes to help disclose his test result to parents or other significant people. Taking up those referrals to secure treatment for HIV and these curable STIs is their choice, as well as disclosure. Our information sharing with specific nurse liaisons at these clinics is guided by what boys want. If boys seek treatment, we offer to facilitate referrals by meeting them at clinics to take them through the linkage to care. There, again, with the boys' permission, we will communicate HIV and/or STI-positive status to nurses with boys present. Nurses will offer the next steps for South Africa's standard public health system protocols for initiating HIV and STI treatment. If boys decide to take up this treatment, we will document that decision. It is important to ensure we document a boy's decision to take treatment for STIs, in particular, to know whether the STIs appearing at the 12-month timepoint are interpretable as new infections (versus existing infections), which may necessitate new offers for referrals to treatment.

South Africa allows for independent consent of HIV testing to be done at age 12 (our eligibility age is 15-17 years, inclusive). South Africa also allows children to independently consent to medical treatment, including pregnancy, HIV testing, and the use of contraceptives. We follow these ethical and legal norms (which also apply to prevention trials), which require test counseling. This test counseling is critical to ensure that we address test anxiety, limit any false sense of protection from acquiring HIV and other STI infections that can lead to risk-behavior disinhibition, and limit distress upon HIV and/or other STI diagnoses. In addition, parent and adolescent consent and assent procedures outline who, how, and why confidentiality would be breached. We safeguard our participants’ confidentiality and privacy. During the consent and assent, we also

explain under what circumstances mandatory reporting is required. It is also made clear in the consent that health information is considered private information regarding the adolescent. We explain that adolescents have a right to keep their health information, including any HIV and/or STI diagnosis, confidential (including from parents). However, we will encourage them to disclose HIV and/or STI status and other serious health concerns to a trusted adult in a reasonable time frame (e.g., three months), as has been written about by South African researchers and ethicists. We make clear to parents that we will not disclose their adolescent's HIV and/or STI status or other health information under any circumstance to them or others (aside from the clinic for referral and treatment based on permission of adolescents).

Plans to promote participant retention and complete follow-up

We gather tracking data for all participants (multiple phone numbers and other contact details). We make attempts to track and retain participants with up to three attempts on different days and times for each timepoint. If participants decide to discontinue participation, they are still included in our intent-to-treat analysis.

Data management

The study uses secure tablet devices running the SurveyToGo app for data collection, ensuring data is automatically calculated and stored securely. Participant eligibility is screened via the app, which applies range checks and exclusion/inclusion criteria automatically to promote data accuracy. Participants' identities are verified through responses to security questions, picture verification, and participant or PID number which are all reused during subsequent study assessments to ensure consistency and identity verification. Additionally, registry tracking forms are used to document eligibility and cross-check data daily.

Data management procedures, including error checks (e.g., duplicate PIDs, incorrect school association) and cross-referencing paper forms with electronic entries, help maintain data quality. Information collected is uploaded to a secure cloud, with further details on data management available in the protocol or subsequent sections of the manual. Daily data checks ensure consistency between manual and digital records, supporting high data quality.

Confidentiality

SPIRIT guidance: How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial.

Personal information about participants is collected securely using the SurveyToGo app on password-protected tablet devices, ensuring confidentiality throughout the study. Participants answer security questions during eligibility screening, with responses used for identity verification at future time points, including the delivery of clinical results. Data is shared and stored only with authorized team members via secure, encrypted systems. Daily cross-checks ensure data accuracy, and personal details are maintained on secure tracking sheets. Participants are informed that their data is confidential and will not be shared outside the study team, ensuring privacy before, during, and after the trial.

We are very explicit on limits of confidentiality including when confidentiality must be broken by law, what information is reported, and who information is reported to. We also discuss the most likely scenarios of research in which these disclosures might occur; the likelihood of these scenarios of disclosure vary depending on what phase of research we are conducting with participants.

Statistical methods/Analytical Plan

Statistical methods for primary and secondary outcomes

We will compare primary outcomes between the two study arms at 4- and twelve months versus baseline to quantify the intervention's short- and long-term effects. We will compare continuous and count outcomes (e.g., frequency of sexual violence perpetration/attempts, IRMAS score) using student's t-test or Wilcoxon rank-sum test (if normality assumption not satisfied), and categorical outcomes (e.g., any STI/HIV infection, reduced IRMAS score at 12-month visit, ever

perpetrated sexual violence) using Chi-square test or Fisher's exact test (if frequencies are sparse). Changes in outcomes from baseline will be tested using a paired t-test, signed rank-rank test, or McNemar's test, which ppr. If multiple visits occur, we will use a unified longitudinal model estimate and draw inferences about the effects of the intervention on the primary outcome. Mod1) is h{E(Y_ij)}=α_i+〖β_1 R〗_i 〖〖+β〗_2 R〗_i×Time_j+〖β_3 X〗_i, where Y_ij is the individindividualdividit closClosesese h(.) is a link function, α_i is a random intercept capturing within-person effect, R_i represents the treatment group membership, Time_j codes the study visit, and X_i denotes baseline covariates. Hence, coefficients β_1 and β_2 represent the difference between the intervention and control and the effect interaction with time; estimation of the two parameters will be our primary interest. Depending on the distribution of primary outcomes, we will choose the appropriate link function for Model(1), e.g., an identity link for the RMA score and a logit link for any HIVSTI infection. As a result, the interpretation of βs will be mean difference or log(odds ratio). We will compare key baseline variables (e.g., age, gender, socio-economic status) between arms to ensure a balance of randomization and make adjustments in the model by adding the term subscript base, beta sub 3, cap X, end base, and treatment effects as needed. Model (1) will be fit using generalized estimating equations (GEE) to account for repeated measures.

For our secondary aim of extending our understanding of why Safe South Africa is efficacious (or not), we will examine mediators, moderators, and mechanisms of how behavior change occurs for primary outcomes. We will investigate mediators that may explain the efficacy of Safe South Africa on the incidence of HIV/STI acquisition, reduction in IPV frequency, and reduction in endorsement of IPV-supportive attitudes. Specifically, based on the theory-driven model of the intervention, we examine whether the extent of impact of Safe South Africa on outcomes is mediated by: 1. Changes in the misperception of social norms relating to sex, condom use, sexual and intimate partner violence, and gender equity; 2. changes in knowledge of protective HIV and IPV behaviors and their effects, knowledge of conditions of sexual consent; 3. motivation for HIV and IPV preventive behaviors including attitudes towards HIV risk, IPV and traditional male gender role script, self-efficacy for HIV and IPV preventive behaviors (e.g., condom use, sexual consent, sexual refusal), and self-efficacy for assertive bystander communication to confront and halt peer IPV behavior among peers. We denote these potential mediators as intermediate factors (IF). We hypothesize that besides a direct effect on the primary outcome, the intervention can cause changes in these IFs at four months, ultimately leading to primary outcomes at twelve months. The entire mediation model fully decomposes the effect of the intervention but contains

multiple pathways whose effects are not simultaneously estimable from a single regression model. We will fit the following submodels, which we expect will indicate the role of mediators in explaining the effect of our intervention. The time ordering of data collection in this longitudinal study is an excellent opportunity to untangle relationships using causal mediation analysis.79-83 Submodel (a) describes the causal effects of intervention on the IF and primary outcomes. Given that the study intervention is randomized, this submodel is identified by data. Submodel (b) focuses on the causal effects on

The primary outcomes. The effect of IF in Submodel (b) is subject to confounding, and hence, its estimation will be based on specific model assumptions (e.g., sequential ignorability). Estimates of submodels (a) and (b) will illustrate the relative degree to which each IF mediates intervention effect. If the two models suggest a causal relationship between intervention and an IF and between IF and primary outcomes, its mediation effect will be considered in the full model (c) that describes the entire process. Thus, from submodels (a) and (b) analyses, we will select the best candidate variables with the most substantial mediation effects from intervention to IF and from IF to the outcome. Statistical modeling will utilize causal mediation models,79 Fit using a wtwelveed two-stage regression approach implemented with SAS macros to estimate the full model (c).84 Our mediation analysis will focus on direct and indirect natural effects.85

We investigate theoretically derived moderators that may explain responsiveness to Safe South Africa on primary outcomes. We examine whether the extent of the impact of the intervention on outcomes is moderated by the effect of sociodemographic (e.g., gender, sexual orientation), structural disparities (e.g., orphanhood, food insecurity), other risks (substance use), and social protections (e.g., government grants). We will build our moderation analysis around Model (1) to quantify the moderation effect of these potential factors on the intervention. We will add the following two terms in Model (1): their main effects sub 3, cap M sub i., as well as their interactions with the stu interveneveβ_4 M_i R_i, where M_idenotes the above potential effect moderators at baseline. Our interest is the interaction coefficientsBetaBeta. β_4, This captures the differential effect of our intervention on the outcome across levels of each potential moderator. We recognize possible limitations. For mediation analysis, we use a causal inference method based on a potential outcomes framework that assumes there is no existing unmeasured confounding. Sensitivity analyses will examine whether assumptions are valid.86-88 Our causal pathway includes multiple mediators, for which statistical methods are limited but are being developed.84 We may need more power for moderation analysis to detect all (three ways or higher) interactions

between intervention and moderators. However, our approach will provide a foundation for future confirmatory analyses.

Interim analyses

SPIRIT guidance: Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial.

We have no interim analyses planned and no pre-specified stopping rules.

Oversight and monitoring

A Data and Safety Monitoring Board (DSMB) has been created with three members has been created and vetted by the funder. Specifically, the DSMB shall be responsible for the following:

1. Reviewing the research protocols and planning for data and safety monitoring.

2. Evaluating the progress of the trial during each phase during active enrollment and treatment. The DSMB will conduct assessments of participant recruitment, accrual and retention, data quality and intervention fidelity, and other factors that may affect study outcomes. They will also review all study adverse events (AEs) and serious adverse events (SAEs). Monitoring may also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or ethical issues related to the study.

3. Maintaining confidentiality during all phases of the trials.

4. Generating a report that will be provided to the investigators, IRBs (as needed), and NIH.

The DSMB will consist of three members including an expert in behavioral interventions, an expert in content (e.g., HIV and/or violence, adolescents, etc.), and a statistician or expert in analysis for these topics. None of the DSMB members will be on the study team. No member of the DSMB will have direct involvement in the conduct of the study. Furthermore, no member will have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. All DSMB members will sign a Conflict of Interest certification to that effect at the time they are asked to participate. At the beginning of every DSMB meeting, the

investigative team will confirm that no conflict of interest exists for DSMB members and will again ask them to sign a Conflict of Interest certification. Meetings will be held by conference calls twice a year (every 6 months). The study team will help to develop the agenda in consultation with the DSMB. Procedures and protocols for notifying the IRBs and NIH Program Official concerning serious adverse events will be discussed at the first meeting.

The first meeting will involve a discussion of the project, any modifications, and to establish guidelines to monitor the project. The DSMB members and the PIs will prepare the agenda to address reviews of the study, modification of the study design, initiation of the project, reporting of accrual, reporting of adverse events, stopping rules, preliminary analysis plan, etc. Meetings will be held twice a year.

The format for DSMB meetings will be an open session (with PIs), followed by a closed session (if needed) where the PIs will be informed of recommendations made by the DSMB. The open sessions will include the PIs and study staff. Issues discussed at open sessions will include conduct and progress of the study, including accrual, compliance with study design, and problems encountered. Only aggregate data, without any treatment arm comparisons, will be presented in the open session. The closed session will include only DSMB members. The DSMB may request others to attend part or all of the closed session, if needed. The discussion at the closed session is completely confidential. If there are differences among DSMB members regarding major study recommendations such as early termination, a vote of the DSMB will be required.

The meeting minutes containing the DSMB meeting summary and recommendations for continuation, modifications, or termination of the study is used as the meeting report. The draft meeting report will be reviewed and approved by the DSMB Chairperson. The final meeting report will be forwarded to DSMB members and the PIs. It will be the responsibility of the investigators to distribute the meeting report to all clinical sites, and to assure that copies are submitted to all the IRBs associated with the study (if needed). All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

Adverse event reporting and harms

SPIRIT guidance: Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.

We have developed a Data and Safety Monitoring Plan focuses on protecting participants in the involvement in all three aims with primary data collection activities which occur in South Africa. Potential risks to subjects are as follows. This research includes a number of sensitive topics. Thus there are some risks due to participation in our study. Concerns include biological testing for HIV and STIs including procedures, anxiety, and distress. Concerns also include risk of retribution against perpetrators disclosing in these studies. The risk of retribution against boys disclosing perpetration is guarded against by using self-completion for disclosure of acts that are socially stigmatizing or involve violence. The other concern is psychological distress; those who have raped or perpetration sexual assault can find discussing it makes them realise that it was wrong. For consent and assent procedures, we will spend significant time discussing what topics will be covered, particularly highlighting what questions will be explored, including HIV status, STI status, and perpetration behaviors. We will emphasize that all participants can halt participation at any time without consequence. We also highlight the legal norms that would require break in confidentiality, and who information would be reported to as laid out by South African law (abuse, neglect, victim of assault or rape, specific cases of sex in within certain age ranges). For some data, we collect it anonymously (as in the school survey in Aim 1), participants will be guaranteed that the information will be kept confidential with no reporting given the anonymized data. In other cases of data for our other Aims, we follow the limits to confidentiality, detailing limits to confidentiality in detail. Although our study protocol does not specifically probe for identifiable victims of perpetration, we recognize that there is the small chance adolescents will disclose this, unprompted by our team and requiring reporting. In anticipation of any possibility of serious adverse events. We have developed a list of vetted referrals to address HIV, mental health, and social support services within South Africa's free public health service system. Furthermore, all adolescents (regardless of eligibility) will receive a list of resources of HIV, IPV, general health, and social services.

We have several procedures in place to protect and minimize risks. For adolescents, during assent procedures, we highlight the legal norms that would require break in confidentiality, and

who information would be reported to. Electronic data, including digital voice recordings and data collected via paper and then scanned digitally, will have several protections. First, all data will be stored on password-protected computers. Second, all files on project computers will be further protected by nCrypted Cloud software which offers two-way encryption with secure access controlled by PIs (who can turn on and off access to password protected files from a central location) and wipe all data from devices remotely in the case of theft. NCrypted Cloud also enables the PIs to control who has access, who can move files from the secured and encrypted cloud serve onto local hard drives (including computers, and external hard drives), and whether and how files can be moved between, providing absolute control over data management and monitoring. Third, all staff will be trained in procedures for maintaining confidentiality of participant information. We are also prepared to address any distress that may arise by referring to South Africa's mental health care within their free public health systems. All serious adverse events will be reported to IRB and NIH. Overall internal monitoring of the safety of human subjects will be conducted by the M-PIs. For non-emergency issues, regular meetings will be held to address study progress, recruitment and retention, data collection, and other factors related to human subjects, and meetings will be held more often if necessary. We put into place additional protections for children. We recognize that children may be a vulnerable group, and extreme care is required to ensure protection and empowerment amongst participants but that exclusion of this group would significantly prohibit scientific development in topic areas of great importance to the health and wellbeing of this group. To ensure informed consent and assent, we will clarify what information will be kept confidential and what will be disclosed to another party. We also build upon our team's extensive research and clinical experience working with adolescents living with HIV in South Africa as well as our team's experience conducting HIV behavioral research with vulnerable populations affected by HIV in South Africa and other international settings. We provide additional protections in consent and assent procedures. All informed assent forms will be read aloud in participants' chosen language, and participants will also be provided copies. To ensure that children do not feel obliged to participate in the research, emphasis will be placed on their ability to refuse to participate, or to cease participation at any point during the research. As has been the practice in our previous studies with this vulnerable population, our research team is trained to recognize that any avoidance by children of the research will be taken as evidence of failure to assent. For adolescents, during the parental passive consent procedures and during the adolescent informed assent procedures, we emphasize that all information shared with us will remain confidential except for life-threatening disclosures or disclosures regarding age-differential partners, exploitative sex, perpetration with identifiable rape victims, being a victim of rape, sexual

abuse or physical abuse which falls under legally mandated reporting to police, social services, and IRB.

The Data and Safety Monitoring Plan for this application will begin by implementing standard procedures for day-to-day monitoring of the study. Also, weekly meetings with the research team will be conducted to evaluate the progress of the trial and to review data quality, recruitment, and study retention and to examine other factors that may affect safety. Participant experiences with the study procedures and the rates of adverse events will also be reviewed to determine any changes in participant risk. The PI will report any adverse events (AEs) that are observed to the local site's IRB (South African Medical Research Council), American University, and to NIH. Serious adverse events (SAEs) will be reported to the local site's IRB by written report within 48 hours of our receipt of information regarding the event; SAEs will also be reported in writing to NIH. Actions taken by the IRB in response to SAEs will also be reported to NIH, as will reports of changes or amendments to the protocol as a result of an SAE. Reports of changes or amendments to the protocol in general must be requested first in writing to the IRB, which then will grant or deny permission to make the requested change or amendment in protocol. Modifications to study aims or design, if applicable as a response to SAEs, will also be submitted to NIH. Finally, significant medical or mental health risks that occur during the study period and are brought to the attention of the study team will be tracked as AEs; significant medical or mental health risks that occur during the study period that have a reasonable possibility of being related to the study will be referred for evaluation by the emergency department to determine whether hospitalization or urgent care is needed. In the event that a research participant either withdraws from the study or the investigator decides to discontinue a research participant due to SAE, the research participant will be monitored by the investigator via ongoing status assessment until either a resolution is reached (i.e. the problem requiring hospitalization has resolved or stabilized with no further changes expected or the SAE is determined to be clearly unrelated to the study intervention). Outcome of all SAEs will be periodically reported to NIH. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIH.

Dissemination plans

SPIRIT guidance: Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions.

Participants and stakeholders at schools will be provided with dissemination of trial results in a format at they prefer. Based on prior engagements with similar participants in these settings, dissemination has taken the forms of school-based meetings, community meetings, oral presentations, and summary written results. Results will be also be dissemination via summary reports to the Department of Education, as well as via conferences and publications.