COVER PAGE PROTOCOL DETAILS

Protocol Title: Integrated Prevention of HIV Risk and Intimate Partner Violence among Adolescents in South Africa
NCT03179982

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This study has been reviewed by the U.S. National Institute of Mental Health (NIMH) under a R34 mechanism (Grant #R34 MH 113484) from 2017-2020. The protocol was approved on April 25, 2017

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Scientific Key words: human immunodeficiency virus (HIV); intimate partner violence (IPV); prevention; perpetration; adolescents; gender

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RESEARCH PROPOSAL EXECUTIVE SUMMARY

Aims

This study will investigate the acceptability and feasibility of Safe South Africa, an integrated intervention to prevent adolescent behavioral risk for human immunodeficiency virus (HIV) and perpetration of intimate partner violence (IPV). *Safe South Africa* is a theory-driven, developmentally-tailored and gender-specific intervention designed for male adolescents 15-17 years of age. The research will be conducted in South Africa, a country with the largest HIV epidemic and some of the highest rates of IPV perpetration in the world. Preventive interventions are urgently needed during adolescence when risk for human immunodeficiency virus (HIV) and intimate partner violence (IPV) increases exponentially. Yet, few behavioral interventions integrate HIV-IPV prevention and are tailored for the unique age and developmental needs of adolescents. We utilize the insights of adolescent development theory in our preventive intervention strategy by capitalizing on adolescents' developmental propensities for maximum prevention gains. Adolescence presents an ideal age and developmental transition period for an integrated intervention targeting prevention of HIV behavioral risk reduction and perpetration of IPV including sexual violence. Developmental hallmarks of adolescence – including for example, the role of social norms in motivating behaviors, the importance of peers in shaping behavioral choices, and the desire for increased responsibility – can all be leveraged for prevention of sexual risk behavior driving acquisition of HIV infection and engagement in IPV. For example, we use social norms marketing insights to shift attitudes and motivations to engage in protective HIV behaviors and prevent IPV. We use positive peer pressure and tap into adolescents' desire to be responsible future leaders to motivate adolescents to intervene as bystanders when their peers are involved in HIV risk behaviors or sexual assault and aggression. The motivation and implementation of these positive behaviors relating to prevention of HIV and IPV perpetration are occurring in a period when identity formation and life-long health patterns are being habituated; our intervention approach leverages the formation of identity and habits during adolescence to support long term prevention behaviors. An integrated approach for prevention of adolescent HIV and IPV perpetration has not yet been tested. We will investigate the acceptability and feasibility of *Safe South Africa*, an integrated HIV-IPV intervention to prevent adolescent HIV behavioral risk and perpetration of IPV among male adolescents 15-17 years of age through three study aims: (1) development aim – create *Safe South Africa*, an integrated male adolescent preventive intervention for HIV risk behavior and IPV perpetration; (2) acceptability aim – evaluate social ecology of HIV and IPV risk with a survey of N=100 of adolescents, and test the acceptability of *Safe South Africa* through an open pilot trial with N=20 male adolescents; and (3) feasibility aim – conduct a randomized controlled pilot trial with 1- and 6-month follow-up in a sample of N=60 male adolescents to assess the feasibility and acceptability for a future fully powered randomized controlled trial to evaluate efficacy of the intervention.

Expected Outcomes

Findings will advance preventive intervention science for young people at elevated risk for HIV and IPV in a high impact setting. The expected outcomes of this study include findings on the acceptability and feasibility data that will inform a future fully-powered RCT to test efficacy of *Safe South Africa* for preventing acquisition of HIV and IPV perpetration. In Year 3, we will submit an R01 application for a fully powered clinical trial to test the efficacy of *Safe South Africa*.

Intended Feedback

Intended feedback and dissemination include peer review papers and conference presentations. In addition, we will develop research briefs for adolescents, school stakeholders, and policy makers.

PROTOCOL NARRATIVE

A. STUDY OBJECTIVE

The purpose of this study is to investigate the feasibility and acceptability of an integrated approach for preventing or reducing risk behavior related to acquisition of human immunodeficiency virus (HIV) and perpetration of intimate partner violence (IPV) among adolescents in South Africa. South Africa faces some of the highest global rates of HIV and IPV with sustained high incidence of HIV and alarming rates of IPV among adolescents. Developing preventive intervention science in this setting and population can advance our scientific understanding of how to intervene early in the life course, and to promote healthy long-term sexual and reproductive lives for adolescents, their future partners, and society.

B. STUDY AIMS, SIGNIFICANCE, INNOVATION

STUDY AIMS

South African adolescents face exponentially greater risk for human immunodeficiency virus (HIV) and intimate partner violence (IPV), with sustained high HIV incidence and unacceptably high rates of IPV. South African adolescents are being infected at a rate of 1.5%,[1] equivalent to 139,000 new infections each year or the largest share of new infections of any age group in the country.[2] South Africa has the largest country population of individuals living with HIV[3] and Southern African adolescents engage in high rates of sexual activity,[4-7] early sexual debut,[4,6] and multiple partners.[6,8] Similar to HIV, prevalence of IPV – defined as sexual, physical, and emotional violence– is also among the highest in the world. Half of African children experienced sexual, physical, emotional violence, bullying, or witnessed violence in the past year.[9] In South Africa, IPV and non-intimate sexual violence is alarmingly high; for example 1 in 3 men (31.9%) perpetrated rape in a population-based survey of N=1,737 South African men 18-49 years.[10] The majority (75%) perpetrated their first rape before age 20, with the average age of first rape at 17.[11,12] This young age of sexual perpetration underscores the need for preventive interventions during adolescence. Preliminary data from our HIV prevention study with South African adolescents 13-15 years (in a community with 33.1% HIV prevalence[13]) indicated high rates of perpetration of unwanted oral sex (15%), sexual touching (14%), anal sex (8%), and vaginal sex (6%) via force or coercion.[14] The synergistic relationship between HIV risk and IPV requires an integrated preventive intervention approach. Yet, no interventions we identified concomitantly target prevention of HIV risk and IPV perpetration among South African adolescents. Gender-tailoring to males is needed because of the majority of IPV is perpetrated by boys and men.[15] Gender-tailoring facilitates males openly discussing attitudes, which may be more difficult when females are present.[16] Developmental-tailoring is also needed because perpetration of violence most often begins during adolescence, and continues within multiple relationships across the lifespan.[17-19] There are unique opportunities to capitalize on developmental aspects of adolescence for larger prevention gains including natural propensities such as forming and retaining preventive health behaviors; the power of positive peer influence to reinforce prevention; and building healthy male identity and gender norms critical to prevention.

Our *long-term goal* is to prevent HIV and IPV perpetration using developmentally- and gender-tailored interventions for male adolescents. In this grant, *our overall objective* is to test the acceptability and feasibility ***Safe South Africa***, an integrated intervention for preventing HIV-IPV perpetration for male adolescents 15-17 years. We will create *Safe South Africa* by integrating best-evidence on adolescent HIV prevention[20,21] into our existing *Safe* intervention,[22-29] a developmentally tailored skills-based IPV prevention program with demonstrated promise among male adolescents. Our existing *Safe* intervention targets attitudes and behaviors that increase proclivity to IPV through evidence-driven social norms messaging combined with proactive bystander behavior training when witnessing inappropriate sexual aggression, IPV, or interpersonal violence among peers.[23] Our *rationale for this study* is that the majority of existing interventions to address HIV-IPV synergies reduce risk for IPV victimization. An explicit focus on preventing IPV perpetration would tackle the root cause of violence related to HIV risk and complement existing risk reduction approaches. We propose 3 aims:

1. **Development Aim: Create *Safe South Africa,* an integrated intervention for prevention of HIV and IPV perpetration.** We begin by reviewing our existing empirically supported *Safe* intervention to identify content, structure, and delivery modalities needing refinement to ensure responsiveness in South Africa.

Then we integrate into *Safe*, best evidence on theoretical and behavioral adolescent HIV prevention to create *Safe South Africa*. We elicit feedback from k=3-5 focus groups with adolescent males on salience of adaptations.

2. **Acceptability Aim: Evaluate adolescent social norms relating to HIV and IPV risk within the school social ecology with N=100 adolescents to inform evidence-based messaging to be used within *Safe South Africa*, then test acceptability of *Safe South Africa* in an open pilot with N=20 male adolescents.** We evaluate social norms relating to HIV and IPV risk to inform evidence-based social messaging tailored to adolescent intervention participants' specific social ecology. Then we test acceptability including participant satisfaction with content, materials, and delivery for make final refinements to *Safe South Africa.*
3. **Feasibility Aim: Assess feasibility of *Safe South Africa* through a randomized controlled pilot trial with 1- and 6-month follow-up with N=60 male adolescents.** We assess feasibility for a future R01 trial including rigor of facilitator implementation by evaluating fidelity and competence, recruitment strategies, and tracking and tracing success. As an exploratory secondary aim, we examine preliminary evidence for hypotheses that the intervention, relative to the control, will produce: (1) reductions in actual or intended HIV risk behaviors; (2) reductions in IPV frequency and decreased endorsement of IPV supportive attitudes; and (3) increased proactive bystander behavior for prevention of IPV perpetration.

The *expected outcomes* of this study include acceptability and feasibility data that will inform a future fully-powered RCT to test efficacy of *Safe South Africa* for preventing acquisition of HIV and IPV perpetration.

STUDY SIGNIFICANCE

The bi-directional relationship between HIV and IPV indicates the need for an integrated intervention. Several systematic reviews and meta-analyses identify causal and non-causal mechanisms linking HIV and IPV. Causal mechanisms linking increased HIV risk with sexual violence – one form of IPV – include increased vaginal or anal tissue trauma associated with increased infection risk. Non-causal mechanisms include positive correlation between HIV infection and those who perpetrate IPV[30] and higher rates of HIV risk behaviors among IPV perpetrators including decreased condom use,[31,32] concurrent and/or multiple sexual partners,[31,33] alcohol and substance use, and higher rates of sexually transmitted infections (STI) co-infection.[34,35] HIV acquisition risk is significantly higher among individuals who have experienced IPV victimization. For example, a global systematic review and meta-analysis of 28 studies with N=331,468 women (including 4 South African studies), indicated that any type of IPV [pooled RR (95% CI): 1.28 (1.00, 1.64)] was significantly associated with HIV infection in cohort studies, and that combination of physical and sexual IPV [pooled OR (95% CI): 2.00 (1.24, 3.22) and any type of IPV [pooled OR (95% CI): 1.41 (1.16, 1.73)] were significantly associated with HIV infection in cross-sectional data.[36] A preventive intervention to address IPV perpetration naturally addresses sexual risk reduction and can yield HIV prevention benefits for potential perpetrators, and current or future partners. Adolescence offers an ideal life-course transition point for integrated HIV-IPV prevention interventions. South Africa provides an appropriate setting to advance the science of concurrent prevention of HIV risk and IPV given high global burdens of HIV and IPV.

South Africa has the largest HIV epidemic of any country in the world,[3] with adolescents accounting for the majority of new HIV infections.[2] Among South African adolescents, HIV incidence increases rapidly during middle adolescence, from 0.25% in the 2-14 year age group to 1.49% in the 15-24 year age group.[1] Adolescents, especially middle adolescents aged 15-17 years, are naturally at increased risk due to normal developmental milestones.[37] Initial sexual experiences frequently occur at this age, corresponding to increased risk for acquisition of HIV, other STIs, and IPV. Behavioral HIV prevention efforts are needed to complement emerging biomedical strategies because 40% of 15-24 year old South Africans did not think they are at risk for HIV, and only 26% correctly identified common modalities of HIV transmission and prevention.[1] Given the gender-specific focus of our proposal (on male adolescents), we highlight data relevant to 15-17 year old males: data from a large South African birth cohort indicated by age 13, 74% of boys reported sexual foreplay or oral sex, and by age 15, approximately half engaged in penetrative sexual debut.[38] We focus on adolescent males starting at age 15 because of the larger proportion of adolescents engaged in penetrative sexual debut by this age. South Africa also has a high global burden of IPV. The majority of IPV perpetrators are male, with over 1 in 3 women (35.6%) experiencing intimate partner or non-partner sexual and/or physical violence in their

lifetime.[39] Globally, the sub-Saharan African region, including South Africa, has the highest prevalence for both intimate partner and non-partner sexual and/or physical violence at 65.6% (95% CI: 53.6-77.7%)[40] and 21% (95% CI: 4.5-37.5%) respectively.[41] We recognize that violence occurs across the lifespan. However, preventive interventions are urgently needed during adolescence, especially in South Africa because 75% of adult perpetrators commit their first rape before the age of 20[11,12] and 31.9% men report rape perpetration.[10] We focus on prevention among adolescent males up to 17 years given this is the average age for first rape perpetration in South Africa.[11,12] Alignment of age of sexual debut with age of perpetration underscores the need for preventive HIV-IPV interventions during adolescence. Given this young age, addressing interpersonal violence and sexual aggression is part of our comprehensive prevention because those who engage in these acts are more likely to engage in IPV.[42]

Empirical data on IPV, especially adolescent sexual violence is rare; South Africa has one of few existing epidemiological surveys of adolescent sexual perpetration which identified a prevalence of 10%.[43] Our own **preliminary data** indicates IPV perpetration is even higher among adolescents at risk for HIV based on results from an adolescent HIV prevention study (PI: Kuo) with N=200 adolescents 13-15 years of age recruited door-to-door from a South African community with 33.1% HIV prevalence.[13,14,44-46] Self-reported perpetration was assessed using the Sexual Experiences Survey - Short Form Perpetration (SES-SFP) using audio computer-assisted self-interviewing (A-CASI).[47] Adolescents reported using coercion, incapacitation, force or threats of force to perpetrate unwanted oral sex at 15%, sexual touching at 14%, anal sex at 8%, and vaginal sex at 6%. Perpetration was more common among males, reinforcing the need for gender-tailored preventive intervention. Development of additional IPV perpetration prevention efforts are needed.[15,48] When we disaggregated preliminary data by gender, males reported perpetrating at much higher rates than females including: oral sex (23%), sexual touching (18.4%), anal sex (11.6%), and vaginal sex (7%). Alarmingly, 14% of boys from our preliminary study engaged in repeat perpetration.[14] Most common perpetration tactics included verbal coercion, followed by incapacitation, threats of violence, and physical assault. Attempted perpetration was also reported at alarming rates for this young age group including: vaginal (8%), oral (8%), and anal sex perpetration (5%).[14]

Our intervention approach integrates prevention of both HIV risk and IPV perpetration, with a purposive focus on male adolescents as potential perpetrators. A focus on preventing IPV perpetration (focused on males) in relation to HIV, as opposed to reducing risk for IPV victimization (most often focused on females), is central to our effort to expand intervention approaches for HIV-IPV. Focusing on perpetration prevention rather than risk reduction permits us to tackle the root cause of violence early in adolescence. There were few randomized controlled trials (RCTs) for prevention of HIV and IPV perpetration in South Africa or other generalized HIV epidemic countries. This included the *Stepping Stones* intervention, a participatory learning intervention tested in a randomized controlled trial; the intervention demonstrated efficacy in reduction of HIV risk factors and reductions of male self-reported perpetration of violence.[49,50] We were only able to find a handful of interventions that combined HIV-IPV in Southern Africa. All focused on risk reduction (rather than IPV perpetration prevention). In South Africa, *PREPARE* led by Dr. Mathews (M-PI of this study) was a multi-component school-based intervention designed to decrease IPV and HIV risk behavior among adolescents. *PREPARE* was tested in a cluster RCT in 42 schools. The 21-session group-based intervention was accompanied by school health and school safety components. At the 12 month follow-up, intervention participants were less likely to report IPV victimization (35.1 vs. 40.9 %; OR: 0.77; 95 % CI 0.61–0.99) but had no changes in HIV risk.[51] Also in South Africa, the *IMAGE* RCT investigated whether a microfinance intervention providing economic stability and complemented with education on male gender norms, domestic violence, sexuality and HIV could reduce IPV among adults. After two years, intervention participants reported lower risk of past-year physical or sexual violence by an intimate partner (adjusted risk ratio=0.45; 95% CI: 0.23-0.91) but no changes in HIV incidence.[52] In Uganda, the *SASA!* intervention tested in a cluster RCT in eight communities, targeted prevention of violence against women and HIV risk reduction by engaging communities in changing attitudes, norms and behaviors related to gender inequality, violence, and women's increased HIV vulnerability. At the four year follow-up, intervention group participants reported fewer events of sexual intimate partner violence (OR: 0.76, 95% CI: 0.33-1.72), and for HIV risk, fewer concurrent partners among men (OR: 0.57, 95% CI: 0.36 to 0.91).[53] There was a fourth trial in Uganda that demonstrated efficacy of *SHARE*, an intervention to reduce IPV towards women and overall HIV incidence.[54] However, *PREPARE,*

IMAGE, SASA!, and SHARE are risk reduction approaches focused on decreasing risk for victimization (as opposed to preventing perpetration which is our approach). The need to integrate best evidence on HIV prevention is indicated by the finding that no HIV and only limited HIV risk behavior change occurred in the trials. We detail how we will integrate the latest evidence on HIV prevention in our intervention under Methods, Aim 1.

We also reviewed the literature to identify RCTs on prevention of IPV, especially sexual perpetration, in South Africa or other settings facing high HIV prevalence. In DeGue et al.'s 2014 systematic review of sexual violence prevention interventions, none integrated prevention of HIV, and no RCTs occurred in South Africa. DeGue's review identified 140 outcome evaluations but only three RCTs[55] All three RCTs were designed and tested in the USA where HIV prevalence is low.[56-58] The study by Boba et al. 2009, took a structural intervention approach focusing on changing legislation and funding for law enforcement, prosecution, arrest policies, and programs to combat domestic violence and child abuse as well as social service support programs. The two other US interventions focused on adolescents; both Foshee et al.'s 2005 intervention, *SAFE Dates*, and Taylor et al.'s 2013 *Shifting Boundaries* intervention used combination intervention approaches of behavioral intervention with adolescents, with changes to school and community environments. Ellsberg et al.'s 2015 review of evidence on prevention of violence against women and girls noted that group-based interventions in school settings have limited success the majority of evidence was generated in high income country settings. Our proposed study contributes to the evidence by examining a group-based approach in a school setting in South Africa (to contribute to the current geographic inequity in studies) and takes a male-tailored approach and integrates bystander intervention elements (neither which were tried in *SAFE Dates* and *Shifting Boundaries*).[48] Since DeGue et al.'s 2014 review, five additional RCTs have been identified. An adolescent dating violence intervention, *Coaching Boys to Men,* used bystander intervention among high school athletes in the USA and showed more likelihood to engage in bystander intervention but no changes in sexual, physical, or psychological perpetration behaviors. A study in India utilized an individual cognitive behavioral intervention approach and showed small but significant reductions in intimate partner perpetration.[59] Another study in the Netherlands showed effective reductions in perpetration behavior using a cognitive behavioral therapy approach and a combined substance use and perpetration prevention approach.[60] We decided not to adapt these US adolescent programs to South Africa given foci on changing school and community environments rather than peers, and because of no perpetration behavior change despite use of a bystander approach. A RCT in Kenya tested *Your Moment of Truth,* a bystander focused intervention for adolescent boys that showed efficacy in increasing intervention when witnessing violence.[61] Finally, we identified one ongoing RCT for perpetration prevention in South Africa; *Skhokho* (Dr. Abrahams, expert consultant on our study was investigator on *Skhokho*) compares a school and family intervention versus a school intervention versus a control. We feel our proposal is distinct from *Skhokho* which does not integrate HIV prevention, and focuses on the family environment (rather than peers, as in our intervention).[62]

INNOVATION

Our study offers several innovations. First, we develop our scientific understanding of developmentally appropriate preventive interventions to address the adolescent intersection of HIV behavioral and IPV perpetration risk. To our knowledge, this will be the first intervention to prevent adolescent HIV risk and IPV perpetration in an integrated manner and in a high priority global setting where prevalence of HIV and IPV is high. DeGue et al.'s 2014 systematic review of interventions to prevent perpetration detailed above failed to identify any RCTs showing efficacy in violence preventive interventions that were integrated with HIV. We were only able to find interventions that combined IPV risk reduction with HIV prevention in southern Africa. All three of these interventions – *PREPARE (led by our M-PI Cathy Mathews), IMAGE, and SASA!* – are IPV risk reduction approaches whereas our intervention specifically focuses on prevention, offering a complement to the existing intervention evidence base. We now integrate the most current global evidence on efficacious HIV preventive approaches for adolescents into a promising existing intervention for IPV. Second, the *Safe* intervention has shown promise in increasing bystander behavior, promoting change in attitudes and behaviors associated with IPV, interpersonal violence, and aggression. Such data indicate the promise of adapting to South Africa. Third, the proposed primary prevention program for IPV is highly innovative in that it targets the

specific risk and protective factors in the social ecology of IPV perpetration; a number of these risk and protective factors are aligned with our HIV prevention goals. Our previous work on *Safe* included the developmental tailoring of the intervention for adolescents, so now we can focus upon HIV and South African adaptations. Fourth, if found to be efficacious, *Safe South Africa* offers not only immediate prevention promise for adolescent males, but also offers long term promise by preventing negative consequences of HIV and IPV on current and future partners as these male adolescents proceed in their life-course. We purposively choose to test acceptability and effectiveness of this HIV-IPV preventive intervention in school settings because a systematic review has shown numerous challenges to reaching youth for sexual health services within health facility settings.[63] Our approach may be congruent with policy changes including South Africa's recent commitment to integrating health services into school settings and outlined in their national Integrated School Health Policy.[64] The leads to our fourth innovation, that our intervention is directly policy relevant, consistent with the government policy encouraging structured after-school health-related activities as part of Integrated School Health Policy.

C. PROPOSED INTERVENTION OVERVIEW

***Safe South Africa*: Integrated adolescent intervention to prevent HIV risk and IPV perpetration**

This Clinical Trial Planning Grant tests the acceptability and feasibility of *Safe South Africa* with an approach that builds on adolescents' natural desire for independence and responsibility as they transition to adulthood. Given the lack of integrated interventions for preventing adolescent HIV and IPV perpetration globally and in South Africa, we utilize a theoretically and empirically supported prevention strategy.

Overview of proposed *Safe South Africa* intervention: The existing *Safe* intervention (tested previously in the USA by co-I Orchowski and consultant Berkowitz)[22-29] will be adapted in this study to create the new *Safe South Africa* intervention. During Development Aim 1, we will integrate best-evidence HIV prevention strategies (HIV intervention elements described below). We retain two components of the existing *Safe* program in our new *Safe South Africa* intervention: (1) Part 1 is a survey with both male and female adolescents to evaluate IPV prevention needs within a specific social ecology (in this case peers within a school) and application of survey data into evidence-driven social norms messaging within the behavioral intervention that occurs as Part 2; and (2) Part 2, a group-based, facilitated behavioral intervention for prevention of HIV risk and IPV perpetration specifically tailored for male adolescents. The behavioral intervention is comprised of 2-hour sessions, held once a week for a total of two weeks. These 2-hour sessions comprise a behavioral intervention that includes the following core components (described in detail under the section titled "Core Components of the *Safe South Africa* intervention"): information and behavioral skills practice to address HIV and STI prevention including HIV and STI content relating to prevention knowledge, attitudes and behaviors; information relating to linkages between HIV and IPV; formation and behavioral skills practice to address IPV prevention including debate, discussion, and information designed to improve victim empathy; debate, discussion, and information designed to support healthy norms regarding masculinity and deep understanding of consent; and development of bystander intervention skills with practice to boost self-efficacy in future implementation of these skills.. The intervention also includes take-home activities to deepen behavioral engagement with week's received session and to "prime the pump" for the upcoming week's session.

Theory driven and conceptual model of *Safe South Africa*: *SAFE South Africa's* HIV risk prevention components will be based on Information-Motivation-Behavioral (IMB) theory. The change strategy of the HIV components of the intervention include: (1) increasing HIV knowledge around protective behaviors (*i.e.,* information), (2) encouraging adolescents to implement protective behaviors through for example, formation of positive peer relationships that impact attitudes towards HIV risk, tying protective HIV behaviors to future goals (*i.e.,* motivation), and (3) building self-efficacy for prevention behaviors including condom use, condom negotiation, and healthy sexual relationships (*i.e.,* behavior).[65-67] See below under Methods, Aim 1 for our proposed integration of best evidence HIV into the existing *Safe* Intervention. ***Safe South Africa's* prevention of IPV components** will be based off a conceptual model called the Integrated Model of Sexual Assault and Acquaintance Rape. This conceptual model was originally proposed by Berkowitz (expert consultant).[68,69] This conceptual model proposes interventions to prevent IPV, interpersonal violence, and sexual aggression are most salient when they target risk and protective factors across social ecology (i.e.,

individual-, peer-, and community-level risk factors). At the individual level, adolescent males must consider their own potential for intimate and interpersonal violence (i.e., attitudes, beliefs and socialization experiences) and take a stand against violence perpetrated by others.[70] Our HIV theoretical model (IMB) is aligned with the violence prevention social-ecological model. At the individual level we focus on changing personal attitudes and beliefs; this aspect of the violence prevention model is aligned with the "I - information" component of our HIV prevention theoretical model. For example, we educate adolescents on situational characteristics that may lead to misperception of sexual interest including "triggers":[71] Triggers might include a pre-existing relationship between the 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;[72] 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;[73-75] assumptions that when a partner says "no" to sexual activity, they really mean "yes" (i.e., token resistance).[76] Accordingly, this research suggests IPV prevention programs benefit from discussions of common assumptions (specific to different contexts) about gender, relationships, sexual situations, consent, and sexual communication. Towards this goal, we explore and challenge males' attitudes and beliefs including stereotypical rape myths, adversarial views towards girls and women, and intimate partner and interpersonal violence.[77-85]

We also address peer-level factors in our prevention model. At the peer level we use bystander intervention techniques.[86-90] Positive peer pressure – as exerted through prosocial bystander action – can prevent IPV in others. Importantly, bystander behaviors can also reinforce the bystanders own prevention behaviors. The bystander approach has promise in correcting misperceptions about IPV[91,92] and decreasing personal engagement in IPV, interpersonal violence, and aggression.[23] This aspect of the violence prevention model is aligned with the "M-motivation" component of the HIV prevention theoretical model because bystander actions involve social learning where peer reinforcement results in self- and social-rewards for positive behaviors. We also build self-efficacy and behavioral skills, including for example, practice in assertive bystander communication (e.g., what to say, how to say it) and behavioral action (e.g., confronting and halting IPV behavior of peers, 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 model is 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, a community is defined as their peers within the school and thus specific to different settings). Data from the survey is used to create evidence-based social norms messaging used in our subsequent behavioral intervention with male adolescents.[93,94] Our discussion of social norms with male adolescents (as derived from a survey of peers within their school) helps adolescents to interrogate their specific social ecology of risk that can serve to inhibit or encourage problem behavior.[95] Social norms contribute to sexual violence in two ways. First, data suggest perpetrators are acting in ways that they (mis)perceive to be occurring within their community[96] For example, men who perpetrate violence are apt to believe that other men ascribe to stereotypical gender role beliefs[97] and support violence against women.[98-100] Men who believe their friends are using coercive behavior to obtain sex are more likely to engage in sexually coercive behaviors themselves.[101] 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 (with normative being defined differently for different contexts – in this case defined by the survey to be conducted in the school setting) and associated with increased status and acceptance.[96,93] Social norms contribute to sexual violence by creating a false misperception of high rates of sexual violence existing in a community.[102,103] Even non-perpetrators believe that peers harbor more rape myths than they actually do.[104] People also underestimate the extent to which their peers feel uncomfortable with sexist or degrading language/actions towards women.[70,91,105] These misperceptions about how many community members accept violence or how few would stand up against it, perpetuates violence by decreasing the likelihood that healthy community members stand up against the expression of inappropriate behavior in their community.[16] Second, men who perpetrate acts of sexual aggression report feeling pressure to engage in sexually aggressive behavior in order to demonstrate their masculinity and avoid humiliation from

peers.[106] This real or perceived pressure is a particularly salient factor for adolescents; notably, 85% of perpetrators, compared to 23% of non-perpetrators, described the "great and considerable" pressure to have sex in high school settings in the USA (data is not available in South Africa).[107] Over-estimations of peer sexual activity contribute to high intentions to initiate early adolescent intercourse especially relevant to our HIV prevention aims,[108] and pressure to be sexually active is a salient correlate of sexual assault perpetration.[107] Accordingly, our social norms messaging corrects misperceived norms as a community-level prevention strategy for both HIV and IPV[109-112] by recognizing: 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;[113] and 4) correcting these misperceptions allows individuals in a community to act in accordance with their actual beliefs, which are most often positive and health promoting.[113] The social norms in our intervention will be defined by survey conducted in the preparatory stages of the study, and also via the participant debate and discussion that occurs as part of the intervention activities. 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, risk sex, etc.) and are more willing to intervene when witnessing inappropriate behavior.[114] Following the acknowledgement that to be effective, prevention efforts must be positive, inclusive and empowering,[115,116] the 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 existing 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: 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 among male adolescents alone. 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. Culturally, this prevention approach is denoted as a topic that should only be discussed by men and boys.[117-119] For IPV perpetration prevention, gender separation decreases defensiveness among participants and promotes salience of program content. Fears of embarrassment make it difficult for males to openly discuss their attitudes when females are present.[16] Given that only perpetrators can truly prevent violence, the importance of specifically engaging males in sexual assault prevention has been emphasized.[16,120-124] We fill a gap in gender-tailored programming with our gender-specific intervention approach since only 8% of existing sexual assault prevention efforts are directed toward males.[15] The single-sex format of our intervention approach 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 propensity of HIV risk and IPV. For example, adolescence is marked by increases in impulsivity, increased risk taking,[125] and exploration of sexual identities[126] leading to naturally heightened sexual risk for HIV.[127] 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.[128] 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,[129]

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:

- **Theory driven, best-evidence intervention approaches for adolescent HIV prevention:** In Aim 1, we will integrate the latest rigorous evidence in efficacious interventions for adolescent HIV prevention into the existing *Safe* intervention to create *Safe South Africa* (described further in Methods). Our choice of adolescent HIV prevention components to integrate is guided by 4 global and South African specific systematic reviews and/or meta-analyses.[20,130-132] It includes content on HIV and STI approaches to increase knowledge, attitudes and motivations, and behavior change related to HIV and STI prevention. This includes for example, age and location specific prevalence data, condom access and use, pre-exposure and post-exposure prophylaxis, medical male circumcision, contraception, HIV testing including testing with partners, HIV disclosure circumcision, early treatment seeking for STIs or HIV, and other relevant sexual and reproductive health information. We combine the latest evidence from these reviews with our own experience of adapting empirically supported interventions to the South African context, and in design and testing of South African adolescent HIV and IPV interventions. These reviews align with our IMB theory (described above).
- **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.[30-35] The intervention also addresses interpersonal violence and aggression, both linked to IPV and critical to address in prevention for this age group.
- **Victim Empathy:** The intervention increases understanding of the impact of IPV by providing local and national statistics, discussing their perception of false accusations, and debunking rape myths.
- **Healthy Norms Regarding Masculinity:** Peer violence and delinquent behaviors are strongly associated with IPV so the social norm components of the intervention creates more healthy norms regarding masculinity and encourages 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. This component is critical given that our **preliminary data from the study described previously** indicates that although rates of perpetration were as high as 15%, only 0.5% of adolescents defined their behavior as rape and 14% engaged in repeat perpetration.[14] Participants are encouraged to share discomfort with aspects of traditional male gender roles and share positive alternatives.
- **Bystander Intervention Skills**: Based on the bystander intervention approach,[86-90] participants are encouraged to intervene when they witness other males engaging in inappropriate dating behavior, including an understanding of consent. Our bystander approach changes both the individual and socio-cultural context from one that supports coercive behavior to one that inhibits it. Since a relatively small group commit the majority of assaults,[129] 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.[16] 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.[22,24,88,90,133-136]

Strong Evidence of Existing Safe Intervention Promise

Our investigative team has conducted three prior evaluations of the *Men's Workshop*, which forms the foundation of the *Safe* intervention. The *Men's Workshop* was developed and evaluated by Dr. Berkowitz (consultant) in concert with Drs. Orchowski (co-I), in a CDC-funded study for college men[22]. The *Men's Workshop* showed efficacy in reducing perpetration of sexual aggression among young men (Gidycz, Orchowski & Berkowitz, 2011). The *Men's Workshop* was then revised into the *Safe* intervention to address

alcohol as a risk factor for sexual aggression by Drs. Orchowski in work funded by NIAAA,[23] and was deemed feasible, acceptable and promising among young men.[28,29] We do not assume that this exact format will be acceptable or feasible in South Africa – our study will examine needs for adaptations and examine the feasibility and acceptability of an adapted intervention in depth to ensure that an intervention has been designed specifically for the South African populations and context in mind. *Safe* taps into the importance of the environmental, social (including the developmental influence of peers), and relational contexts in which adolescent perpetration occurs. Through CDC funding, the *Men's Workshop* is also currently being tailored for administration among adolescent males in the USA. The *Men's Workshop* showed 50% reductions in sexual assault perpetration among college men over four months[22]. Dr. Orchowski and Dr. Berkowitz trained and supervised interventionists in the prior trial ($N = 635$). In all, 83% returned for a four-month follow-up, and 78% returned for a seven-month follow-up. These data reflect our ability to recruit and maintain adolescents and men in an evaluation of an intervention of similar format and comparable length. Notably, the sexual assault prevention workshop evaluated in this study was associated with a 50% decrease in rates of sexual assault perpetration among men in the treatment group, relative to the control. This was the first large-scale evaluation of a sexual assault prevention program that reduced rates of sexual aggression among men.

D. INVESTIGATIVE TEAM

Our multidisciplinary team consists of highly qualified, accomplished personnel with extensive experience in the areas of adolescent preventive interventions for HIV and IPV in South Africa and globally. Our investigative team currently has multiple projects in South Africa on adolescent HIV and IPV. Dr. Caroline Kuo (M-PI) will contribute social and behavioral expertise in adolescent HIV prevention including adaptation of empirically supported HIV interventions from outside of South Africa to South Africa, and in mixed-methods formative intervention development research that will yield appropriately tailored interventions for adolescents. She has 4 ongoing studies in Cape Town as an investigator (NIH grants: K01 NIMH 096646, R24 NICHD 077976, R21 NIAID 116309, R21 NIAID118393) and 1 other study (iLink: Incentives for Linkage to Care for HIV positive individuals) in a mentor role. Dr. Kuo directly collaborates with Dr. Cathy Mathews on 2 of these studies (K01 NIMH 096646 and R24 NICHD 077976), and Dr. Harrison on 3 studies (R24 NICHD 077976, R21 NIAID118393 and iLink). Dr. Cathy Mathews (M-PI) is a public health scientist with expertise in adolescent interventions for HIV and IPV, and specializing in school-based intervention trial design and testing. Her research is specifically focused on testing interventions for scale-up in school and health systems, and designed to inform national policies related to adolescent sexual and reproductive health in South Africa. Dr. Abigail Harrison (co-I) will contribute her substantial expertise in qualitative sexual and reproductive health research with South African adolescents. She has served as M-PI or co-I for multiple NIH-funded awards in South Africa. She has investigated the social context of adolescent HIV risk and preventive behaviors in South Africa (R01 HD41721) and is experienced in the design and evaluation of interventions for adolescents (R01 HD37343). Dr. Lindsay Orchowski (co-I) will bring her substantial expertise in the *Safe* violence preventive intervention being used in the study. She is PI of a large-scale, CDC-funded evaluation of sexual assault prevention programming for high school boys, as well as middle school boys. She is currently the PI of an NIAAA R34 grant designed to evaluate the *Safe* program for men in the military. She served as the study coordinator for a large-scale (N =1285), CDC-funded evaluation of sexual assault prevention programming (with Dr. Alan Berkowitz) and has published extensively on sexual assault risk reduction and prevention programs. Dr. Alan Berkowitz (consultant) is an expert in social norms theory, bystander intervention, and engaging men in sexual assault prevention. A collaborator on the design of the *Men's Workshop* (which forms the basis of the *Safe* program), he has worked with Dr. Orchowski in three evaluations of the model. Dr. Naeemah Abrahams (consultant) is an expert in violence risk reduction and prevention in South Africa as well as gender norms and relationships. She brings significant content expertise in IPV and interpersonal violence research within South Africa and has extensive knowledge of the South African ethical challenges of violence research with adolescents. Dr. Kuo, Mathews, Abrahams and Orchowski recently collaborated on an edited volume on sexual violence which has been accepted for publication by Elsevier entitled, "Sexual Assault Risk Reduction and Resistance: Theory, Research, and Practice."

E. METHODS

In this proposed Clinical Trial Planning Grant, we will focus on testing the acceptability and feasibility of *Safe South Africa* in preparation for a future R01 clinical trial. Given the acceptability and feasibility aims of this study, we are underpowered to gather biomarker data on HIV and STI incidence but plan to incorporate collection of biologically verifiable data on HIV incidence – as aligned with NIH HIV research strategy in a future fully powered RCT. See study will take a total of 3 years from start to finish. For more details on the

Table 1. Study Timeline	**Year 1**				**Year 2**				**Year 3**			
3 month quarters	1	2	3	4	5	6	7	8	9	10	11	12
Development Phase (Aim 1)												
Theoretical and empirical HIV prevention adaptation of	✓	✓	✓									
Focus group discussions with adolescents		✓	✓									
Qualitative analysis to finalize intervention		✓	✓	✓								
Acceptability Phase - Open Pilot (Aim 2)												
Translation and programming of electronic data systems					✓							
Interventionist training and supervision						✓	✓					
Social ecology survey (N=100) with males and females in the school community						✓						
Open Pilot (N = 20) with further *Safe South Africa* refinement							✓					
Feasibility Phase – Trial RCT (Aim 3)												
Interventionist supervision							✓	✓	✓			
Trial RCT (N = 60)							✓	✓	✓			
1-month follow-up								✓	✓			
6-month follow-ups									✓	✓	✓	
Outcome, mediation and moderation analysis										✓	✓	
Future Study Preparation Analysis Phase												
Preparation of manuscripts											✓	✓
Submission of R01											✓	✓

study timeline, including a breakdown of activities for the 3 study aims appears in **Table 1**:

Language. All study materials and procedures will be conducted in English or isiXhosa, the local language in our school study sites. Study materials will be translated by a professional translator, then back-translated to ensure accuracy. Participants will identify language of preference and multi-lingual research assistants (RAs) will conduct procedures in the preferred language. We draw from our established research networks to hire a team experienced in intervention development and testing research with adolescents including qualitative research and cognizant of linguistic precision needed in our research.

Site Selection. We build on our team's extensive experience conducting school-based interventions, adolescent HIV and IPV interventions, and prevention research in South Africa. We work off our established network of 40 school research sites in Western Cape Province of South Africa, focusing on high schools in high HIV risk communities based off of M-PI, Dr. Mathews' previous school-based research. We select the highest HIV prevalence schools from among 40 public high schools in Western Cape where we have previously worked with success in our school-based intervention trials with this age group.[51,137-139] In each of these 40 schools, we have established relationships with school stakeholders including principals and other educators. These relationships allow us to run our after-school HIV-IPV prevention program on school premises. Dr. Mathews, in consultation with Dr. Abrahams will utilize their extensive experience to lead our team in the process of securing permissions to work within schools including the process of engagement and consultation with stakeholders such as referral sources, Department of Education, principals, the student Representative Council of Learners (RCLs), and School Governing Body (SGB).

SPECIFIC AIM 1: DEVELOPMENT PHASE – HIV PREVENTION INTEGRATION AND ADOLESCENT FOCUS GROUPS

Goals. In **Development Phase (Aim 1)** we will review our existing empirically supported *Safe* program to identify content, structure, and delivery modalities needing refinement and adaptation to South Africa. Then we will integrate best-evidence on theoretical and behavioral adolescent HIV prevention to create *Safe South Africa*. Finally, we will finalize adaptations guided by k=3-5 qualitative focus groups with adolescent males.

Review of Existing Safe Intervention and Contextual Adaptations. We begin by evaluating the existing *Safe* intervention for adaptations needed for the South African context. Our focus of the adaptation process is to adapt content to be relevant to South African populations and settings. We also evaluate whether adaptations are needed to delivery approach (facilitators, setting, format of materials, activities). We also adapt based on the logical aspects that will affect the intervention such as location and scheduling keeping in mind the safety and ease of attendance by participants. We have specifically chosen this intervention because it has a conceptual model aligned with our chosen HIV prevention theory, has been empirically been developmentally adapted to adolescents in prior work, and also because of the potential for adaptation to South Africa. Specifically, the intervention has intensive but manageable numbers of sessions due to South African challenges related to poverty and community crime that might affect transport and attendance by participants. In our adaptation, we retain core active components of *Safe*, but examine material, content, and modalities of delivery that may result in non-response and non-engagement due to unique characteristics of the population and setting. We consider how high HIV prevalence, social determinants of HIV and IPV risk, culture, and language need to be integrated into material, content, and delivery, drawing from our experience of adapting or testing interventions for adolescents in South Africa.[46,51,140-148] This will result in an initial draft of *Safe South Africa.*

Theory and evidence-based adaptation for HIV. In the next phase, we will integrate the IPV perpetration and HIV prevention material. This stage will be guided by IMB theory-guided adaptation for an initial draft of *Safe South Africa*. Our choice of IMB theory-guided adaptation is further strengthened with integration of adolescent HIV prevention components based on 4 global and South African specific systematic reviews and/or meta-analyses that align with our theoretical IMB approach. The first meta-analysis evaluated effective HIV preventive interventions for South African youth aged 9-26 years. This meta-analysis was comprised of ten studies (k = 11; N = 22,788) and showed interventions were efficacious in delaying sexual intercourse (fixed-effects: d+s =0.07, 0.15), increasing condom use (fixed-effects: d+s =0.17, 0.19), reducing the number of sexual partners (fixed-effects: d+s =0.95, 0.44) relative to those in a control condition, and lowering incidence of HSV-2 (k = 2, d+ = 0.17, 95% CI = 0.09, 0.25).[130] Based on this adolescent and youth South African review, we will include the following successful intervention components: delivery by facilitators who are not professionals (e.g., not nurses); delivery over fewer sessions (e.g. length was not important); content covering social norms and gender inequalities (synchronizing with our planned *Safe South Africa* intervention); and incorporation of intensive behavioral skills training such as condom use. The finding that number of sessions was not important, was relevant for our choice of the *Safe* intervention; we further examined whether brief interventions for HIV prevention have a clinically significant effect using a second meta-analysis. The second meta-analysis evaluated effectiveness of single-session behavioral interventions to prevent STIs. This meta-analysis was comprised of 29 single-session interventions (k = 20; N = 52,465) and showed intervention participants relative to controls had significantly lower risks with an odds ratio of 0.65 (95% CI=0.55-077) even when control groups were active controls (e.g. stringent controls where control participants received risk reduction materials). Because this meta-analysis indicated brief preventive (individual, group-based, computer delivered) interventions can have clinical salience, we will focus on a brief but behaviorally intensive intervention in our approach.[131] The third meta-analysis evaluated effectiveness of HIV interventions for adolescents 11-19 years globally and was comprised of 98 interventions (k = 67; N = 51,240). Results showed adolescents who received interventions compared to controls showed significant reductions in incident STIs, frequency of sex, number of partners, and significant increases in abstinence or delay of intercourse, condom use, safer sex communication skills, and acquisition of condoms. Based on this global adolescent HIV prevention review, we will include the following successful intervention components: motivational training for behavior change and condom skills training but no emphasis on abstinence given abstinence focused interventions were ineffective.[20] The fourth global meta-analysis was on the efficacy of behavioral interventions

to increase condom use and reduce STIs. The meta-analysis was comprised of forty-two studies (k = 67; N = 40,665 and showed intervention effects of increased condom use (d=0.17, 95% CI 0.04 to 0.29; I^2=94%), fewer incidents of STIs (d=0.16, 95% CI 0.04 to 0.29; I^2=90%) and lowered cases of HIV (d=0.46, 95% CI 0.13 to 0.79; I^2=99%). Based on this meta-analysis, we will include the following intervention components: for motivation, focusing on distal motivation components (i.e., future orientation for adolescents); and content with behavioral skills training (i.e., condom skills and interpersonal skills).[132]

Sampling Plan, Recruitment, Inclusion/Exclusion. We describe the sampling plan including inclusion and exclusion criteria for recruitment, and retention strategies. Aim 1 involves focus groups (k=3-5) with male adolescents, 15-17 years of age. We recruit male adolescents for k=3-5 adolescent focus groups to further refine our initial *Safe South Africa* intervention draft. Participant recruitment will follow procedures used previously in our research on best ethical procedures with adolescents in South Africa.[149] We recruit a convenience sample of male adolescents through flyers providing contact details for study staff in the school setting and recruit in-person with permissions of school principals and teachers. Inclusion criteria include: (1) male adolescent; and (2) 15-17 years of age inclusive. Adolescents are excluded if parents do not provide consent or adolescents do not provide informed assent.

Informed consent/assent. Interested adolescents will speak privately with the study team to gather parent contact details to proceed with the parental consent process. All interested adolescents will be sent home with written parental consent and adolescent assent forms. Study staff will speak with parents by phone or in person to secure consent. In our study, we use the term parent broadly to describe adults serving in a parental role and may include biological parents as well as surrogate parents (caregivers serving in the parental role). Diverse child caring arrangements are common in the South African context, where a large number of non-biological caregivers take on the parental role. The South African Child Gauge 2013 Report by the Children's Institute shows that approximately a quarter of all children in South Africa do not live with either biological parent. More importantly, among the populations which we are working with (largely black African), approximately two-thirds of children do not live with either biological parent. Biological parents may not present in children's lives due to cultural norms, personal family choice, labor migration, parental neglect, social circumstances, etc. These diverse family structures result from historical adaptations due to separation of families during apartheid, economic migration, etc.[150,151] Furthermore in our study setting, many children have experienced the death of biological parents due to HIV/AIDS or other causes. In HIV-affected communities, informal caregiving arrangements, in which non-biological individuals playing a parental role are particularly prevalent.[152,153] We have utilized consent from adults serving in the parental role in our previous studies which have been reviewed and approved by South African universities (University of KwaZulu Natal, University of Cape Town and provincial Departments of Health and Education) and also by Oxford University. During this conversation, the parent will receive information on the study. Parents will have time to consider the information. Then they will be asked if they give consent for the adolescent to proceed with assent. Study staff will request a written informed consent form from each parent and prompt them to keep the second copy for their records. Then study staff will assess eligibility for adolescent focus groups. Inclusion criteria include: (1) male adolescent; and (2) 15-17 years of age inclusive. We will include adolescents regardless of sexual activity, HIV, or IPV status. This is because developmentally, prevention may alter the trajectory of possible engagement in new (not yet experienced) risk behaviors, or risk for those already engaged in unsafe behaviors. We consider all definitions of dating to be “intimate partners” at this young age. We are not specifically screening for intimacy in our eligibility in this study because South African data shows by age 13, 74% of boys reported sexual foreplay or oral sex, and age 15 is the median age for penetrative sexual debut.[38] We will use this study to determine if a future fully powered randomized controlled trial needs a stricter eligibility criteria. Adolescents are excluded if parents do not provide consent or adolescents do not provide informed assent. If the potential participant meets the inclusion criteria for the study, we will inform them that they are eligible. If eligible, a participant locator form will be filled out to help schedule focus groups. Adolescents will be given an assent form at initial point of contact but go through assent procedures at the focus group to give additional time to consider assent. Our consent and assent procedures for this portion of the study and all subsequent portions include specific discussion of mandatory disclosures and reporting based on law which is also detailed in forms. We specifically acknowledge the significant potential harms and negative consequences that such disclosures

may present for participants and families if systems of reporting are initiated.

Adolescent focus group procedures. We will conduct a total of k=3-5 male adolescent focus groups with final focus group numbers dependent upon data saturation. Each focus group will contain a minimum of 4, and maximum of 8 participants. We will begin each group by confirming receipt of consent forms from parents/caregivers, and verbally go over assent procedures followed by written assent. Assent procedures specifically detail permission for recording and the need to avoid use of real names. Then we will gather a brief socio-demographic survey to gather details on age, family situation, and behavioral data relating to HIV and IPV to contextualize focus group data. Each group will last approximately 1.5 hours; when combined with informed consent procedures and the demographic questionnaire, we anticipate that each participant will spend approximately 2 hours involved in the study. Two members of the study team will facilitate each group with one study team member directing the flow of discussion, and the other taking notes and prompting with additional questions as needed. Focus groups will follow the semi-structured agenda exploring the following themes: (1) perceptions of HIV including knowledge of protective behaviors, and barriers/facilitators to engaging in protective behaviors; (2) perceptions of IPV including attitudes and norms around gender roles, relationships, and violence; (3) exploration of community and context specific factors relating to HIV and IPV behaviors; (4) feedback on core elements of *Safe South Africa*, including appeal, clarity and appropriateness of content, especially newly adapted material and content; and (5) anticipated barriers/facilitators in uptake of the intervention including delivery preferences and suggestions for optimizing recruitment, data collection, and retention procedures. These specific thematic areas will guide our approach to adaptations made to the intervention model. Our goal is to ensure that we consider the design of an intervention that is appropriate for this male adolescents from South Africa in the specific setting where this intervention is being tested. These thematic areas will guide the intervention team in developing a final draft intervention to be trialed including areas such as content, material, format, timing, delivery, and more. All focus groups will take place in a private room in the school or community setting with compensation for time and transportation. Food and refreshments will also be offered during the focus groups. Focus group discussions will be recorded using a digital voice recorder (DVR). Audio files will be stored in the password-protected project drive. Audio files will then be translated and transcribed verbatim by a transcriptionist. After transcription, the study team will edit out any information that might be used to identify a participant personally. A bilingual RA will compare 10% of transcripts to audio files for accuracy.

Participant Reimbursement. At the close of the focus group, we will thank participants and provide reimbursement. Each participant will be provided with reimbursement of 75 Rand (approximately $7.50) (comprised of 50 Rand for time and 25 Rand for travel). This reimbursement may be provided in the form of a voucher. If the focus group is under-enrolled, we still offer a reimbursement for travel of 25 Rand.

Analyses. We will conduct ongoing saturation analyses, based on iterative coding during data collection.[154] Each audio recording is transcribed word-for-word and translated if necessary. Transcriptions are checked for accuracy and entered into NVivo. We will also enter all observational notes as memos. Data analysis is iterative including techniques of open and axial coding based on manual coding prior to coding in NVivo.[155] We will distill qualitative intervention components into thematic categories to guide refinement of intervention material, content, and delivery for Aim 2.

SPECIFIC AIM 2: ACCEPTABILITY PHASE – TEST ACCEPTABILITY OF SAFE SOUTH AFRICA IN OPEN PILOT TRIAL

Goals. **Acceptability Phase (Aim 2)** involves two sets of data collection. First, we conduct a school-wide survey of N=100 male and female adolescents, of any age (anticipated to be 13-18 years) to evaluate the social ecology of HIV and IPV risk (focusing on social norms of peers within the school). We will use survey data to create evidence-based social messaging tailored to address male adolescent's specific social-ecological risk and protective factors for HIV and IPV – data from the survey used to generate content for debate and discussion within the behavioral intervention itself. Second, we will elicit feedback on *Safe South Africa* via an open pilot trial with N=20 male adolescents. This open pilot trial will assess acceptability including participant

satisfaction with intervention content, materials, and delivery prior to a more in-depth test of the intervention in the randomized pilot trial.

Survey of Social Ecology. In preparation for later stages of Aim 2 and for Aim 3, we begin by conducting a school-wide survey to better understand the social ecology of the school community with N=100 male and female adolescents. This survey comprises Part 1 (preparations for the *Safe South Africa* Intervention), by providing a data-driven evaluation of risk and protective factors for HIV and IPV. The results of the survey of social ecology will help to generate evidence-driven social norms messaging used as content for the intervention being tested in Part 2, the stage corresponding to actual roll-out of the male adolescent behavioral intervention (the open pilot test of the intervention and the randomized pilot trial of the intervention). For the survey, we will recruit a convenience sample of both male and female adolescents attending our chosen intervention school by visiting classrooms, briefly explaining the purpose of the anonymous survey.

Recruitment for Survey. This survey will guide the development of intervention content that is specifically tailored to the adolescents that are the population being targeted in this intervention. The survey generates specific age and contextual data that will be integrated into a final intervention model that is adapted for the South African population and setting where the intervention is being tested. We will recruit a convenience sample of both male and female adolescents attending our chosen intervention school site by visiting classrooms, briefly explaining the purpose of the anonymous survey. Inclusion criteria include: (1) adolescents attending the high school will be included regardless of gender and age. Interested adolescents go through assent procedures if they are under 18 years of age. Adolescents are excluded if parents fail to provide consent or adolescents do not provide informed assent. We anticipate the age to be 13-18 years but school-going ages vary widely in South Africa due to delayed start of school and pass/fail criteria that may hold back students based on performance. We focus on all adolescents in the school environment. Although the target of the *Safe South Africa* intervention itself focuses on male adolescents 15-17 years of age (for the open pilot in the second half of Aim 2, and the randomized pilot trial in Aim 3), we feel that expanding our survey of social ecology to include all students regardless of age in the high school environment is warranted. We specifically chose to include adolescents who are both younger and older than our target intervention age group in this survey of the social ecology to provide a more complete picture of norms in the school community. This information on how norms develop and are shaped in the ages leading up to, and immediately after, our actual intervention target population age range of 15-17 years, is relevant to the developmental-tailoring of intervention content. We also purposively include females as well as males in this school ecology survey even though the intervention itself targets males. This is because norms around HIV risk behavior, IPV, and gender are not shaped only by male adolescents (who are the target of our gender-specific intervention). Females also shape the social ecology relating to HIV and IPV behaviors among males. As such, we feel that including females in the survey of social ecology will provide more detailed information on how both female and male perspectives shape the social environment including roles, norms, and expectations relating to male-specific HIV risk behavior and IPV perpetration. Thus, we feel that eliciting female, as well as male perspectives, in the social ecology survey during Aim 2 enriches the scientific data that we generate to refine the intervention that will be piloted in Aim 3.

Consent and assent for survey. After visiting classrooms to explain the purpose of the anonymous survey, we will follow the subsequent consent and assent process, which we have given careful consideration based on our own research of the most appropriate consent procedures for low-risk research with adolescents in school settings.[156] We will follow active parental consent procedures for this anonymous school ecology survey. Our team will visit classrooms to describe the survey to students, explaining parents/caregivers need to indicate in writing whether they want their child to participant. We will provide parents/caregivers a letter about the nature of the research seeking their permission for their child's participation, Then we revisit high school classes 1 week later. Then study staff will assess eligibility for adolescent surveys. Inclusion criteria include receipt of signed parental consent forms combined with the following: (1) adolescents attending the high school, anticipated to be 13-18 years of age. We include adolescents attending the school regardless of gender and age to get a full assessment of social ecology (rather than just focusing on 15-17 year old males). Interested adolescents go through assent procedures. Adolescents are excluded if parents provide dissent or adolescents do not provide informed assent. Then we provide a brief school social ecology climate survey assessing: (1) IPV

and HIV behavior data; (2) predicted prevalence of IPV and sexual behaviors in their school; (3) norms and attitudes around sex, gender, and IPV. We then analyze this survey data and use this to generate content for the behavioral intervention materials and activities. We will conduct bivariate analyses using chi-square, Fisher's exact and t-tests to examine the associations between participant demographic characteristics, and actual or predicted IPV behaviors. Then we will use multivariate regressions to identify variables predictive of IPV. Findings inform our social norms messages within the behavioral intervention, tailored to meet the specific HIV, IPV, interpersonal violence, and aggression prevention needs of adolescent's social ecology.

Training Intervention Facilitators. Our investigative team will train facilitators in preparation for the behavioral intervention that occurs as Part 2 of the *Safe South Africa* intervention. We will recruit facilitators through our pool of experienced adolescent HIV and IPV intervention facilitators used in our previous trials, supplemented by advertising, community-flyers, and outreach with NGOs/CBOs, community meetings, clinics, and schools. Training will involve 5 modules. Module 1 includes: 1) introductions and ice-breaking exercises, 2) project overview and training objectives, 3) education regarding HIV prevention and IPV with a focus on perpetration prevention, communication, gender roles and social norms particularly in regards to sexual relationships, and sexual relationship negotiations. Module 2 focuses on intervention delivery skills: 1) public speaking and 2) communication of sensitive topics. Module 3 involves training in use of the intervention protocol guided by a manual: 1) demonstrations of intervention modules, 2) education on core intervention elements, and 3) role-play sessions. Module 4 involves: 1) testing implementation skills in short mock scenarios, 2) feedback from the PI. Module 5 involves role-playing participants in a mock intervention. We incorporate challenges that may arise during implementation including delivery of intervention content and inter-personal interactions to assess paraprofessional facilitators' mastery of core skills and performance. We rank performance using the fidelity forms we will use in the trial. If an interventionist is not deemed qualified, additional training will be provided until competent. Interventionists who are deemed unqualified after additional training will be replaced.

Open Pilot Trial. We will recruit N=20 male adolescent who meet study inclusion criteria to participate in the behavioral intervention that comprises Part 2 of the *Safe South Africa* intervention. This is the group-based, facilitated behavioral intervention for prevention of HIV risk and IPV perpetration held in 2-hour sessions, once a week for a total of two weeks after school, on school premises. This after school program is a behavioral intervention that includes the following core components (described in detail under the section titled "Core Components of the *Safe South Africa* intervention"): information and behavioral skills practice to address HIV and STI prevention including HIV and STI content relating to prevention knowledge, attitudes and behaviors; information relating to linkages between HIV and IPV; formation and behavioral skills practice to address IPV prevention including debate, discussion, and information designed to improve victim empathy; debate, discussion, and information designed to support healthy norms regarding masculinity and deep understanding of consent; and development of bystander intervention skills with practice to boost self-efficacy in future implementation of these skills.

Recruitment for Open Pilot Trial. For the open pilot trial with N=20 adolescent males, 15-17 years, we recruit a convenience sample of male adolescents through flyers providing contact details for study staff in the school setting and recruit in-person with permissions of school principals and teachers. Inclusion criteria include: (1) male adolescent; and (2) 15-17 years of age inclusive. Adolescents are excluded if parents do not provide consent or adolescents do not provide informed assent. Retention is not an issue in Aim 2. Eligibility are same as Aim 1 Focus Groups.

Consent and Assent for Open Pilot Trial. Consent and assent are the same as describe above for Aim 1. Interested adolescents will speak privately with the study team to gather parent contact details to proceed with the parental consent process. All interested adolescents are sent home with written parental consent and adolescent assent forms. Study staff will speak with parents/caregivers by phone or in person to secure consent. During this conversation, the parent will receive information on the study. Parents will have time to consider the information. Then they will be asked if they give consent for the adolescent to proceed with assent. Study staff will request a written informed consent form from parents and prompt them to keep the second copy for their records. Then study staff will assess eligibility. If the potential participant meets the inclusion criteria for the study, we will inform them that they are eligible. If eligible, a participant locator form will be filled out to help

schedule the intervention. Adolescents have been given an assent form at the initial point of contact but go through assent procedures prior to the intervention to give additional time to consider assent. We begin enrollment into the open pilot by confirming receipt of consent forms from parents/caregivers, and verbally go over assent procedures followed by written assent.

Open Pilot Trial Procedures. For participant acceptability, participants will complete 3 sets of assessments. The first set of assessments will reflect the outcome questionnaire used at baseline, 1- and 6-months (also used in Aim 3). The second set of assessments will be session and overall intervention satisfaction forms. These satisfaction forms gather opinions on content, material, delivery, format, length, time, and location (also used in Aim 3). The third set of assessments will evaluate participant opinions of final draft material and messages derived from the social-ecology survey (Part 1) including suggestions for refinement of images and social norms messages in a facilitated group discussion. Finally, our investigative team will evaluate fidelity, ranking integrity and competency of session delivery in real time (also used in Aim 3). Fidelity assessments will also be used in the trial RCT (Aim 3) but in this open pilot, rankings will be used to make final refinements to intervention facilitator training prior to launch of the trial RCT. These fidelity assessments will follow recommendations issued by the Treatment Fidelity Workgroup of the NIH Behavior Change Consortium to ensure rigorous coding of fidelity based on a standardized monitoring checklist to assess facilitator adherence/drift from fidelity.[157] Measures and assessment timelines for Aims 2 and 3 appear in **Table 2** (below).

Analysis and Further Intervention Refinement. We will check all forms for missing data in field and during entry, with at least 2 telephone calls to participants to get missing data. We will examine key variables for skewness, variability, missing data, and outliers, with transformations to achieve normality if needed. For our outcomes questionnaire (baseline version used in this pilot), we will examine descriptive statistics for main outcomes and mediators/moderators. This analysis will focus on correcting any errors prior to Aim 3 and trialing the data systems. Then, we will assess acceptability, setting 80% reporting positive ratings as a marker of acceptability and examining process data on satisfaction with format, length, etc. We will use this acceptability data to make final adjustments to the *Safe South Africa* intervention prior to Aim 3. We will assess fidelity of facilitator implementation, setting 80% as acceptable fidelity, and using data to make final adjustments to training.

Reimbursement. For the brief school social ecology climate survey, adolescents will a pen/pencil (worth 10 Rand) as appreciation. In the open pilot, adolescents will receive 50 Rand (consisting of 25 Rand to offset time and 25 Rand to offset travel costs) for the baseline outcome assessment, 60 Rand (consisting of 35 Rand to offset time and 25 Rand to offset travel costs) for the 1-month outcome assessment and 70 Rand (consisting of 45 Rand to offset time and 25 Rand to offset travel costs) for the 6-month outcome assessment. In the open pilot, adolescents in the intervention arm only, also fill out questionnaires to help us evaluate the acceptability of the intervention; these questionnaires will occur after each session. Adolescents in will receive50 Rand (consisting of 25 Rand to offset time and 25 Rand to offset travel costs) for attending the enrollment session and the satisfaction assessments filled out in the first session. Adolescents in the intervention arm only, will also receive 60 Rand (consisting of 35 Rand to offset time and 25 Rand to offset travel costs) for filling out satisfaction assessments after the second session. The second session requires a slightly higher reimbursement rate because participants fill out both questionnaires on their satisfaction with the second session as well as the overall program.

SPECIFIC AIM 3: FEASIBILITY PHASE – ASSESS FEASIBILITY OF *SAFE SOUTH AFRICA* IN TRIAL RCT

Goals. In **Feasibility Phase (Aim 3)** we will assess feasibility for a future R01 trial including the rigor of facilitator implementation of the intervention protocol by evaluating fidelity and competence, recruitment strategies, and tracking and tracing success. We will assess feasibility by testing *Safe South Africa* in a randomized controlled pilot trial with 1- and 6-month follow-up. Participants include a sample of N=60 male adolescents who will receive a behavioral group-based intervention to prevent HIV risk, IPV perpetration, and increase bystander behavior). Intervention participants will be compared to a control of ordinary usual care. The ordinary usual care condition will consist of a packet of existing available brochures on HIV and other sexually

transmitted diseases including testing, prevention, and treatment; IPV prevention and intervention; and places to access prevention, care, and support for these outcomes and related health outcomes. This packet includes existing resources in South Africa including Childline (an adolescent tailored health resource), Stop Gender Based Violence helpline, HIV helpline, and the South African Depression and Anxiety Group (SADAG) helpline for mental health. We considered alternative treatments as a control but there are no existing rigorously tested HIV-IPV perpetration preventive interventions exist for adolescents in South Africa. This is not a treatment study but has a prevention focus. We explore preliminary evidence for hypotheses that the intervention, relative to the control, will produce the following outcomes: (1) reductions in actual or intended HIV risk behaviors; (2) reductions in IPV frequency and decreased endorsement of IPV supportive attitudes; and (3) increased proactive bystander behavior for prevention of IPV perpetration.

Design. This is a randomized controlled trial where participants are prospectively assigned to two arms (Safe South Africa) versus the control of ordinary usual care. This will be a single blind study. Intervention participants will not be blinded to the condition they are in (the intervention group will receive the intervention first, with the control group given standard usual care. Study staff (e.g. intervention team) will not be blinded to the condition. Study staff (e.g., outcome assessment team) who assess outcomes after the experimental intervention has been delivered will be blinded to the condition participants have been assigned to. Blinding will be broken for data analysis. To reduce the risk of contamination, or that blinding will be broken by participants communicating to each other, we will request that participants in the intervention keep all activities and discussions to themselves. We will also assess whether blinding was successful by checking for contamination at the outcome assessments at 1- and 6-months. There is no chance that participants in the control group would participate mistakenly in the intervention so we assess for contamination in terms of sharing of intervention materials between the intervention and control group. Participants assigned to the control group will be screened for contamination. We will adjust for any contamination effects in analyses. Although this is a feasibility and acceptability trial, thus not designed to be fully powered to measure effects, we set out to create a study design that carefully adheres to elements outlined in the Consolidated Standards of Reporting Trials (CONSORT) Statement.[158] This pilot study adheres to a single blind, randomized pilot trial design with the end goal of informing a future fully powered RCT corresponding to a Phase III clinical trial.

Recruitment, eligibility, and informed consent/assent. We will recruit N=60 male adolescents (30 in each of 2 arms) to test *Safe South Africa* in a pilot RCT to generate data for a future fully-powered RCT. This pilot RCT consists of a behavioral group-based intervention (10-20 adolescents per group) delivered by a facilitator in 2-hour sessions, once a week for a total of two weeks after school, on school premises with take home activities to deepen behavioral practice and engagement. We implement recruitment, consent and assent procedures, and eligibility criteria same as Aim 1 (see above). Consent and assent procedures will occur twice during Aim 3. First, consent and assent will occur at the first point of contact, after screening for eligibility and prior to gathering baseline assessment. We seek consent and assent prior to gathering baseline assessment because this data will provide valuable feasibility and acceptability data on who is eligible for the community based intervention but who choose not to proceed to enrollment. Second, consent and assent will be sought at the enrollment session which includes a behavioral run-in an intensive methodological approach for discussing pros and cons of trial participation, detailed at the NIH Randomized Behavioral Clinical Trials Institute (attended by M-PI Kuo).[159] This method focuses on thoroughly discussing ethical considerations prior to randomization (and in doing, also optimizing recruitment and retention in the trial). This procedure involves a discussion of pros and cons in the order shown in Figure 1 as part of study orientation, prior to randomization.

Figure 1: Study orientation and ethical discussion		
	Enrolling in the study	**NOT enrolling in the study**
Pros of participation	3 – Discuss third *pros* of enrolling in the study	2 – Discuss second *pros* of *not* enrolling in the study
Cons of participation	4 – Discuss last *cons* of enrolling in the study	1 – Discuss first *cons* of *not* enrolling in the study

The idea of this behavioral run-in is to provide a more in-depth orientation session after participants have been

given time to consider the study in depth (following an initial consent and assent at baseline). In this behavioral run-in, we provide a thorough discussion of ethical considerations to complement traditional consent/assent procedures. This discussion focuses upon eliciting potential participants' perspectives of pros and cons of their potential trial enrollment to help them consider risks and benefits thoroughly, to explicitly acknowledges study challenges, and to engage in a meaningful interactive dialogue to overcome any misunderstandings of the study (including confusion on trial design and objectives, prevention misconception, and other ethical challenges documented by studies on related topics in similar settings).[160,161] The approach avoids a "hard sell" or "pro-change" positions, but instead, focuses on enriching the informed consent and assent process to ensure meaningful informed and voluntary consent and assent.

Randomization & Retention. We will randomize adolescents in this 2-arm trial to an intervention arm (testing our *Safe South Africa* intervention, n=30) or a control arm (n=30) from a different school consisting of ordinary usual care (information on existing community resources for HIV and IPV). We considered comparing to a more stringent control, such as an existing rigorously empirical preventative interventions targeting prevention of HIV-IPV perpetration but this does not exist for adolescents in South Africa. We will randomize based on permuted blocked randomization chosen off careful consideration of randomization possibilities and training received at the NIH Randomized Behavioral Clinical Trials Institute. Permuted blocks will be based off of varying block lengths. This process will be repeated until target baseline enrollment is achieved. To retain participants, one data enterer will devote 50% time to tracking including: 1) at baseline, documenting multiple participant contact details and three individuals who know how to contact the family; 2) monthly contact via telephone or text; 3) follow up at least five times using different days, times, and methods. These strategies were successful in maintaining 100% attrition in Dr. Kuo's recent acceptability and feasibility trial with adolescents of similar age and similar South African communities.

Assessments. All measures utilized in the current study are well established, with adequate reliability and validity and tested in our prior studies. See **Table 2**.

Table 2: Outcome Measures and Assessment Timeline

Outcome	Measures	Baseline	Session 1	Session 2	1-month	6-month
Acceptability	• Session Evaluation Form[162] • Client Satisfaction Questionnaire[163]		✓	✓		
HIV Risk Behavior & Intentions: HIV and STI status; HIV testing; frequency sex; number and type of partners; use of condoms	• Items taken from South African trials & NIH's Adolescent Medicine Trials Network for HIV/AIDS Interventions	✓			✓	✓
IPV Perpetration Behaviors: type, frequency and severity of IPV; sexual perpetration and aggression, dating violence	• Childhood Sexual Victimization Questionnaire (CSVQ)[164,165] • Sexual Experiences (SES-SFP)[47] • Assault Characteristics Questionnaire (ACQ)[164] • Conflict in Adolescent Dating Relationships[166]	✓			✓	✓
Bystander Intervention Behaviors: proactive bystander behavior; bystander efficacy and readiness	• Sexual Social Norms Inventory (SSNI)[167] • Bystander Behavior Scale[168-170] (BBS) • Intent to Help Scale (IHS) [168,170] • Bystander Efficacy Scale[169,170] (BES) • Interpersonal Reactivity Index (IRI)[171] • Stages of Change Scale (SOC) [90,172,173]	✓			✓	✓

	• Decisional Balance Scale (DB) [169]					
Co-variates: socio-demographics; economic status; household characteristics	• Items from the South African 2011 Census Questionnaire & World Health Organization Food Security Questionnaire [174] • Verbal Autopsy Questionnaire for AIDS orphanhood[175]	✓			✓	✓
Mechanisms & Moderators: • HIV knowledge; HIV stigma; condom attitudes, self-efficacy, and skills; family interactions • Resilience; mental health; substance use • Sexual aggression norms; endorsement rape myths, traditional gender roles; social norms regarding violence; identification of sexual consent; empathy for victims	• South African HIV Knowledge[176]; AIDS Related Stigma Scale and Internalized AIDS-Related Stigma Scale (IA-RSS)[177,178]; Condom Attitudes Scale - Adolescents (CAS-A)[179]; Condom Use Self-Efficacy Scale (CUSES)[180]; Condom-use skills checklist[181]; Alabama Parenting Questionnaire-Short Form[182] • Connor-Davidson Resilience Scale (CD-RISC)[183]; Center for Epidemiologic Studies Scale - Revised (CESD-R)[184,185]; Alcohol Use Disorders Identification Test (AUDIT-C)[186]; Drug Use Disorders Identification Test (DUDIT)[187] • Illinois Rape Myth Acceptance Scale (IRMAS) [188]; Hypergender Ideology Scale—Short Form (HIS)[189]; Boeringer's Social Norms Measure (BSN)[190]; Marlowe-Crowne Social Desirability Scale (MCSDS[191]; consent scenarios[23]	✓			✓	✓

All administration systems (paper and smartphone modalities) and data software come with rigorous human subjects protections (Teleform, SurveyToGo, Filemaker). All have worked well as international data systems in our previous collaborative USA-South African trials. We conduct a first set of assessments to evaluate acceptability using paper forms which will be scanned into computerized data using TeleForm Software. Acceptability will be evaluated with session satisfaction and overall intervention satisfaction forms. These satisfaction forms gather opinions on content, material, delivery, format, length, time, and location. We conduct a second set of assessments to evaluate feasibility. We will examine the rigor of the intervention by evaluating fidelity for 10-15% of total sessions using a neutral coder, ranking integrity and competency of session delivery in real time, and following recommendations issued by the Treatment Fidelity Workgroup of the NIH Behavior Change Consortium[157] We also track recruitment, retention, and attrition data using FileMaker Software to inform future studies. This will include gathering characteristics on who is eligible (from baseline data) but do not attend the enrollment session; data on who fills out baseline, post 1-month, and 6-month assessments; as well as who attends scheduled intervention sessions. The count-down clock for the 1- and 6- month post intervention assessment will occur after the last intervention session has occurred. We will also conduct exit questionnaires for early exiters and full completers probing for: 1) intervention drop out/facilitators including logistical, job or family related barriers, 2) perceived burden of intervention and assessment, and 3) satisfaction with interactions with the research team in scheduling, etc. For early exiters who we are unable to identify at intervention sessions, we will complete exit evaluations by phone. We will conduct a third set of assessments for our exploratory aims, our examination of direction of outcomes regarding whether the intervention, relative to the control, will produce: (1) reductions in actual or intended HIV risk behaviors; (2) reductions in IPV frequency and decreased endorsement of IPV supportive attitudes; and (3) increased proactive bystander behavior for prevention of IPV perpetration. For these assessments we use an outcome questionnaire at baseline, 1- and 6-months. We collect outcomes on a smartphone using SurveyToGo, anticipating assessments lasting 1-1.5 hours. To diminish social reporting bias we administer questions via earphones plugged into smartphone devices using A-CASI.

Reimbursement. Adolescents will receive 50 Rand (consisting of 25 Rand to offset time and 25 Rand to offset travel costs) for the baseline outcome assessment, 60 Rand (consisting of 35 Rand to offset time and 25

Rand to offset travel costs) for the 1-month outcome assessment, and 70 Rand (consisting of 45 Rand to offset time and 25 Rand to offset travel costs) for the 6-month outcome assessment. In addition, adolescents will receive 50 Rand (consisting of 25 Rand to offset time and 25 Rand to offset travel costs) for the enrollment session and filling out the satisfaction assessments that occur after the first session Adolescents in the intervention arm only, will receive 60 Rand (consisting of 35 Rand for time and 25 Rand for travel) for satisfaction assessments filled out after the second session.).

Sample Size and Power Considerations. The primary objective of this pilot is to test feasibility, acceptability, and generate meaningful effect size estimates for a future fully-powered RCT. A fully-powered study is not our aim. We believe 60 adolescents (30 adolescents per arm) is adequate to examine feasibility and acceptability. We increase sample size by 10% as a conservative estimate during baseline recruitment to 66 adolescents to account for loss to attrition; our previous HIV intervention trial with similar aged adolescents in similar settings had 100% retention at the last follow-up timepoint.[45,192] We considered sample size needed based on the goals of increased condom use at last sex by a third or double as shown in other adolescent HIV behavioral trials,[20,193,194] and reduced sexual assault by half as shown in our previous trials of the SAFE intervention. To examine moderate effects (*e.g.,* 0.50) we would need 200 adolescents, or 100 adolescents per arm, beyond the scope of this pilot. Thus, we focus on rigorously testing acceptability and feasibility.

Analysis. For acceptability, we conduct the same analysis as described for Aim 2, setting 80% reporting positive ratings as a marker of acceptability and examining process data on satisfaction with clarity, structure, content, delivery, location, and timing of the intervention. For feasibility, we evaluate fidelity, setting 80% fidelity as a marker of acceptability. We also evaluate feasibility in regards to attendance rates, treatment retention rate, retention during outcome timepoints, and balance during randomization. For these data, individual ANOVA will be conducted to compare groups (*SAFE South Africa* vs. Control) on the continuous variables of number of sessions attended. For treatment retention rate (dichotomous), a chi-square analysis will be used. For success of random assignment in equating groups, we compare groups on demographic characteristics and primary risk factors for HIV and IPV. If groups differ on any variables that show a relation to outcomes, outcome analyses will be conducted both with and without adjusting for these covariates. For trial outcomes, preliminary analyses will include studies of patterns of missing data, dropout rates, and correlations effect size estimates with small samples have large standard errors so we use pilot data to assess hypothesized intervention effects.[195] We will examine key variables for skewness, variability, missing data, and outliers, with transformations to achieve normality if needed. We will examine descriptive statistics for main outcomes and mediators with extreme scores or deviations from normality to be addressed in subsequent analyses. Baseline differences between groups on demographic variables will be examined using *t*-tests and variables that show differences will be included as covariates in outcome analyses. Generalized estimating equations (GEE) will be used to compare intervention and control group on the main study outcomes following intention-to-treat principles. In exploratory analysis, we look at directions of hypothesized effects for our outcomes. While we are underpowered to test mediation effects directly, we will explore differences between study arms in hypothesized mediating and moderating variables. We will obtain the between treatment condition effect size estimates (with 95% confidence intervals) at each assessment (*e.g.,* Cohen's d or h) to help determine necessary sample size for future fully-powered RCT.[196]

Dissemination. In addition to peer review papers and conference presentations, we will develop research briefs for adolescents, school stakeholders, and policy makers. In Year 3, we will submit an R01 application for a fully powered clinical trial to test the efficacy of *Safe South Africa*.

F. Other Ethical Considerations

Additional ethical reviews. We have submitted an ethical review application to Brown University and provide their letter providing detail that we are able to proceed with Aim 1 with a planned re-review prior to Aim 2 and 3 (see Appendices).

Inclusion of Children. This study will include children. In Aim 1, we will include male adolescents aged 15-17 years (inclusive) for focus groups. In Aim 2, we will include male and female adolescents ages 13-18 (inclusive) for a brief school climate survey, and male adolescents aged 15-17 years (inclusive) for an open

pilot trial of the intervention. In Aim 3, we will include male adolescents aged 15-17 years (inclusive) for a randomized controlled pilot trial of the intervention. The topic under investigation necessitates inclusion of adolescents; we are developing and testing the acceptability and feasibility of an intervention tailored to meet the specific HIV and IPV prevention needs of adolescents. Without adolescent participants, we will be unable to accomplish the study objective of developing knowledge on the acceptability and feasibility of SAFE South Africa, a male adolescent-tailored intervention to prevent HIV risk behaviors and IPV perpetration. 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 informed 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 which falls under legally mandated reporting to police, social services, and IRB including perpetration with identifiable rape or sexual assault victims, being a victim of rape, sexual, emotional, or physical abuse which falls under legally mandated reporting to police, social services, and IRB.

Collaborating Sites. All primary data collection occurs in South Africa, based out of the South African Medical Research Council (SAMRC) via a contractual arrangement with Brown University. Dr. Mathews, M-PI is based at SAMRC. Data will be obtained, managed, and protected through a data agreement between Brown University and SAMRC. M-PI's Drs. Kuo and Mathews will oversee all standard operating procedures including study protocols including ethics; quality control and assurance; and data collection, management, and analyses procedures. In regards to data collection, data will be protected by unique research identification numbers (RINs). Data will be managed in the following manner. First, documents identifying participants by name will be included on password-protected computers and files. Second, these identifiable data will be kept separate from documents containing other participant data. Third, electronic data 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 data remotely on electronic devices). Fourth, paper documents relating to patient data will be kept in locked cabinets accessible only to essential study personnel. For data analyses, analyses procedures will only focus on data associated with RIN. All other identifiers will be expunged from transcripts. Any names or pseudonyms used during focus groups will be replaced with the RIN. To guard against accidental data loss, the project data will be backed up.

Access to Individually Identifiable Information & Data Collection, Management, and Protections. Only PIs, co-Is and other essential project staff will have access to project data. Drs. Orchowski, Abrahams, and Berkowitz will only have access to de-identified participant data. All data will be protected by unique RINs. Identifiable data will be kept separate from documents containing other participant data. Paper documents relating to participant data will be kept in locked cabinets accessible only to essential study personnel. Data will also be backed up by the data enterer and transferred via two-way encryption via the nCrypted Cloud program for PIs and Co-Is to oversee for quality control. Participants' names will never appear in any report resulting from the project. Electronic data, including digital voice recordings and data collected via ACASI on our electronic computer devices (android smartphones) will have several protections. Staff will be trained in procedures for maintaining confidentiality of participant information. Data analyses will only focus on data associated with RIN. All other identifiers will be expunged from transcripts. To ensure data quality, we will implement several quality procedures. These include the following procedures: 1) for quantitative data, quality

checking weekly with our experienced data team for synchronization electronic data, and backup of this data; 2) for qualitative data, transferring of digital files to computers checking of DVR recordings within 48 hours; after transcriptions, a check of transcripts for accuracy and to facilitate cleaning of transcripts.

We use several data systems to protect our data. First is **Filemaker**, our tracking database. This is stored on Brown University's encrypted server and this database is only available to staff tracking participants. It is password protected (in addition to accessibly only by a password protected computer. We also utilize **SurveyToGo Software (http://www.dooblo.net/stgi/surveytogo.aspx).** SurveyToGo will be used to screen for eligibility, and to collect data at baseline, 6- and 12-months. Data center security is protected by state-of-the-art servers hosted by Amazon AWS. Amazon AWS datacenters are housed at nondescript facilities protected by biometric locks and round-the-clock interior and exterior surveillance monitoring. Data center is limited to authorized personnel, who must pass a two-factor authentication a minimum of two times to access the datacenter floors. The software and infrastructure are updated regularly with anti-virus protection and regular security updates. Network security includes an enterprise-level firewall that protects two way data flows. This includes SSL encryption to protect device to server communications and management applications to server communications. SSL certificates are also utilized and al data passes through a checkpoint firewall product to prevent network attacks. All network traffic is stopped at the firewall and monitored with Intrusion Detection and Prevention Systems. Data is strictly regulated. This includes security measures to ensure that data is tied to, owned by, and accessible only by our project team for each specific project. Access to SurveyToGo system for our project team and project is done via user name and password which authenticates authorized access. In addition, we can grant various levels of security and access with delineated rights to data in the project. This role based security can provide a combination of access features including combinations of the following: creating users for the SurveyToGo project, managing storage of data, managing rights to access, viewing rights. This includes the ability for our project team to delete and wipe all data from SurveyToGo servers. Data collection security includes the ability to collect data from the field (in our case using android devices that are password protected and with ncrypted cloud security). SurveyToGo data systems on Android devices will route encrypted data to a secured local database; this data is automatically uploaded to the SurveyToGo remote server and deleted from the device whenever network is detected. If network fails, data can still be collected in offline scenarios and is fully encrypted in this scenario. SurveyToGo allows us to disable devices that may be lost or stolen by de-linking devices to the specific SurveyToGo project immediately or using the auto-sync option of 10 minutes to pull any remaining data from the device. Data stored on a PC includes a built-in encryption mechanism of the Microsoft SQL Mobile to encrypted data on the local hard drive of the machine. We use a scanned TeleForm system for paper data collection. All paper versions are stored in locked study cabinets in project offices upon scanning. The scanned versions are stored on **Ncrypted Cloud** which offers similar state of the art protection as detailed for SurveyToGo. Ncrypted Cloud includes double encryption, zipping of files, password protected entry to folders and files each and every time or once, authorization of every user by the PI. This program also allows the PI to track which authorized individual has accessed files and when and changes that have occurred including deletions, copies. The PI can bar all copying or set limits to copying of files. Importantly, data is wipeable via "unlink" function from a central location in case of theft or loss. To guard against accidental data loss, the project data will also be backed up.

Potential Risks to Subjects. This research includes a number of potential risks. We highlight these and the steps we take to minimize risk.

1) *Sensitive Information*. Participants may feel uncomfortable with the sensitive nature of some of the survey and/or interviews or research staff's questions. For example, we ask about sexual and reproductive health questions. To minimize discomfort, we use a highly trained team (hiring from our pilot study team) who have experience conducting sensitive research to gather outcomes data. We also use a computerized mobile smartphone to collect data, which offers privacy both visually and in regards to sound in our deployment of Audio Computer-Assisted Self-Interviewing Software (ACASI) for sensitive questions to limit social desirability bias in participant reporting of data. The scientific team will train and supervise the RAs in these procedures and techniques to gather data sensitively. If any such moments of sensitivity occur during the study, the M-PIs will be available for consultation. Further, if participants experience discomfort, they will be given the option of taking a break, or rescheduling. Further, any distress will be minimized by assurances

that participants can refuse to provide any data and that they can withdraw from the study at any time without penalty. For group based intervention sessions, we will protect against the risk of loss of confidentiality during the group intervention by extensively training intervention facilitators in the importance of maintaining confidentiality of participant information. Topics discussed in the program are personal and sensitive in nature. Participants may disclose personal information in the group programs that other participants may not otherwise have known. Although participants will not be encouraged to do so, participants may also disclose sexual experiences and prior engagement in coercive sexual behavior during a group session. To minimize these risks, the interventionists will detail under what circumstances they will maintain confidentiality (and when they will not due to legally mandated disclosures). Furthermore, interventionists will minimize participant disclosure within the group session. Participants will be informed that they may refuse to participate in the group at any time. Consistent with standards of practice for administering group interventions, the interventionists will emphasize the importance of group members protecting one another's confidentiality in the group and throughout the course of the study. Prior to participating in the group, participants will be provided with a statement noting the nature of the group process. Some participants may choose to attend the groups but not make verbal comments during the sessions. Participants will also sign an agreement of group confidentiality, which reinforces the confidential nature of group discussions. However, we cannot guarantee protection of confidentiality by other group members and will make this clear.

2) There is a small risk of *loss of privacy or confidentiality of data*, including sensitive data on sexual behaviors, other risk behaviors, and psychological characteristics. This risk increases in the focus group discussion (in Aim 1). We take this risk seriously, and we will take steps to protect participants' identities. As outlined in the previous section, we will ensure that all personal identifiers are removed from the data and any publications arising from the study. We will make clear prior to the start of the focus group discussion that we cannot guarantee the absolute confidentiality of participant statements made in the group setting, and we will encourage them to use aliases for the group discussion. The informed consent and assent documents will highlight confidentiality risks. We will inform both adolescents and parent during the informed consent and assent process that we will not share information about anything disclosed in focus groups unless in a case of self or other harm and legally mandated reporting requirements. We will ensure that personal identifiers are never included in any research or analytical datasets, or any publications arising from the study. The informed consent documents will bring confidentiality risks to participants' attention and situations under which disclosure can occur (and to who). Names and any other specific personal identifiers will not be included in any datasets: only a unique participant RIN. Tracking information (including names and telephone numbers) will be available solely to the project staff in charge of planning and organizing follow-up visits. We explain the extensive data protections put into place for our data above.
3) Participants may experience *stigma or discrimination* due to sexual behaviors, self-report HIV status, or IPV perpetration behaviors. We have taken steps to minimize the risk due to association with our pilot study through careful wording of the consent and assent forms emphasizing prevention (meaning participants are not selected based on IPV perpetration of HIV status) and through careful discussion of participation in group settings and the limits we have in protecting information disclosed in group settings with other participants being present. We also put in place data handling, storage, and analysis practices to protect participants' anonymity. We will provide training for all project staff on the needs and strategies for maximizing participants' anonymity.
4) *Psychological distress or retribution:* Thus are concerns including 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. The scientific team has extensive experience in interviewing participants, including adolescents around these topics and rarely have participants reacted to these types of questions with more than temporary embarrassment or mild discomfort in group discussion because they can decide what to discuss. For other data collection, we gather data using sensitive self-report methods including anonymized surveys and ACASI. The scientific team will train and supervise the RAs in these

procedures and techniques to gather data sensitively. If any such moments of sensitivity occur during the study, the M-PIs will be available for consultation. Further, if participants experience emotional discomfort, they will be given the option of taking a break or rescheduling the focus group discussion or other data collection for another date and time. Further, any distress will be minimized by assurances that participants can refuse to answer any particular question they do not feel comfortable addressing and withdraw from the study at any time without penalty. For consent and assent procedures for Aims 1, we will spend significant time discussing what topics will be covered, particularly highlighting what questions will explore including HIV-status, perpetration behaviors. We will emphasize that adolescents can halt participation at any time without consequence. We will also emphasize that although study staff will protect confidentiality of participants, this is not guaranteed in group settings. 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. We balance these legal norms from South Africa on protecting the best interests of the child. For some data, we collect it anonymously (as in the school climate survey in Aim 2), 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 detailed above. 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 will refer adolescents to appropriate HIV support, mental health, and social support services, and for various psychological issues to the specific DCAPs within catchment areas after gaining permission for research from the Department of Education. In our weekly team meetings, we explicitly probe for any unanticipated ethical situations which do not need immediate emergency attention. All ethical emergencies requiring urgent attention are reported to the PIs immediately. All procedures will be reviewed by institutional IRBs.

Planned Procedures for Protecting Against or Minimizing Potential Risks

Overview. For adolescents, during assent procedures, and for parents during consent procedures, we highlight the legal norms that would require break in confidentiality, and who information would be reported to. For both adolescents in focus groups, we will minimize loss of privacy by limiting access to individually identifiable information using unique RINs on all paper, electronic data, and analyses. Electronic data, including digital voice recordings and data collected via ACASI will have several protections. First, all data will be stored on password-protected computers including smartphones and files. Second, all files on project computers and android smartphones 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, smartphones, and external harddrives), 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 African'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, a weekly meeting 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.

Unanticipated Problems or Adverse Events. If an Unanticipated Problems or a Serious Adverse Event occurs at the study site and is more likely than not related to the research activity, and places participants or others at a greater risk of harm than was previously known or recognized, the M-PIs will report the event in writing using the appropriate forms to IRB. The M-PIs will also report Serious Adverse Events in writing to the sponsor. The M-PIs will review the Adverse Event report with the entire study team and gather any information needed to investigate the event and to determine subsequent action. The M-PIs will document and report any subsequent action to IRBs. We will also generate a brief report of Adverse Events for the study record each year, and we will forward the report to Brown University IRB, SA MRC HREC, and NIH.

Potential Benefits of the Proposed Research to Human Subject and Others. There may be little or no direct benefit to participants from the study. Some possible benefits may include informing HIV and IPV prevention science. Adolescent participants will be given information on HIV, IPV, general health, and social services and referrals if necessary. The risks associated with this research are reasonable in relation to the anticipated benefits of advancing empirical knowledge adolescent prevention approaches for this high priority population and setting.

Importance of Knowledge to be Gained. To our knowledge, this will be the first intervention to prevent adolescent HIV risk and IPV perpetration in an integrated manner and in a high impact setting (South Africa).

Data and Safety Monitoring Plan

Data Protected by Unique Research ID Number (RIN). Every individual that expresses interest in our study and is deemed eligible will be assigned a RIN. All data they provide will be identifiable only by the RIN, which will not contain any personal identifiers. During this study, we will take precautions to separate any documents that identify participants by name from documents that contain participant data. Documents that identify participants by name will include the password-protected file containing participants' signed informed consent/assent forms and signed documentation that participants have received reimbursement. These documents will be kept entirely separate from any documents containing participant data. Paper documents that identify participants by name will be kept in locked cabinets in the offices of study personnel. Data will also be backed up on a weekly basis and transferred via two-way encryption via the nCrypted Cloud program for PIs and Co-I to oversee for quality control. Participants' names will never appear in any report resulting from the project.

Electronic data, including digital voice recordings and data collected via ACASI on android smartphones will have several protections. First, all data will be stored on password-protected computers and phones and files on these electronic devices will store data within electronic files that are further protected via nCrypted Cloud, approved by Brown's Computing, including their information security division. NCrypted Cloud software offers two-way encryption with secure access controlled by M-PIs (who can turn on and off access to password protected files from a central location) and wipe all data from devices. NCrypted Cloud also enables the M-PIs to control who has access, who can move files from the secured and encrypted cloud serve onto local hard drives (including computers, smartphones, 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. Fourth, audiotapes will be transferred to a secure computer within 48 hours of recording. Encrypted data on the nCrypted Cloud server can be downloaded daily from any location in the world (via secure password) and if authorized by the PIs, saved to password protected hard-drives on computers dedicated solely to the project. Data analyses will only focus on data associated with RIN. All other identifiers will be expunged from transcripts. Any names or pseudonyms used during focus groups will be replaced with the RIN. To guard against accidental data loss, the project data will be backed up onto a secure server weekly.

Encouraging Focus Group Participants to Maintain Confidentiality. At the start of each focus group, we will emphasize the need for confidentiality and discuss the need for participants to refrain from sharing others' comments with any other person after the group ends. We cannot completely safeguard the confidentiality of participants' statements during focus group sessions, because these sessions involve multiple participants. We will state this fact explicitly when we obtain informed consent and assent from focus group participants. We will strongly encourage focus group participants to use aliases during the group discussion to protect their names.

Training in Confidentiality. The M-PIs will provide the study team with training in all ethical procedures including informed consent/assent, maintaining confidentiality, and protecting confidential data. This training includes for example, the importance of securing participants' privacy, the separation of data from identifiers, and protocols for using locked offices, filing cabinets, and password-protected files to avoid unauthorized use of participant data. The study team will meet regularly to discuss protocols for maintaining participants' privacy. The study team will also follow institutional policies at Brown University for requiring mandatory training in human subjects protection before conducting any study activities.

Protocols for Audio Files. Focus group discussions will be recorded on digital voice recorders. Given our precautions to maintain confidentiality, the risk of a confidentiality breach related to recorded data is minimal, and that it is reasonable in relation to the benefits to be gained by recording focus groups. This risk is also reasonable in relation to the importance of the knowledge to be gained from our study. After each day of recording, the group facilitator will transfer all new recordings to a project drive on a password-protected computer. He or she will label files with the number of each focus group and ensure that files are password-protected. To guard against accidental data loss, the project data will be backed up weekly. All original recordings will be removed from the digital voice ecorders immediately after transferring the recording to a password protected and secure project drive and before starting a new focus group. Transcript files will also be stored securely in password-protected files, on password-protected computers. The transcript file has been "cleaned" after it has been reviewed by project staff who participated in the focus group for accuracy, and to expunge any identifying information other than a participant's RIN (e.g., name, address, name of school, etc.). After a transcript file has been "cleaned", this will be the primary document for analysis in NVIVO. RAs will receive ongoing supervision and training in regular meetings, which will also ensure continued compliance with data safety protocols. The M-PIs will be responsible for ensuring that study protocols for maintaining confidentiality are followed. Serious adverse events will be reported to and written reports will also be provided NIH.

Data and Safety Monitoring. Aim 1 is comprised of qualitative focus groups. Aim 2 is an open pilot of our intervention to assess acceptability. Aim 3 is a randomized controlled pilot trial of our intervention to assess feasibility. For both Aim 2 and Aim 3, this is a pilot of a prevention trial (thus not a treatment) and not requiring interim analysis for safety and monitoring. Thus our focus is on identifying Unanticipated Problem or a Serious Adverse Events that may occurs at the study site and is more likely than not related to the research activity, and places participants or others at a greater risk of harm than was previously known or recognized.

M-PIs are responsible for monitoring the safety and efficacy of this trial and complying with the reporting requirements. The safety of participants will be monitored during each contact with study participants. There will also be regular team meetings monitoring of the safety of participants. If Serious Adverse Events, Unanticipated Problems occur, M-PIs will report the event in writing using the appropriate forms to IRB. For Serious Adverse Events that require clinical care, referral for appropriate care for subjects will be conducted for them to access care within South Africa's free at point of care public health care system.

The M-PIs will review the Adverse Event report with the entire study team and gather any information needed to investigate the event and to determine subsequent action. The M-PIs will document and report any subsequent action to IRBs. We will also generate a report of Adverse Events for the study record each year, and we will forward the report to Brown University IRB, SA MRC HREC and NIH.

G. MANAGEMENT DETAILS

Staff and Scientific Collaboration

Our multidisciplinary team consists of highly qualified, accomplished personnel with extensive experience in the areas of adolescent preventive interventions for HIV and IPV in South Africa and globally. Our investigative team currently has multiple projects in South Africa on adolescent HIV and IPV. Dr. Caroline Kuo (M-PI) will contribute social and behavioral expertise in adolescent HIV prevention including adaptation of empirically supported HIV interventions from outside of South Africa to South Africa, and in mixed-methods formative intervention development research that will yield appropriately tailored interventions for adolescents. She has 4 ongoing studies in Cape Town as an investigator (NIH grants: K01 NIMH 096646, R24 NICHD 077976, R21 NIAID 116309, R21 NIAID118393) and 1 other study (iLink: Incentives for Linkage to Care for HIV positive individuals) in a mentor role. Dr. Kuo directly collaborates with Dr. Cathy Mathews on 2 of these studies (K01 NIMH 096646 and R24 NICHD 077976), and Dr. Harrison on 3 studies (R24 NICHD 077976, R21 NIAID118393 and iLink). Dr. Cathy Mathews (M-PI) is a public health scientist with expertise in adolescent interventions for HIV and IPV, and specializing in school-based intervention trial design and testing. Her research is specifically focused on testing interventions for scale-up in school and health systems, and de-signed to inform national policies related to adolescent sexual and reproductive health in South Africa. Dr.

Abigail Harrison (co-I) will contribute her substantial expertise in qualitative sexual and reproductive health research with South African adolescents. She has served as M-PI or co-I for multiple NIH-funded awards in South Africa. She has investigated the social context of adolescent HIV risk and preventive behaviors in South Africa (R01 HD41721) and is experienced in the design and evaluation of interventions for adolescents (R01 HD37343). Dr. Lindsay Orchowski (co-I) will bring her substantial expertise in the Safe violence preventive intervention being used in the study. She is PI of a large-scale, CDC-funded evaluation of sexual assault prevention programming for high school boys, as well as middle school boys. She is currently the PI of an NIAAA R34 grant designed to evaluate the Safe program for men in the military. She served as the study coordinator for a large-scale (N =1285), CDC-funded evaluation of sexual assault prevention programming (with Dr. Alan Berkowitz) and has published extensively on sexual assault risk reduction and prevention programs. Dr. Alan Berkowitz (consultant) is an expert in social norms theory, bystander intervention, and engaging men in sexual assault prevention. A collaborator on the design of the Men's Workshop (which forms the basis of the Safe pro-gram), he has worked with Dr. Orchowski in three evaluations of the model. Dr. Naeemah Abrahams (consult-ant) is an expert in violence risk reduction and prevention in South Africa as well as gender norms and relation-ships. She brings significant content expertise in IPV and interpersonal violence research within South Africa and has extensive knowledge of the South African ethical challenges of violence research with adolescents. Dr. Kuo, Mathews, Abrahams and Orchowski recently collaborated on an edited volume on sexual violence which has been accepted for publication by Elsevier entitled, "Sexual Assault Risk Reduction and Resistance: Theory, Research, and Practice."

Management Approach

We propose a multiple PI leadership plan that involves sharing responsibility by two M-PIs, Dr. Caroline Kuo (Brown University) and Dr. Catherine Mathews (Medical Research Council). This scientific collaboration is stronger than a study conducted by either the USA-based or South African-based team alone. We are able to consolidate expertise with South African adolescents at risk for HIV and IPV. This collaboration also illustrates our philosophy of multidisciplinary and equitable international research partnerships. Dr. Kuo contributes significant expertise in adolescent behavioral and social risk. She also brings expertise in mixed-methods for intervention development and adaptation of empirically supported programs to the South African context as well as international data systems and mobile data collection in South African community contexts. Her experience will facilitate tracking and tracing of adolescents for collection of data in the community setting, and high quality data collection from adolescents on sensitive topics. Dr. Mathews contributes significant experience in adolescent HIV, sexual and reproductive health, and IPV. She brings vast expertise in intervention trial design, implementation, analyses, and dissemination for maximum health systems and policy impact. She is also an expert in trial implementation among South African adolescents in school settings.

Dr. Kuo will have oversight of Brown University activities including the subcontract to the University of Cape and submission of reports to NIH. Dr. Mathews will have oversight over Medical Research Council sub-contract activities, in close collaboration with Dr. Kuo. Project progress will be summarized weekly in order coordinate scientific, fiscal and administrative management of the project, setting priorities for allocation of resources and funds. Together, Drs. Kuo and Mathews will ensure adequate systems, working with their experienced institutional financial and grants management teams, to ensure that grant activities are in compliance with US laws, and DHHS and NIH policies, including biosafety, the protection of Human Subjects, data and facilities, as well as parallel applicable laws and policies in South Africa. In the case of unanticipated serious adverse events, and with the permission of children and parents, we will refer to services by tapping into the extensive social service and clinical networks that we have worked with for adolescent health in South Africa including both Drs. Kuo and Mathew's respective affiliation with the Medical School at University of Cape Town.

Authorship for peer-reviewed manuscripts, book-chapters, scientific conference presentations, policy and clinical briefs, and child-friendly dissemination briefs resulting from project activities will be determined prior to creating drafts for these outputs. Authorship will be negotiated based on the relative scientific contributions of the PIs, Co-I, consultants, and key personnel, following international guidelines set by the International Committee of Medical Journal Editors (ICMJE). All decisions regarding the technical aspects of

the project will be decided jointly in weekly Skype meetings by the M-PIs and Co-Is. In the unlikely case of conflicting opinions regarding the technical approach of the study, the M-PIs, Drs. Kuo and Mathews will consult with co-Is (Drs. Harrison and Orchowski).

Facilities

The South African Medical Research Council (SAMRC) will serve as the South African site for this proposed study. Dr. Catherine Mathews (M-PI) is Chief Specialist Scientist and Director of the Health Systems Re-search Unit. She is co-Director of the Adolescent Health Research Unit at the University of Cape Town. She is a member of the Cochrane Sexually Transmitted Infections Review Group. She also holds an appointment as Honorary Associate Professor in the School of Public Health and Family Medicine and in the Department of Psychiatry and Mental Health at University of Cape Town. Dr. Mathews shared appointment at the University of Cape Town has provided many opportunities to collaborate with Drs. Kuo and Harrison. Dr. Kuo (M-PI) also holds an appointment in the Department of Psychiatry and Mental Health at the University of Cape Town; Dr. Harrison (co-I) also holds an appointment in the School of Public Health and Family Medicine at University of Cape Town. Dr. Naeemah Abrahams (expert consultant) is Chief Specialist Scientist and Deputy Unit Director of the Gender and Health Research Unit, also based at the SAMRC. She also holds an appointment as Honorary Associate Professor with University of Cape Town's Faculty of Health Sciences in the School of Health and Rehabilitation Sciences, as well as Extraordinary Professor with University of Western Cape's Faculty of Community Health Sciences in the School of Public Health.

The SAMRC is a South African and international leader in research on adolescents including HIV, adolescent sexual and reproductive health, and IPV. There is strong interdisciplinary collaboration between research units at SAMRC, with Dr. Mathews' and Abrahams' respective units located adjacent to each other and their offices several doors away from each other. Such close physical proximity facilitates collaboration on this proposed study. SAMRC provides an exceptional research environment, particularly in regards to HIV and IPV including sexual violence prevention research. The SAMRC was established in 1969 with a man-date to improve the health of the South African population, through research, development and technology transfer, so that people can enjoy a better quality of life. Both Drs. Mathews and Abrahams bring decades of experience and hold leadership positions in research units within SAMRC focused on adolescent HIV and sexual health and IPV research.

SAMRC offers a full administrative and grants management staff to assist in pre- and post-award management. Speaking to SAMRC's capacity to address post-award financial management, including review, approval and processing of all transactions associated with the sub-contract of this award, SAMRC currently manages over 100 active research grants. The Professional Sup-port Services team at SAMRC manages all its research contracts by complying to all research contract conditions as well as statutory and legislative requirements.

SAMRC has robust access to a physical library housed on their campus as well as electronic access to the majority of academic databases related to this proposal. Investigators from SAMRC will also utilize their affiliations at University of Cape Town to access library resources (where both Drs. Mathews and Abrahams have appointments). University of Cape Town has 9 libraries spanning across three campuses including a dedicated Health Sciences Library. The University of Cape Town library system houses 1.2 million volumes. Journal volume holdings alone consist of over 72,000 e-journal titles and more than 28,500 print journal titles. In addition, University of Cape Town faculty and students have access to 190 high-quality electronic databases. The libraries have fully staffed user service desks with knowledgeable library professionals to assist with research needs.

SAMRC will provide fully equipped office space dedicated to Drs. Mathews and Abrahams and their research team. The SAMRC research campus is secured at all times with both physical security and 24 hour security personnel. All offices are secured and include locked filing cabinets. SAMRC offices are fully equipped with high speed laser printers, scanners, fax machines, and photocopy machines.

Computing at SAMRC is linked to high-speed networks. SAMRC has a fully staffed information technology support team. We have coordinated our information technology teams to facilitate. SAMRC also offers a wide range of applications for office computers including the software needed for research (i.e.,

Microsoft Office, NVIVO, SPSS, etc.). Data will be captured onto password protected computers and backed up daily onto a secure server. Data on this server can be downloaded daily from any location in the world using two-way encryption and saved to password protected computers dedicated solely to the project. Data will also be backed up onto an encrypted hard-drive on a weekly basis and transferred via two-way encrypted files to the M-PI's quality control. Drs. Mathews, Kuo, and Harrison have worked extensively on past collaborative projects to develop a user-centered, real time data system capable of collecting secure human subjects data in an adolescent friendly manner.

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Ensayo clínico randomizado por clusters para determinar la efectividad del 'Stepping Stones' en la prevención de infecciones por VIH y promover un comportamiento sexual más seguro entre jóvenes de la zona rural del Cabo del Este, Sur África: Diseño del estudio, métodos y hallazgos basales. Tropical Medicine & International Health 2006;11:3-16.
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