STUDY PROTOCOL

Tough Talks: Virtual Support for Difficult Conversations: Using Artificial Intelligence to Increase HIV Disclosure among Young Men Who Have Sex with Men

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Tough Talks

Virtual Support for Difficult Conversations: Using Artificial Intelligence to Increase HIV Disclosure Among Young Men Who Have Sex With Men

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List of Abbreviations and Definitions of Terms

AE	Adverse event
AI	Artificial Intelligence
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral treatment
ASSIST	The Alcohol, Smoking, and Substance Involvement Screening Test
BSI	Brief Symptom Inventory
CAI	Condomless Anal Intercourse
CASI	Commuter Assisted Self-Interview
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CRF	Case report form
DAIDS	Division of AIDS
GCP	Good Clinical Practices

HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IGHID	Institute for Global Health & Infectious Diseases
IRB	Institutional Review Board
MSM	Men who have sex with men
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
PI	Principal Investigator
PrEP	Pre Exposure Prophylaxis
OHRP	Office of Human Research Protection
RCT	Randomized controlled trial
RNA	Ribonucleic acid
SAE	Serious adverse event
SCT	Social cognitive theory
SID	Study ID number
SMART	Study Management and Retention Tool
SOC	Standard of care
SRV	Study Recruitment Venue
SSL	Secure Socket Layer
UNC	University of North Carolina
US	United States
VAS	Visual analogue scale
VBI	Virtually Better, Inc.
VL	Viral Load

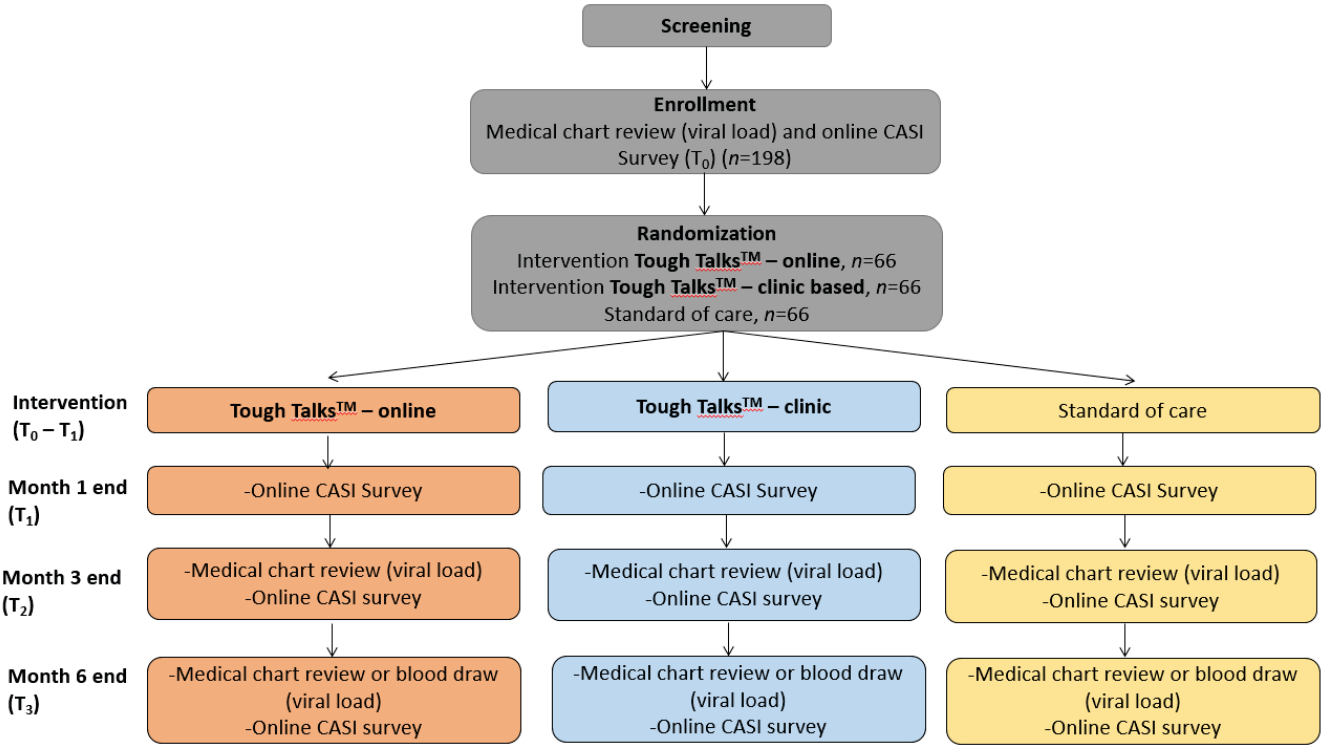
VR	Virtual Reality
YMSM	Young men who have sex with men

Study Abstract

Protocol Title	Tough Talks - Virtual Support for Difficult Conversations: Using Artificial Intelligence to Increase HIV Disclosure Among Young Men Who Have Sex With Men
Design	This study includes 2 phases: Phase 1: a technical pilot to optimize functionality and technical performance; and Phase 2: a three-arm RCT to evaluate efficacy and effectiveness of **Tough Talks** among HIV-positive YMSM.
Intervention Description	Tough Talks is an application (app) for smartphones or tablets for young men living with HIV to learn about and practice HIV disclosure in a safe space. Tough Talks helps young men living with HIV to think about and practice disclosing. The app includes four sections (Understanding disclosure; Should I disclose? How do I disclose?; Preparing for the outcome) with information about disclosure, activities to encourage YMSM to think about their own disclosure values and style, choose your own adventure style games, and virtual reality scenarios for them to practice disclosing their status safely.
Protocol Duration	24 weeks for Phase 2
Sample Size	We will recruit approximately 210 YMSM (8-16 in Phase 1; 198 in Phase 2) across 6 study sites (Chapel Hill, NC; Houston, TX; Tampa, FL; Bronx, NY; Atlanta, GA; Charlotte, NC) that have extensive experience engaging, enrolling and retaining HIV-positive YMSM. For Phase 2, we will also recruit and enroll YMSM nationwide to participate remotely.
Population	1) age 16-29 years; 2) assigned male sex at birth; 3) male-identified; 4) HIV positive; 5) owns and has reliable access to a mobile device (smartphone) or tablet; 6) able to understand, read, and speak English; 7) reports ≥1 episode of anal intercourse with a male partner in past 6 months OR reports a sexually transmitted infection (STI) diagnosis in the last six months; 8) For RCT only: have a viral load measurement within 12 months prior to enrollment (or on day on enrollment). As this is a minimal risk study, we will use a waiver of parental consent for YMSM under age 18.
Data Collection	During the piloting and RCT stages, YMSM will complete computer-assisted self-interviews (CASI). Pilot trial participants and a sub-set of RCT intervention participants will complete a post-intervention qualitative interview. During the RCT, data will also be collected via chart review. Audio recorders will be used to record the content of the discussions during the qualitative interviews.

	The data collected from individuals will be stored using a numerical system to identify each subject. Only the staff working on this study will have access to the records and identities of the subjects. This includes the Principal Investigators, Co-Investigators, and additional members of the research team.
Objectives	1. A technical pilot to optimize functionality and technical performance. 2. A three-arm RCT to evaluate efficacy and effectiveness of **Tough Talks** among HIV-positive YMSM.
Outcomes	**Primary outcome**: Viral load (VL) suppression defined as HIV RNA < the lower limit of detection as per the laboratory at each clinical site. **Secondary outcomes**: We will also assess intervention efficacy on a panel of self-reported outcomes including sexual risk, STI infections, disclosure behaviors, intentions and self-efficacy.
Number of sites	6 in-person (Houston, TX; Bronx, NY; Tampa, FL; Chapel Hill, NC; Atlanta, GA; Charlotte, NC); nationwide recruitment for remote procedures
Clinical Samples	Viral load suppression: Viral loads will be assessed through chart review, blood draw, or participant shared documentation at baseline, 3 and 6 months. Participants with no VL result in their medical record in the 2 months prior to or 3 months after their 6-month follow up visit will have one drawn for the study. Participants may also self-report viral load at 6 month. Viral load suppression will be defined as HIV RNA < lower limit of detection as per the laboratory processing the sample.

Phase 2 (RCT) Study Schema



1.0 INTRODUCTION

1.1. Background

Men who have sex with men (MSM) account for nearly two-thirds all of new HIV diagnoses in the United States (US) and young MSM (YMSM) continue to be disproportionately affected[1]. Among youth living with HIV, 67 percent report not disclosing to their first-time sex partners[2]. Disclosing of one's HIV status is important for accessing support which can lead to improved medication adherence and retention in care. Those who disclose are more likely to use condoms with HIV-negative sex partners[3] and mathematical modeling estimates that increased HIV status disclosure to sex partners may reduce transmissions by 40-60%[4,5]. Further, disclosure may motivate HIV-negative sex partners to seek testing and reduce their own HIV transmission behaviors. Given the potential benefits and challenges associated with disclosure, there is a need for sophisticated interventions that can assist MSM with the disclosure process. Virtual reality provides a unique environment for users to practice HIV disclosure. Artificial intelligence (AI) driven disclosure may offer advantages over in-person role play through the use of realistic avatars that represent potential romantic partners, and probabilistic settings where users envision having disclosure conversations. Users have the opportunity to practice disclosing and experience a variety of responses and outcomes. During Phase I of this project we developed an iPad-based virtual reality system that features three avatars, two virtual locations and three disclosure scenarios which represent a variety of common disclosure experiences and contexts experienced by YMSM[6]. In Phase II, we will further enhance **Tough Talks** and develop a full-feature automated version to test via a multi-site, randomized controlled trial (RCT).

1.2. Rationale

HIV status disclosure is a stressor in the lives of many HIV-positive persons[7]. Failure to disclose HIV status can negatively impact health, impeding adherence to care or medications and hindering reduction of sexual risk behaviors[8,9]. Moreover, individuals who fail to disclose miss the positive effects of post-disclosure support[9,10]. Disclosure to sexual partners, friends, and family can lead to social support, closer relationships, antiretroviral therapy (ART) initiation, adherence, and improved psychological well-being[9,11]. Notably, one study of 373 HIV-positive patients in Seattle found an independent association between disclosure of HIV and increased CD4 T-cell counts over time[12]. A study by Kalichman et al. found that among 538 sexually active HIV+ MSM, engaging in sex without a condom with undisclosed non-concordant partners was associated with worse ART adherence and greater likelihood of unsuppressed HIV[13].

Among MSM, many studies have found that disclosure of HIV status leads to a reduction in sexual risk[14,15] and increased social support[9,10]. Most data show that individuals who can communicate with sex partners about sexual health topics, including disclosure of HIV status, are more likely to engage in condom use behaviors[14-17]. Furthermore, disclosure may motivate sex partners to seek HIV testing and reduce their own HIV transmission behaviors, as well as influence other risk-reduction strategies such as strategic positioning (choosing insertive or receptive anal intercourse based on serostatus), serosorting (limiting sexual partners to those of the same serostatus) and the use of pre-exposure prophylaxis (PrEP)[18-20].

Stand-alone eHealth interventions are potent tools for public health. Unlike traditional in-person interventions, stand-alone eHealth interventions are not limited by cost or availability of interventionists to deliver them. Further, eHealth interventions are scalable and accessible, especially for youth who engage with technology on a regular basis and are early adopters[21]. In addition, eHealth interventions have the potential to be customizable to the unique participant based on user input.

Virtual Reality (VR) has great potential as an educational tool by offering participants a safe, situated learning space where they can learn-by-doing and problem solve in a realistic environment that enables the transfer of skills learned in VR into real life[22-24]. VR allows participants to practice disclosing to realistic virtual characters that represent potential romantic partners, as well as in realistic settings. Participants have the opportunity to practice disclosing using a variety of strategies and experience different outcomes including acceptance, confusion, lack of HIV knowledge, and rejection.

VR is a technological tool that can be used to enhance learning by eliciting participant emotions and invoking affective experiences through interaction with its contents. It provides several key advantages over current methods of delivering HIV prevention interventions, such as role-play and video vignettes[25]. Specifically, the sensory-rich, immersive environments of VR (virtual characters, visual ambience, directional audio, culturally specific content) provide a realistic avenue for YMSM for mental rehearsal and performance of HIV disclosure behaviors in a controlled environment where new challenges can be gradually introduced. Further, VR environments provide a standardized setting that can be controlled and replicated to deliver the intervention in a systematic manner. Additionally, incorporating interactivity and game mechanics (e.g. customizable virtual characters, virtual conversations) is highly innovative and will provide participants with a compelling, engaging experience that will motivate and support behavior change.

Scientific Premise: Disclosure impacts adherence in care, viral suppression, HIV transmission and mental and physical health. There are no stand-alone sexual partner disclosure interventions, much less any that can be delivered wholly online. **Tough Talks**, a VR HIV disclosure intervention, shows the potential for theoretically backed VR interventions to work as a tool to build self-efficacy. A similar strategy could be applied to other topics that impact an individual's health and wellbeing - from coming out about one's sexual or gender identity, to training doctors to improve delivery of difficult diagnoses, and to helping their patients learn to talk with their families about a variety of medical conditions.

Table 1: Description of Tough Talks application

Module	**Description**	**List of Activities**
Understanding Disclosure	Participants go through activities that set up what it means to disclose your HIV status, while reminding them that they are not defined by their status and that disclosure is a choice. Activities in this module include exercises about disclosure laws across the country, thinking about different situations in which you may have to disclose or not (to an employer? To a roommate? To a sex partner? Etc.), and a mock texting activity	• Choose your own adventure: It's Like Coming Out…Again • What is disclosure? (video) • Disclosure and the Law • Do I have to disclose if… • HIV doesn't change who I am • Disclosure Advice • Virtual Disclosure Practice

	where they give advice about disclosure to a friend.	
Should I disclose?	Participants are led through a series of activities that model different ways to think about and decide if they want to disclose to someone. Activities in this module include reviewing a list of items and assigning them as pros or cons of disclosing, and thinking about the right time and place to disclose.	• Choose your own adventure: Learning the Ropes • Past Disclosure Experiences • To disclose, or not to disclose? • Disclosure experience videos • Right Time, Right Place • Virtual Disclosure Practice
How do I disclose?	Participants are presented with different ways to disclose to someone and encouraged to think about what ways feel best to them. Activities in this module include reviewing different ways to go about disclosure, and what disclosure can look like depending on what feels right to the participant.	• Choose your own adventure: He Likes Me…He Likes Me Not • Ways to Tell Someone • Texting Disclosure • Would I say that? Conversation Starters • How to Deal with Someone Finding Out • Virtual Disclosure Practice
Preparing for the outcome	Participants explore activities that help them think about the outcome after disclosure, from receiving support, to how to handle a poor reaction. Participants are reminded that they aren't responsible for how others respond. Activities in this module include reviewing a list of commonly asked questions and answers (ex. Is there anything I can do to protect myself? What does undetectable mean?) and thinking about what they feel comfortable answering.	• Choose your own adventure: Worst Case Scenario • Are You Prepared for the Questions? • After you tell them. What are you willing to answer? • How Would YOU answer? • What am I most afraid of? • How to exit "gracefully" if things go awry • Virtual Disclosure Practice

2.0 STUDY OBJECTIVES

2.1 Primary Outcome

The primary outcome is viral load (VL) suppression. Viral load suppression will either be obtained by chart review, or drawn for the study. Viral load suppression will be defined as HIV RNA < the lower limit of detection as per the laboratory processing the sample.

2.2 Secondary Outcomes

We will also assess intervention efficacy on a panel of self-reported outcomes including condomless anal intercourse (CAI), STI infections, and disclosure behaviors, intentions and self-efficacy. For binary outcomes, we define intervention efficacy as a difference in proportions, while for continuous outcomes, we define efficacy as a difference in means. (See Table 2 on page 45)

2.2.1 Cost Outcomes and Cost Effectiveness

To compare costs between the intervention arms, we will collect information on (1) time spent by study staff for training and supervision of delivering the clinic VR intervention; (2) time participants spend in the clinic sessions; and (3) costs associated with the delivery of both home and clinic arms. The procedures we will use to quantify the resources required to deliver the interventions will be organized in standard expenditure categories: personnel, supplies, equipment, services, space, and overhead. Incremental cost effectiveness ratio between the 2 intervention arms will be defined as $\Delta C/\Delta E$, where ΔC denotes the estimated difference in mean costs of the intervention and ΔE reflects the estimated difference in mean effectiveness of proportion suppressed between the interventions.

2.3 Hypothesis

We have the following hypotheses:

A. Participants in both intervention arms will be more likely to be virally suppressed at 6 months compared to participants in the SOC arm.
B. Participants in both intervention arms will report less CAI with potentially susceptible partners at six months compared to participants in the SOC arm.
C. Participants in Arm 2 (clinic) will report greater intervention satisfaction and immersion but Arm 2 will be costlier.

3.0 STUDY DESIGN

This study includes 2 phases:

1) A technical pilot to optimize functionality and technical performance of the intervention; and
2) A three-arm RCT to evaluate efficacy and effectiveness of **Tough Talks** among HIV-positive YMSM.

3.1 Study Population

The total study sample is approximately 210 YMSM, of which the following will be enrolled for each phase: 1) a technical pilot will be conducted with 8-16 HIV+ YMSM in North Carolina; 2) and an RCT will be conducted with 198 HIV+ YMSM by study staff at 6 study sites (Houston, TX; Bronx, NY; Tampa, FL, Chapel Hill, NC; Atlanta, GA; Charlotte, NC). For the RCT phase, participants may also be enrolled remotely from any state in the United States.

3.2 Sample Size

We will recruit approximately 210 YMSM (8-16 in Phase 1; 198 in Phase 2). To ensure inclusion of diverse youth who are representative of the US epidemic, we will attempt to oversample YMSM of color, with a goal of enrolling two-thirds of the cohort YMSM of color.

3.3 Study Randomization, Stratification, or Description of Non-Random Assignment Procedures

Technical Pilot: Participants will be recruited from UNC-Chapel Hill. We will enroll 8-16 participants. After participants are consented, they will complete a web-based computer assisted survey instrument (CASI) using Qualtrics software. Participants will be randomized to either use Modules 1 and 2 or Modules 3 and 4. Participants will receive a short orientation to the program before use. Participants will be provided with a notebook to take notes on each activity, as well as take a survey on each activity. At the end of each module, participants will do a short qualitative semi-structured interview. At the end of the second module, they will take a post survey. They will receive $75 for their participation in this aim of the study. Participants can choose to re-enroll and complete the other two Modules of Tough Talks as well.

RCT*:* Participants will be recruited from across the country. We will enroll a total of 198 participants. After participants are consented, they will complete a baseline web-based computer assisted survey instrument (CASI) survey using Qualtrics software and be randomized in a 1:1:1 fashion into one of three arms: 1) the Tough Talks fully-online intervention, 2) the Tough Talks clinic-based intervention or 3) the SOC control condition, based on a randomization sequence developed by UNC and administered through REDCap. The randomization sequence will be stratified by study site. Participants may enroll in-person or remotely via video teleconferencing system.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Inclusion Criteria for All Aims

- Age 16-29 years
- Assigned male sex at birth
- Born male and male-identified
- Able to understand, read, and speak English

Additional Criteria for Technical Pilot:

- Reports ≥1 episode of CAI with a male partner in past 6 months
- HIV-positive (self-report)

Additional Criteria for RCT:

- HIV-positive (medical chart review)
- Viral Load measure within 12 months of screening date (assessed by chart review, blood draw, or shared by participant via video teleconferencing or Qualtrics)
- Owns and has reliable access to a smartphone or tablet
- Has reliable internet access
- Reports ≥1 episode of anal sex with a male partner in past 6 months (self-report) OR reports STI diagnosis (urethral/rectal gonorrhea or chlamydia or syphilis) in the last six months (self-report OR medical chart review)

As this is a minimal risk study, we will seek a waiver of parental consent for YMSM under age 18 (see Human Subjects section).

4.2 Exclusion Criteria

Exclusion Criteria for All Aims:

- Under 16 years of age
- Over 29 years of age
- Assigned female at birth
- HIV negative
- Reports 0 episodes of anal sex with a male partner in the last 6 month AND reports no new STI diagnosis (urethral/rectal gonorrhea or chlamydia or syphilis) in last 6 months.
- Currently enrolled in another HIV behavioral intervention study; previous or future enrollment in another HIV behavioral intervention study is permissible, as is participation in any standard of care intervention(s) within the clinical study site.

4.3 Recruitment

We will recruit approximately 210 YMSM (8-16 in Phase 2; 198 in Phase 3) across six in-person study sites that have extensive experience engaging, enrolling and retaining HIV-positive YMSM. Participants will be recruited through a variety of strategies, including online and via social media strategies (e.g. Craigslist, Grindr and Facebook ads); distributing posters, flyers, and palm cards about the study; and direct outreach at local venues frequented by YMSM, including community-based organizations and clinics providing care and services to HIV-positive youth. YMSM will also be recruited to participate remotely; site staff will enroll people from anywhere in the country to complete all study procedures online.

For the RCT, we will also follow respondent-driven sampling (RDS) methods and use a long-chain referral method to supplement recruitment, especially with the adolescents (15-17) who may be harder to reach than young adults (18-24).

4.4 Informed Consent

Informed consent/assent: Individuals interested in screening for study participation will be consented/assented for screening after reading information about the study and screening procedures. Those who meet initial eligibility criteria and schedule an enrollment visit will undergo a detailed informed consent/assent process where study staff will explain all study procedures and answer questions concerning the study and consent/assent process. The research staff member will give the participant as much time as needed and will address any questions or concerns they may have. The research staff member will ask the participant questions to gauge comprehension. The consent/assent form describes all study procedures, including confidentiality and privacy; information about potential risks, discomforts, and benefits of participation; a section on HIPPA consent for medical chart abstraction; and information regarding who they can contact with further questions. It also states that participation is voluntary, that participants may decide to not take part or to withdraw from the study at any time without penalty or loss of any benefit to which they might otherwise be entitled, and that study participation is in no way related to being able to access or continue getting care or services at any participating study site. Participants can refuse to answer any question and can withdraw from the study at any time. The PIs, Co-PIs, or designee at each site will review all informed consents and assents.

Assessing for decisional capacity: Study staff will review the informed consent/assent to make a formal assessment of the youth's decisional capacity and ability to provide consent/assent prior to signing, using a 2-step process. First, the study staff determines if the person understands the study goals by asking "Can you tell me what this study is about?" In step 2, potential participants will be asked questions designed to assess their capacity to understand, appreciate, reason with, and express a choice about participation in our specific protocol. We will use a modified version of the widely used Evaluation to Sign Consent Form in which participants are asked to: **1)** name things they will be expected to do during the study; **2)** explain what they would do if they no longer wished to participate in the study**; 3)** explain what they would do if they experienced distress during the study; and **4)** identify potential risks for participating in the study. Potential participants will be enrolled only if they are able to provide clear and correct answers to each of these items, without prompting or correction. If the enrollment process occurs online, research staff will talk with potential participants via phone or HIPAA compliant video teleconferencing to assess for decisional capacity and to address any questions or concerns the person may have.

Waiver of parental consent*:* We will request that the UNC-CH IRB as the central IRB (IRB of Record) grant a waiver of parental consent to participate in this research study for youth participants who are 16 to 17 years of age. The research team has been granted waivers of parental permission for prior studies with sexual minority youth. Under 45 CFR 46.408 (c), an IRB has the authority to waive parental permission if it determines that "a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects" and "an appropriate mechanism for protecting the children who will participate as research subjects is substituted" and "that the waiver is not inconsistent with Federal, State, or local law." A waiver of parental permission for studies with lesbian, gay, bisexual, transgender, and questioning (LGBT) youth

that do not involve greater than minimal risk is a common practice among researchers working in the area of gay and lesbian health/mental health. This is done to avoid the selection biases operating in only recruiting youth whose parents are both aware of and comfortable with their sexual orientation. Commonly these youth have explored their sexual orientation without their parents' knowledge as the youth struggle with issues of disclosure and its consequences within the social, religious, and economic context of their families. A requirement for parental permission in this type of study could not only affect a person's willingness to participate, but could also potentially impact the ability of researchers to engage in this type of research with sexual minority youth. Additionally, minors can often seek sexually transmitted infection (STI) and HIV prevention services without parental/legal guardian permission, depending on each site's state laws.

If the purpose of requiring parental permission as stated in CFR is to protect the minor subject, then requiring parental permission for youth in these circumstances is not a reasonable requirement. Additional privacy protections are provided in that all assessments, notes, reports, and other records will be identified by only a coded number to maintain participant confidentiality. These records and any forms that do contain identifying information will be kept in a locked, limited access area (such as a locked file cabinet) at the participating site. A waiver of signed consent will be requested from UNC-CH IRB.

Once all eligibility is confirmed, study details will be discussed, and questions answered during the informed consent process. Informed consent/assent will be obtained before any study-related procedures are performed

For the technical pilot, consent/assent may be obtained up to 30 days prior to or on the day of enrollment, prior to implementing any study activities. If more than 30 days has elapsed, consent/assent must be reaffirmed on the day of enrollment.

For the RCT, consent/assent must be obtained on the day of enrollment, prior to implementing any study activities.

4.5 Screening

Potential participants recruited in any of the aforementioned ways will be directed to the study screening webpage. The webpage will include information about the study. Those who express interest in the study will be asked to provide informed consent/assent for eligibility screening. Those who provide consent/assent will view the eligibility screener. The webpage can be viewed on participants' own device (smartphone, tablet, or computer) or on a computer or tablet located in a confidential room at the study site to determine if they meet eligibility criteria (technical pilot, RCT).

For those who meet eligibility criteria and express interest in participating, we will ask for and record the first name, e-mail, and phone number of the individual via the online screener. We also collect preferred means of contact (e.g. call, text, email) and permission to leave a message. We use SSL encryption for

transfers of information online and data will be stored in the secure, HIPPA-compliant servers of the University of North Carolina at Chapel Hill. The CASI data will be stored in a secure database at Qualtrics.

Qualtrics uses Transport Layer Security (TLS) encryption (also known as Hypertext Transfer Protocol Secure (HTTPS)) for all transmitted data. Survey data are protected with passwords and HTTPS referrer checking. The data is hosted by third party data centers that are Statement on Standards for Attestation Engagements (SSAE)-16 Service Organization Control (SOC) II certified. All data at rest are encrypted, and data on deprecated hard drives are destroyed by U.S. Department of Defense methods and delivered to a third-party data destruction service.

Qualtrics deploys the general requirements set forth by many Federal Acts including the Federal Information Security Management Act (FISMA) of 2002. They meet or exceed the minimum requirements as outlined in Federal Information Processing Standards (FIPS) Publication 200.

Health Insurance Portability and Accountability Act (HIPAA) Statement: With some restrictions, Qualtrics may be designated as a Business Associate when the Qualtrics BA Agreement is signed with a Covered Entity—those organizations that are required to comply with HIPAA privacy rules. All client data are considered confidential, and treated as such.

Related to HIPAA, Health Information Technology for Economic and Clinical Health Act (HITECH) are updated assessment rules to ensure that data are properly protected and best security practices are followed. By using secure and certified data centers, Qualtrics ensures the highest protection and testing as per HITECH requirements.

Individuals may first screen eligible either through medical chart review or via responses to the eligibility screener mentioned above. The study recruitment venue (SRV) staff will contact individuals who screen eligible for the study and schedule them for an enrollment visit using the Study Management and Retention Tool (SMART). SMART Web, a study management and retention database managed by UNC, will aid study staff in ensuring retention. SMART Web maintains participant follow-up timelines, tracks participant communications, and automates sending of e-mail, text reminders, and calendar invites to participants for follow-up survey and visit completion. Eligibility for all participants will be confirmed at enrollment visit based on confirmation of VL in the last year up to the date of enrollment.

5.0 STUDY PROCEDURES

5.1 Enrollment Procedures

Technical Pilot

We will enroll 8-16 participants. The technical pilot only consists of one in-person session. After being consented, all participants will be given brief instructions on the purpose of Tough Talks and an overview of how to use the program. They will complete an online assessment at baseline and a paper assessment at the end of using the program. Participants will also be asked to provide feedback during

interviews conducted by study staff about intervention content, technical performance, errors and bugs encountered, overall experiences using Tough Talks, and feedback for further refinement. Participants will receive $75 for participation.

RCT

We will enroll a total of 198 participants. Study staff will review the consent in person or over Zoom (or another HIPPA compliant system) and if the participant decides to enroll, he can sign the paper copy or electronic copy programmed in Qualtrics. After participants are consented, they will complete the baseline web-based CASI survey using Qualtrics software and then be randomized into the Tough Talks online/at-home intervention (Arm 1), the Tough Talks clinic-based intervention (Arm 2) or the SOC control condition (Arm 3). At this visit, those randomized to the online intervention (Arm 1) will download the Tough Talks app onto their personal mobile phone or tablet, have their unique App ID recorded by study staff, set up their preferred email login and password information, and receive information on how to contact study personnel for any technical issues. Arm 1 participants will have access to all of the intervention features upon download. Participants randomized into this arm are expected to proceed through the entire intervention within 30 days. Arm 1 participants who have not completed the app around 2 weeks after enrollment, around 3 weeks after enrollment, and during week after enrollment will be reminded via text or email via SMART to use the Tough Talks app.

Those randomized to the in-clinic condition (Arm 2) at this visit will download the Tough Talks app onto their personal mobile phone or tablet, have their unique App ID recorded by study staff, set up their preferred email login and password information, and immediately begin using the program. At this in-person or remote visit, they will complete both Modules 1 and 2, which includes completion of four virtual reality practice scenarios. These scenarios will be conducted with the assistance of research staff controlling the avatar responses (e.g. clinic-assisted sessions). For the remote visits, staff will do this privately while on video teleconference. During the in-person visits, the staff would control the avatar responses from a separate room. After completion of both Modules 1 and 2 of the program, participants will schedule their follow-up visit for approximately two weeks and receive information on how to contact study personnel for any technical issues when using the first half of the program at home. For those completing the modules remotely, they will receive a list of national resources for mental health support. Their two-week visit can happen anywhere during week 2 or week 4 of the study period. At their follow-up visit, participants will complete the second half of the program (Modules 3 and 4), which also includes completion of the virtual reality practice scenarios as described above (clinic-assisted sessions). Research staff will also be available to troubleshoot with participants in person or for the remote visits they will be on video teleconference and available via text if need be.

Those randomized to the SOC control arm (Arm 3) at this visit will receive an informational, paper or electronic packet of information on disclosure based on available CDC guidance.

Participants will be allowed to enroll in-person at the site or remotely via Zoom or another HIPPA compliant system. All participants who enroll remotely will be asked to download the necessary app to aid the enrollment process. They will receive all forms via text or email. Participants who enroll from across the country (in states where there are no SRVs) will be assigned to an SRV by region. For example, the Houston site staff may enroll the participants from western states, whereas the Tampa site staff may enroll participants from the southern states. The regional division of enrollments is subject to update

depending on volume of enrollments from each state, so that no site is enrolling significantly more remote participants than another.

One month after study enrollment, all participants will complete an online survey to assess intervention acceptability as well as to assess social cognitive framework (SCT) model constructs related to disclosure. Three months after study enrollment, all participants will complete a second online survey. Study staff will perform a chart abstraction to record any VL measures in the six weeks prior to the three-month study visit, or any measures since BL. Six months after study enrollment, all participants will complete a third online survey. Study staff will perform a chart abstraction to record any VL measures since the 3-month assessment and in the 2 months before the six-month study visit. If a current VL is not documented in the medical record (2 months prior to 6-month mark, or 3 months after), participants will be asked to have blood drawn to ascertain a VL measure as part of the study.

All participants will receive $50 after their baseline visit, and Arm 2 participants will receive $50 for completing the baseline modules, and $50 for attending their follow-up visit. All participants will receive $25 after completing the online CASI given at one month, $25 after completing the online CASI given at three months, and $50 for completing their 6-month CASI and VL measure. All participants asked to attend the clinic site as part of the study will also receive a travel reimbursement based on their location and site standards. A subset of participants in the intervention arms will do a qualitative exit interview ($50) beginning at the one-month follow up. For participants who refer members of their social network to participate in the study, for each person they recruit who screens eligible and completes initial enrollment steps, they will receive an incentive of $10 for up to 3 referrals for a maximum of $30. If a participant completes all study-related procedures, they can earn up to between $200-$300 dollars, depending on the study arm; if a participant completes all referrals in addition to study procedures, they can earn between $230-$330, depending on their study arm.

5.2 Locator/Contact Information

Once a participant has been consented and enrolled, designated site study staff will collect Locator/Contact Information from the participant. Participants will be asked to provide a working phone number or valid email address through which they can be reached. Participants will also be asked to provide valid contact information for a family member and/or friend who can be called in the event the participant cannot be reached by phone or email. Participants will be asked if messages can be left at the numbers provided. Participants will also be asked to provide their physical address and whether they can receive mail related to their study participation at that address. Study staff will not leave messages or send mail unless expressly permitted to do so by the participant, which also will be documented on this form. If permission is given to leave messages or send mail, site staff will assure participants that messages only ask the participant to contact study staff and will not include any protected health information or information related to study participation. This information may be entered directly into SMART or collected on the Locator/Contact Information form first and then entered into SMART by SRV staff.

The Contact Information Form will not contain any study data and will be maintained under double locks at the study site, separate from all study records, with access limited to designated site research personnel.

5.3 Randomization Procedures

Participants will be randomized in a 1:1:1 ratio into either the Tough Talks fully online intervention, the Tough Talks clinic-based intervention, or the SOC control condition, based on a robust randomization sequence developed by UNC. The randomization sequence will be stratified by study site.

The randomization sequence will be setup in REDCap such that study staff may use the randomization feature to determine study arm assignment for each participant. Staff will not be aware of the randomization sequence, and therefore will not know what preceding or subsequent assignments will be.

5.4 Intervention/Investigation Procedures

5.4.2 Technical Pilot

After development is complete and internal beta testing performed, both the Tough Talks intervention and intervention procedures will be evaluated and revised during a technical pilot with a small group of YMSM participants (8-16) at one site (Chapel Hill, NC). All participants will be given brief instructions on the purpose of Tough Talks and an overview of how to use the program. They will complete an online assessment at baseline and a post survey after using the program. Participants will also be asked to provide feedback during qualitative interviews conducted by study on intervention content, functionality, technical performance, errors and bugs encountered, overall experiences using Tough Talks, and feedback for further refinement. We will solicit feedback about the acceptability and utility, and assess how the intervention components could be strengthened, identifying areas needing improvement for future iterations. Participant feedback will be specifically sought on the subjective impact of the intervention on HIV disclosure, engagement in care and ART adherence. Participant feedback will also be solicited on the acceptability of the assessments with respect to duration and relevance. Both the qualitative and quantitative data from the technical pilot will be used to refine the Tough Talks program, the intervention protocol and the assessment tools prior to the RCT pilot (Aim 3) using a concurrent triangulation approach, taking advantage of the strengths of both data types to cross validate results.[62] These data will be used to further refine the intervention protocol and instruments to be tested in the pilot RCT (Aim 3).

5.4.3 RCT

Recruitment for the RCT will occur from the 6 study sites (Tampa, FL; Houston, TX; Bronx, NY; Chapel Hill, NC; Atlanta, GA; Charlotte, NC), as well as through online channels such as social media. Identifying, screening and enrolling potential participants for the RCT will proceed as described in sections 4.3, 4.4, 4.5, and 5.1. After eligibility is confirmed, and consent/assent is obtained, participants will be assigned a study ID, complete the baseline CASI survey, and then be randomized to a study arm. Next, participants will be walked through a brief description of their study arm (clinic, at home, control). Participants will be compensated $50-$100 at the conclusion of the enrollment visit (depending on arm) and reminded

that they will be asked to complete follow up assessments online at one, three, and six months, in addition to a two week visit after enrollment for the in-clinic arm only.

The study team will conduct a combined efficacy/effectiveness trial to compare the intervention delivered online, in the clinic or SOC disclosure materials. Primary and secondary outcomes will be assessed at intervention completion (one month), three months, and at six months, and will include HIV VL information (abstracted via chart review, shared by participant via Qualtrics, or blood draw), self-report data based on the CASI surveys and staff completion of costing tools and CRFs. Mathematical modeling will estimate transmissions averted and costs of each arm.

A sub set of participants in both intervention arms will complete a qualitative exit interview to evaluate the program in-depth and document a more nuanced understanding of intervention acceptability and impact. Participants in both interventions will be eligible to participate in an interview after completion of their one-month follow-up survey. The interviews will be conducted in person or online using a HIPAA-compliant, IRB-approved videoconferencing software program. Online interviews will be recorded by the software program and back-up recorded using an external digital audio recorder. In-person interviews will be recorded using two digital audio recorders. Interviews will last 45-60minutes and will be transcribed by an IRB-approved, HIPAA-compliant transcription service. Transcripts will be checked for quality control by study staff against original recordings. Participants can opt to include video chat, but no video will be recorded. Interviews will be semi-structured and focus on participants' evaluation of the program (e.g. likes, dislikes, technical problems), how they used the program over the course of the month, what impact (if any) they perceive using the program had or would have on them (probing for status disclosure, HIV care and medication adherence, social support and sexual behavior choices), and suggestions for changes to the program. We aim to interview 20-30 participants (10-15 in each arm, with approximately even distribution across the 4 study sites). Based on previous similar study designs, we are confident that we can recruit a sufficient number of interviewees from the pool of 112 possible intervention participants (112 = 66 in each of the two intervention arms, less 15% attrition). Participants will receive an additional $50 for completing a qualitative exit interview. Transcribed exit interviews will be analyzed thematically for both a priori and emergent themes using Dedoose qualitative data analysis software, or an equivalent program. We will follow similar analytic procedures used in the Technical Pilot in order to identify possible areas for program improvement in the RCT and to provide additional context for interpreting the intervention's quantitative results.

5.4.4 Research and Training Staff

All proposed study staff have participated in the required trainings in participation and conduct of studies that involve human subjects, and any future study staff will do so upon hiring. Research staff at individual SRVs who interact with participants at assessments do not need to be clinicians. A research assistant (RA) level position should be sufficient to verify eligibility during both study aims, obtain informed consent, be available for questions during the CASI, abstract viral load information via chart reviews, take a blood sample for viral load, control the AI during clinician assisted virtual reality sessions, and explain the Tough Talks intervention. Research staff at SRVs will be trained in person and/or via videoconferencing on the intervention components and will be given a script and checklist to review with participants. If a participant asks a question that study staff do not feel equipped to answer, SRV study staff will contact research staff at the University of North Carolina at Chapel Hill and/or Duke University and then follow up with the participant.

5.4.5 Intervention Monitoring/Quality Control

Because the Tough Talks intervention is an app, intervention fidelity is assured for all activities, except for the virtual reality activities (i.e., all participants will receive the intervention in the same way and have access to all of the same resources). For the virtual reality activities, Arm 1 participants will have the avatar controlled by the AI and Arm 2 participants will have the avatar controlled by staff. However, for both VR activities, the same utterance database is being used so while we anticipate that the staff controlled avatar may perform better, the types of conversations and specifics on what words/phrases can be said in both arms will be the same. To maintain quality control the study team will train and score practice VR scenarios and retrain if needed prior to enrollment visits. The UNC study team will also review the first 10 VR session transcripts performed at each SRV site, and then 20% of the sessions on an ongoing basis. Site staff with issues will be re-trained.

6.0 EVALUATIONS AND MEASURES

THIS SECTION CONTAINS RELEVANT EVALUATIONS AND MEASURES FOR THE RCT ONLY

Overviews of the administration of clinical and behavioral measures are shown in the Schedule of Evaluations with a full list of study measures. Presented below is additional information on visit-specific measure administration and procedures.

6.1 Screening

Online, phone-based, and in-person screeners will be used to determine if individuals meet initial eligibility criteria. Individuals may be screened for eligibility by accessing the study's online screener using their own laptop or mobile device (e.g., if responding to online or community recruitment) or may complete the online screener on a local clinic tablet or computer. The online screener may also be administered by study staff to potential participants in person or over the phone. All potential technical pilot participants who meet the initial eligibility criteria (based on the screener) must arrange an in-person enrollment visit to confirm eligibility. Potentially eligible RCT participants can select an online visit if needed. Eligibility will be confirmed at the enrollment visit based on the confirmation of screener completion in past 30 days, and VL measure within the past year of screener completion (or up until the enrollment visit date).

6.1.1 Administrative and Behavioral Procedures

- Screening assessment, in-person, by phone, or online

6.2 Enrollment

Participants must be scheduled for an enrollment visit within 30 days of online, phone, or in-person screening; otherwise they will need to be re-screened. Individuals who meet initial eligibility criteria

based on the online screener will be scheduled for an enrollment visit, where screener completion, including recent VL measure will be confirmed.

6.2.1 Administrative and Behavioral Procedures

- Informed Consent/Assent
- Randomization to Arm 1 (online), Arm 2 (clinic delivery) or Arm 3 (SOC)
- Baseline CASI Assessment
- Introduction and orientation to Tough Talks
- For Arm 1 and Arm 2 participants, unique Tough Talks account creation, download and set up of Tough Talks on participant's mobile device
- For Arm 2 participants, completion of 1st half of Tough Talks program
- Remuneration for enrollment completion (including BL survey)

6.3 Two-Week Follow Up (Arm 2 only)

Participants in the clinic arm (Arm 2) will be scheduled for a two-week follow up to complete the second half of the program. The eligible window for completing the two-week follow up is any time during week 2 to week 4 of their intervention.

6.3.1 Administrative and Behavioral Procedures

- Completion of 2nd half of Tough Talks program
- Remuneration for completion

6.4 One-Month Assessment (Immediate Post Intervention)

The intervention will last for 1 month. The 1-month assessment should occur as soon after their 1-month enrollment period as possible. However, given that the one-month assessment is the only one that includes measures of overall intervention acceptability, the assessment may occur up to 160 days after the ideal 1-month assessment time point (e.g. up until the end of follow-up period). SMART will aid study staff in ensuring retention. SMART maintains participant follow-up timelines, tracks participant communications, and automates sending of e-mail, text reminders, and calendar invites to participants for follow-up survey and visit completion. An appointment for the 1-month assessment visit will be scheduled to complete the following procedures listed below.

At one month, all participants will complete an online survey to assess intervention acceptability as well as to assess SCT model constructs. Participants will receive $25 for completion.

A sub-set of participants (20-30 total) in both intervention arms (10-15 in each arm) will complete a qualitative exit interview to evaluate the program in-depth and document a more nuanced understanding of intervention acceptability and impact. Participants in both interventions will be eligible to participate in an interview after completion of their one-month follow-up survey. The interviews will be conducted in person or online using a HIPAA-compliant, IRB-approved videoconferencing software program. Online interviews will be recorded by the software program and back-up recorded using an

external digital audio recorder. In-person interviews will be recorded using two digital audio recorders. Interviews will last 45-60 minutes and participants will receive an additional $50 for completing a qualitative exit interview.

6.4.1 Behavioral Evaluations

- One-month CASI assessment
- Qualitative exit interview (for subgroup of participants)
- Remuneration for survey completion
- Updates to contact/locator information

6.5 Three-Month Assessment

A second assessment should occur 90 days (3 months) after study enrollment. However, the assessment may occur 15 days prior to or 30 days after the ideal three-month assessment time point. SMART will aid study staff in ensuring retention. SMART maintains participant follow-up timelines, tracks participant communications, and automates sending of e-mail, text reminders, and calendar invites to participants for follow-up survey and visit completion. At three months, all participants will complete a second online survey and staff will conduct a medical chart abstraction for VL results in the week window surrounding the three-month follow up visit (both before and after). Participants will complete the 3-month follow up survey remotely and will receive $25 for completion. Payment is not contingent upon having a VL result in the required window. Participants who miss their 1-month follow up are eligible to complete their 3-month visit.

6.5.1 Behavioral Evaluations

- Three-month CASI assessment
- Remuneration for online survey completion

6.5.2 Clinical Procedures

- Viral load measure, taken from chart (if within six weeks prior to or following three-month follow up)

6.6 Six-Month Assessment

The final assessment should be conducted 6 months after study enrollment. However, the assessment may occur two weeks prior to or 30 days after the ideal final assessment time point. At six months, all participants will complete a third online survey and undergo a medical chart review to abstract VL data. If participants have had a viral load taken in the two months prior to their six-month follow up appointment, they can complete the six-month follow-up survey remotely and receive their follow-up incentive. If they do not have a VL result from the prior two months, they can still complete their survey remotely but will be asked to provide a blood sample to assess viral load within three months of completing the six-month survey. Participants will receive $50 for completion. Participants must complete both their survey and have an eligible viral load (either through chart review in last two months, self-report, or blood sample within three months after survey) to receive their incentive.

Participants who miss their one and/or three-month follow up are eligible to complete their final six-month visit.

6.6.1 Administrative and Behavioral Procedures

- Six-month CASI assessment
- Remuneration for visit completion (dependent on both survey and viral load)
- Documentation of viral load measure (blood draw, self-report or chart review)

6.6.2 Clinical Procedures

- Viral load measure, abstracted from medical chart or blood sample

6.6.3. Laboratory Procedures

- Blood specimen analysis for viral load (if not in chart review)

7.0 DATA COLLECTION AND SITE MONITORING

7.1 Development of Protocol and Case Report Forms

The protocol team is responsible for the development of this protocol as well as the Case Report Forms (CRFs) needed to collect the information required to implement this protocol. All Case Report Forms are input in REDCap, where study staff will complete all relevant fields.

7.2 Data Records

Participant-related study information will be identified through a study ID number (SID) and participant code on all participant CRFs, audio files, transcripts, and CASI files. Participant names or other personally-identifying information will not be used on any study documents other than the Contact Information Worksheet (stored in double-locked office separate from other study information only accessible by designated study staff) and informed consent form and will be redacted from usability and field trial interview transcripts. All study-related information will be kept in double-locked, limited access areas at each study site. Participant names and their SID and participant code will be stored in in SMART Web, accessible only to designated study staff, and representatives from the NICHD. SIDs will not be entered into the mobile app and instead a unique app ID will be assigned to each participant and used when setting up the app. These unique App IDs will be provided by the UNC Study Team and recorded into the Intervention Delivery Form during enrollment. Original source documents (e.g., Contact Information Worksheet) for individual participants will be maintained at the respective SRV and will be accessible only to the study staff. Data from original source documents will be transcribed with SMART or on CRFs in REDCap as applicable. Electronic data will be stored on a secure server at UNC.

7.3 Data Collection

7.3.1 CRFs

Study monitoring data, including information about eligibility, demographic data, and monitoring untoward effects will be collected on CRFs. All CRFs for this study must be entered into REDCap. Hard copies will be made available for download from a UNC-run secure cloud management platform, to be used if needed (i.e. technical issues preventing use of REDCap).

7.3.2 CASI Survey Data

Technical Pilot: Self-administered surveys will be completed by participants at the baseline and 1-month assessment time points. Participants will complete an online computer assisted self-interview (CASI) via survey hosts on Qualtrics.

RCT: Self-administered surveys will be completed by participants at the baseline, 1-month, 3-month and 6-month assessment time points. Participants will complete an online computer assisted self-interview (CASI) via survey hosts on Qualtrics.

Data collected using a CASI method at the clinic sites will be entered on a portable computer or mobile phone via an internet-based application. All data collected using CASI will remain confidential; no personal identifying information will be collected during the computer session. The participant's unique SID number will be used in order to link the interview responses to the participant's CRF data. This unique SID will also be used to link participant completed follow-up Qualtrics surveys

7.3.3 CASI Data Security

CASI Data Security

Only authorized users with a login name and password will be able to access and open the online HIPPA-compliant online CASI platform administered survey.

7.3.4 Video Platform Description

A HIPPA-compliant video platform will be used for this study. Either Zoom or a comparable platform may be used to conduct qualitative interviews remotely and/or to enable remote enrollments. For the qualitative interviews, participants will have the option to conduct face-to-face video chat, video chat in which they can see the interviewer, but the interviewer cannot see them, or audio chat only. In order to ensure privacy, participants will be asked to complete the interview within a private room. Zoom is compatible on PCs, tablets, and smartphones; as well as maintains the option to conduct an audio conference without the video component.

End-to-end encryption: Zoom encrypts all presentation content at the application layer using the Advanced Encryption Standard (AES) 256-bit algorithm. Zoom end-to-end (E2E) chat encryption allows for a secured communication where only the intended recipient can read the secured message. Zoom uses public and private keys to encrypt the chat session with Advance Encryption Standard (AES256), and session keys are generated with device unique hardware ID to avoid data being read from other devices. This ensures that the session cannot be eavesdropped on or tampered with.

Cloud Control Infrastructure: A distributed network of low-latency multimedia routers (software) resides on Zoom's communications infrastructure. With these low-latency multimedia routers, all session data originating from the host's device and arriving at the participants' devices is dynamically switched — never stored persistently through the Zoom communications infrastructure. Zoom's communications infrastructure for real-time video, audio, and data communications resides on Zoom dedicated servers, which are housed in SSAE 16 SOC2 compliant datacenters on opposite sides of the US. Zoom sessions are completely temporary and operate analogously to the popular mobile conversation over the public mobile network. In addition to unique security benefits, Zoom's

communications infrastructure also enables an extremely scalable and highly available meeting infrastructure unrestricted by the limitations of physical data centers.

The Zoom client communicates with the multimedia router to establish a reliable and secure connection. At the time of instantiation, the Zoom client will determine the best method for communication, attempting to connect automatically using udp and tcp port 8801, 8802 and 8804 or HTTPS (port 443/TLS).

The Zoom sessions will contain identifying information, but this information will be stripped from the recorded Zoom sessions by the study team immediately post completion.

7.3.5 Back Up Recording

All qualitative interviews may also be recorded using a back-up digital audio recorder. Audio files will be erased after being transcribed and transcripts will be de-identified. All audio files will be kept confidential and stored in a locked/limited access folder on secured servers, which is only accessible to designated study staff. All members of the research team will be trained in confidentiality and have signed confidentiality agreements. A professional transcription service, experienced in the handling of confidential data, will be used to fully transcribe verbatim all audio files. Prior to receipt of the first audio file, the transcription service will be instructed to exclude from the typed transcript identifying information (e.g., a name) that may have been verbalized during the course of the interviews.

7.4 Data Submission

7.4.1 CRFS

Although Tough Talks will involve substantial online follow-up, forms on REDCap will be used to collect key study visit data (e.g., enrollment and randomization assignment), study milestones such as completion or discontinuation, study laboratory results, and adverse events (AE). During active study conduct, the study sites will maintain the CRFs within REDCap and any hard-copy CRFs will be stored in secured locations and later entered into REDCap.

7.4.2 Audio-recorded Data

Audio recorded data from the technical pilot exit interviews will initially be stored as a digital file on a secure encrypted UNC server. Exit interviews will be transcribed verbatim from the digital audio recording and de-identified by assigning unique numerical codes. After transcripts are verified by the research team and one year after the study is over, audio files will be destroyed.

All CASI data will only be identified with a unique SID and stored on a secure encrypted server by the UNC team. Only study site research staff and the research team at the University of North Carolina/Duke will have access to the data.

7.4.3 CASI Data Transmission

Only authorized users with a login and password will be able to access and open the survey through the internet site. Survey data will be stored in secured databases on a UNC server.

7.4.4 Retention Data

The study will use a HIPAA-compliant web-based platform entitled Study Management and Retention Toolkit (SMART), which is a SaaS (Software as a Service) based mobile application aiding studies with various aspects of participant recruitment, study implementation, and retention. The application has the ability to securely manage participant information across multiple studies and customers simultaneously, stratifying participant information by study and site. SMART includes an admin web portal and a participant facing mobile app (optional), which allows for secure messaging, study calendar management, self-scheduling by participants, secure photo uploads, and longitudinal tracking of participants from screening to study completion. The ability to designate specific roles to all SMART users allows for greater control around permissions and accessibility to participant information. Users can even be limited to a reporting only role, which allows for study oversight through real time aggregate reporting, but no access to PHI. SMART is a licensed service of the Center for AIDS Research (CFAR) at Emory University, Prevention Science Core. Utilization of the mobile app is optional and the admin web portal will fully function without it.

The following information outlines the security of the three SMART components: (1) the admin web portal, (2) the participant app, and (3) a web service that acts as a liaison between the mobile app and the study database.

Admin Web Portal: The admin web portal is a web-based application developed using Microsoft .NET technologies. It uses SQL server as backend database. The application requires two servers to host: (1) Web server [Windows server with IIS] and (2) SQL server [Standard or Enterprise version]. Both these servers are to be placed behind a firewall. Web server will have a public IP to access the server using VPN. SSL certificate is to be installed on the web server. The admin website will be rendered over SSL (https). The application uses form authentication (no integrated authentication such as AD). All passwords are stored encrypted within the database. The system will also be using database level encryption, which will prevent any copying of information from one database to another. The web application also uses an automatic logout feature after a certain period of inactivity. By default, the inactivity duration is set to three minutes.

Study staff can only first gain access to the admin web portal if granted by a study or site administrator. Their assigned user role will determine their permissions to perform different actions and even view PHI. Email notifications are sent from the system (without the need to login) when: (1) a staff member requests to reset their password, (2) role assignments to a study are made, (3) an event/visit that staff are scheduled to work is nearing, (4) a new task is assigned to a staff member, or (5) they are designated as a staff member to receive alerts of positive test results. All participant communications are performed using secure messaging through the message center (inbox) implementation within the mobile app. If the mobile app is not utilized by a study, communications are sent as standard email or text messages to participants.

Mobile App: The mobile app, developed natively for iOS and Android platforms and available for free in the App Store and Google Play Store, is an optional feature the study can utilize for self-scheduling,

communication, photo uploads, and updating contact information. The study will indicate during the initial setup within the admin web portal whether the participant mobile app is utilized or not. If the app is utilized, participants will receive download instructions after their information is entered into the admin web portal. Only participants listed in an active study who validate their email or phone number against the contact information listed in the admin web portal will be able to proceed into the app. For validation, the app uses both traditional form authentication as well as social login (Facebook and Google). The social login feature will only work if the email associated with either social account matches the contact information within the admin web portal. The app does not request anything other than basic information from these authentication services. Participants cannot "remember" their password on the mobile device for automatic logins to ensure privacy. All participant data and activity status is maintained within a secure and encrypted SQL Server database. To create the connection between the admin web portal and the mobile app, each participant is assigned a unique ID within the application, which is associated with their login credentials. When a participant has been successfully authenticated through the mobile app, the admin web portal will send their specific information to their phone through the established secure session (web APIs using SSL). The app will not store the information presented locally on the phone. Local data storage is used only for storing some minimal non-PHI information, such as app settings. The mobile app implements an automatic logout when there is inactivity for more than three minutes. If a participant should need to re-download the app on a new device, login and password authentication will be required again.

The mobile app has push notifications that are primarily used for reminders and notifications of new messages. Push notifications displayed on the participant's phone will be generic in nature and not contain any PHI. Reminders and notifications within the mobile app inbox will also be generic in nature, with any message containing sensitive information requiring a pin, established during registration as a secondary authentication, to open within the mobile app. Firebase cloud-messaging service is used as a communication channel for these notifications. No PHI is passed through Firebase. Push notifications are customizable in the study setup, and samples of system notifications include: "You have a new message in your inbox," "You have an upcoming event for March 7, 2018," and "You have a pending task."

Web Service: A web service will also be hosted on the web server. This service is used by the mobile application to retrieve and store data. The service will utilize secure socket layer (SSL) for communication.

7.5 Data Quality Assurance

Investigators receiving federal funding must adhere to the Code of Federal Regulations (CFR) to protect research participants and produce reliable study information. Sites participating in research sponsored by the NIMH need to have an internal quality assurance (QA) plan that will identify problems and correct errors in research study records.

7.6 Role of Data Management

UNC will provide instructions concerning the recording of study data on CRFs, and the entry and transmission of the data, and administration and transmission of CASI data.

7.7 Study Site Monitoring and Record Availability

Site monitors at UNC may visit participating study sites to review a selected portion of the individual participant records, including assent/consent forms, CRFs, and supporting source documentation to ensure the protection of study subjects, compliance with the protocol, and accuracy and completeness of records. Regulatory files, as required, will also be inspected to ensure that regulatory requirements are being followed.

The site investigator will make study documents (e.g., assent/consent forms, case report forms) *and pertinent hospital or clinic records* readily available for inspection by the local IRB, the central IRB, the site monitors, the NIMH, the Office for Human Research Protections (OHRP), or the sponsor's designee for confirmation of the study data.

8.0 PARTICIPANT MANAGEMENT

8.1 Tracking Participants / Follow-up

All subjects will be contacted before each follow-up study visit/assessment (i.e., enrollment, 2-week visit for Arm 2 participants, one-month, three-month, and six-month time points). Multiple contact methods will be used for youth who are difficult to reach (e.g., mail, alternate phone numbers, e-mail, text message, Facebook). Doximity, a HIPAA compliant app, may be used to call participants. Subjects will be asked whether or not messages can be left for each of the phone numbers that they provide. They will be informed that messages will not contain any information regarding the nature of the project. The SMART participant management system will be used.

8.2 Compensation

Technical pilot participants: Compensated with $75 for participation.

RCT participants: Compensated with $50 at enrollment visit, $50 for completing baseline modules (Arm 2 participants only), $50 for the 2-week visit (Arm 2 participants only), $25 at the one-month visit, $25 at the 3-month visit, and $50 at the six-month visit. Participants who do a qualitative interview will receive an additional $50. ($200-300 total). Compensation will be provided in person, sent digitally or can be mailed to subjects, if allowed by the SRV.

8.3 Intervening on "Social Harms"

We identified the following items as possible risks to subjects and describe how we plan on addressing those risks:

1) Breach of Confidentiality: A potential risk to participants is violation of confidentiality. We will take the utmost caution to protect the confidentiality of all responses. We will minimize this risk by maintaining confidentiality and discretion throughout the usability testing, field testing and RCT. Files – audio, paper and electronic– will not have any identifying information about the study participants and will be tracked through a unique SID. All audio recordings will be downloaded and stored on a password-protected, encrypted computer in locked offices at UNC-CH and subsequently transferred to UNC encrypted servers. Transcription of audio files will be conducted using a HIPAA-compliant transcription service. Any names mentioned in the audio files will be redacted during transcription. Interview transcripts will be kept on UNC secure servers. Analysis of transcripts will be conducted on a password-protected, encrypted computer. Hard copies will be kept in locked files. This research specifically targets a vulnerable population, children (YMSM ages 16-17). We will take every available step to minimize the risk of identifying/linking data being subpoenaed, stolen, or inadvertently released. First, the Tough Talks has acquired a Certificate of Confidentiality from the NIH.. Second, the study will safeguard against the risk of the linking information being stolen by keeping such information in a locked Excel spreadsheet on a secure server at UNC to which only essential study personnel who have completed CITI certification for human subjects research ethics training (http://citiprogram.org) will have access. We have also included numerous features to ensure app security and privacy. All relevant app communications (e.g. those between participants or those between participants and staff) will be secured via industry standard encrypted SSL communications links. These connections will ensure that all communications are inaccessible to unauthorized third parties. Furthermore, the app can be updated regularly to address any unforeseen security updates to the software libraries underlying the secured communication links. Beyond encrypting communication, we users will need to log in with a username and password to access the app, even if the use of their phone is “unlocked”. This will allow the user to share their phone generally with others without granting access to Tough Talks. These software security solutions will provide the layers of both communications security and physical access security to ensure that only authorized users have access to the information stored on the phone as well as the information being shared over communications links. We will take special care to ensure that Tough Talks addresses participant privacy. We have chosen the app name, Tough Talks, because it does not relate to health care and is therefore designed to be non-stigmatizing and un-interpretable by anyone observing a participant using the app on their mobile phones. During app onboarding, study staff will assist youth in choosing a discreet and anonymous username. Moreover, mobile phone screens themselves are also constructed to prevent surreptitious observation.

2) Emotional discomfort: It is possible that the study may precipitate discomfort and/or an emotional response when YMSM answer questions about potentially sensitive topics such as HIV disclosure. Further, participants may feel embarrassed about discussing sensitive issues. All participants will be told during the informed consent process that their participation is voluntary and that they can chose to stop participating at any time without any consequences. Based on our experiences using similar data collection methods with YMSM in past studies, the likelihood and seriousness of this risk is minimal and we will strive to create a safe and comfortable environment for all study participants.

3) Discomfort during collection of blood specimen: The risk of discomfort due to blood sample collection is considered minimal. Physical harms are minimal. Blood samples will be collected based on best clinical practices in each of the SRV sites by trained staff. Subjects could experience dizziness, diaphoresis and nausea associated with the procedure but in prior clinical studies using blood sample collection, adverse events have been rare.

All sites have specific policies governing the treatment of human subjects. These policies specify that medical and psychological assistance will be available in the immediate environment in the event a participant should experience any adverse reactions resulting from study procedures.

While participants will be informed that they may refuse to answer any question at any time, responses or reactions to certain questions may indicate distress on the part of the participants. If at any time during the study a participant divulges that they are at risk for harm, including but not limited to being abused or experiencing violence, if harm is suspected or likely, or if the participant states they are suicidal/homicidal, measures will be taken to ensure their safety. Reporting will be done as appropriate to the situation and the legal statutes, including reporting to child protection agencies or other appropriate agencies, and referrals will be provided to appropriate support, counseling, or treatment resources.

8.4 Criteria for Premature Study Discontinuation

The principal investigator has the authority to withdraw any participant at any time if in their opinion it would be in the best interest of the participant. The participant will be informed of this withdrawal and explained the rationale. Withdrawal will be documented in the study tracking system.
Subjects will be prematurely discontinued from the study if any of the following occurs:

- The subject withdraws consent/assent;
- The study is cancelled by the *NIH*;
- The study is cancelled for other administrative reasons;
- The subject becomes incarcerated or placed in detention during the study; or
- Death of the subject.

Participants may end their participation in the study at any time. No further data collection will occur from the date the decision is made to permanently discontinue the subject from the study. Participants who experience distress during the study while in the study site clinic will be offered counseling on site. Participants who experience distress during the study and do not come to the clinical site for a visit will be provided a list of community referrals via phone or e-mail. Any unexpected adverse events that meet the new safety information reporting criteria will be immediately reported to the UNC-CH IRB and the respective sites' IRBs if applicable. The *Study Stop and Adverse Event Forms* will be completed at this time.

9.0 MONITORING UNTOWARD EFFECTS ASSOCIATED WITH OR RESULTING FROM STUDY

Site research staff must first follow both the UNC IRB and their own IRB's procedure for reporting and managing untoward effects.

There are three types of untoward effects to be identified: 1) those related to the participant, 2) those related to the study staff, and 3) those related to the neighborhood/community *(if applicable).*

First, the study will catalogue any untoward effect related to the participant. Reporting is required for occurrences including social harms, psychological distress, and serious life-threatening events such as suicide attempts. These may be immediately apparent to the study staff, such as the participant's emotional upset state requiring referral for counseling; or they may be delayed and reported later to study staff, such as physical harm to an individual for having participated in the study. Study staff will notify the UNC/Duke teams via secure email with a subject line stating that immediate response is necessary. Study staff will be briefed with best practices and trainings on the scope of possible untoward effects and how to report events.

Second, study staff may encounter untoward events during sessions that personally affect them. Training and guidance will seek to minimize this risk. Nonetheless, an assessment of the cost of conducting this study must include cataloguing these events as well. The UNC/Duke team will be notified of these events so that they may be immediately addressed, evaluated, and then modify guidance or expanded to minimize similar risk to other study staff.

Third, a critically important area that any community-based study intends to evaluate is the impact, including untoward effects, of the project on the community. This will be done informally for this protocol with untoward events being reported to the protocol team.

All untoward effects/adverse events/unanticipated problems will also need to be reported to the UNC IRB if they meet all three of the following criteria:

"Unanticipated problems involving risks to subjects or others" (UPIRSO) refers to any incident, experience, or outcome that:

1) is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2) is related or possibly related to a subject's participation in the research; and
3) Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Events that meet the criteria for an UPIRSO and are also serious adverse events should be reported to the UNC IRB within one (1) week of the investigator becoming aware of the event. Any other events that meet the criteria for a UPIRSO should be reported to the IRB within two (2) weeks of the investigator becoming aware of the problem.

If the report cannot be completed in its entirety within the required time period, a preliminary report should be submitted. The report should be amended once the event is resolved and/or more information becomes available.

10.0 STATISTICAL/ANALYTIC CONSIDERATIONS

10.1 Overview of analytic strategy

10.1.2 Technical Pilot

To evaluate the functionality, technical performance, errors and bugs encountered, overall experiences using Tough Talks, and provide feedback for further refinement.

10.1.3 RCT

Conduct a combined efficacy/effectiveness trial to compare the intervention delivered online, in the clinic, or SOC clinic disclosure messaging. The primary outcome of HIV viral suppression will be assessed at six months. We will also assess intervention efficacy on a panel of self-reported outcomes including CAI, STI infections, disclosure behaviors, intentions and self-efficacy assessed at baseline, 3 months, and 6 months. Cost effectiveness of both intervention arms will also be assessed.

The primary analysis will be based on intention-to-treat principles, where all participants are assumed to have followed their randomized assignment; secondary analyses will account for observed intervention completion. Additionally, we will develop a mathematical model to estimate secondary HIV transmissions and potential transmissions averted as a result of the intervention's effect on viral suppression and CAI with susceptible partners.

10.2 Power Estimates

10.2.2 Technical Pilot Power Considerations

Power is not a concern for the technical pilot as it is performed to collect feedback from a small number of members from the target population about the functionality of the near final version of the intervention.

10.2.3 RCT Power Considerations

Power and sample size. The sample size calculation is based on the primary aim examining a change in the probability of **viral load suppression** from baseline to six months of follow-up between the standard of care arm and each of the two intervention arms. Using data from previous work, we estimate the probability of viral load suppression to be 0.66 in each of the three trial arms at baseline, and a change in this probability to 0.88 in each of the two intervention arms at six months of follow-up. Assuming this absolute change of 0.22, a two-sided alpha level of 0.05, and 15% loss to follow-up over the six-month study period, we estimate we will need 66 participants in each of the 3 study arms (n=198) to achieve 80% power to detect this change in the probability of viral load suppression between SOC and the two intervention arms. While our sample size is not powered to detect a difference between the two intervention arms, precise estimates of the efficacy for each arm are critical for subsequent costing analyses.

Power calculations were performed using PASS v.13 software (NCSS, LLC. Kaysville, Utah).

10.3 Statistical Analysis Plan

10.3.2 Technical Pilot Analysis Plan

All data collected during Phase 1, the Technical Pilot, will be qualitative in nature and therefore not have a statistical analysis plan.

10.3.3 RCT Primary Analysis Plan

The study is a multi-site randomized 3-arm parallel group, longitudinal trial. The primary analysis will be based on intention-to-treat principles where we assume that all participants have followed their randomized assignment. The primary outcome is the probability of viral load suppression at six months, defined as less than the lower limit of detection as per the laboratory at each clinical site. At baseline, the most recent viral load will be abstracted from participants' medical records, within a specified time window (per trial eligibility criteria). At six months, participants' most recent viral load will be abstracted if one is available in the 2-month window prior to the six-month follow-up visit; if none is available within that window, a blood draw will be done for the study to ascertain viral load, or participant can have viral load measure as part of normal care within three months after six-month visit. We will use a binomial regression model (with identity link) for the risk difference (RD) in 6-month viral suppression, comparing each of the intervention groups with the SOC group. Due to random assignment, we expect that the probability of viral suppression at baseline will be balanced between the intervention and control groups. However, if baseline differences occur by chance, we will use inverse probability of treatment weights to correct imbalances in baseline viral suppression. Additional baseline covariates may be included in the model to increase the precision of treatment effects. The treatment weights may be combined with censoring weights if loss to follow-up exceeds 15% or if there is evidence of differential censoring by treatment group.

All analyses will be conducted using R (R Foundation for Statistical Computing, Vienna, Austria).

10.3.3 RCT Secondary Analysis Plan

The occurrence of CAI with a potentially susceptible partner in the last three months will be assessed at baseline, three-months, and six-months following the intervention. At each time point, participants will complete the web-based CASI survey that will include items on sexual risk behaviors over the prior three months. These items will ask about frequency of insertive and receptive anal intercourse, condom use, and number and HIV status of partners. CAI with a potentially susceptible partner will be defined as ≥1 act of condomless anal intercourse with a partner who is not known to be HIV-positive. To assess intervention effect at the time point of primary interest (six months), we will use a binomial regression model (with identity link) for the RD in any CAI with a susceptible partner (vs. none) at six months, comparing the intervention groups to the control group. Similar to viral suppression, we expect that the probability of CAI with a susceptible partner will be similar for intervention and control groups at baseline. We will use inverse probability of treatment weights to correct any imbalances in baseline CAI with a susceptible partner. In addition, baseline covariates may be included in the model to improve precision of treatment effects. Censoring weights may also be included if loss to follow-up exceeds 15% or if there is evidence of differential censoring by treatment group.

In addition to the main six-month CAI outcome (any CAI with a potentially susceptible partner in the last 3 months), we will conduct a separate analysis in which "potentially susceptible partner" is defined as a partner who is not known to be HIV-positive or taking HIV medications (including PrEP). Additionally, we will compare the intervention and control arms with respect to the number of CAI acts in the last three months according to partner HIV and PrEP status (known HIV-positive, HIV-negative and not on PrEP, HIV-negative and on PrEP, unknown HIV status). Finally, linear mixed models will be fitted to all continuous outcome measures (i.e., self-regulation, self-efficacy to disclose, disclosure outcome expectations, consequences of disclosure, and intentions to disclose) to estimate the relative change in mean response from baseline to 6 months between intervention and SOC groups. Before fitting all models we will look for balance between treatment arms to assess the success of randomization, and we will adjust for possible confounding variables to improve precision and validity where needed. In the event that loss to follow-up is differential across treatment arms, we will employ inverse probability weighting to correct for this selection bias. We will test hypotheses using the likelihood ratio test, and goodness-of-fit among models will be assessed using the likelihood-ratio test, AIC and BIC criteria. Intervention completion and acceptability will be assessed at 1 month, and sensitivity analyses will evaluate how our findings for primary outcomes are influenced when we account for observed intervention completion.

Transmission Model

We will use a modified Bernoulli process mathematical model[26] to estimate the expected number of secondary sexual HIV transmission events for study participants. The estimated number of transmissions expected from each participant in each three-month interval (months -3 to 0, months 1 to 3, months 4 to 6) will be based on his viral load, specific risk behaviors, reported numbers of partners and acts within those partnerships, and partner HIV/PrEP status in that interval. In addition to the study data, we will review the literature to obtain model parameters for per-act HIV transmission probabilities, the effect of viral load and condom use on transmission probabilities, and expected HIV prevalence among partners whose HIV status was unknown. To account for uncertainty in model input parameters, we will run 10,000 simulations of the model, varying the input values for parameters obtained from the literature. The main output of each model run is the expected number of secondary transmissions for each participant over the six months after baseline, which will be summarized as the mean value (with 95% credible interval) in that period across all simulations. We will compare the estimated transmission events for the intervention and control groups to estimate transmissions averted due to the Tough Talks approach.

10.3.4. Program cost data collection

We will use the program costing approach described by Kim and colleagues (2014)[27] combined with standard cost weights derived from the analysis of Medicaid or other archival billing data sources, if needed. Detailed resource use for the interventions will be collected for both the intervention groups and the usual treatment group[28]. These data will be assigned standard cost weights developed using the data collection framework provided by Kim and colleagues (2014)[27]. We will use the individual site data collected by the Excel model from Kim, combined with study contract and expenditure records to estimate the intervention costs and of resource use differences by treatment. The Kim Excel model is a standardized instrument that is used to capture the economic cost treatment programs (e.g., personnel, facilities, supplies) to calculate a cost per visit or other type of service[27]. Study case flow and expenditure data will be used to determine the average cost/subject for each service type, average cost per technology-related resource used, and overall cost of technology to be amortized over the interventions

in the study. We will examine the effect of software amortization and market uptake assumptions on the ICERs estimated by the model.

10.3.5 Qualitative exit interviews

Transcribed exit interviews will be analyzed thematically for both a priori and emergent themes using Dedoose qualitative data analysis software (or equivalent). We will follow similar analytic procedures used in Phase 1 in order to identify possible areas for program improvement in Phase 2 and to provide additional context for interpreting the intervention's quantitative results.

10.4 Missing Data

Several procedures will be used to conduct data analysis when data for either outcomes or covariates are missing. The first step will be to assess the extent and pattern of missing data. If data are missing for only a few cases, then data analysis will be conducted only on study participants with complete data. However, when such a strategy would result in loss of data from a substantial proportion of participants, or if this approach would lead to biased or inaccurate results, then some form of imputation will be performed. The form of imputation used will depend on the nature of the data that are missing. For example, data that are collected repeatedly might be imputed using the "last value carried forward" method; and in some instances, interpolation between neighboring points might also be used.
When the primary endpoint is missing, one data analysis will be conducted using only cases with the endpoint. Subsequent analysis will be done where missing endpoints are imputed. Hot-deck imputation or regression imputation may also be used in this context.

11.0 HUMAN SUBJECTS

This study will be conducted in compliance with the protocol, ICH Good Clinical Practice (GCP) guidelines, and 45 CFR Part 46.

11.1 Participants' Confidentiality

All laboratory specimens, questionnaires, evaluation forms, reports, transcripts, and other records will be identified by SID and participant initials only, to maintain participant confidentiality. All paper records with personally-identifying information will be kept in a locked file cabinet in a limited secure access area at each study site. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the protocol team or NICHD. Every effort will be made to ensure that study participants are protected from risks.

Breach of Confidentiality: A potential risk to participants is violation of confidentiality. We will take the utmost caution to protect the confidentiality of all responses. We will minimize this risk by maintaining confidentiality and discretion throughout all research procedures and data management and analysis.

Participants may be concerned about the security of their data, particularly since it is collected and stored electronically. UNC and Duke have significant experience developing security protocols for

Internet-based studies, and we will take a variety of steps to ensure participant security, including using a dedicated server behind a firewall, encryption of data, separation of identifiers from responses, and password-protected access to data. Therefore, we believe that this risk will be minimal.

For both Tough Talks intervention arms, participants will create a unique username that does not contain any identifying information but will be their username on the app. Participants will not be able to privately communicate with each other on the app. Trained research staff at the University of North Carolina will monitor the website daily to ensure violations to privacy.

11.2 Certificate of Confidentiality

This research specifically targets a vulnerable population, children – YMSM ages 15-17. We will take every available step to minimize the risk of identifying/linking data being subpoenaed, stolen, or inadvertently released. First, the Tough Talks has secured a Certificate of Confidentiality from the NIH. Second, all research staff members are required to complete ethical clearance certification regarding protection of human subjects through their relevant IRBs. Third, all studies will have documented procedures to safeguard against the risk of the linking information being stolen by keeping such information in locked spaces to which only essential study personnel who have completed CITI certification for human subjects research ethics training (http://citiprogram.org) will have access. Per Section 2012 of the 21st Century Cures Act as implemented in the 2017 NIH Certificates of Confidentiality Policy, all ongoing or new research funded by NIH as of December 13, 2016 that is collecting or using identifiable, sensitive information is automatically issued a CoC. As noted on the NIH website (http://grants.nih.gov/grants/policy/COC/faqs.htm#187), a Certificate of Confidentiality will help the research team "...avoid compelled 'involuntary disclosure' (e.g., subpoenas) of names and other identifying information about any individual who participates as a research subject (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect."

11.3 Risks and Benefits

11.3.1 Risks

To minimize the risk of participants feeling uncomfortable about answering personal questions, we will use Computer Assisted Self Interview (CASI) methods for the study's assessments. In CASI, participants read assessment questions on a laptop computer or mobile phone and use a combination of mouse click and keyboard/touchscreen entry to input the answers themselves. Study staff may be available to assist participants with questions or technical difficulties on the CASI. Participants will also be able to refuse to answer any question that makes them uncomfortable. In-depth interviews will be conducted face-to-face or online.

To minimize risks to confidentiality, we will secure study data with all appropriate physical, electronic and operational protections. Data will be stored in a physically secure environment. All data files will have encryption and strong password protection. Any identifiable data will either be stored on UNC secure servers or will be on fully encrypted laptops. CASI assessments and online eligibility screening will take place on Qualtrics. Access to data will be on a role-based standard; only those study staff who require access to each type of data to complete their study-related roles will be allowed access. All study staff will be trained in security and confidentiality procedures, and will sign a confidentiality agreement before receiving access to any participant data.

We will also develop procedures to minimize indirect disclosure that a participant is participating in an HIV- related research study, or a study that enrolls MSM. For each mode of contact information, we will ask specifically whether anyone else potentially has access to that mode of communication, and if it is acceptable to leave a non-specific message about participation in a health study. No study-related messages will ever mention HIV prevention or the nature of the research study.

We use SSL encryption for transfers of information online, and Qualtrics has a business partner HIPAA agreement with UNC. Qualtrics is HIPAA compliant.

UNC will use Dedoose software to perform all qualitative analyses. Dedoose is a web-based application for organizing and analyzing textual, audio, and video data (qualitative) along with outstanding functionality for their integration with survey, test score, ratings, and demographic data (quantitative). Dedoose employs the highest levels of data encryption available for a web application in all data storage, back up, and transmission. Dedoose allows for project specific encryption feature.

In addition to a Certificate of Confidentiality, we will protect participants in the following ways (which correspond to the potential risks described in A.3):

1) Breach of confidentiality. We will take every precaution to minimize risks to study participants. All research staff members are required to complete ethical clearance certification regarding protection of human subjects through UNC-CH and Duke University or at their participating study site. We also have a strong data and safety monitoring plan in place to protect participants. Adverse events will be reported to the UNC-CH and Duke University and study site-specific IRBs using the Adverse Event Reporting Forms. Reports will be sent within 24 hours of notification by the PIs. Annual updates on enrollment and retention will also be sent to the IRBs.

   All data collection will take place in secure and supervised clinical settings. All study personnel names on this protocol have completed training and received certification in Human Subjects Research Protection (CITI Program) and HIPAA regulations. They will continue to renew this training in compliance with institutional policies. Participants will be asked to provide informed written consent to audio recording (usability testing, field testing) and HIV testing, and medical chart abstraction. To assure confidentiality and protection of the participants during audio recording, all files and transcripts will be stored on a password protected, encrypted computer in a locked file cabinet in a secured office. To additionally preserve confidentiality, we will only use participants' SIDs and names will not be used in data analysis. Informed consent forms, audio files, and transcripts will be kept in locked files and password-protected databases in a locked office accessible only to investigators. Audio files will be destroyed within one year of study completion.

2) Emotional discomfort during the assessment and/or while using the mobile app. While participants will be informed that they may refuse to answer any questions at any time, responses or reactions to certain questions may indicate distress on the part of the participants. If at any time during the study, a participant divulges that he is at risk for harm, including but not limited to being abused or experiencing violence, if harm is suspected or likely, or if the participant states he is suicidal/homicidal, measures will be taken to ensure his safety locally. Reporting will be made as appropriate to the situation and the legal statutes, and referrals will be provided for appropriate support, counseling or treatment resources.

3) Discomfort during collection of blood specimen. Whenever possible, we will conduct a medical chart review in order to minimize the need for blood sample collection for participants. There are only two time points in the study that require a potential blood draw if VL is not provided in the participants' medical chart (enrollment and 6-month assessment). All necessary blood sample draws will be executed by trained professionals within the SRV sites or independent laboratory.

In addition to a Certificate of Confidentiality, we will protect participants in the following ways:

We will take every precaution to minimize risks to study participants. Adverse events will be reported to the UNC-CH IRB, individual research PI institutional IRBs, and STUDY site-specific IRBs per each institution's IRB reporting requirements using Adverse Event CRF. When possible, reports will be sent within 24 hours of notification by the PIs. Annual updates on enrollment and retention will also be sent to the IRBs.

All data collection will take place in secure and supervised clinical settings. All study personnel have completed training and received certification in Human Subjects Research Protection (CITI Program) and HIPAA regulations. They will continue to renew this training in compliance with the UNC IRB policy as well as their individual institutional policies.

11.3.2 Benefits

The risk to individual participants is small and the potential benefit to both the individual and society is substantial. The main benefit of the proposed study to society is the development of a potentially feasible and acceptable mobile app that improves HIV disclosure. Participants may experience improvements in their own experiences disclosing their HIV status, thereby potentially reducing their risk for transmitting HIV and risks and costs to society. Therefore, the risk/benefit ratio is favorable. Study participants will be compensated for their time.

YMSM account for nearly two thirds of all new HIV infections in the US and YMSM are the only risk group experiencing a significant increase in HIV incidence. If successful, our intervention will improve these outcomes in our subject population. Given this high potential impact and low potential hazards to participants, we find that a clear examination of these research questions outweighs the previously mentioned risks. The effectiveness of a novel, scalable, technology driven, intervention to address HIV disclosure is understudied with this population. Given the significant health outcomes associated with HIV infections, and the paucity of intervention programs for this population of young adults, the knowledge to be gained from this research is significant. The risks to participants are reasonable in relation to the importance of the knowledge to be gained.

11.4 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed assent/consent documents, and any subsequent modifications will be reviewed and approved by the UNC IRB who is responsible for the oversight of the study. The informed assent/consent will describe the purpose of the study, the procedures to be followed, and the risks and

benefits of participation. Consent/assent will be obtained to explain the nature, significance, and risks of the study. Sample informed consent/assent forms are included.

11.5 Waiver of the Requirement for Parental Permission for Special Circumstances

The site IRBs and the UNC IRB as the central IRB will be requested to grant a waiver of parental permission to participate in this research study for youth participants under (not inclusive of) the age of 18.
Under 45 CFR 46.408 (c), an IRB has the authority to waive parental permission if it determines that "a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects" and "an appropriate mechanism for protecting the children who will participate as research subjects is substituted" and "that the waiver is not inconsistent with Federal, State, or local law."

A request for a waiver of the requirement for parental permission is requested for 2 reasons: 1) many youth would be reluctant to participate in this study – which focuses on HIV and risks for poorer medication adherence – if they are required to get parental permission; and 2) many of the youth in our study are likely to be gay, bisexual, or have an attraction to persons of the same gender, but may not be out to their parents; requiring parental permission may place participants at risk for outing themselves as part of the LGBT community or having HIV. For these reasons, we believe it is important to be granted a waiver for parental permission for this study population.

11.6 Waiver of the Requirement for Signed Consent Form

11.6.1 For Eligibility Screening

An online consent process for the eligibility screening is proposed. The introduction to the screening interview includes all the required elements for consent (45 CFR 46.116). No identifying information on volunteers is recorded during the online screening until a participant is determined eligible (i.e., by marking "I do consent to be screened for eligibility"). Therefore, there will be no identifying link of who agreed to be screened or not screened for the study. In addition, the screening presents minimal risk to participants and involves no procedures that would require written consent outside of a research context. Under these conditions the IRB is authorized to modify the requirements to obtain a signed consent form for some or all subjects (45 CFR 46.117 [c]).

11.7 Prisoner Participation

NIMH has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in human subjects research and should NOT be considered by local IRBs for the recruitment of prisoners. Subjects enrolled who subsequently become incarcerated or are placed in detention may not continue study participation. Study visits cannot be conducted during the period of incarceration or detention.

11.8 45 CFR Parts 160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" Pursuant to the Health Insurance Portability and Accountability Act - HIPAA)

Each site is responsible for adherence to their individual institution's HIPAA policies and procedures.

11.9 Study Discontinuation

This study may be discontinued at any time by the UNC IRB, NICHD, or other government agencies as part of their duties to ensure that research participants are protected.

12.0 PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the study sponsor(s) prior to submission.

Schedule of Events

Table 2: Schedule of Study Evaluations and Outcomes

			BL	One-month	Three-months	Six-Months
Primary Outcomes						
Viral load suppression	Viral load suppression will be defined as HIV RNA < lower limit of detection as per the laboratory at each clinical site.	Medical Chart review or blood draw for study	X		X	X
Secondary Outcomes						
Condomless anal sex (CA) with potentially susceptible partner	≥1 act of CAI with a partner who is not known to be HIV-positive in the last 3 months.	CASI	X		X	X
Disclosure Self-Regulation (Behaviors)	Measure of desire and actual disclosure behaviors to family, peers and sex partners	CASI	X	X	X	X
Self-efficacy to disclose	Adapted version of disclosure self-efficacy measure for MSM (6 items)[14].	CASI	X	X	X	X

Disclosure outcome expectations	Adapted version of disclosure outcome expectations measure for MSM (2 domains: self-evaluative expectancies - 6 items, and hedonistic outcome expectancies – 3 items)[14].	CASI	X	X	X	X
Intentions to disclose	Adapted version of disclosure intentions measure for MSM (1 item)[14].	CASI	X	X	X	X
Consequences of disclosure	Measure indicating how important each of a list of possible consequences concerning disclosure was to them when considering disclosing to a specific person[29].	CASI	X	X	X	X
Potential Moderators						
Brief Symptom Inventory (BSI)	The BSI yields nine primary symptom scales and global indices and has norms for adolescents and adults[30].	CASI	X		X	X
The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)	Individuals respond to eight items assessing the frequency and consequences of drug and alcohol use[31].	CASI	X		X	X
Other Outcomes of Interest						
Retention in Care	# missed and scheduled visits over last 6 months	CASI	X		X	X
STIs	New diagnosis of rectal/urethral gonorrhea or chlamydia or syphilis in last 6 months.	Medical Chart abstraction CASI	X		X	X
Adherence	A visual analogue scale (VAS) will be used to assess antiretroviral therapy adherence over the last 3 months[32].	CASI	X		X	X
PrEP uptake in serodiscordant partners	Participants will be asked to report on any known PrEP use among their serodiscordant partners.	CASI	X		X	X
Feasibility/Acceptability and Cost						

Feasibility (participants)	Records on recruitment, retention (missed assessments) and follow-up attempts will be kept. Intervention usage will include: # of times participant accessed the intervention, average time spent on the site, and # of activities completed.	App Metrics		X		
Acceptability	Both a scale adapted from Horvath et al[33]. and The System Usability Scale is a validated 10-measure scale that assesses subjective usability of a system. It is scored from 0 to 100, and a score of 68 or greater indicates that the online intervention is acceptable[34,35].	CASI		X		
TT specific Acceptability	Features liked, disliked with some write in questions, avatar specific acceptability	CASI		X		
Cost	Resources used to provide standard of care visits, installation and orientation to Tough Talks, clinic visits, and any unexpected consequences of the two intervention approaches recorded as part of the feasibility data collection.	CRFs, staff tools	X	X	X	X

13.0 References

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