Version 4.1

July 16, 2021

ATN 160 – TechStep: Technology-based Stepped Care to Stem Transgender Adolescent Risk Transmission

Funded by:
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development (NICHD)

with co-funding from:

The National Institute on Drug Abuse (NIDA)

The National Institute of Mental Health (NIMH)

The National Institute on Minority Health and Health Disparities (NIMHD)

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Trial Registration: ClinicalTrials.gov NCT04000724

ATN 160 – TECHSTEP: TECHNOLOGY-BASED STEPPED CARE TO STEM TRANSGENDER ADOLESCENT RISK TRANSMISSION

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

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Print/Type

Signed: _____ Date: _____

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AC	Analytic Core
ACASI	Audio Computer Assisted Self-interview
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretoviral Therapy
ATN	Adolescent Medicine Trials Network for HIV/AIDS Interventions
CASI	Computer Assisted Self-Interview
CFR	Code of Federal Regulations
CRF	Case Report Form
DHHS	U.S. Department of Health and Human Services
EC	Ethics Committee
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MC	Management Core
MSM	Men who have Sex with Men
NICHD	National Institute of Child Health and Development
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
PI	Principal Investigator
OHRP	Office for Human Research Protections
QNS	Query and Notification System
RCG	Radiant Creative Group
RCT	Randomized Controlled Trial
RDC	Remote Data Capture
SRV	Subject Recruitment Venue
SSL	Secure Sockets Layer
TC	Technology Core
Trans	transgender feminine, transgender masculine, gender non-conforming
TWM	Thrive With Me
UMN	University of Minnesota
VL	Viral Load
YAB	Youth Advisory Board
YLWH	Youth Living With HIV
YO	Years Old
YT	Youth Thrive
YYA	Youth and Young Adults

STUDY ABSTRACT

DESIGN:	TechStep is a three-arm, technology-based randomized controlled trial (RCT), with a stepped care approach, among high-risk HIV-negative trans youth and young adults (YYA) for reducing sexual risk behaviors and increasing PrEP uptake.
DURATION:	Trans YYA are enrolled for 9 months in the RCT.
SAMPLE SIZE:	Total study sample is 355 of which the following will be enrolled for each phase: 1) up to 80 participants for focus groups to inform intervention adaption; 2) 275 participants for a randomized controlled trial of TechStep, with participants randomized to either text messaging stepped care (n=108), WebApp stepped care (n=83) or control (n=83) condition.
POPULATION:	Participants will include YYA who are self-identified trans feminine, trans masculine or gender non-conforming or whose birth sex and current gender do not match; ages 15 to 24 years; HIV-negative; and sexually active. For Phase 1, participants must self-report never having received a positive HIV test result; participants age 15-20 must report any kind of sex in the previous 12 months, while participants age 21-24 must report vaginal or anal sex (either insertive or receptive; excluding sex toys) in the previous 12 months. For Phase 2, participants must have a confirmed HIV negative serostatus and report anal or vaginal sex (either insertive or receptive; excluding sex toys) in the previous 12 months. For Phase 2, participants will be recruited from SRVs in Houston, Los Angeles, New York City, Philadelphia, and Boston.
STRATIFICATION:	Focus group discussions will be stratified by age (50% 15-20 years old; 50% 21-24 years old).
DATA COLLECTION:	Focus group discussions will be conducted in-person, digitally recorded, and professionally transcribed. There will be five data collection (screening, baseline, 3-month, 6-month, and 9-month) time points for the RCT. Visits will

be conducted in-person at the SRV, online, or some combination of in person or online. The ACASI will be completed using online survey tools. An HIV test, STI panel, urine screen for recent illicit drug use, and blood microsampling, for those who report PrEP uptake, to verify PrEP adherence will be collected in-person at the participant's SRV or via mailed self-collection kits. HIV testing during enrollment is mandatory, and encouraged during follow-ups. All biological specimen collection with the excepton of HIV testing at enrollment is optional but encouraged. Process data of participant activity at each step of the intervention, as well as the control intervention, will be collected.

OBJECTIVES:

Primary Aim 1: Conduct formative research to develop the stepped care (text messaging, WebApp, and eCoaching) interventions and refine iterations through input from focus groups with trans YYA at the four study sites (n=80) and a youth advisory board (YAB).

Primary Aim 2: In a 3-arm RCT (N=275), assess the differential immediate and sustained effects of a low intensity information ("Info") arm compared to a text messaging stepped care intervention (text messaging plus step to eCoaching for YYA with continued high risk) arm compared to a WebApp stepped care intervention (WebApp plus step to eCoaching for YYA with continued high risk) arm for reducing sexual risk behaviors and increasing PrEP uptake among high-risk, HIV-negative trans (15-24 years old).

Secondary Aim 3: Determine the added benefit of text messaging plus eCoaching versus text messaging alone and of WebApp plus eCoaching versus WebApp alone for reducing sexual risk behaviors and increasing PrEP uptake.

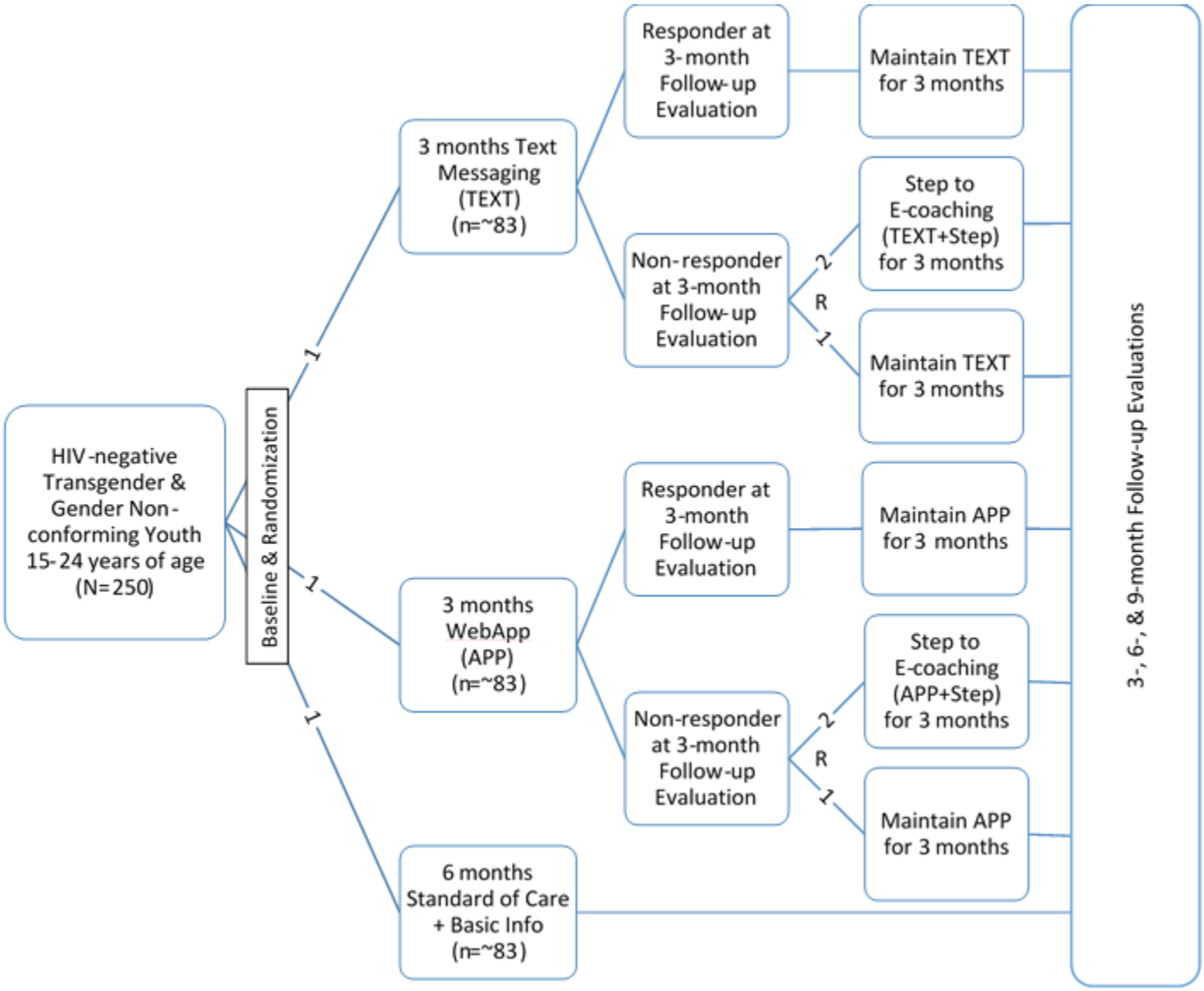
Secondary Aim 4: Assess the differential immediate and sustained effects of low intensity information compared to text messaging only compared to WebApp only for reducing sexual risk behaviors and increasing PrEP uptake.

Secondary Aim 5: Determine the impact of structural- (e.g., transphobia, housing insecurity, educational attainment, access to healthcare) and individual-level (e.g., identity formation, gender transition, gender expression,

stigma, discrimination) trans-specific factors as moderators of intervention outcomes.

STUDY DESIGN OR SCHEMA

Figure 1. TechStep Study Design



Note: Text arm increasing from 83 to 108 as of February 2021.

1.0 INTRODUCTION

1.1 Background

National evidence suggests that as many as 8% of US youth self-identify as either "transgender," "gender nonconforming," or "other gender".[7] Evidence further demonstrates that trans youth face a "health syndemic," i.e., a set of reinforcing structural, cultural, and behavioral factors that place trans youth at dramatically increased risk for negative physical, social, and mental health outcomes.[8-11] For example, trans youth demonstrate significantly elevated rates of sexual risk-taking relative to their cisgender/gender-conforming peers,[9,12,13,14] including rates of condomless anal intercourse ranging from 27-59% and rates of engagement in sex work ranging from 24-75%.[1,14] Increased rates of sexual risk behavior(s) among trans youth are associated with the population's increased experiences of physical/sexual abuse and victimization, mental health disorder, incarceration, and homelessness,[9,14,15] as well as substance use, sex work, and substance use during sex.[2,9,14] Due to this health syndemic, trans youth are at substantially increased risk for HIV infection, as well as other STIs, relative to their cisgender youth counterparts.[1,2] Despite these needs, there is persistent evidence of inadequate training regarding the care of trans youth among traditional healthcare providers;[16] the difficulties trans youth report accessing traditional healthcare[13,17] and the frequent reports by trans youth of prejudice/discrimination when receiving traditional healthcare[17,18] demonstrate the critical need for avenues of sexual health information and intervention which extend beyond traditional brick-and-mortar service and which cater to the special needs of trans youth.

Mobile technology-based intervention approaches have the unique advantages of being unleashed from traditional face-to-face requirements within brick-and-mortar settings, and therefore are highly scalable. Because of this, mobile interventions may be delivered anywhere and at any time, so long as users have their mobile device with them. This "always on" feature allows mobile interventions to be delivered during times when users need relevant intervention the most. Finally, interventions delivered via mobile phone can also be delivered at no/low cost, provide a high degree of confidentiality, and cultivate motivational communication among users, all elements of special relevance to trans youth populations.[28]

All adolescents, including trans youth,[19] demonstrate frequent use of text messaging and mobile Internet-enabled technology to seek out protective sexual health information.[20] Trans youth explicitly cite mobile phones as critical tools in their ability to engage with sexual health information, as text messaging conversations, mobile apps, and other mHealth delivery modalities provide portals where trans youth report feeling comfortable to seek out health-related knowledge specific to trans individuals (e.g., hormone therapy, pubertal suppression[21]) adopt and express new and different identities, connect to other trans youth to seek out information and resources.[19,22,23] Evidence demonstrates that youth find text messages about sexual health easy to understand, trustworthy, friendly, convenient, and that the text message format promotes the ability to assimilate and share sexual health information at their own pace; youth also indicate that sexual health messages delivered via text increase confidence and reduce sexual stigma.[24] In-depth interviews with trans youth revealed overwhelming endorsement of digital spaces, particularly those accessible for free or at low cost via mobile phones,[23] as critical sources of transgender-specific health information[25,26] and resilience in the face of prejudice and perceived discrimination.[22,23] Among mobile deliverable intervention modalities, text messaging and smartphone apps in specific have been identified as particularly well-suited to the needs of trans populations, whose gender expression may serve as an obstacle to standard brick-and-mortar treatment.[27]

Although systematic review indicates that mobile health interventions are particularly efficacious at increasing HIV protective behaviors among vulnerable and key HIV risk populations such as trans youth,[28] a recent systematic review revealed that only 18% of mobile phone-based HIV prevention/care interventions provide any information tailored to LGBT populations, and none were tailored specifically to trans individuals.[29] One digital intervention designed for LGBT youth, but not specifically tailored for trans youth, successfully increased safer sex outcomes among participants,[30] and another intervention designed for young African American/Black MSM and trans women, but was not specifically for trans women, demonstrated significant improvements in participant social support, social isolation, and depressive symptoms.[31,32] The TechStep study will fill a critical gap in the scientific advancement of technology-based interventions for trans youth by a) creating the first technology-based trans youth-specific HIV prevention interventions optimized for mobile phone delivery; and, b) employing the two intervention delivery modalities identified as most promising for use among trans YYA (i.e., text messaging and mobile app).

As part of the UNC/Emory Center for Innovative Technology (iTech), we propose to test the efficacy of TechStep for trans YYA. In this 4-year study, 275 high-risk trans YYA between the ages of 15-24 will be randomized to receive text messaging, a WebApp, or an information-only control intervention for 6 months, with assessments occurring at baseline and 3-, 6- and 9-months. YYA who do not evidence improvements in sexual risk and/or PrEP uptake at the 3-month assessment will be randomized to either receive weekly eCoaching sessions in addition to their assigned text messaging or WebApp intervention, or remain in the original intervention in a 2:1 ratio. The primary endpoint is reduced sexual risk behaviors and/or PrEP uptake, adherence and persistence at month 6.

1.2 Rationale

There is a clear need to develop effective prevention interventions that meet the needs of trans YYA. Trans YYA – especially racial and ethnic minorities – are at very high risk for acquiring HIV and other STIs, the impact of which is compounded by the lack of culturally competent healthcare providers. For this reason, the suite of technology-based interventions developed in TechStep and assessed for effectiveness in a 3-arm RCT represents an important advance in intervention science toward developing tailored and scalable interventions for this population.

1.2.1 Youth Advisory Boards (YAB) of trans YYA

Two Youth Advisory Boards will be convened. There will be a physical YAB in Los Angeles, and a virtual cross-site YAB via telecommunication comprised of members from the Houston, New York, and Philadelphia SRVs. The YABs will meet biannually throughout the course of the study and will provide feedback on all aspects of the TechStep study including the technology-based interventions, stepped care design, recruitment strategies, culturally competent study materials, and implementation. YAB participants provide expert advice and are not considered human subjects under the IRB.

1.2.2 Focus groups with trans YYA

Eight focus groups (two each in Houston, Los Angeles, New York and Philadelphia) will be conducted to gain feedback from trans YYA about the existing text messaging and WebApp interventions that will serve as the starting points for adapting these intervention approaches. Focus groups will be conducted at four SRVs (Houston, Los Angeles, New York City, and Philadelphia), two of which (Houston & Los Angeles) will focus on gaining feedback on the WebApp and two of which (New York & Philadelphia) will focus on gaining feedback on the text

messaging intervention. Feedback on these intervention strategies will help to ensure that they are culturally tailored to trans YYA.

1.2.3 RCT of TechStep

A 3-arm RCT of TechStep will be conducted with the following conditions: 1) a text messaging stepped care intervention, 2) a WebApp stepped care intervention, and 3) a low-intensity information control group. Those in either of the active technology-based intervention conditions who do not report a reduction in sexual risk and have not started PrEP, or those who report a reduction in sexual risk but have discontinued PrEP since their last assessment will be randomized to either step up to receive the technology-based intervention (text or WebApp) plus weekly eCoaching sessions or to remain on the original intervention.. The control group will consist of information about trans health, HIV/STI information and local resources for trans persons. A RCT was chosen since it is the gold standard for assessing the effectiveness of an intervention under tightly controlled conditions. The intervention and control groups will have access to information and intervention content for 6 months, with ACASI performed at baseline, and every 3 months thereafter for 9 months (i.e., 3-month, 6-month, & 9-month follow-up assessments). At all follow-up assessments, trans YYA will be assessed for their sexual risk behaviors and PrEP uptake, adherence and persistence. Assessments will include self-reported behavioral data, and biomarkers for HIV, STIs, current drug use, and PrEP adherence and persistence.

2.0 STUDY OBJECTIVES

Primary Aim 1: Conduct formative research to develop the stepped care (text messaging, WebApp, and eCoaching) interventions and refine iterations through input from focus groups with trans youth and young adults (YYA) at the four study sites (n=80) and a youth advisory board (YAB).

Primary Aim 2:

In a 3-arm RCT (N=275), assess the differential immediate and sustained effects of a low intensity information (“Info”) arm compared to a text messaging stepped care intervention (text messaging plus step to eCoaching for YYA with continued high risk) arm compared to a WebApp stepped care intervention (WebApp plus step to eCoaching for YYA with continued high risk) arm for reducing sexual risk behaviors and increasing PrEP uptake among high-risk, HIV-negative trans (15-24 years old).

Hypothesis 1a: There will be significantly greater reductions in sexual risk behaviors among those in the Text+Step and App+Step arms compared to the low intensity Info arm.

Hypothesis 1b: There will be significantly greater uptake of PrEP among those in the Text+Step and App+Step arms compared to the low intensity Info arm.

Secondary Aim 3:

Determine the added benefit of text messaging plus eCoaching versus text messaging alone and of WebApp plus eCoaching versus WebApp alone for reducing sexual risk behaviors and

increasing PrEP uptake.

Secondary Aim 4: Assess the differential immediate and sustained effects of low intensity information compared to text messaging only compared to WebApp only for reducing sexual risk behaviors and increasing PrEP uptake.

Secondary Aim 5: Determine the impact of structural- (e.g., transphobia, housing insecurity, educational attainment, access to healthcare) and individual-level (e.g., identity formation, gender transition, gender expression, stigma, discrimination) trans-specific factors as moderators of intervention outcomes.

> *Hypothesis 2*: Structural- and individual-level trans-specific factors will moderate intervention outcomes, such that participants who report higher amounts and degrees of these factors will require more intensive intervention steps (i.e., eCoaching).

3.0 STUDY DESIGN

3.1 Study Phases

We will develop and evaluate TechStep in two phases. In Phase 1, we will establish Youth Advisory Boards (YABs) to inform intervention features and content, as well as conduct focus groups to seek input into intervention components. In Phase 2, TechStep will be evaluated in a randomized controlled efficacy trial (see TechStep Schema). For Phase 1, all participants (n=80) must meet the eligibility criteria listed in Section 4. A recruitment target of 275 HIV-negative trans YYA will be enrolled in Phase 2 to assess whether Text+Step or WebApp+Step is more effective in reducing sexual risk behaviors and increasing PrEP uptake, adherence and persistence for HIV-negative trans YYA than a low-intensity control condition. Trans YYA will be recruited from 5 SRVs (Boston, Houston, Los Angeles, Philadelphia, New York), screened, and randomized to receive either the Text+Step intervention, the App+Step intervention, or basic information on HIV/STIs, trans health, and referrals only in the control condition. The step component may provide weekly eCoaching sessions in addition to the original intervention (i.e. text or app) for YYA who do not evidence improvement in sexual risk and/or PrEP uptake. Sexual risk behaviors and PrEP uptake, adherence, and persistence will be assessed at the enrollment visit, and 3-, 6-, and 9-month follow-up assessment time points.

Phase 1: Formative Research and Community Input
Two Youth Advisory Boards will be convened. There will be a physical YAB in Los Angeles, and a virtual cross-site YAB via telecommunication comprised of members from the Houston, New York, and Philadelphia SRVs. The YABs will meet at least biannually throughout the course of the study and will provide feedback on all aspects of the TechStep study including the technology-based interventions, stepped care design, recruitment strategies, culturally competent study materials, and implementation.

We will conduct two focus groups with up to 10 trans YYA per group, at 4 SRVs (8 focus groups total). At each SRV, one focus group will consist of participants between the ages of 15-20 and the other focus group will be with participants between the ages of 21-24. Focus groups in Houston and Los Angeles will be used to gain feedback on the WebApp (also referred to in this protocol as an “app”) component of the intervention, while focus groups in New York and Philadelphia will be used to gain feedback on the text messaging component of the intervention.

Focus groups will be transcribed verbatim and a content analysis will be assisted by the Analytic Core (AC).

Phase 2: Randomized Controlled Trial to Test Efficacy of TechStep
Trans YYA will be recruited from 5 SRVs (Boston, Houston, Los Angeles, New York, and Philadelphia) to participate in a 3-arm RCT to determine immediate and sustained effects of the Text+Step intervention versus the App+Step intervention compared to an information-only control condition ("Info" arm). All participants will receive one of the interventions for 6 months, with assessments occurring at baseline and every 3 months thereafter until month 9. Trans YYA randomized to either of the technology-based intervention arms (Text or WebApp) will be evaluated at the 3-month follow-up assessment time points to determine if they remain at the current level of intervention, or if they are eligible for randomization to also receive eCoaching sessions in addition to their originally assinged intervention. All participants assigned to the Text+Step intervention arm will begin with the text messaging intervention. Participants assigned to the App+Step intervention arm will begin with the WebApp intervention. At the first follow-up assessment time point, information about their sexual behavior in the past 3 months and whether they began or stopped using PrEP will be used to determine if they require a more intensive intervention approach. Participants who do not demonstrate intervention responsiveness at the 3-month follow-up assessment will be re-randomized, in a 2:1 ratio, to either remain in the original technology-based intervention (i.e., Text or App) or add eCoaching to the original technology-based intervention (i.e., Text+eCoaching or App+eCoaching). This re-randomization will allow for a comparison of intervention effects between the technology-based interventions (i.e., text or app) plus eCoaching to the technology-based intervention alone. The control condition will receive the same information-only intervention for the entire 6-month intervention period.

3.2 Study Population

We propose to enroll 355 trans YYA for the purposes of this study. Up to 80 participants will be recruited for focus group discussions (with the goal of 5-7, a minimum of 3 and a maximum of 10 per group), and 275 participants (n=108 Text+Step, n=83 App+Step and n=83 control) will be recruited to participate in the TechStep RCT.

Inclusion criteria for the focus groups and RCT are described in Section 4.0 (note: the Youth Advisory Board members are not considered human subjects for research and, therefore, inclusion criteria are not listed for YABs).

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

3.3.1 Focus Groups

Focus groups will be stratified by age such that 2 focus groups (1 consisting of youth 15-20 year olds and 1 consisting of young adults 21-24 years old) will be conducted at 4 SRVs. Study staff at each SRV will oversee that approximately 5-7 participants (with a minimum of 3 and a maximum of 10) are recruited for each of the 2 focus groups conducted at that site.

3.3.2 RCT

In the RCT, participants will be randomized 1:1:1 to the Text+Step intervention or App+Step

intervention or control condition. Randomization procedures are further explained in Section 5.2.

4.0 SELECTION AND ENROLLMENT OF STUDY PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Inclusion Criteria for Phase 1 Focus Groups with Youth (15-20 years old)

- Self-identified as trans feminine, trans masculine or gender non-conforming OR birth sex and current gender differ;
- Between the ages of 15 to 20 years old;
- Reports any sex with another person in the previous 12 months;
- Self-report HIV negative serostatus.
- Live in the area and availability to meet with research staff at either the Baylor College of Medicine (BCM) Adolescent Medicine Trials Unit in Houston, Children's Hospital of Philadelphia, Children's Hospital Los Angeles, or the Center for HIV Educational Studies and Training (CHEST) in New York City;
- Have a mobile device with SMS and Internet access capabilities; and
- English-speaking (since the intervention will be built in English).

4.1.2 Inclusion Criteria for Focus Groups with Young Adults (21-24 years old)

- Self-identified as trans feminine, trans masculine or gender non-conforming OR birth sex and current gender differ;
- Between the ages of 21 to 24 years old;
- Reports vaginal or anal sex (either insertive or receptive) with another person in the previous 12 months;
- Self-report HIV negative serostatus.
- Live in the area and availability to meet with research staff at either the Baylor College of Medicine (BCM) Adolescent Medicine Trials Unit in Houston, Children's Hospital of Philadelphia, Children's Hospital Los Angeles, or the Center for HIV Educational Studies and Training (CHEST) in New York City;
- Have a mobile device with SMS and Internet access capabilities; and
- English-speaking (since the intervention will be built in English).

4.1.3 Inclusion Criteria for Randomized Controlled Trial Inclusion Criteria

- Self-identified as trans feminine, trans masculine or gender non-conforming OR birth sex and current gender differ;

- Between the ages of 15 to 24 years old;
- Report vaginal or anal sex (either insertive or receptive; excluding sex toys) with another person in the previous 12 months;
- Negative HIV test;
- Availability to meet with research staff in person or online at the Baylor College of Medicine (BCM) Adolescent Medicine Trials Unit in Houston, Children's Hospital of Philadelphia, Children's Hospital Los Angeles, PRIDE Health Research Consortium New York City, or the Fenway Institute in Boston;
- Have a mobile device with SMS (text messaging) and Internet access capabilities; and
- Read and speak English (since the intervention will be built in English).

4.2 Exclusion Criteria

4.2.1 Exclusion Criteria for Focus Groups with Youth (15-20 years old)

- Does not self-identify as trans feminine, trans masculine or gender non-conforming OR birth sex and current gender match;
- Younger than 15 years of age or over 20 years of age;
- Does not report sex with another person in the previous 12 months;
- Does not self-report a HIV negative serostatus.
- Doesn't live in the area or is unable to meet with research staff at either the Baylor College of Medicine (BCM) Adolescent Medicine Trials Unit in Houston, Children's Hospital of Philadelphia, Children's Hospital Los Angeles, the Center for HIV Educational Studies and Training (CHEST) in New York City ;
- Does not have a mobile device with SMS and Internet access capabilities;
- Not English-speaking and/or does not read English (since the intervention will be built in English);
- Unwilling or unable to comply with protocol requirements;
- Unable to understand the Informed Consent/Assent Form.

4.2.2 Exclusion Criteria for Focus Groups with Young Adults (21-24 years old)

- Does not self-identify as trans feminine, trans masculine or gender non-conforming OR birth sex and current gender match;
- Younger than 21 years of age or over 24 years of age;
- Does not report vaginal or anal sex (either insertive or receptive; excluding sex toys) with another person in the previous 12 months.

- Does not live in the area or is unable to meet with research staff at either the Baylor College of Medicine (BCM) Adolescent Medicine Trials Unit in Houston, Children's Hospital of Philadelphia, Children's Hospital Los Angeles, the Center for HIV Educational Studies and Training (CHEST) in New York City;
- Does not have a mobile device with SMS and Internet access capabilities;
- Not English-speaking and/or does not read English (since the intervention will be built in English);
- Unwilling or unable to comply with protocol requirements;
- Unable to understand the Informed Consent/Assent Form.

4.2.3 Exclusion Criteria for Randomized Controlled Trial

- Does not self-identify as trans feminine, trans masculine or gender non-conforming OR birth sex and current gender match;
- Younger than 15 years of age or over 24 years of age;
- Does not report vaginal or anal sex (either insertive or receptive; excluding sex toys) with another person in the previous 12 months.
- Reactive or indeterminate HIV test;
- Unable to meet in person or online with research staff at the Baylor College of Medicine (BCM) Adolescent Medicine Trials Unit in Houston, Children's Hospital of Philadelphia, Children's Hospital Los Angeles, PRIDE Health Research Consortium in New York City, or the Fenway Institute in Boston for the Baseline and 3 month assessment;
- Does not have a mobile device with SMS (text messaging) and Internet access capabilities;
- Not English-speaking and/or does not read English (since the intervention will be built in English);
- Unwilling or unable to comply with protocol requirements;
- Unable to understand the Informed Consent/Assent Form.

4.3 Recruitment

The following recruitment strategies will be utilized to ensure enrollment targets are met and a diversity of participants are enrolled. 1) Online Recruitment: Online banner ads targeting trans YYA will be placed through geo-mapping on websites and social media in SRV cities. We will also distribute digital flyers to community leaders who will inform their email distribution lists with information on how to participate in the study. Additional online recruitment may also be conducted, including but not limited to recruiting via online social media outlets (e.g., Facebook,

Instagram, Snapchat, etc.). 2) SRV and other Community-based Outreach: flyers and posters will be created and distributed in SRVs and other community-based organizations and clinic settings that cater to trans YYA. The flyers and posters will contain details about how to contact a SRV Research Assistant for further information or how to screen online for the RCT. 3) Peer Referral: Participants who screen eligible for the RCT will be asked to refer friends who are also trans YYA. For the RCT, we will 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) Clinic-based recruitment may include reviewing medical charts of existing patients for potential eligibility, or referrals from other providers in the clinic. 5) Former participants who have previously given consent to be contacted for future research may also be directly contacted for recruitment and screening. 6) Print Media: Ads will be placed in print media that trans YYA read. 7) Street- and Venue-based Outreach: Research Assistants will utilize a semi-structured time-space sampling methodology to conduct street- and venue-based outreach identified through the Trans Youth Community Advisory Board and ongoing community mapping at locations where young trans YYA congregate. Research Assistants will be trained on appropriate outreach strategies, how to build and maintain ongoing trust and rapport, and how to conduct confidential screening.

4.4 Screening

All potential participants (whether recruited online, in-person or over the phone) will complete an online screening survey to obtain consent/assent to be screened and verify all inclusion criteria. Screening may occur on the same day as enrollment or beforehand. The online screening survey will begin with a script that will be read by participants to explain the purpose of screening and clarify that if they are eligible, they will be invited to participate in the study. The script will also provide general information about the research study, the nature of the screening questions and related potential risks, the approximate length of the screening (~5 minutes), the confidentiality of the screening information, the use of any screening information obtained, the ability to skip any questions or withdraw at any time, and contact information of key study personnel. After reading this screening script, participants will be asked if they are interested in participating and agree to voluntarily complete the screening procedure. Participants will electronically indicate their agreement and then take the screening survey.

SRV staff may also screen participants using the online screener in person, over the phone, or over a teleconferencing platform such as Zoom or a comparable platform. The SRV staff will obtain verbal consent from the participant to screen, read the screening questions from the the online survey to the participant, and record the participant's responses in the online screener.

The online survey is hosted on Alchemer and we will use SSL encryption for transfers of information online and data will be stored in the secure, HIPAA-compliant servers of Alchemer. The Emory AC team maintains a business partner HIPAA agreement with Alchemer. For those who meet eligibility criteria, the survey will ask if they are willing to provide their first name, e-mail, and a phone number. Potential participants who do not meet eligibility criteria will be asked if they would like to be contacted about other research studies and, if so, to provide contact information.

The Analytic Core will securely share the contact information of eligible participants with SRV sites via a secure Box or Microsoft OneDrive account. SRV staff will enter the eligible participant into SMART for scheduling and contact participants to schedule an in-person visit at the SRV or an online enrollment visit. Study staff also have the option of scheduling and completing some study visit activities in person and some of the study visit activities online to provide flexibility during the COVID-19 pandemic and afterwards and to be responsive to participant needs.

YYA who screen eligible and provide contact information will be contacted by SRV staff and provided with information about the date and time of the focus group (in Phase 1) or to schedule an in person or online baseline enrollment visit (in Phase 2). An email will be sent to potential focus group participants immediately after they are scheduled for the focus group that includes the focus group date, time, location and staff contact information. Potential focus group participants will be sent a reminder three days prior to the focus group, as well as on the day of the focus group.

YYA who screen ineligible (see section 4.2 for exclusion criteria) will be informed at the conclusion of the screener that they are not eligible for the study.

4.4.1 Contact Info

Once the participant is consented/assented, designated site study staff will complete a Locator/Contact Information Worksheet with the participant and/or enter the participant's contact information directly into SMART Web during the enrollment visit. Participants will be asked to provide a working phone number and/or valid email address through which they can be reached. Participants will also be asked to provide social media contact information. Participants will also be asked to provide valid contact information for two family members and/or friends 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. Study staff will not leave messages unless expressly permitted to do so by the participant which also will be documented on this form. If permission is given to leave messages, site study staff will assure participants that messages left with a family member or friend will only ask the participant to contact study staff and will not include any protected health information or information related to study participation. For participants randomized to the eCoaching intervention, the eCoaches based at PRIDE will ask participants in the eCoaching intervention to provide them with contact information similar to what the participant provided to the SRV when they were enrolled.

4.5 Informed Consent

Informed consent/assent. The informed consent process will occur on the day the enrollment visit is held. Consent may be done online, in person, or over the phone. A teleconference platform such as Zoom (see Section 7.3.6 for description of the Zoom platform) or other comparable platform will be used for online study visits and consenting. Interested persons will be guided through the informed consent process by study staff, who will explain all study procedures, answer questions concerning the study and consent process, and offer a copy of the informed consent/assent form. The research staff member will give the participant as much time as needed and will address any questions or concerns they may have. The participant will be allowed to take the consent/assent form home and review it before enrolling in the study if the participant needs more time to review the form. 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, benefits of participation, and information regarding who they can contact with further questions. It also states that participation is voluntary, that participants may decide not to 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. The informed consent/assent form may be on paper or online

via a HIPAA-compliant, secure online platform, such as Alchemer or Qualtrics (see Section 7.3.7 for details on Qualtrics).

Assessing for decisional capacity. For all participants, the research assistant (RA) reviews the informed consent/assent to make an assessment of the participant's decisional capacity and ability to provide consent/assent prior to signing, using a 2-step process. First, the RA determines if the person understands the study goals by asking a question such as, "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. Participants will be asked to: name things they will be expected to do during the study; explain what they would do if they no longer wished to participate in the study**;** explain what they would do if they experienced distress during the study; and identify potential risks for participating in the study. For YYA who cannot answer these questions, the RA will go back and review the relevant elements of consent with the participant again and repeat the process. YYA who appear not to understand after repeated review will not be enrolled in the study. If the enrollment process occurs online, research staff will talk with potential participants via phone or online teleconference platform such as Zoom (see Section 7.3.6 for description of the Zoom platform) or other comparable platform 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 15 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 signed consent and parental/legal guardian permission will be sought given that minor individuals can often seek sexually transmitted infection (STI) and HIV testing without parental/legal guardian permission, depending on each site's state laws, and given that many of the trans youth in our study are likely to be gender and/or sexually fluid 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 disclosing as part of the LGBT community or being at risk for HIV infection. A waiver of parental permission for studies with 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 or gender identity. Commonly, these youth have explored their sexuality or gender expression 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 gender and sexual minority youth.

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 (e.g., consent/assent forms,

contact information) will be kept in a locked, limited access area (such as a locked file cabinet) at the participating site.

5.0 STUDY PROCEDURES

5.1 Enrollment Procedures

5.1.1 Focus group enrollment

Screening procedures are explained above in section 4.4. All persons who screen eligible for the study will be guided through the informed consent process (section 4.5) on the day the focus group is held. Research staff administering the consent process will pay particular attention to whether the potential participant appears confused or otherwise unable to complete the informed consent process, and will stop enrollment of that participant in the focus group.

Following informed consent, trans YYA will be walked to the focus group room where they will complete a brief paper-and-pencil Focus Group Participant Survey (e.g., additional demographics and technology use survey) before the focus group begins. After informed consent/assent is obtained and the Focus Group Participant Survey is completed, participants will be deemed enrolled in the study.

Participants will be compensated for their time once the focus group has ended. Participants who leave the focus group early will be compensated the same amount regardless of how long they are present.

5.1.2 RCT Enrollment

Screening procedures are explained above in section 4.4. All persons who screen eligible for the study will be guided through the informed consent process (section 4.5) on the day of their enrollment appointment. Research staff administering the consent process will pay particular attention to whether the potential participant appears confused or otherwise unable to complete the informed consent process, and will stop enrollment of that participant in the RCT.

Following informed consent, trans YYA will go through baseline assessment procedures of having HIV testing, blood microsampling analysis for those who self-report PrEP use, screening for STIs and drug use through a urine screen (note: HIV testing is the only required biological specimen collection, all others are voluntary), and the survey measures through an ACASI. Biological specimen collection may be done in person during the study visit or via self collection kits mailed to participants. For mailed self collection, the biological specimens may be collected after the baseline enrollment visit and must be returned within 90 days. After randomization, participants will receive more information about the arm they are randomized into (e.g. how to use the WebApp, the frequency of text messages, or how to access the resources and information). For in person enrollment visits, participants will be deemed enrolled in the study after baseline procedures and the enrollment visit are completed. For online enrollment visits, participants will be deemed enrolled in the study after they are randomized and onboarded.

5.2 Randomization Procedures

For the purpose of Phase 1 focus groups, participants will not be randomized.

Randomization for the RCT is explained in section 3.3.2.

During the RCT, after completion of the baseline ACASI, participants will be randomized 1:1:1 to the Text+Step intervention or App+Step intervention or control condition, based on a randomization sequence developed by the AC lead statistician and loaded into DFexplore (see section 7.4.1 for more details on DFexplore). The randomization sequence will be stratified by city and use random permuted blocks of size 3.

5.3 Intervention/Investigation Procedures

5.3.1 Focus Groups

Focus groups will be conducted in person and at 4 SRVs (Houston, Los Angeles, New York, and Philadelphia). Two focus groups will be conducted at each of the 4 SRVs. Focus groups are anticipated to last approximately 120 minutes, and light refreshments and food will be served at each group. Research staff will conduct the focus groups. The focus groups conducted in New York and Philadelphia will be used to gain feedback from trans YYA on the text messaging intervention of TechStep, while the focus groups in Houston and Los Angeles will be used to gain feedback on the WebApp. All focus groups will be audio recorded (equipment provided by the research staff). The Protocol Chair will coordinate with SRV staff to arrange participant compensation at the end of each focus group. A minimum of 3 persons must be present at the beginning of the focus group to conduct the focus group. If 1 or 2 persons are present at the beginning of the focus group, we will ask that it be rescheduled and they will be compensated for transportation costs.

5.3.2. Focus Group Recruitment

Focus group participants will be recruited from SRVs, other community settings, online, and through peer referrals. Specifically, focus group participants may be recruited through poster advertisement placed at each SVR or at community sites that collaborate with the SRV. The posters will contain details about how to contact a Research Assistant for further information regarding the focus groups. Ads will be posted on social media and with brief information about the purpose of the focus groups as well as information about compensation. Interested individuals can screen online or can email the SRV Research Assistant to find out more and get screened for eligiblity over the telephone or in-person. When a participant screens eligible to participate in a focus group, they will be asked to refer any friends who are also trans YYA. If the SRV has a YAB, some participants may be recruited directly from the YAB

5.3.3 RCT

Enrollment for the RCT will be conducted in person or or online at 5 SRVs (Boston, Houston, Los Angeles, New York, and Philadelphia). Online study visits may be carried out via an online videoconferencing software, such as Zoom (see Section 7.3.6 for description of the Zoom platform) or a comparable platform.

Enrollment procedures are anticipated to last approximately 120 minutes and consists of informed consent/assent, the baseline ACASI survey, and HIV, STI and drug screen testing, and blood microsampling for those who self-report PrEP use (of the biological specimen collection, only HIV

testing is mandatory). For online enrollment visits, some or all of the biological specimen collection may be done via mailed self-collection kits after the enrollment visit. Participants, if they choose to do so, will be able to meet with research staff via live, secure video chat, to answer questions about the at-home self-collection kit components and procedures. Particularly, study staff will be able to answer questions and go over results of rapid HIV test results if participants prefer to self-administer a rapid test in addition to or in lieu of a lab processed HIV test. Rapid HIV test results will be confirmed with research staff via secure video chat, or by uploading a photo of the test results to a secure online survey hosted by Alchemer. During enrollment, participants will be randomized into either the Text+Step arm, the App+Step arm, or the information-only (i.e. “Info”) arm. Participants randomized into the Text+Step arm will be given information about the frequency of text messages they should expect. Participants randomized into the App+Step arm will be guided by research staff to log onto the WebApp for the first time and obtain basic information on how to navigate the app. Participants randomized into the “Info” arm will learn how they will gain access to the information available in that arm and the basic description of that information. At the end of the enrollment visit, all participants will be invited to schedule their 3-month follow-up appointment.

Participants can schedule and attend a 3-month follow-up visit in person or online as early as 14 days prior to the calendar date that falls three months after their enrollment date, and as late as 75 days after the calendar date that falls three months after their enrollment date. At the 3-month follow-up visit, participants will undergo additional HIV, STI and drug screen testing, blood microsampling for those who report PrEP uptake or continued PrEP use, as well as take another ACASI survey. Biological specimen collection may be done in person during the study visit or via self-collection kits mailed to participants. For mailed self-collection, the biological specimens may be collected and returned at any point during the visit window. Participants, if they choose to do so, will be able to meet with research staff via live, secure video chat, to answer questions about the at-home self-collection kit components and procedures. Particularly, study staff will be able to answer questions and go over results of rapid HIV test results if participants prefer to self-administer a rapid test in addition to or in lieu of a lab processed HIV test. Rapid HIV test results will be confirmed with research staff via secure video chat, or by uploading a photo of the test results to a secure online survey hosted by Alchemer. Participants in the technology-based intervention groups (i.e. the Text+Step or the App+Step arm) that do not reduce sexual risk behaviors or self-report a recent STI diagnosis and do not initiate PrEP or adhere to PrEP at effective levels will be randomized 2:1 into either additional eCoaching with their technology-based intervention or remain with their originally assigned intervention. Stepping will be determined using a series of questions: 1) participants that self report PrEP adherence (4+ doses taken per week for each of the past 2 weeks) will not step, otherwise: 2) participants who self-report a new STI (syphillis, chlamydia, or gonnorhea) diagnosed outside of the study in the past 3 months will be eligible for step by randomization, otherwise; 3) participans who self-report sexual risk in the form of: a) condomless anal or vaginal sex, b) sex with exchange partners, c) sex while feeling the effects of stimulants (methamphetamine, powder cocaine, or crack cocaine) or d) sex after binge drinking (5+ drinks at one time) in the past three months will be eligble for step by randomization. Those that are randomized to step up to additional eCoaching will meet the eCoach online at the 3-month visit or during the 3-month visit window for an introductory visit and to schedule their next eCoaching session.

Participants can schedule and attend a 6-month follow-up visit in person or online as early as 14 days prior to the calendar date that falls six months after their enrollment date, and as late as 75 days after the calendar date that falls six months after their enrollment date. At the 6-month follow-up visit, particpants will undergo additional HIV, STIs and drug screen testing, blood microsampling for those who report PrEP uptake or continued use, as well as take another ACASI survey. Of the biological specimen tests, only HIV testing is required, however the others (i.e.,

STI testing, uring screening, and blood microsampling for those reporting PrEP use) are encouraged. Biological specimen collection may be done in person during the study visit or via self-collection kits mailed to participants. For mailed self-collection, the biological specimens may be collected and returned at any point during the visit window. Participants, if they choose to do so, will be able to meet with research staff via live, secure video chat, to answer questions about the at-home self-collection kit components and procedures. Particularly, study staff will be able to answer questions and go over results of rapid HIV test results if participants prefer to self-administer a rapid test in addition to or in lieu of a lab processed HIV test. Rapid HIV test results will be confirmed with research staff via secure video chat, or by uploading a photo of the test results to a secure online survey hosted by Alchemer. The active intervention period ends after 6 months, and therefore participants will no longer have access to their intervention to which they were assigned after month 6.

Participants can schedule and attend a 9-month follow-up visit as early as 14 days prior to the calendar date that falls nine months after their enrollment date, and as late as 90 days after the calendar date that falls nine months after their enrollment date. Participants will return to the SRV at the 9-month follow up for HIV, STI, and drug screen testing, blood microsampling for those report PrEP uptake or use, as well as a final ACASI to measure sustained effects of the intervention. Of the biological specimen tests, only HIV testing is required, however the others (i.e. STI testing, uring screening, and blood microsampling for those reporting PrEP use) are encouraged. Biological specimen collection may be done in person during the study visit or via self-collection kits mailed to participants. For mailed self-collection, the biological specimens may be collected and returned at any point during the visit window. Participants, if they choose to do so, will be able to meet with research staff via live, secure video chat, to answer questions about the at-home self-collection kit components and procedures. Particularly, study staff will be able to answer questions and go over results of rapid HIV test results if participants prefer to self-administer a rapid test in addition to or in lieu of a lab processed HIV test. Rapid HIV test results will be confirmed with research staff via secure video chat, or by uploading a photo of the test results to a secure online survey hosted by Alchemer.

5.3.4 Research and Training Staff

Research staff at individual SRVs who interact with study participants at assessments do not need to be clinicians. A research assistant (RA) level position is sufficient to obtain informed consent, oversee administration of the brief survey, and assist with the focus groups as needed. If a participant asks a question that the RA does not feel equipped to answer, the RA will contact research staff at Friends Research Institute or San Diego State University and then follow-up with the participant. SRV study staff and research staff at Friends Research Institute and San Diego State University will monitor for participant self- or other harm ideation or behaviors during the focus group that may require involvement from the clinical team at the SRV.

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. Training for all research staff includes (but is not limited to) an overview of the study, study procedures and human subjects issues (informed consent process, confidentiality), a demonstration of all technology components, methods for establishing comfort with the sensitive issues, including discussion of sexual behaviors, that will likely arise in the course of the focus groups or assessments, review of the study instruments, their required elements and the inherent flexibility built into them, Human Subjects Protection, Good Clinical Practice, informed consent, quality management, confidentiality, and reporting of adverse events.

5.3.5 Intervention Monitoring/Quality Control

A focus group summary form will be completed by SRV staff and the Protocol Chairs. The form will include focus group id, date, city, age group, and the number of participants scheduled and in attendance, as well as a space to write any comments about the focus group for later reference.

6.0 EVALUATIONS AND MEASURES FOR PHASE 1 FOCUS GROUPS

6.1 Screening

All local sites will use the methods described in section 4.4 to screen participants for eligibility characteristics that meet inclusion criteria for the youth and young adult focus groups (see section 4.1). Participants must be screened for inclusion prior to the scheduled focus group day and time.

6.1.1 Administrative and Behavioral Procedures

- Screening assessment
- Collection of contact information

6.1.2 Clinical Procedures

- None

6.1.3 Laboratory Procedures

- None

6.2 Focus Group

Potential participants will receive reminders to attend the focus group through email and/or text the day they screen eligible for the study, 3 days in advance of the focus group, and 1 day in advance of the focus group. The following are a list of procedures that will be conducted before the focus group begins.

6.2.1 Administrative and Behavioral Procedures

- Informed Consent
- Focus Group Participant Survey

6.2.2 Clinical Procedures

- None

6.2.3 Laboratory Procedures

- None

6.3 RCT

Eligible participants will be contacted to schedule an enrollment appointment through email and/or text within one or two business days following their screening. Reminders to attend the enrollment appointment will be sent via email and/or text 3 days in advance of their appointment, and 1 day before their appointment. The following data will be collected for each study visit time point (enrollment/baseline, 3-, 6-, and 9-month follow-up). Biological specimen collection may be done in person during the study visit or via self-collection kits mailed to participants. For mailed self-collection, the biological specimens may be collected and returned at any point point during the visit window. Some specimens may not be collected if the participant objects or if study staff determine that it would not be feasible and/or safe for the participant to receive a mailed self-collect kit.

6.3.1 Administrative and Behavioral Procedures
- Informed consent/assent (enrollment only)
- ACASI

6.3.2 Clinical procedures
- HIV testing (required)
- STI testing (not required)
  - Gonorrhea
  - Syphlilis
  - Chlamydia
- Blood microsampling for PrEP uptake/use (not required)
- Urine drug screen for current drug use (not required)

6.3.3 Laboratory Procedures
- HIV testing for HIV status (required)
- STI testing to detect the presence of: (not required)
  - Gonorrhea
  - Syphlilis
  - Chlamydia
- Urine drug screen for current drug use (not required)

6.4. Premature Discontinuation/Off-Study Evaluations/Measures

Participants who discontinue study participation during the focus group will be asked to provide a reason for discontinuing the study and paid the full compensation amount. Participants who discontinue study participation during the RCT will be asked to provide a reason for discontinuing the study and provided compensation consistent with their participation up to that point.

7.0 DATA COLLECTION AND SITE MONITORING

7.1 Development of Protocol and Case Report Forms

The Management Core, in collaboration with 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.

7.2 Data Records

Participant-related study information will be identified through a study ID number (SID) and participant code comprised of the first initial of the participant's first name and their two digit day of the month born on all participant CRFs, audio files, transcripts, and survey data files. Participant names or other personally identifying information will not be used on any study documents and should be redacted from focus group 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 the SMART system which is separate from other study information, and is accessible only to designated study staff, iTech site monitors, and representatives from the NICHD. Original source documents 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 on CRFs as applicable.

7.3 Data Collection

7.3.1 Focus group data collection

Focus group discussions will be transcribed verbatim from the digital audio-recording and de-identified by assigning unique numerical codes.

Two independent researchers will analyze the focus group data using the qualitative software program Dedoose (or equivalent software) to code, sort, search, and extract text to develop and explore emergent themes. To calculate an inter-rater reliability score, each researcher will independently develop themes to compile into a preliminary codebook that will be refined during multiple iterations of transcript review. After which notes, themes, and subthemes will be compared and reviewed, and inconsistencies will be reconciled.

7.3.2 CRFs

Study monitoring data for all study phases, including information about eligibility, demographic data, and monitoring untoward effects will be collected on CRFs. All CRFs for this study will be available for download from Box or Microsoft OneDrive, a secure content management platform, and/or available electronic in DFexplore.

7.3.3 Survey Data

Online surveys will be hosted on Alchemer. We use SSL encryption for transfers of information online and data will be stored in the secure, HIPAA-compliant servers of Alchemer. The Emory AC team maintains a business partner HIPAA agreement with Alchemer.

All data collected via the online screener, photo uploads of HIV test results into Alchmer, and in the ACASI during the RCT will remain confidential; no personal identifying information will be collected. The participant's unique SID# will be used in order to link the survey information entered to the participant's CRF data.

Photos of participant HIV rapid test results uploaded into Alchemer. The results will be made available by Emory to SRV staff via a site-specific live "portal" download CSV spreadsheet that is accessible through a password protected link that Emory provides to each SRVs. The password protected CSV file download will have the participant's study ID and a url link to the photo.

7.3.4 Online Survey Data Security

Only authorized study staff will have access the online screener data through the Internet site. To ensure data privacy, as data are entered in real time, it will be encrypted during transmission to the Alchemer server, and that data will be regularly downloaded by AC staff and stored in a secure database within the AC data center at Emory University.

7.3.5 VSee Platform Description

VSee is a private video-chat software that the study may use for private and confidential meetings between participants and eCoaches. When using VSee, participants will have the option to use VSee in several formats: face-to-face video chat, video chat in which they can see the coach but the coach cannot see them, audio chat only, or a text based conversation. VSee is compatible on PCs, tablets, and smartphones. Unlike other video-chat platforms (e.g., Skype), VSee is HIPAA-compliant. VSee includes the following functions to protect users:

*End-to-end encryption without a man-in-the-middle listener***.** In WebEx, Vidyo, Tandberg, and Polycom architectures, media is sent to a server (also called a video relay or MCU). Although encryption is applied from the user's computer to these servers, the servers still have full access to the user's media. In contrast, VSee uses end-to-end encryption where no server, including VSee servers, has the decryption key. VSee uses public/private RSA keys to exchange a 256-bit AES session key with the property that only the endpoints have the AES session key. VSee uses FIPS 140-2 certified 256-bit AES encryption.

*One port***.** VSee uses a single port for call signaling and media. The VSee protocol is structured so that only the outgoing port needs to be open because return traffic is always structured as responses to outgoing traffic. This allows administrators to set a policy where if users inside their network are using VSee, then their firewall lets VSee traffic securely cross the firewall; however, if users inside their firewall stop using VSee, then the firewall will block external port scans.

*Automatic HTTP/SSL tunneling***.** VSee prefers to use UDP since it allows higher performance video. However, if the firewall does not allow UDP, VSee will automatically switch to HTTP/SSL tunneling.

*Cloud Control***.** VSee's cloud solution allows enterprises to maintain central control of their security policies to a large number of end points even though the service is hosted by VSee. It does this by having VSee clients always connect first to VSee servers in the cloud, where the policies are controlled. The cloud servers determine whether any of these security policies should be applied and enforces them as the VSee client. This allows us to set our own security settings and to record the sessions.

*No-install client***.** Video conferencing software clients tend to be large and to leave a big footprint on the user's system. Almost all of them require administrator permissions to install. Once the client software gains administrator permissions, they can severely compromise computer security. VSee is a lightweight client that does not require administrator permissions or installation.

VSee offers the HIPAA-required Business Associate Agreement (BAA) where VSee agrees to be responsible for keeping all patient information secure and to immediately report any breach of personal health information. In this study, the iTech Technology core will enter into a BAA with VSee, and this will be extended to cover the proposed activities. The VSee sessions will include identifying information (e.g. images of the participant, voice recordings). All identifying information will be stripped from the recorded VSee sessions before they are sent to the analysis team for content analysis.

7.3.6 Zoom Platform Description

Zoom software may be used to conduct online study visits, consenting, and eCoaching sessions remotely. Participants will have the option to conduct face-to-face video chat, video chat in which they can see the study staff, but the study staff cannot see them, or audio chat only. Zoom is compatible on PCs, tablets, and smartphones; as well as maintains the option to conduct an audio conference without the video component. Emory University has entered into a BAA with Zoom, where Zoom agrees to be responsible for keeping all patient information secure and report any breaches of protected health information (PHI).

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 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, as in VSee above, but this information will be stripped form the recorded Zoom sessions before they are sent to the analysis team for content analysis.

7.3.7 Qualtrics Platform Description

Qualtrics may be used for study surveys and online informed consent/assent forms.

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.

7.4 Data Submission

7.4.1 CRFs

Although the iTech projects will involve substantial online follow-up, CRFs 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). AC staff will work with study investigators and the MC to develop and design the CRFs. During study conduct, the SRVs will maintain the CRFs in secured locations, and transmit CRF data to the AC either electronically using DFexplore or by submitting scanned paper forms using DFSend. DFexplore and its DFdiscover platform is a leading multi-site database environment for HIV RCT that can receive and transcribe CRF data via scanned PDFs, or allow for direct electronic data entry. It provides for monitoring form completion and data quality, and a system for data querying and resolution with SRVs, while maintaining an audit trail. The AC uses DFexplore for MSM studies and RCTs and data is maintained by the parent company DF/net on a cloud-based server with Microsoft Azure.

7.4.2 Audio Data

Audio-recoded data for the focus groups will initially be stored as a digital file on a secure encrypted server. All focus group discussion may also be recorded using a back-up digital audio recorder. 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. Focus group discussions 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 survey data will only be identified with a unique study number and stored on a secure encrypted server by the AC team. Only SRV research staff, the AC team, and the research team at Friends Research Institute, San Diego State University and the University of Minnesota will have access to the data.

eCoaching sessions will be audio recorderd for fidelity checks and supervision.

7.4.3 Online Survey Data Transmission

Only authorized users will be able to access the online screeners and other surveys through the Internet site. See section 7.3.2 on online survey data security.

7.4.4 Participant Contact Database

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. System will also be using database level encryption, which will prevent any copying of information from one database to another. 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 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.

SMART 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 NICHD 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

The AC and MC will provide instructions concerning the recording of study data on the CRFs, submission of CRFs, and administration and transmission of ACASI data.

7.7 Study Site Monitoring and Record Availability

Site monitors from the MC and AC will 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) readily available for inspection by the local IRB, the central IRB, the site monitors, the NICHD, 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

Study staff will verify participant contact information at baseline and update this information if needed at time of follow up.

Study staff will contact participants prior to their target date to complete follow-up study procedures. Study staff will use both a preferred and, if necessary for YYA who are difficult to reach, backup method of contact as indicated at baseline (e.g. mail, alternate phone numbers, e-mail, text message, social media contact information), to contact participants to complete follow up study procedures. Additional reminders will be provided on/after the target date as needed to ensure completion of study visit procedures. Participants 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.

8.2 Compensation

The method and amount of compensation will be determined separately by each site, listed in the site's informed consent/assent form, and approved by the central IRB (the UNC-CH IRB). RCT participants will be compensated at each of their appointments at the SRV, including the enrollment/baseline visit and each of the 3-, 6-, and 9-month assessment points.

8.3 Intervening on "Social Harms"

We identified the following 3 items as possible risks to subjects for the overall study period and described how we plan on addressing those risks:

1. Protecting against others finding out about their gender identity during focus groups. Participants will be alerted to this given that the focus groups are in person. The description of the purpose of the study will clearly state that the study is designed to promote face-to-face discussion with other trans YYA, and we will recommend that persons who are highly uncomfortable with such exchanges may be better served by not enrolling in the study. Once enrolled, we also minimize this risk of identification to participants by asking participants to come up with a pseudonym that do not contain personally identifying information. Additionally, we will establish "group rules" that include requesting that no information about the identity of participants or what is said in the focus group is shared outside of the focus group. Although we cannot guarantee their anonymity, we will take appropriate safeguards to minimize this risk.
2. Protecting against discomfort in answering personal questions during the focus group discussions. This risk is similar to #1 above, and we will use comparable safeguards to protect against it. Thus, we intend to fully inform participants of the purpose and nature of the study prior to their participation. Participants are informed that they are free not to answer questions, and they may stop participation at any time. Since a "decline to answer" option is provided to the survey completed just before the focus group, there is a constant reminder of their participant rights throughout the study. Thus, we believe the risk to participants is minimal and we have adequately anticipated and set into place protocols to address potential risks that may arise.
3. Protecting against concerns about the security of their data during focus groups and RCT. Well-established security processes will be followed, that include the following:
    - Participants' identifying information is housed in a separate cloud-based password-protected study management platform, SMART, which is separate from survey data and other collected outcome data. Only authorized study staff will be granted access

to the platform through requests initially made to the Analytic Core at Emory University, or subsequently through the designated study coordinator. SMART regulates staff permissions to view participant information based on assigned user roles, which also stratifies participant data by site/location, such that staff from other sites will not be able to view participant data except from their site/location. Study staff will not be able to download participant data from the cloud-based platform. Only designated analysts at the Analytic Core at Emory University will have access to data downloads from SMART for reporting purposes.

- At the end of the study, the identifying information (participants' names and contact information) is destroyed. The original data records will be archived for a minimum of 3 years following the conclusion of the study or longer if institutional requirements dictate, and three copies of the de-identified dataset will be maintained (a working one and two archived at different sites).
- All project staff will be required to complete the NIH online training in research ethics. Further training and supervision will focus research staff on confidentiality concerns both during and after the study. The project coordinator in conjunction with the Protocol Chairs are responsible for ensuring that all research staff involved in this study document their NIH training.

There are two risks associated with receiving the WebApp:

1. Protecting against going to the site by mistake. We have a secure site (https:) with an introductory page clearly specifying the nature of the study. Sensitive survey or intervention content is protected behind screening questions and a username/password, and therefore in the opening study webpage, we could not think of anything that would be deemed offensive by any persons or those who might be vulnerable. In this way, we have minimized the risk to a level that is negligible.

2. Protecting against hostile interactions and inaccurate information from one participant to another. Participants will be informed during the onboarding process of the "group rules" regarding interactions with one another (e.g., "Honesty is important; however, hostile or abusive language will not be tolerated and may be grounds for immediate removal from the study"). These "rules" will also be available with a link on all intervention web pages for review by participants at any time. The project coordinator will manually review an automated compilation of posts participants make on a daily basis to flag hostile interactions and inaccurate information. Hostile interactions between participants will be handled by, first, reminding the participants in the interaction of the "group rules" regarding appropriate interactions. If the hostility continues, the offending participants will be given a warning that the continued hostility will result in withdrawal from the study if it continues. On the third offense, the participant may be withdrawn from the study after discussion of the offense. Text containing hostile exchanges will be removed from the study website and unavailable to view. In cases in which inaccurate information is found, project staff be guided by experts on the team to post a comment that provides accurate information on the topic. In extreme cases, the Protocol Chairs or SRV Site PIs may decide to withdraw a participant before the third offense. We will ensure all clinic sites have a clear clinical protocol to address major issues that may come up at study visits or in online interactions. The major issues addressed in the procotol will be suicidal ideation, homicidality or violent ideation, emotional and cognitive disregulation, violent/aggressive or disruptive behavior, and intoxication. If research staff see concerning comments or messages online from participants regarding self-harm or harm of others, they will contact study site staff and take immediate precautions.

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 he or she 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 or she is suicidal/homicidal, measures will be taken to ensure his or her 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.

See section 11.3.1 for more information on potential social harm-related risks.

8.4 Criteria for Premature Study Discontinuation

The Protocol Chairs and SRV Site PIs have the authority to withdraw any participant at any time if it 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. If a participant is withdrawn due to seroconversion, they will be offered referrals and linkages as necessary, and may be referred to an ATN study for HIV+ participants.

Participants will be prematurely discontinued from the study if any of the following occurs:

- The participant withdraws consent/assent
- The participant is unwilling or unable to comply with study procedures
- The participant fails to return or confirm HIV negative test results with research staff within 90 days of their enrollment visit
- The participant returns a HIV positive test result at the 3- or 6-month follow-up time point.
- The participant seroconverts
- The Protocol Chairs or Site PIs believe that ongoing participation may cause harm to the participant or study staff
- The Protocol Chairs of Site PI believe that ongoing participant may impact the integrity of the study dataThe study is cancelled by the NIH (or iTech, or other administrative entity);
- The study is cancelled for other administrative reasons;
- Death of the participant

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 SRV clinic will be offered counseling on site. Participants who experience distress during the study and do not come to the SRV clinic for a visit will be provided a list of community referrals via phone or e-mail. Any unexpected adverse events that meet the unanticipated problem (UP) reporting criteria will be immediately reported to the UNC-CH IRB and the respective sites' IRBs if applicable. The *Study Stop CRF* will be completed at this time.

9.0 MONITORING UNTOWARD EFFECTS ASSOICATED WITH OR RESULTING FROM STUDY

9.1 Site research staff must first follow 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 iTech team of these untoward effects using the iTech QNS accessible through the iTech website (www.iTechnetwork.org) within 24 hours of becoming aware of these untoward effects. Study staff will be briefed during the training on the scope of possible untoward effects and instructed to report events.

Second, study staff may encounter untoward events during the focus groups or RCT 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 protocol chairs should be notified of these events so that they may be immediately addressed, evaluated, and guidance modified or expanded to minimize similar risk to other study staff.

Third, a critically important area 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 Introduction

10.1.1 Focus Groups Overview

We will conduct eight focus groups with up to 10 trans YYA (one group with youth 15-20 years old and one group with young adults 21-24 years old) at 4 SRVs (Houston, Los Angeles, New York, and Philadelphia). Focus groups in Houston and Los Angeles will be used to obtain information specific to the Web App. Topics covered in those focus groups include: 1) challenges to obtaining culturally appropriate and comprehensive sexual health and other health services; 2) feedback from trans YYA about the "look and feel" and content of the original TWM and YouTHrive interventions; 3) suggestions for adapting the intervention for trans YYA similar to themselves. Focus groups in New York and Philadelphia will be used to obtain information specific to the text messaging intervention. Topics covered in those focus groups include: 1) feedback from the trans YYA about the adaptation of the *Text Me, Girl!* text-message library for HIV-positive young trans women to high-risk trans feminine, trans masculine, and gender non-conforming HIV-negative YYA; 2) specific editing of text messages for content that is culturally appropriate and relevant to HIV-negative trans YYA; 3) suggestions on content and appropriateness of text messages related to trans-specific sexual health; 4) suggestions on content and appropriateness of text messages related to biobehavioral HIV prevention strategies (e.g., PEP/PrEP). Focus groups (as opposed to in-depth quantitative interviews) were chosen to gain feedback in these areas because this setting will allow participants to explore together the ways in which the TechStep intervention meets their needs and how the intervention can be adapted to be community appropriate.

10.2 Power Estimates

10.2.1 Focus Groups Power Considerations

The purpose of focus groups is not to obtain generalizable data, but rather to obtain collective qualitative information to inform adaptation of the existing interventions for trans YYA. We are balancing feasibility with the need to obtain information from a spectrum of trans youth. As such, we will conduct 8 focus groups, targeting youth (ages 15-20) and young adults (ages 21-24) at 4 different SRVs with the goal of reaching a maximum of 80 trans YYA. Given our prior experience and best practices for the conduct of focus groups, this will provide us with information from enough YYA to inform the adaptation process.

10.2.2 RCT Power Considerations

We performed extensive Monte Carlo simulations to assess the power for our primary analysis. We examined scenarios involving different dropout rates (5-15%), different relative efficacies of first-line (text or app) interventions relative to the eCoaching intervention, and different levels of strength of predictive covariates to be included in the analysis. Across a wide range of scenarios, we determined that we will have >80% power to detect a clinically meaningful effect, defined as an average decrease of at least 1.5 risky sexual encounters over the course of the study.

10.3 Statistical Analysis Plan

10.3.1 Analyses of Focus Group Data.

Focus group discussions will be transcribed verbatim from the digital audio-recording, de-identified by assigning unique numerical codes, and entered into Dedoose software to assist with theme identification, coding textual data, and describing relationships among codes (via code co-occurrence and memoing functions). Following established focus group analysis guidelines, we will create a codebook of a priori and emergent themes including operational definitions of all codes and sample quotations to illustrate how to apply each code. Two study team members will then use the codebook to independently code the compiled user profiles while a third team member will review these sections of coded data and resolve discrepancies. We will draw a random sample of 20 instances for the coders to begin with and calculate an inter-rater reliability score based on their code assignments. If this score is <95%, we will refine the codebook definitions and retrain the coders. Coders will then complete the coding of the remaining instances and we will calculate an inter-rater reliability score. Discrepancies will then be reviewed and resolved by the research team. Coding and analytic activities will be discussed during weekly team meetings.

10.3.2 Analyses of RCT

Outcomes understudy include rates of condomless anal and vaginal sex, number of exchange partners, reports of sex while feeling the effects of stimulants (i.e. methamphetamine, powder cocaine, crack cocaine) or after binge drinking (5+ drinks at one time), self-report and confirmed STI diagnoses, and PrEP adherence measured through self-report and verified by blood microsampling. We will analyze both the primary and secondary questions in the RCT using longitudinal targeted minimimum loss-based estimation (LTMLE).[38] This approach has several advantages over standard techniques for longitudinal data analysis. First, it appropriately accounts for the fact that only high-risk participants are eligible for randomization into the eCoaching intervention. Second, the method accounts for predictive and prognostic time-varying participant-level covariates, thereby increasing the power to detect intervention effects. Third, the method accounts for possibly informative missingness reducing bias in the estimates of causal effects. Implementation of LTMLE involves fitting several covariate adjusted models. First, a sequence of regressions are fit to model cumulative sexual risk behaviors at each time point adjusting for baseline and time-varying covariates. Second, a regression is fit to model the cumulative probability of participant dropout adjusting for baseline and time-varying covariates. These models will be fit using the super learner, a cross-validation-based estimator selection technique. This method aggregates results from a library of candidate regression estimators to build the most powerful predictor given the data at hand. In large samples, the method is guaranteed to perform as well as the unknown best-performing regression in the library. We will use Wald-style tests of each of the relevant null hypotheses using cross-validated influence-function-based standard error estimates.

10.4 Missing Data

Given the primary aim of the focus groups is to collect qualitative data, we do not anticipate missing data. That said, to protect against malfunction or user error in operating the audio recorders, we will have 2 audio recorders at each focus group. In addition, written notes the focus group discussion will be obtained.

For the RCT, as mentioned in Section 10.3.2, the LTMLE approach used in the primary analysis will account for missing data.

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 a coded number only, to maintain participant confidentiality. All records with personally identifying information will be kept in a locked file cabinet in a limited secure access area at each SRV site, or in a secure limited access study database. 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 MC or NICHD.

Every effort will be made to ensure that study participants are protected from risks. The main risk specific to the role of the AC is breach of confidentiality.

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 iTech 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. The AC has significant experience developing security protocols for technology-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. All of the apps and websites included in the iTech have features to ensure security and privacy.

11.2 Certificate of Confidentiality

This research specifically targets a vulnerable population, trans YYA between the ages of 15-24. We will take every available step to minimize the risk of identifying/linking data being subpoenaed, stolen, or inadvertently released. First, the iTech has obtained 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

Risks to participants in this research study may include:

Potential participants or participants enrolled in the study may have concerns about others finding out about their gender identity or other personal behavior (e.g., sexual behavior or substance use). We anticipate that the likelihood of this occurring is high for those randomized into the App+Step arm given that a major feature of the WebApp is for participants to network with one another and that eligibility for enrollment in the study requires participants to be a trans youth or young adult. We anticipate that the likelihood of this occurring is high during the focus groups as well, since they will be meeting in-person with other trans YYA for the focus groups. Subjects will be informed of the inclusion criteria and general questions that will be asked during focus groups during the recruitment period. Since subjects will be recruited directly within SRVs, they will have the opportunity to discuss with staff whether they feel comfortable being a part of such discussions. Clear consent procedures will also give opportunities for subjects to withdraw if they no longer feel comfortable participating in focus group discussions. For those in the RCT, subjects will be informed during the consent process of the basic features of the WebApp intervention and those who are not comfortable interacting with other trans YYA will be encouraged to not participate in the study.

To minimize the risk of participants feeling uncomfortable about answering personal questions, we will provide an option for online methods for screening. For assessments, we will use ACASI methods for the study's surveys. In ACASI, participants read and hear aloud survey questions on a computer 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 online screener of the ACASI. Participants will also be able to refuse to answer any question that makes them uncomfortable.

Participants in the focus groups will be told of "group rules" at the beginning of the focus group, which includes asking them to not share the identities of attendees or content shared during the focus group.

The measurements that are involved in this study require venipuncture to collect blood samples for syphilis testing. Syphilis is tested by serum RPR performed by a trained and certified phlebotomist. This procedure may cause local discomfort, bleeding, or bruising; rarely small clot or infection can occur at the blood draw site. This measurement should not be considered greater than minimal risk in and of itself given its routine use in general health care delivery.

Urine samples will be provided to test for gonorrhea, Chlamydia, and current drug use and will be collected under monitored conditions (i.e., using an FDA approved temperature strip to verify the specimen integrity). Pharyngeal swabs are taken from the back of the throat to test for gonorrhea and Chlamydia and participants self-administer rectal swabs for gonorrhea and Chlamydia.

Trained and certified research assistants will perform dried blood spot extraction. The procedure will only require a finger prick to extract a small amount of blood, and threfore the risk of infection or bruising is small. If needed, clinical staff will be on site to assist with any medical problems that may arise from this procedure.

Participants randomized into the App+Step arm may receive hostile communications or incorrect information from other participants during the course of the WebApp component. It is possible that some participants may respond aggressively or with hostility to other participants. Likewise, although well-intended, participants may provide inaccurate information about adherence or its risk factors to other participants by interactions through the website message boards/social networking wall. The WebApp intervention will include a clear section on Community Guidelines and will be monitored daily by research staff. Users have the option to "flag" objectionable content. We have protocols in place for addressing hostile interaction in the site up to and including termination of participation in the study.

Some participants in the Text+Step arm may not want others to see that they are getting messages related to sexual health or their gender identity. Participants will be given assistance with strategies for minimizing unauthorized access to their phone. Participants will be shown how to lock their phone, how to hide messages on the locked screen, establish and use a pin code to password protect their phone, and will be instructed to periodically delete the intervention text messages after they have been read.

To minimize risks to confidentiality of focus group and RCT data, 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 Emory University's secure servers or will be on fully encrypted laptops. Surveys and online eligibility screening will take place on an encrypted commercial survey website, Alchemer. This site has been used by the investigators for thousands of online surveys with vulnerable populations with no data security breaches. 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 a HIV-prevention research study, or a study that enrolls trans persons. 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. Additionally, all scripts for email, text message, and telephone contact with participants will be reviewed and approved by the UNC IRB before being used for contact with participants.

We use SSL encryption for transfers of information online, and Alchemer has a business partner HIPAA agreement with Emory. Alchemer's servers are HIPAA compliant.

The AC 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. When using this feature, only Dr. Kate Muessig or her designee will hold the additional encryption key needed to be entered in order to view the project. This gives Dr. Muessig exclusive control over who can view the project under any circumstances.

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

1. Breach of confidentiality. We will take every precaution to minimize risks to study participants.

All AC research staff members are required to complete ethical clearance certification regarding protection of human subjects through UNC-CH or Emory University. 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 Emory IRBs, and SRV site-specific IRBs per each institution's IRB reporting requirements using Adverse Event Reporting Forms created by the AC. When possible, reports will be sent within 24 hours of notification by the Protcol Chairs. Annual updates on enrollment and retention will also be sent to the UNC IRB, and institutional IRBs if required.

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 institutional policies.

11.3.2 Benefits

There are no direct benefits of participating in the focus groups. Participation in the RCT technology-based intervention arms (i.e., Text+Step and App+Step) may provide participants with information and exercises that help them locate and access trans-relevant local resources, build motivation to start or restart PrEP, build peer social support, and identify and address individual, social, structural, and cultural barriers to HIV risk reduction. Participants in the control arm (i.e., Info) may gain basic knowledge about HIV and trans-specific health issues and links to outside local resources. In either the experimental or control conditions, the primary benefit is access to health information that may assist participants to improve access to culturally appropriate HIV risk reduction resources, increase quality of life, reduce high-risk sexual behaviors and lower the risk of acquiring HIV. Secondary benefits include positive feelings related to having assisted in the development of a novel technology-based HIV risk reduction intervention for trans YYA.

Compensation for participation is not considered a benefit, because we are simply reimbursing participants for their time, effort, and expenses.

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 in the IRB submission.

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 trans youth would be reluctant to participate in this study – which focuses on HIV prevention and PrEP uptake, adherence and persistence – if they are required to get parental permission; and 2) many of the trans youth in our study are likely to be gender and/or sexually fluid 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 disclosing themselves as part of the LGBT community or being at risk for HIV infection. 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 Study Participation

In order to maintain the anonymity of the survey and fully protect the privacy of the volunteer study participants, the UNC IRB will be requested to waive the requirement for a record of a signed consent form. A written consent form will be reviewed with each potential study participant and provided to each consenting one. This form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

Under 45 CFR §46.117 (c) (1) and (2), an IRB may waive the requirement for the investigator to obtain a singed informed consent for some or all of the subjects if it finds either: (1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant will be asked whether they want documentation linking them with the research, and the participant's wishes will govern; or (2) that the research presents no more than minimal risk of harm to the participants and involve no procedures for which written consent is normally required outside the research context."

The protocol team believes that both #1 and #2 applies to this study and, both combined, justify a waiver of written consent.

11.6.2 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

NICHD 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.

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.

13.0 REFERENCES

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