STUDY PROTOCOL

ATN 142: P3 (Prepared, Protected, emPowered): A Study to Test the Efficacy of a Social Networking, Gamification, and Adherence Support App to Improve PrEP Adherence

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ATN 142: P3 (Prepared, Protected, emPowered): A Study to Test the Efficacy of a Social Networking, Gamification, and Adherence Support App to Improve PrEP Adherence.

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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.

Investigator of Record: _____
Print/Type

Signed: _____ Date: _____

Title: _____

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AC	Analytic Core
AIDS	Acquired Immunodeficiency Syndrome
ATN	Adolescent Medicine Trials Network for HIV/AIDS Interventions
CASI	Computer assisted self-interview
CFR	Code of Federal Regulations
CRF	Case report form
DBS	Dried blood spot
DHHS	U.S. Department of Health and Human Services
FTC-TP	Emtricitabine Triphosphate
GCP	Good Clinical Practices
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
MC	Management Core
MSM	Man who has sex with men or 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
NSC	Next Step Counseling
P3	Prepared, Protected, EmPowered
PrEP	Pre-exposure prophylaxis
PI	Principal Investigator
OHRP	Office of Human Research Protection
QNS	Query and Notification System
RCT	Randomized controlled trial
SID	Study ID number
SMART	Study Management and Retention Tool
SRV	Subject Recruitment Venue
SSL	Secure Socket Layer
TAF	Tenofovir Alafenamide
TFV-DP	Tenofovir Diphosphate
TC	Technology Core
TW	Transgender women
TWSM	Transgender woman who has sex with men
YAB	Youth Advisory Board
YMSM	Young men who have sex with men
YTWSM	Young transgender women who have sex with men

STUDY ABSTRACT

DESIGN: This study is a three arm, randomized-controlled trial (RCT) that will test the efficacy of P3, a novel, theory-based mobile app that utilizes game mechanics and social networking features to improve PrEP adherence, retention in PrEP clinical care, and PrEP persistence among young men who have sex with men (YMSM) and young transgender women who have sex with men (YTWSM), ages 16-24. We will test the efficacy of P3 and P3+, which adds Next Step Counseling delivered by an adherence counselor through the app, against PrEP standard of care. Participants will be randomized to P3, P3+, or standard of care. The study will evaluate the efficacy of P3, P3+. A cost comparison between P3 and P3+ will be conducted.

DURATION: The total duration of study participation for each RCT subject is 6 months. The duration of the P3 intervention arms is 3 months.

SAMPLE SIZE: Total study sample is ~265 of which the following will be enrolled for each phase: 1) Usability testing with 8-12 total youth at 2 iTech subject recruitment venue (SRV) cities (Boston, Massachusetts; Chicago, Illinois); 2) Field testing will be conducted with 15 total youth who have recently initiated PrEP or are PrEP non-adherent at 3 iTech SRV cities (Bronx, New York; Houston, Texas; Philadelphia, Pennsylvania); The RCT will be conducted with 240 youth who plan to initiate PrEP or are on PrEP at 9 iTech SRV cities (Atlanta, Georgia; Boston, Massachusetts; Bronx, New York; Chapel Hill, North Carolina; Charlotte, North Carolina; Chicago, Illinois; Houston, Texas; Philadelphia, Pennsylvania; Tampa, Florida). The P3, P3+, and standard of care arm will each include 80 participants.

POPULATION: Usability Testing: Eligible participants: 1) are self-reported HIV-negative; 2) are ages 16-24 years; 3) were assigned male sex at birth; 4) self-identify as a man who has sex with men (MSM) or transgender woman who has sex with men (TWSM): 5) are able to speak and read English; 6) are familiar with Android or iOS smartphone; 7) have previously taken, are currently taking or considering taking PrEP; 8) are recruited from one of 2 iTech SRV cities (Boston, Massachusetts; Chicago, Illinois); 9) have the ability to attend a usability session on dates specified by the research team. Not eligible: unable to be consented due to active substance use or psychological condition.

Field Testing
Eligible participants: 1) are aged 16-24; 2) were assigned male sex at birth; 3) report sex with men; 4) are able to speak and read English; 5) have reliable daily access to an Android or iOS smartphone with a data plan; 6) are HIV-uninfected (self-report); 7) initiated PrEP within the last 60 days and have an active PrEP prescription (prescription confirmed by study staff) OR on PrEP >60 days but self-report adherence on average < 6 pills per week over the past month and have an active PrEP prescription (prescription confirmed by study staff); 8) recruited from one of 3 iTech SRV cities (Bronx, New York; Houston, Texas; Philadelphia, Pennsylvania). Not eligible: unable to be consented due to active substance use or psychological condition. Individuals who participated in the field trial will not be eligible for the RCT.

RCT : Eligible participants: 1) are aged 16-24; 2) were assigned male sex at birth; 3) report sex with men; 4) are able to speak and read English; 5) have reliable daily access to an Android or iOS smartphone with a data plan; 6) are HIV-uninfected (self-report); 7) are not currently on PrEP but plan to initiate in the next 7 days and have an active PrEP prescription (prescription confirmed by study staff) OR on PrEP and have an active PrEP prescription (prescription confirmed by study staff); 8) recruited from one of 9 iTech SRV cities (Atlanta, Georgia; Boston, Massachusetts; Bronx, New York; Chapel Hill, North Carolina; Charlotte, North Carolina; Chicago, Illinois; Houston, Texas; Philadelphia, Pennsylvania; Tampa, Florida). Not eligible: 1) unable to be consented due to active substance use or psychological condition; 2) participated in the field trial.

STRATIFICATION: Participants in the usability testing and field trials will not be stratified. RCT participants will be randomized in a 1:1:1 ratio to the P3, P3+, or standard of care study arms stratified by SRV.

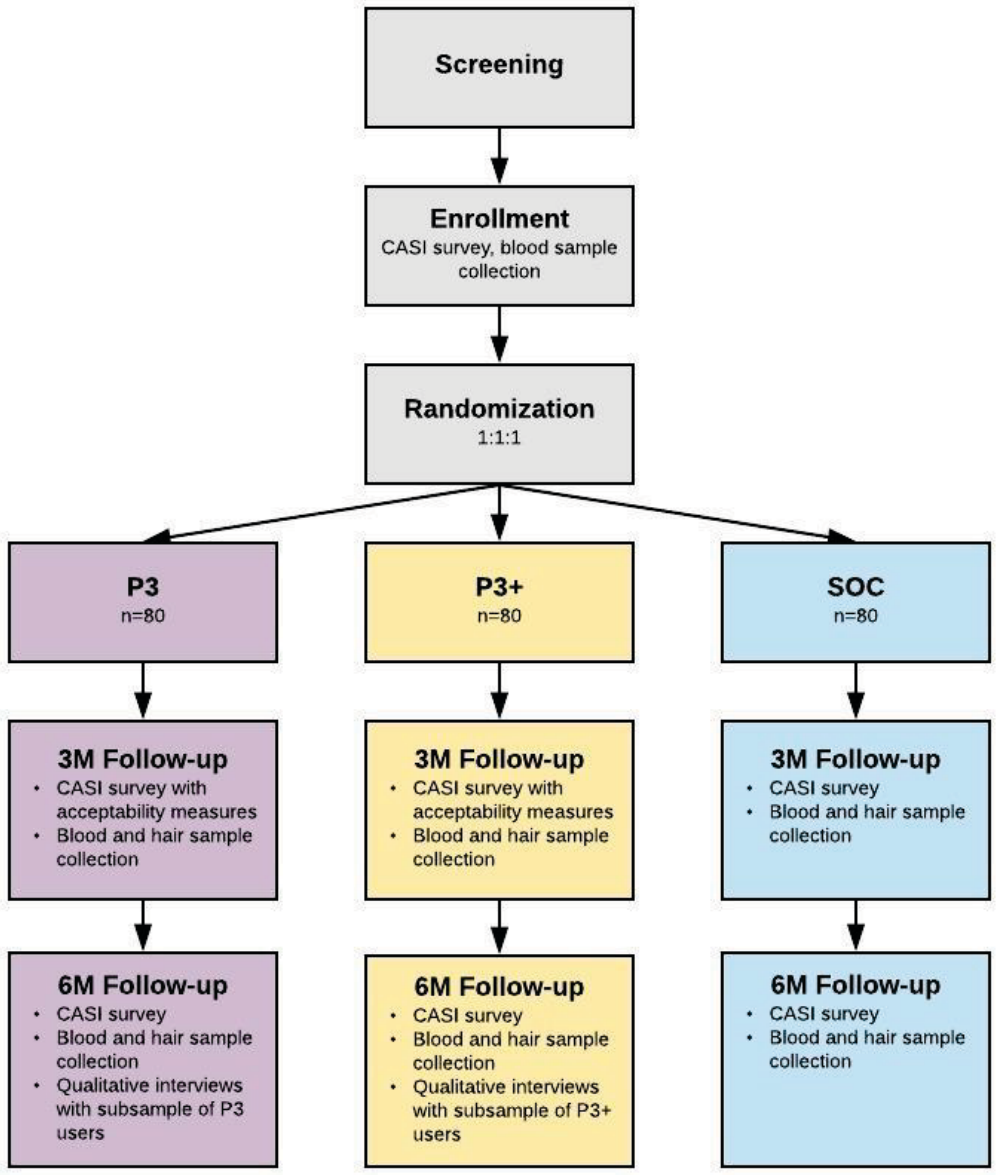
DATA COLLECTION: Study visits are conducted in-person at the SRV or remotely via video teleconferencing for the RCT. Usability testing will consist of one in-person visit. Audio recordings will be digitally recorded and transcribed. Pre-and post-usability testing surveys will be administered using AlchemerAlchemer (online, HIPPA compliant computer-assisted self-interviewing [CASI] platform). Field testing will consist of two visits, baseline and 1-month follow-up. At each visit, surveys will be administered using Alchemer; whole blood will be collected via dried blood spot (DBS) or a Mitra microsampling device to measure TFV-DP/FTC-TP or TAF/FTC-TP concentrations, and hair samples will be collected to measure FTC concentrations. Post-field testing interviews will be conducted online using a HIPPA-compliant secure online videoconferencing platform. Audio recordings will be digitally recorded and transcribed. The RCT includes three data collection time points (months 0, 3, 6). At each time point, surveys will be administered using Alchemer and a whole blood sample will be collected. Hair samples will be collected from participants at months 3 and 6. At the 6-month follow-up, a subset of participants (n=20) from P3 and P3+ who are classified as either high or low users will participate in a qualitative exit interview, using a HIPPA-compliant secure online videoconferencing platform. Process data of participant activity on P3 and P3+ from baseline to month 3 will include app usage and engagement data (e.g. numbers of times per week participants access app, average time spent on app, completion of app activities, number and content of social wall posts, amount of virtual currency collected and narratives unlocked). Costing data will be collected about the human and material resources expended to deliver the interventions.

STUDY OBJECTIVES: 1. To optimize the final components of P3 and P3+ (adherence counseling) intervention through usability and field testing.

2. To test the efficacy of the P3/P3+ intervention apps among 240 YMSM and YTWSM, ages 16-24, by conducting a three-arm RCT with assessments at baseline (month 0), month 3 (end of intervention phase) and months 6 (post-intervention phase). The primary outcome measures are PrEP adherence measured by blood sample levels of tenofovir diphosphate and emtricitabine

triphosphate (TFV-DP/FTC-TP) with blood concentration consistent with > 4 doses/week at 3- and 6- month follow-ups
3. To conduct a cost comparison between P3 and P3+.

STUDY DESIGN OR SCHEMA



1.0 INTRODUCTION

1.1 Background

Between 2002 and 2011, rates of new HIV infections declined by more than 30% overall in the United States (US) but increased by 132% among young men who have sex with men (YMSM) ages 13-24.[1] Regional studies suggest that HIV prevalence among transgender women (TW) are among the highest of all risk groups, especially TW of color, and African-American TW in particular.[2-4] Despite overwhelming scientific evidence of the efficacy and safety of pre-exposure prophylaxis (PrEP) to prevent HIV infection in YMSM and young transgender women who have sex with men (YTWSM)

efficacy in all PrEP studies has been strongly correlated with drug levels, and drug monitoring indicates that adherence has been suboptimal in a substantial proportion of participants.[5-7] Adherence to medications, including PrEP, is known to be a significant challenge for adolescents and young adults.[8-14] in a recent study of PrEP use among 200 YMSM (mean age 20.2 years, 54.5% Black, 26.5% Latino) at week 4, 56% had protective levels of intracellular tenofovir-diphosphate (TFV-DP) (i.e., consistent with ≥4 pills/week). This decreased to 48% at week 24 and 34% at week 48. PrEP adherence rates were lower among African American YMSM and below the protective threshold at all-time points measured.[14] To date, there are no proven interventions for YMSM and YTWSM to promote consistent and persistent PrEP adherence. Interventions that improve PrEP adherence are urgently needed to maximize HIV prevention benefits for YMSM and YTWSM.

1.2 Rationale

The use of smartphones to deliver HIV prevention and care interventions has grown substantially in recent years due to: a) wide-scale adoption of smartphone technology among high-risk groups, b) the ability to deliver interventions in real-time within risk contexts, and c) low implementation costs.[15-19] A smartphone-delivered PrEP adherence intervention is well suited for YMSM and YTWSM, given they have a high-uptake and utilization of smartphone technology.[20-22] P^3 (Prepared, Protected, emPowered) is an interactive smartphone app for HIV-uninfected YMSM and YTWSM that utilizes social networking and game-based mechanics to improve PrEP adherence. P3 is a product born from the collaborative effort of researchers and health game developers working closely with members of the target population. Built on a successful, evidence-based platform designed and tested by our collaborating technology partner, Ayogo, P^3 is flexible and responsive to changes in technology and emerging PrEP practice standards and guidelines.

Social engagement and provision of support are powerful tools for behavior change – both of which can be achieved with smartphone technologies. Social networking sites often provide venues for health-related activities including searching for information and connecting with peers by sharing information, posting questions, and joining special interest groups.[23] While some web-based interventions have provided HIV prevention information through existing social networking sites,[24,25] to our knowledge, no app-based interventions have been designed to capitalize on social involvement as a means through which HIV-uninfected YMSM and YTWSM can receive information and social support, experience more positive social norms and reflective appraisals, and feel a sense of connectedness to peers.[26,27] P3 provides anonymity so that YMSM and YTWSM on PrEP can feel comfortable sharing their thoughts or experiences related to PrEP within the safety of a respectful, affirming on-line environment.

Although smartphone apps can deliver individualized, tailored content through complex algorithms, added individual adherence counseling delivered by trained counselors may provide a degree of personalization that may improve outcomes. Further, the available literature suggests that some tools, including technology based tools, may be more beneficial to patient adherence when combined with education or counseling.[28-30] Online text-based counseling offers a convenient, confidential, and user-controlled experience, providing support to YMSM and YTWSM who otherwise may not be willing or able to access services in person. Interacting the adherence counselor in the P^3+ arm may heighten participants' sense of accountability, enhance motivation, and allow participants to have their unique adherence and related needs addressed dynamically.

1.2.1 Usability Testing

The purpose of usability testing is to gain feedback about the intervention once a functional version of the intervention is available. It is primarily intended to get feedback from the target population about any technical issues they encountered, as well as to obtain any feedback about the educational content, understanding and use of intervention features, and overall impressions of app functionality. Iterative content development based on actual app usage allows for system refinement and improvements prior to the launch of the efficacy trial. As we have done in prior technology-based

studies, we will recruit up to 10 youth to participate in usability testing. Ongoing adjustments require an agile, iterative approach throughout usability testing with members of the target population.

1.2.2 Field Testing
To ensure that the features, platform and content of P3 and P3+ are acceptable to the target population and that there are no technical challenges or user concerns with either the app or DBS or Mitra or hair collection, we will conduct a one-month technical field trial of use with 15 participants.

1.2.3 Randomized Controlled Trial (RCT)
We will test the efficacy of the P3 app among 240 YMSM and YTWSM, ages 16-24, by conducting a three-arm RCT (P3, P3+, standard of care), with assessments at baseline (month 0), month 3 (end of intervention phase) and months 6 (post-intervention phase). The primary outcome measures are PrEP adherence measured by intracellular TFV-DP/TAF levels and adherence measured by intracellular FTC-TP levels, both collected from whole blood specimens via finger stick at months 3 and 6. Secondarily, we will assess efficacy of P3/P3+ at improving PrEP adherence by analyzing self-reported PrEP use, namely weekly PrEP use and monthly PrEP use at both 3 and 6 months follow-up. Secondary outcomes of interest also include self-reported retention in PrEP clinical care; PrEP persistence; sexual risk behaviors; and, (self-reported) sexually transmitted infection (STI) incidence. As a secondary analysis, we will provide validation data on the use of hair specimens for the detection of FTC in YMSM and YTWSM at levels of 'any' and 'protective' usage. We will also conduct a cost comparison between P3 and P3+. Qualitative exit interviews will be conducted with a subset of P3 (n=10) and P3+ (n=10) users who are classified as either low or high users.

2.0 STUDY OBJECTIVES

2.1 Primary Objective
To test the efficacy of P3/P3+ among 240 YMSM and YTWSM, ages 16-24, recruited from participating SRV cities by conducting a three-arm RCT (P^3, P^3+, standard of care) with assessments at months 0, 3, and 6. The primary outcome measure is PrEP adherence which is measured in two different ways (1) by blood sample levels of tenofovir diphosphate (TFV-DP) with blood concentration consistent with >4 doses per week and (2) by blood samples of emtricitabine triphosphate (FTC-TP) with blood concentration consistent with > 4 doses/week, both will be assessed at 3- and 6- month follow-ups.

2.2 Secondary Objective
Secondary objectives include testing the efficacy of P3 and P3+ in terms of the primary outcomes above, but with the interventions considered separately against standard of care. We will also assess differences between P3/P3+ versus standard of care in terms of self-reported weekly PrEP use and self-reported monthly PrEP use to see if these results align with the primary results. Additional secondary outcomes of interest for P3/P3+ include self-reported retention in PrEP clinical care, PrEP persistence, sexual risk behaviors, and (self-reported) STI incidence.

A cost comparison between P3 and P3+ will be conducted to assess the incremental cost effectiveness ratio across intervention arms.

2.3 Study Hypotheses/Research Questions
H1: A greater proportion of participants in the P3 *and* P3**+** *arms will have protective levels of TFV-DP/FTC-TP or TAF/FTC-TP (measure of adherence) at months 3 and 6 compared to those in the standard of care arm.*

H2: P3**+** *will cost more to implement than* P3*, however, we expect the additional* P3**+** *costs to result in meaningful differences in outcomes.*

3.0 STUDY DESIGN

3.1 Study Phases

Phase 1: Conduct usability testing with up to 12 YMSM and YTWSM at 2 iTech SRVs to assess users' comprehension of the educational content, understanding and use of intervention features, and overall impressions of app functionality.

Phase 2: Conduct field-testing of P3 and P3+ with 15 YMSM and YTWSM who have recently initiated PrEP or are PrEP non-adherent at 3 iTech SRV sites. Using an iterative process of feedback and continuing quality improvement, final app refinements and enhancements will be made to ensure full technological functionality prior to the RCT. We will also assess and refine procedures for collection of whole blood and hair samples to ensure feasibility and acceptability within the target population.

Phase 3: Conduct a three-arm randomized controlled trial to test intervention efficacy with 240 YMSM and YTWSM who are initiating PrEP, recently initiated PrEP or are PrEP non-adherent. Initial study arms will include standard of care, P3 and P3+.The primary outcome measures are PrEP adherence measured by intracellular TFV-DP/TAF levels and adherence measured by FTC-TP levels, both collected from whole blood specimens at months 3 and 6. Secondarily, we will assess the efficacy of P3/P3+ at improving PrEP adherence by analyzing self-reported PrEP use, namely weekly PrEP use and monthly PrEP use at both 3- and 6- months follow-up. Secondary outcomes for P3/P3+ include self-reported retention in PrEP clinical care; PrEP persistence; sexual risk behaviors; and, (self-reported) STI incidence. As a secondary analysis, we will provide validation data on the use of hair specimens for the detection of FTC in YMSM and YTWSM at levels of 'any' and 'protective' usage. Conduct qualitative exit interviews with a subset of P3 (n=10) and P3+ (n=10) users who are classified as either low or high users.

3.2 Study Population

Total study sample is ~267 of which the following will be enrolled for each phase: 1) Usability testing with 8-12 total youth at 2 iTech SRV cities (Boston, Massachusetts; Chicago, Illinois); 2) Field testing will be conducted with 15 total youth who have recently initiated PrEP or are PrEP non-adherent at 3 iTech SRV cities (Bronx, New York; Houston, Texas; Philadelphia, Pennsylvania); 3) The RCT will be conducted with 240 youth who are on or planning to initiate PrEP in 9 iTech SRV cities (Atlanta, Georgia; Boston, Massachusetts; Bronx, New York; Chapel Hill, North Carolina; Charlotte, North Carolina; Chicago, Illinois; Houston, Texas; Philadelphia, Pennsylvania, and Tampa, Florida). The P3 and P3+ study arms and the standard of care arm will each include 80 participants.

Inclusion criteria for each phase of the study are described below:

Usability Testing Eligibility Criteria: 1) self-reported HIV-negative; 2) ages 16-24 years; 3) assigned male sex at birth; 4) self-identify as MSM or TWSM: 5) able to speak and read English; 6) familiar with Android or iOS smartphone; 7) have previously taken, are currently taking or considering taking PrEP; 8) recruited from one of 2 iTech SRV cities (Boston, Massachusetts; Chicago, Illinois); 9) ability to attend a usability session on dates specified by the research team. Not eligible: unable to be consented due to active substance use or psychological condition.

Field Testing Eligibility Criteria: 1) ages 16-24; 2) assigned male sex at birth; 3) report sex with men; 4) able to speak and read English; 5) reliable daily access to an Android or iOS smartphone with a data plan; 6) HIV-uninfected (self-report); 7) initiated PrEP within the last 60 days and have an active PrEP prescription (prescription confirmed by study staff) OR on PrEP >60 days but self-report adherence on average < 6 pills per week over the past month and have an active PrEP prescription (prescription confirmed by study staff); 8) recruited from one of 3 iTech SRV cities (Bronx, New York; Houston, Texas; Philadelphia, Pennsylvania); 9) willing to adhere to study collection of whole blood

and hair specimens. Not eligible: unable to be consented due to active substance use or psychological condition. Individuals who participated in the field trial will not be eligible for the RCT.

RCT Eligibility Criteria: 1) ages 16-24; 2) assigned male sex at birth; 3) report sex with men; 4) able to speak and read English; 5) reliable daily access to an Android or iOS smartphone with a data plan; 6) HIV-uninfected (self-report); 7) not currently on PrEP but plan to initiate in the next 7 days and have an active PrEP prescription (prescription confirmed by study staff) OR on PrEP and have an active PrEP prescription (prescription confirmed by study staff); 8) recruited from one of 9 iTech SRV cities (Atlanta, Georgia; Boston, Massachusetts; Bronx, New York; Chapel Hill, North Carolina; Charlotte, North Carolina; Chicago, Illinois; Houston, Texas; Philadelphia, Pennsylvania; Tampa, Florida); 9) willing to adhere to study collection of whole blood specimens. Not eligible: 1) unable to be consented due to active substance use or psychological condition; 2) participated in the field trial; 3) participating in any other experimental PrEP adherence intervention.

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

3.3.1 Usability Testing

Usability testing participants will be recruited without stratification or random assignment. However, participant demographics for this phase will be closely monitored to ensure that diversity in age and race/ethnicity is achieved.

3.3.2 Field Testing

Field testing participants will be recruited without stratification or random assignment. However, participant demographics for this phase will be closely monitored to ensure that diversity in age and race/ethnicity is achieved.

3.3.3 RCT

Participants will be randomized in a 1:1:1 ratio into the standard of care, P3 or P3+ condition, based on a randomization sequence developed by the AC and loaded into DFexplore clinical data management software. The randomization sequence will be stratified by SRV.

4.0 SELECTION AND ENROLLMENT OF ALL STUDY PARTICIPANTS

4.1 Inclusion Criteria for all phases

- Ages 16-24, inclusive
- Male sex at birth
- Report sex with men
- Able to speak and read English
- HIV-negative (self-report)

Additional inclusion criteria for usability testing

- Familiarity with an Android or iOS smartphone
- Have previously taken, are currently taking or considering taking PrEP
- Recruited from one of 2 iTech SRV cities (Boston, Massachusetts; Chicago, Illinois)
- Ability to attend usability session on dates specified by the research team

Additional inclusion criteria for field testing

- Reliable daily access to Android or iOS smartphone with a data plan
- Initiated PrEP within the last 60 days and have an active PrEP prescription (prescription confirmed by study staff) OR on PrEP >60 days but self-report adherence on average < 6 pills

per week over the past month and have an active PrEP prescription (prescription confirmed by study staff)
- Recruited from one of 3 iTech SRV cities for field testing (Bronx, New York; Houston, Texas; Philadelphia, Pennsylvania)
- Willing to adhere to study collection of whole blood and hair specimens.

Additional inclusion criteria for RCT
- Reliable daily access to Android or iOS smartphone with a data plan
- Willing to download video teleconferencing application, such as Zoom
- Not currently on PrEP but plan to initiate in the next 7 days and have an active PrEP prescription (prescription confirmed by study staff) OR on PrEP and have an active PrEP prescription (prescription confirmed by study staff)
- Recruited from one of 9 iTech SRV cities for RCT (Atlanta, Georgia; Boston, Massachusetts; Bronx, New York; Chapel Hill, North Carolina; Charlotte, North Carolina; Chicago, Illinois; Houston, Texas; Philadelphia, Pennsylvania; Tampa, Florida)
- Willing to adhere to study collection of whole blood specimens, including self-collection

4.2 Exclusion Criteria all phases

- Aged younger than 16 years or older than 24 years
- Not available to meet with project staff for planned study visit(s)
- Non-English speaking
- Unable to be consented due to active substance use or psychological condition
- HIV-positive (self-report)

Additional exclusion criteria for field testing and RCT

- Not currently prescribed PrEP (study staff unable to verify participant has an active PrEP prescription by a health provider)
- Anticipate not having reliable access to a smartphone with a data plan for 2 or more days during field testing or 1 or more weeks during the RCT intervention period
- Planning to move out of study area during the study period
- Unwilling or unable to comply with protocol requirements.

Additional exclusion criteria for RCT

- Participation in the field trial
- Participating in any other experimental PrEP adherence intervention.

4.3 Recruitment/Screening

For all aims: We will work closely with the participating SRVs and the iTech Management Core (MC) and Technology Core (TC) to engage youth who are initiating PrEP, have recently initiated PrEP, or are PrEP non-adherent. For usability testing, we will also recruit youth who are considering PrEP initiation or have taken PrEP in the past. This includes utilizing in person, venue-based (including recruitment from locally specific PrEP clinics/providers) and online recruitment mechanisms. All participating SRVs either provide PrEP or have close relationships with sites in their community that prescribe. Recruitment procedures may vary slightly depending on the SRV and study phase, which

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

4.4 Screening

Potential participants recruited in any of the aforementioned ways will be directed to the study screening survey (hosted on Alchemer.com). The screening survey will include information about the study. Those who express interest in the study will be asked to provide informed consent/assent for eligibility screening. Those who provide consent/assent will view the aim-specific eligibility screener questions. The Alchemer screener survey can be viewed on participants' own device or on a computer or tablet located in a confidential room at the SRV to determine if they meet eligibility criteria (usability) or initial eligibility criteria (field testing, RCT).

For those who meet eligibility criteria, and express interest in participating, we will ask for and record the first name, e-mail, and phone number of the individual via the online screener. We also collect preferred means of contact (e.g. call, text, email) and permission to leave a message. We use SSL encryption for transfers of information online and data will be stored in the secure, HIPPA-compliant servers of Alchemer. The Emory AC team maintains a business partner HIPPA agreement with Alchemer. A list of participants who meet eligibility criteria (usability) or initial eligibility criteria (field testing, RCT) will be updated twice weekly on each SRV's secure Box or Microsoft OneDrive folder. The list is password protected; only the data manager at Emory and SRV staff can access the file. The SRV staff then contacts individuals on the list and schedules them for an enrollment visit using the Study Management and Retention Tool (SMART Web). Only those in the field testing or RCT will be informed of the need to bring verification of PrEP prescription to the enrollment visit.

4.5 Informed Consent

Informed consent/assent. Individuals interested in screening for study participation will be consented/assented for screening after reading information about the study and screening procedures. Participants who meet eligibility criteria will undergo a detailed informed consent/assent process in which study staff explain all study procedures and answer questions concerning the study and consent/assent process. The research staff member will give the participant as much time as needed and will address any questions or concerns they may have. The research staff member will ask the participant questions to gauge comprehension. The consent/assent form describes all study procedures, including confidentiality and privacy, information about potential risks, discomforts, 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.

Assessing for decisional capacity. The study staff reviews the informed consent/assent to make a formal assessment of the youth's decisional capacity and ability to provide consent/assent prior to signing, using a 2-step process. First, the staff members determine if the person understands the study goals by asking "Can you tell me what this study is about?" In step 2, potential participants will be asked questions designed to assess their capacity to understand, appreciate, reason with, and express a choice about participation in our specific protocol. We will use a modified version of the widely used Evaluation to Sign Consent Form in which participants are asked to: **1)** name things they will be expected to do during the study; **2)** explain what they would do if they no longer wished to participate in the study**; 3)** explain what they would do if they experienced distress during the study; and **4)** identify

potential risks for participating in the study. Potential participants will be enrolled only if they are able to provide clear and correct answers to each of these items, without prompting or correction.

Waiver of parental consent. We will request that the UNC-CH IRB as the central IRB (IRB of Record) grant a waiver of parental consent to participate in this research study for youth participants who are 16 to 17 years of age. The research team has been granted waivers of parental permission for prior studies with sexual minority youth. Under 45 CFR 46.408 (c), an IRB has the authority to waive parental permission if it determines that "a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects" and "an appropriate mechanism for protecting the children who will participate as research subjects is substituted" and "that the waiver is not inconsistent with Federal, State, or local law." A waiver of parental permission for studies with lesbian, gay, bisexual, transgender, and questioning (LGBT) youth that do not involve greater than minimal risk is a common practice among researchers working in the area of gay and lesbian health/mental health. This is done to avoid the selection biases operating in only recruiting youth whose parents are both aware of and comfortable with their sexual orientation. Commonly these youth have explored their sexual orientation without their parents' knowledge as the youth struggle with issues of disclosure and its consequences within the social, religious, and economic context of their families. A requirement for parental permission in this type of study could not only affect a person's willingness to participate, but could also potentially impact the ability of researchers to engage in this type of research with sexual minority youth. Additionally, minors can often seek sexually transmitted infection (STI) and HIV prevention services without parental/legal guardian permission, depending on each site's state laws.

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

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

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

For the field trial and RCT, consent/assent must be obtained on the day of enrollment, prior to implementing any study activities. When the RCT procedures are being completed remotely, consent/assent is obtained during the first phone call/video teleconferencing contact with a potential participant, prior to implementing any study activities.

Individuals who are eligible but do not consent to participate will be asked if they are willing to provide their reason for declining participation; responses will be logged. Individuals assessed as ineligible for enrollment will have the reason(s) for ineligibility recorded. Study ID (SID) and participant code (first initial and two-digit date of birth) will be entered in the study-specific log for individuals that do not enroll in the study. Individuals are asked if they would like to provide contact information to be re-contacted for eligibility assessment for other iTech studies. When study accrual ends, study staff will obliterate all information belonging to individuals who did not consent to participate in the study.

The Protocol Team may request tabulated information from the AC on individuals who participated in the recruitment process, including reasons for ineligibility and, for those eligible, reasons for declining participation. These data will provide general information on the population that was recruited but not enrolled in the study.

5.0 STUDY PROCEDURES

5.1 Enrollment Procedures

Usability Testing

Youth that are eligible will be scheduled for an enrollment visit at the SRV. Consent/assent can be obtained up to 30 days prior to the scheduled usability session. Usability sessions will be conducted at the SRV.

Field Testing

Youth that meet initial eligibility criteria will be scheduled for an enrollment visit at the SRV. SRV staff will verify that the individual meets the initial eligibility criteria. Individuals will be asked to bring their smartphone with them to the enrollment visit. To confirm an individual meets the smartphone eligibility criteria, study staff will confirm that the individual has a smartphone with a data plan at the visit and ask if they anticipate lack of smartphone access for >2 days during the field trial. To confirm an individual meets the study PrEP eligibility criteria, they will be asked to bring their non-expired PrEP pill bottle, or a photograph of their non-expired pill bottle to the enrollment visit (expiration date must be visible in the photograph), or staff will check in their chart for a filled PrEP prescription. Study staff will confirm individual identity by photo ID (driver's license, state ID, school ID card) to confirm the PrEP prescription belongs to the individual. Study staff will document the inclusion and exclusion criteria and eligibility status for each participant using the Screening and Enrollment Case Report Form (CRF).

The checklist for the Enrollment Visit is detailed in the Baseline Field Testing Checklist. During the enrollment visit, youth who are confirmed as eligible for the study will be guided through an informed consent/assent process by research staff. Study staff will document whether consent was obtained and the participant's enrollment status on the Screening and Enrollment CRF. Next, participants will complete a computer-assisted baseline survey (CASI), programmed by AC staff and hosted on Alchemer, a secure, HIPAA-compliant platform.

Next, participants will be guided through the app download process by SRV staff and given an app site tour to highlight features. They will also be provided with information about the Next Step Counseling component (adherence counseling) including information about how the counselor will contact them through the app. Lastly SRV staff will collect the hair and whole blood specimen from participants. Participants will be considered enrolled upon meeting all field testing eligibility criteria, signing the enrollment field testing consent/assent form, completing the CASI at the enrollment visit, successfully downloading the P3 app to their phone, and providing biological specimens. Once participants have completed these tasks (see Baseline Checklist), they will be compensated $50 for their time.

RCT

SRV staff will verify that the individual meets the initial eligibility criteria. Individuals will be asked to bring their smartphone with them to the in-person enrollment visit. To confirm an individual meets the smartphone eligibility criteria, study staff will confirm that the individual has a smartphone with a data plan at the visit and ask if they anticipate lack of smartphone access for ≥1 week during the RCT. To confirm an individual meets study PrEP eligibility criteria, they will be asked to bring their non-expired PrEP pill bottle OR a photograph of their non-expired pill bottle to the enrollment visit (expiration date must be visible in the photograph) OR a non-expired paper PrEP prescription OR a picture of non-

expired paper prescription (expiration date must be visible in the photograph) OR documentation from the medical record of non-expired PrEP prescription (HIPAA waiver to access medical record will be obtained). Study staff will confirm individual identity by photo ID (driver's license, state ID, school ID card) to confirm the PrEP prescription belongs to the individual. Study staff will document the inclusion and exclusion criteria and eligibility status for each participant using the Screening and Enrollment Case Report Form (CRF). For enrollment visits that take place remotely, participants will be asked to self-report their smartphone version and to show proof of their PrEP prescription and ID during the introductory videoconference.

The checklist for the Enrollment Visit can be found in the Baseline RCT Checklist. During the in-person enrollment visit, youth who are eligible for the study will be guided through an informed consent/assent process by research staff. After participants are consented, whole blood specimen will be collected and it will be documented on the Specimen Collection CRF. Next, they will complete a computer-assisted baseline survey (CASI), created by AC staff and hosted on Alchemer, a secure, HIPAA-compliant platform. Study staff will document whether consent was obtained and the participant's enrollment status on the Screening and Enrollment CRF.

Next, participants who are enrolled will be randomized 1:1:1 ratio into the P3 and P3+, or standard of care arm based on a randomization sequence developed by the AC and loaded into DFexplore clinical data management software. The randomization sequence will be stratified by SRV. Participants randomized to the P3 or P3 + arms will be guided through the app download process by SRV staff and given an app site tour to highlight features. Those in P3+ arm will be provided with additional information about the Next Step Counseling component (adherence counseling) including information about how to contact the counselor through the app. Participants will be considered enrolled upon meeting all RCT eligibility criteria, signing the enrollment RCT consent/assent form, being randomized to P3, P3 + or control and for P3, P3 + group, completing the baseline CASI, successfully downloading the app on their phones. Once participants have completed these tasks (see Baseline Checklist), they will be compensated $50 for their time.

For remote enrollment visits, potential participants will have an introductory call with study staff via phone or video teleconference, and will be guided through the informed consent form prior to signing electronically. Study staff will confirm the participant's address, and will have a blood self-collection kit mailed to the address of participant's choice to complete self-collection of baseline specimen, as well as specimen collection survey. Study staff will send the potential participant a link to the baseline survey after this initial call. Once the baseline specimen is received, study staff will contact the participant again and complete the enrollment visit. During this second contact, participants will be randomized and onboarded onto the app or sent standard of care materials. This entire process should be done within 30 days of the participant screening eligible. Participants will be sent $50 for completing the specimen collection and $50 for completing the baseline survey and for intervention onboarding.

5.2 Locator/Contact Information

Once consented and enrolled, designated site study staff may complete a Contact Information Worksheet with the participant to collect additional contact information. 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 valid contact information for a family member and/or friend who can be called in the event the participant cannot be reached by phone or email. Participants will be asked if messages can be left at the numbers provided. Participants will be asked to provide their physical address and whether they could receive mail related to their study participation at that address. They will also be asked to provide social media contact info and whether study related communications can be sent to those. Study staff will not leave messages or send mail unless expressly permitted to do so by the participant, which also will be documented on this form. If

permission is given to leave messages or send mail, site staff will assure participants that messages only ask the participant to contact study staff and will not include any protected health information or information related to study participation. The information from the Contact Information Worksheet will be entered into the SMART Web study management and retention database by SRV staff. Alternatively, this information may be entered directly into SMART Web by SRV staff.

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

5.3. Randomization Procedures

Participants in the usability testing and field testing will not be randomized.

Participants in the RCT will be randomized 1:1:1 ratio into the P3 and P3+ or standard of care condition, based on a randomization sequence developed by the AC and loaded into DFexplore clinical management software. The randomization sequence will be stratified by SRV.

5.4 Intervention/Investigation Procedures

5.4.1 Usability Testing

Eight to 12 youth will be recruited at 2 SRVs (Boston, Massachusetts; Chicago, Illinois) to participate in usability testing (Usability Testing Checklist). Usability testing will involve identifying, screening and enrolling potential participants as described in Sections 4.3, 4.4, 4.5 and 5.1. Individuals who are eligible for usability testing based on the online screener will be scheduled for an in-person visit to enroll in the study and review the P3 intervention. Once enrolled, participants will complete a brief demographic, technology use and PrEP awareness and utilization survey on Alchemer using a tablet or computer provided by SRV staff. Participants will then receive an overview of the intervention and will be taken through a brief tutorial of the P3 intervention pre-loaded on a study smartphone (Usability Testing Script), and then asked to think aloud as they explore the app. Testing will be conducted by members of the research team in accordance with NIH usability guidelines.[40] The main goals of usability testing are to assess users' comprehension of the educational content, understanding and use of intervention features, and overall impressions of app functionality. A post-usability survey will be completed. Participants will be paid $50 at the end of the session. The session is anticipated to take 90 minutes.

5.4.2 Field Testing

Fifteen youth initiating PrEP will be recruited at 3 SRVs (Bronx, New York; Houston, Texas; Philadelphia, Pennsylvania) to participate in a field test of the app. The purpose of field testing is to ensure that the features, platform and content of P3 and P3+, including Next Step Counseling, are acceptable to the target population and that there are no technical challenges or user concerns with either the app or the whole blood and hair collection. Field testing will involve identifying, screening and enrolling potential participants as described in Sections 4.3, 4.4, 4.5 and 5.1.

Once eligibility is confirmed and consent/assent is obtained, a baseline survey will be administered using CASI (Alchemer) that will include items planned for use in the RCT survey. Study staff will then facilitate app download and login onto participants' phones, and provide an app site tour to highlight features. They will be provided information about the NSC and informed that they will be contacted by the counselor to schedule an adherence counseling "chat" session. In addition, they will be asked to engage in two-way texting with the adherence counselor to ensure full technological functioning of the texting portal. Participants will be provided information regarding the virtual bank account and told that their account will be initially seeded with $30. For each day (of the 30 day trial) that participants

log-in and engage with the three required app activities, they will be awarded $0.50. For each day that they do no log-in and engage with the three required app activities, they will lose $1.00. The money will be visible on the profile page of the app. A participants' bank account will never be able to drop below $0.00. Individuals will be instructed to contact study staff immediately to report difficulties with any app components or to report any problems with their phone or phone service. After being onboarded onto the app, DBS, Mitra, and head hair samples are collected (hair samples will include 10 fibers of hair at least 1cm long taken as close to the scalp as possible).

Participants will be compensated $50 for participation at the end of the enrollment visit and reminded that they will be asked to return in one month for follow-up.

> At the end of the one-month field trial, participants will return to the SRV to complete post-trial procedures. This will include:
>
> *DBS, Mitra, and hair collection procedures*: DBS and Mitra collection (via a finger stick using a lancing device) and hair collection (hair samples will include 10 fibers of hair at least 1cm long taken as close to the scalp as possible).
>
> Completion of a follow-up survey (Alchemer) that will include questions planned for follow-up surveys in the RCT. The survey will also include questions regarding the acceptability of the DBS, Mitra and hair collection procedures.
>
> Complete a qualitative exit interview, conducted using HIPPA-compliant videoconferencing software that will allow for an in-depth and nuanced understanding of intervention feasibility and acceptability (both the app itself and the adherence counseling component). This debriefing session will be conducted by members of the research team at UNC/Duke. The online interview will last 45-60 minutes and audio only will be recorded using the software platform and transcribed by a secure transcription service. Participants can opt to include video chat, but no video will be recorded. Interviews will be semi-structured and focus on how participants used P3/P3+ over the one-month field-trial, any usability challenges, and how they perceive that use of the intervention could translate into behavior change. In the event that a participant does not have enough time at the post-trial visit to complete the interview or the UNC/Duke team is not available for an interview at the scheduled time, the SRV staff will work with the participant to schedule the participants' interview (conducted using the same procedures outlined above) within one month of the visit.

Participants will be compensated $50 for participation at the follow-up visit if all activities are completed. If the qualitative exit interview cannot be completed at the visit, they will receive $25 at the follow-up visit and $25 after the exit interview is completed. Based on app usage they could also receive an additional $45 at the follow-up visit.

5.4.3 RCT

Recruitment for the RCT will occur in nine SRV cities/locales (Atlanta, Georgia; Boston, Massachusetts; Bronx/NY, New York; Chapel Hill, North Carolina; Charlotte, North Carolina; Chicago, Illinois; Houston, Texas; Philadelphia, Pennsylvania; Tampa, Florida). Identifying, screening and enrolling potential participants for the RCT will proceed as described in Sections 4.3, 4.4, 4.5 and 5.1.

After eligibility is confirmed and consent/assent is obtained, whole blood specimens will be collected. Participants will then complete a CASI survey (Alchemer) and be randomized into a study arm. Next, participants will be walked through a brief description of their respective study arm (Control Group Script, P3 Intervention Group Script and P3+ Intervention Group Script). Participants will be compensated $50 at the conclusion of the enrollment visit, and reminded that they will be asked to complete3 and 6 month follow-up surveys and specimen collections. Participants completing procedures remotely will be compensated $50 for specimen collection and $50 for visit activities (i.e.

surveys, intervention onboarding). For participants completing their RCT enrollments remotely via phone or video teleconference, eligibility confirmation and consent/assent will happen prior to their blood specimen collection, baseline survey completion, randomization, and overview of study arm.

P3 *and* P3+ *arms*: After giving a brief description of the relevant intervention study arm, SRV site staff will help the participant download and install P3 on the subject's phone and provide a guided tour of the app. If the visit is done remotely, the participant will be sent a link to a video to guide them through downloading, installing, and reviewing the app. They will be sent their App ID through text in SMART. The adherence counselor texting portal will be unlocked and demonstrated for those in the P3+ arm. The participant will then be instructed to send an introductory text to the adherence counselor through the portal and encouraged to schedule their first adherence counseling session. SRV site staff will provide assistance if needed. Each individual will be given SRV staff phone number and email address and instructed to contact them immediately to report difficulties with any app components or to report any problems with their phone or phone service. P3 arm participants will have access to all features of P3 except the adherence-counseling component**.** P3+ participants will have access to all features of P3. The duration of the intervention is 3 months for both intervention arms. However, participants will still have access to the P3 app after the completion of 3 months until the end of the trial. They will not have access to the adherence counselor feature (in either the P3 or P3+arm) and the virtual bank account feature will not be active (e.g. they will not receive additional monetary incentives for using the app)

Qualitative interviews: A sample of 20 users (10 in P3 and 10 in P3+) including both high/low users will complete a qualitative exit interview, conducted using HIPPA-compliant videoconferencing software, which will allow for an in-depth and nuanced understanding of usage of P3/P3+ over the 6-month trial. High users for the P3 arm are defined as those who use the app on average $\geq$4 days during the intervention period; moderate to low users are those who use the app on average $\leq$3 days. High users for the P3+ arm include those who use the app $\geq$4 days on average and participate in $\geq$3 adherence counseling sessions; moderate to low users are those who use the app $\leq$3 days and participate in <3 counseling sessions. The online interview will last 45-60 minutes and audio only will be recorded using the software platform and transcribed by a secure transcription service. Participants can opt to include video chat, but no video will be recorded. Interviews will be semi-structured and focus on how participants used/didn't use P3/P3+ over the six-month trial, and what additional components (either technology-based or in-person) might be useful to further impact behavior change.

Standard of Care arm: SRV staff will inform participants of standard of care services available to them at the clinic or through community partners. According to CDC guidelines, medication adherence counseling is a key part of PrEP standard of care, should occur at PrEP initiation and at 3-month intervals, and should include education about PrEP (i.e., medication dosage and schedule, management of common side effects), adherence support, and monitoring of medication adherence (i.e., identify factors interfering with adherence and develop a plan to address them, reinforce success, normalize occasional missed doses). Medication adherence counseling should be conducted at each PrEP follow-up visit.[41] SRV staff will also provide participants with written or online materials/resources that provide information about taking PrEP.

5.4.4 Research and Training Staff

All proposed study staff have participated in the required trainings in participation and conduct of studies that involve human subjects, and any future study staff will do so upon hiring. Research staff at individual SRVs who interact with P3 participants at assessments do not need to be clinicians. A research assistant (RA) level position should be sufficient to verify eligibility (field testing, RCT), obtain informed consent, collect whole blood and hair specimens, be available for questions during the CASI, and explain the P3 intervention. Research staff at SRVs will be trained in person, at an ATN meeting and via videoconferencing on the intervention components, whole blood and hair specimen collection,

and will be given a script and checklist to review with participants. If a participant asks a question that study staff do not feel equipped to answer, SRV study staff will contact research staff at the University of North Carolina/Duke and then follow-up with the participant. Research staff at the University of North Carolina/Duke will monitor the app daily. Since this is a social networking site, users may post information (such as suicidal ideation) which would require involvement from the clinical team at the SRV, as described in Clinical Protocol for User Postings.

5.4.5 Intervention Monitoring/Quality Control

Because the P3 intervention is an app, intervention fidelity is assured (i.e., all participants will receive the intervention in the same way and have access to all of the same resources). P3+ will include provision of Next Step Counseling (NSC), an interactive, client-centered motivational intervention to improve PrEP adherence, delivered via texting through the app. A NSC protocol will be developed during formative work and implemented in field testing and the RCT. During the RCT, we will review 20% of sessions every quarter. The adherence counselor(s) will document all sessions on the fidelity form developed by the NSC research team.[42] Dr. Muessig will assess quality and fidelity by reviewing counseling transcripts and the accuracy of fidelity forms. Dr. Muessig will retrain the counselor(s) if any quality or fidelity issues are detected.

6.0 EVALUATION AND MEASURES

THIS SECTION CONTAINS RELEVANT EVALUATIONS AND MEASURES FOR THE RCT ONLY

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

6.1 Screening

Online or in-person screeners will be used to determine if individuals meet initial eligibility criteria. Individuals may be screened for eligibility by accessing the screening webpage using their own mobile device (e.g., if conducting online or community recruitment) or may complete the online screener on a local clinic tablet or computer. All potential field testing and RCT participants who meet the initial eligibility criteria (based on the online screener) must arrange an in-person or teleconference enrollment visit. Participants will complete a short screener consenting to provide evidence of having an active PrEP prescription. For those that provide this initial consent, study staff will verify that they meet the PrEP prescription criteria (active prescription confirmed through staff visualization of pill bottle or a photo of pill bottle or medical record review and verification of participant ID) and that they are HIV-negative (self-report).

6.1.1 Administrative and Behavioral Procedures

Consent to be screened

Consent for PrEP Rx verification

Screening assessment using Alchemer

6.2 Enrollment

Participants must be scheduled for an enrollment visit within 30 days of online screening; otherwise they will need to be re-screened. Individuals who meet initial eligibility criteria based on the online screener will be scheduled for an enrollment visit. Participant eligibility will be confirmed at the enrollment visit and recorded on the Screening and Enrollment CRF. Study enrollment will occur only after participants have provided appropriate documentation of a PrEP prescription consistent with eligibility criteria (verified by site

study staff) and self-report a HIV-negative status. For remote visits, participants must be enrolled within 30 days of screening. When completing procedures remotely, a participant is considered enrolled once they have successfully mailed back a self-collected blood sample, completed the baseline and been randomized

6.2.1 Administrative and Behavioral Procedures

Confirmation of active prescription by pill bottle, photograph of pill bottle, or chart review of filled prescription and verification of ID through either the medical record or with photo ID (driver's license, state ID, school ID card) to confirm the PrEP prescription belongs to the individual.

Informed Consent/Assent

Baseline Assessment using CASI

Randomization to P3, P3+ or control

For P3 and P3+ intervention participants, download and set-up of P3 app

For P3 and P3+ intervention participants, tour and training on the P3 app

For P3+ intervention participants, training and initiation on the NSC feature

For control participants, provision of control materials/resources

Completion of participant contact/tracking information

Remuneration for survey completion

For remote participants, mailing of self-collection specimen kit and specimen collection CASI

6.2.2 Clinical Procedures

Whole blood collection: (see whole blood collection guidelines for detailed methods for collecting and sending specimen to the Molecular Testing Lab and/or UNC Chapel Hill School of Pharmacy, Clinical Pharmacology and Analytical Chemistry Laboratory)

6.2.3 Laboratory Procedures

Whole blood specimen analysis for measurement of TFV-DP/ FTC-TP or TAF/FTC-TP

6.3 3-month Assessment (Immediate Post-Intervention)

The intervention will last for a total of 3 months. The 3-month assessment should occur as soon after their 3-month enrollment period as possible. However, the assessment may occur within 30 days after the 3-month assessment time point. (For example: A participant enrolls on September 1, 2018. Their 3-month enrollment date is December 1, 2018. They may complete their 3-month assessment any day on or between December 1, 2018 and December 31, 2018).SMART Web, a study management and retention database managed by the Analytic Core (AC), will aid study staff in ensuring retention. SMART Web maintains participant follow-up timelines, tracks participant communications, and automates sending of e-mail, text reminders, and calendar invites to participants for follow-up survey and visit completion. Retention data will be collected by the AC and monitored by the MC. An appointment for the 3-month assessment visit will be scheduled to complete the following procedures listed below. Participants completing their 3-month assessment remotely will receive the survey link emailed to them. Blood specimen self-collection kits will be mailed to participants prior to their window opening. Participants will have 60 days to return their

3-month specimen collection kit and complete their remote 3-month assessment as well as a specimen collection survey.

6.3.1 Administrative and Behavioral Procedures

3-month assessment using CASI

Remuneration for visit completion ($50 for survey and $50 for blood specimen sample if self-collected) and app usage (if virtual account has a positive balance).

Update SMART Web

For remote participants, mailing of self-collection specimen kit

6.3.2 Clinical Procedures

Whole blood collection

Hair collection (hair samples will include 10 fibers of hair at least 1cm long taken as close to the scalp as possible)

6.3.3 Laboratory Procedures

Whole blood specimen analysis for measurement of TFV-DP or TAF and FTC-TP

Hair analysis (see Whole Blood and Hair specimen collection guidelines for detailed methods for collecting and sending hair samples to the UNC Chapel Hill School of Pharmacy, Clinical Pharmacology and Analytical Chemistry Laboratory)

6.4 6-month Assessment (Post-Intervention)

The 6-month assessment should occur as soon after their 6-month enrollment period as possible. However, the assessment may occur within 30 days after the 6-month assessment time point. (For example: A participant enrolls on September 1, 2018. Their 6-month enrollment date is March 1, 2019. They may complete their 6-month assessment any day on or between March 1, 2019 and 31, 2019.) SMART Web, managed by the Analytic Core (AC), will aid study staff in ensuring retention. SMART Web maintains participant follow-up timelines, tracks participant communications, and automates sending of e-mail, text reminders, and calendar invites to participants for follow-up survey and visit completion. Retention data will be collected by the AC and monitored by the MC. An appointment for the 6-month assessment visit will be scheduled to complete the following procedures listed below. Participants completing their 6-month assessment remotely will receive a link emailed to them. Blood specimen self-collection kits will be mailed to participants prior to their window opening. Participants will be able to complete 6-month specimen collection, specimen collection survey, and follow-up survey 30 days prior and up to 90 days after their 6-month window.

Participants who miss their 3-month follow up are eligible to complete their 6-month visit.

6.4.1 Administrative and Behavioral Procedures

6-month assessment using CASI

For remote participants, mailing of self-collection specimen kit and specimen collection CASI

Remuneration for visit completion ($50 for survey and $50 for blood specimen sample if self-collected)

Update SMART Web

Qualitative exit interview (for subset of participants)

6.4.2 Clinical Procedures

Whole blood specimen collection

Hair collection (hair samples will include 10 fibers of hair at least 1cm long taken as close to the scalp as possible)

6.4.3 Laboratory Procedures

Whole blood specimen analysis for measurement of TFV-DP/ FTC-TP or TAF/FTC-TP

Hair analysis

7.0 DATA COLLECTION AND SITE MONITORING

7.1 Development of Protocol and Case Report Forms

The MC and AC, 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 on all participant CRFs, audio files, transcripts, and CASI files. Participant names or other personally-identifying information will not be used on any study documents other than the Contact Information Worksheet (stored in double-locked office separate from other study information only accessible by designated study staff) and will be redacted from usability and field trial interview transcripts. All study-related information will be kept in double-locked, limited access areas at each study site. Participant names and their SID and participant code will be stored in separate tabs in SMART Web, accessible only to designated study staff, iTech site monitors, and representatives from the NICHD. SIDs will not be entered into the mobile app and instead a unique app ID will be assigned to each participant and used when logging into the app. These unique App IDs will be provided by the developer and recorded into SMART Web during enrollment. Original source documents (e.g., Contact Information Worksheet) for individual participants will be maintained at the respective SRV and will be accessible only to the study staff. Data from original source documents will be transcribed on CRFs as applicable. Electronic data will be stored in Box, Microsoft OneDrive or on a secure server at Emory.

7.3 Data Collection

7.3.1 CRFs

Study monitoring data, including information about eligibility, demographic data, and monitoring untoward effects will be collected on CRFs. All CRFs for this study will be available for download from the iTech Box or Microsoft OneDrive account, a secure content management platform.

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7.3.2 CASI Survey Data

Field trial: Self-administered surveys will be completed by participants at the baseline and 1-month assessment time points. Participants will complete an online computer assisted self-interview (CASI) via survey hosts on Alchemer.com. 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 HIPPA agreement with Alchemer.

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

Data collected using a CASI method will be on a portable computer or mobile phone via an internet-based application. All data collected using CASI will remain confidential; no personal identifying information will be collected during the computer session. The participant's unique SID# and participant code will be used to link the survey responses to the participant's CRF data.

7.3.3 CASI Data Security

CASI Data Security

Survey data will be stored in secure databases on an AC server within the Emory AC data center.

7.3.4 VSee Platform Description

For the qualitative interviews being conducted, the Analytic Core will rely on VSee platform. 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 interviewer but the interviewer cannot see them, audio chat only, or a text based conversation. The consent form for each research project will include a full description of VSee, their options for using VSee, and will also make it clear what they can opt not to do. 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 at 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.

7.3.5 Zoom Platform Description
In addition to VSee, the Zoom platform may be used to conduct qualitative interviews remotely. Participants will have the option to conduct face-to-face video chat, video chat in which they can see the interviewer, but the interviewer cannot see them, or audio chat only. Zoom is compatible on PCs, tablets, and smartphones; as well as maintains the option to conduct an audio conference without the video component. Zoom offers HIPAA-compliant versions of its platform. Study staff will use HIPAA-compliant version of Zoom for study activities.

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.

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

7.4 Data Submission

7.4.1 CRFS

Although 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-recorded Data

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

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

7.4.3 CASI Data Transmission

Survey data will be stored in secure databases on an AC server within the AC data center.

7.4.4 Retention Data

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

The 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.

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

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

The site investigator will make study documents (e.g., assent/consent forms, case report forms) *and pertinent hospital or clinic records* readily available for inspection by the local IRB, the central IRB, the site monitors, the 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
All subjects will be contacted before each follow-up study visit/assessment (i.e., enrollment, 3-month, and 6-month time points). Multiple contact methods will be used for youth who are difficult to reach (e.g., mail, alternate phone numbers, e-mail, text message, Facebook). Subjects will be asked whether or not messages can be left for each of the phone numbers that they provide. They will be informed that messages will not contain any information regarding the nature of the project. The SMART participant management system will be used.

8.2 Compensation
The method for compensation will be determined separately by each site and approved by each site's IRB. Participants at all sites will be compensated using the following cash or cash equivalent:

Usability test participants: Compensated with $50.

Field test participants: Compensated with $50 at first visit and $50 at second visit. Possible to earn an additional $45 for app usage over the 4-week field trial ($145 total).

RCT participants: Compensated with $50 at enrollment visit, $50 at the 3-month visit, $50 at the 6-month visit. Participants randomized to the P3 or P3+ arms have the possibility of earning an additional $135 for app usage over the 3-month app intervention period ($150 total control group/$325 P3/P3+ group). Participants who complete an exit interview will earn an additional $50. Participants who complete enrollment remotely will receive $50 for specimen collection and $50 for survey completion and intervention onboarding. Participants who began the study in-person and had to continue follow-ups remotely will receive $50 for specimen collection and $50 for survey completion.

Compensation will be provided in person or can be mailed to subjects, if allowed at the SRV.

8.3 Intervening on “Social Harms"

We identified the following 5 items as possible risks to subjects and described how we plan on addressing those risks:

1) Breach of Confidentiality: A potential risk to participants is violation of confidentiality. We will take the utmost caution to protect the confidentiality of all responses. We will minimize this risk by maintaining confidentiality and discretion throughout the usability testing, field testing and RCT. Files – audio, paper and electronic– will not have any identifying information about the study participants and will be tracked through a unique SID and participant code. All audio recordings will be downloaded and stored on a password-protected, encrypted computer in locked offices at UNC-CH and subsequently transferred to Emory’s secure Box or Microsoft OneDrive platform. Transcription of audio files will be conducted using a HIPAA compliant transcription service. Any names mentioned in the audio files will be redacted during transcription. Interview transcripts will be kept on Emory’s secure Box or Microsoft OneDrive platform. Analysis of transcripts will be conducted on a password-protected, encrypted computer. Hard copies will be kept in locked files. This research specifically targets a vulnerable population, children (YMSM ages 16-17). We will take every available step to minimize the risk of identifying/linking data being subpoenaed, stolen, or inadvertently released. First, the iTech has acquired a Certificate of Confidentiality from the NIH. Second, all research staff members are required to complete ethical clearance certification regarding protection of human’s subjects through the UNC-CH and/or Duke University. Third, the study will safeguard against the risk of the linking information being stolen by keeping such information in a locked Excel file store on a secure server at Emory University to which only essential study personnel who have completed CITI certification for human subjects’ research ethics training (http://citiprogram.org) will have access. We have also included numerous features to ensure app security and privacy. All relevant app communications (e.g. those between participants or those between participants and staff) will be secured via industry standard encrypted SSL communications links. These connections will ensure that all communications are inaccessible to unauthorized third parties. Furthermore, the app can be updated regularly to address any unforeseen security updates to the software libraries underlying the secured communication links. Beyond encrypting communication, we will allow users to enable an extra PIN to secure the app within their phone beyond the PIN required to unlock the phone itself. This will allow the user to share their phone generally with others without granting access to P3. These software security solutions will provide the layers of both communications security and physical access security to ensure that only authorized users have access to the information stored on the phone as well as the information being shared over communications links. We will take special care to ensure that P3 addresses participant privacy. We have chosen the app name, P3, because it does not relate to health care and is therefore designed to be non-stigmatizing and un-interpretable by anyone observing a participant using the app on their mobile phones. During app onboarding, study staff will assist youth in choosing a discreet and anonymous username. Moreover, mobile phone screens themselves are also constructed to prevent surreptitious observation.

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

3) Discomfort during collection of whole blood and hair specimen: The risk of discomfort due to blood and hair sample collection is considered minimal. Physical harms are minimal. The type of safety lancet selected for use in the study was designed to minimize the potential for infection or significant injury. Cleaning the area with an alcohol pad first lowers the already low infection risk further; pads are included in every kit. The spring-loaded lancet retracts fully after one firing, and thus does not pose a risk for "needle stick" injury to anyone after the device has been used. Subjects could experience dizziness, diaphoresis and nausea associated with the procedure but in prior clinical studies using dried blood spots, adverse events have been rare. The risk of discomfort due to hair sample collection is considered minimal. Physical harms are minimal. There is some possibility of discomfort during the procedure related to lifting the hair away from the occipital region of the scalp. There is also the possibility of small nicks to scalp with scissors that may result from cutting the hair sample.

4) Protecting against hostile interactions and inaccurate information from one participant to another. Field trial participants and RCT participants assigned to the intervention study arms will be informed during the consent 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 "terms of use" will also be available with a link on the app for review by participants at any time. The UNC based project coordinator and/or research assistant will manually review participants posts on a daily basis to identify any hostile interactions or 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 offending participant will be withdrawn from the study. Text containing hostile exchanges will be removed from the study app and unavailable to view. In cases in which inaccurate information is found, project staff will be guided by experts on the team to post a comment that provides accurate information on the topic. In extreme cases, the PI's may decide to withdraw a participant before the third offense. We will ensure all SRVs 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 from the University of North Carolina see concerning comments or messages online from participants regarding self-harm or harm of others, they will contact clinicians at the site 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 they are at risk for harm, including but not limited to being abused or experiencing violence, if harm is suspected or likely, or if the participant states

they are suicidal/homicidal, measures will be taken to ensure their safety. Reporting will be done as appropriate to the situation and the legal statutes, including reporting to child protection agencies or other appropriate agencies, and referrals will be provided to appropriate support, counseling, or treatment resources.

8.4 Criteria for Premature Study Discontinuation

The principal investigator has the authority to withdraw any participant at any time if 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.

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

- The subject withdraws consent/assent;
- The subject reports testing HIV-positive at follow-up assessments;
- The study is cancelled by the *NIH (or iTech, or other administrative entity)*;
- The study is cancelled for other administrative reasons;
- The participant repeatedly posts hostile or inflammatory information on the app (see Section 8.3)
- The subject becomes incarcerated or placed in detention during the study; or
- Death of the subject.

Participants may end their participation in the study at any time. No further data collection will occur from the date the decision is made to permanently discontinue the subject from the study. Participants who experience distress during the study while in the 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 new safety information reporting criteria will be immediately reported to the UNC-CH IRB and the respective sites' IRBs if applicable. The *Study Stop and Adverse Event Forms* will be completed at this time.

9.0 MONITORING UNTOWARD EFFECTS ASSOCIATED WITH OR RESULTING FROM STUDY

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

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

First, the study will catalogue any untoward effect related to the participant. Reporting is required for occurrences including social harms, psychological distress, and serious life-threatening events such as suicide attempts. These may be immediately apparent to the study staff, such as the participant's emotional upset state requiring referral for counseling; or they may be delayed and reported later to study staff, such as physical harm to an individual for having participated in the study. Study staff will notify the protocol team of these untoward effects using the iTech query notification system (QNS) accessible through the iTech website (https://itechnetwork.org). Study staff will complete CRFs to further document adverse events and social harms. 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 sessions that personally affect them. Training and guidance will seek to minimize this risk. Nonetheless, an assessment of the cost of conducting this study must include cataloguing these events as well. The 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 Usability Testing Overview

We will conduct usability testing with 8-12 YMSM/YTWSM who have sex with men to assess users' comprehension of the educational content, understanding and use of intervention features, and overall impressions of app functionality.

10.1.2 Field Testing Overview

We will conduct field-testing of P3 and P3+ with 15 YMSM/YTWSM recently initiating PrEP or are PrEP non-adherent. Using an iterative process of feedback and continuing quality improvement, final app refinements and enhancements will be made to ensure full technological functionality prior to the RCT. In addition, DBS, Mitra and hair collection procedures will be assessed for feasibility and acceptability prior to the RCT.

10.1.3 RCT Overview

We will conduct a three-arm RCT to test intervention efficacy, with 240 YMSM/YTWSM initiating PrEP, recently initiated PrEP or are PrEP non-adherent. Study arms will include standard of care, P3 and P3+. The primary outcome measures are PrEP adherence measured by intracellular tenofovir-diphosphate (TFV-DP) or tenofovir alafenamide (TAF) levels and PrEP adherence measured by emtricitabine (FTC-TP) levels. Both will be obtained from whole blood specimen collected at months 3, and 6. Secondarily, we will assess the efficacy of P3/P3+ at improving PrEP adherence by analyzing self-reported PrEP use, namely weekly PrEP use and monthly PrEP use at both 3 and 6months follow-up. Additional secondary outcomes include self-reported retention in PrEP clinical

care, PrEP persistence, sexual risk behaviors, and (self-reported) STI incidence. Secondary outcome measures will be assessed at baseline, 3 and 6 months. We will also conduct a cost comparison between P3 versus P3+. As a secondary analysis, we will provide validation data on the use of hair specimens for the detection of FTC in YMSM and YTWSM at levels of 'any' and 'protective' usage.

10.2 Power Estimates

10.2.1 Usability Power Considerations

Power is not a concern for usability testing as it is performed to collect feedback from a small number of members from the target population about a preliminary version of the intervention.

10.2.2 Field Testing Power Considerations

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

10.2.3 RCT Power Considerations

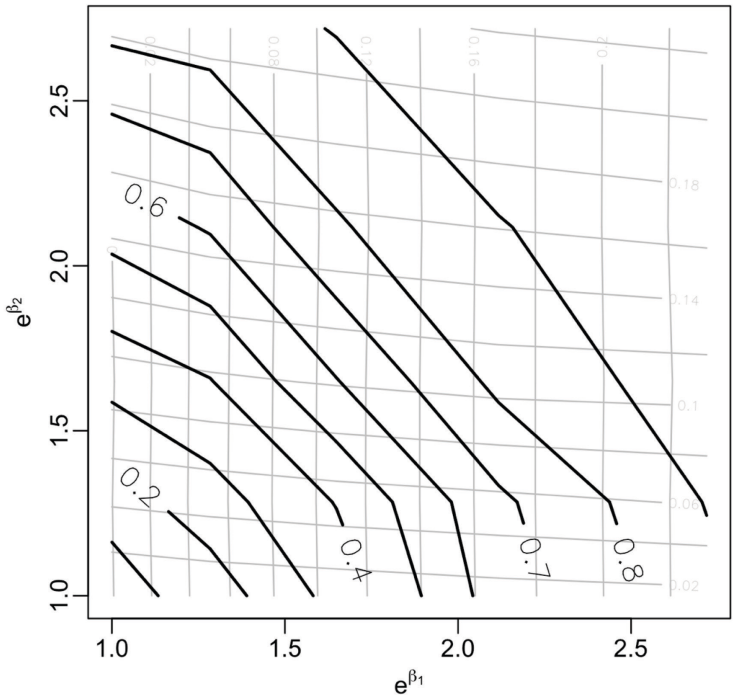
A total of 240 participants will be enrolled at baseline to account for a 20% expected loss to follow-up during the first 3 months of the study leaving an estimated 192 individuals (64 per arm) for analysis. Power was assessed via Monte Carlo simulation. Data were simulated as follows. A single binary baseline variable $W$was drawn from a Bernoulli (1/2) distribution to represent patient-level characteristics included in the analysis. A binary intervention variable A was drawn from a Bernoulli (2/3) distribution to mimic the 1:1:1 treatment allocation. A binary intermediate variable I_1 was drawn from a Bernoulli (3/4) distribution to mimic participant app utilization. A censoring variable $C_1$for the month three visit was drawn from a Bernoulli (1/20) distribution, with the value 1 indicating a participant was lost-to-follow-up before the three-month visit. For uncensored participants, PrEP adherence at month three Y_1 was drawn from a Bernoulli distribution with adherence probability equal to$logit^{-1}(-1 + \beta_1 A)$. Thus, approximately 27% of participants in the SOC arm were assumed to be adherent at the three-month visit. Note that the parameter β_1 describes the log-odds-ratio of adherence comparing treatment to SOC. Next, we drew L_2 from a Bernoulli (3/4) distribution to mimic participant app utilization after the three month visit, and drew C_2 from a Bernoulli (1/20) distribution, where again a value of 1 indicated a participant was lost-to-follow-up between the three- and six-month visit. For uncensored participants, PrEP adherence at month six Y_2 was drawn from a Bernoulli distribution with adherence probability equal to$logit^{-1}(-1.5 + \beta_2 A + 1.5\, Y_1)$. Thus, approximately 18% of participants in the SOC arm who were not adherent at month three, were adherent at month six, while 50% of participants in the SOC arm who were adherent at month three were again adherent at month six. Note that the parameter β_2 describes the log-odds-ratio of adherence at month six comparing treatment versus control for participants with the same month three adherence.

We generated 200 simulated data sets of 240 participants from this mechanism and analyzed each data set using longitudinal targeted minimum loss-based estimation (TMLE). This process was repeated across a range of values for(β_1, β_2). Results for our analysis are shown in Figure 1. This figure shows power (thick black lines) as a function of(β_1, β_2). Because the analysis is not conducted on the odds ratio scale, we have also included grid lines (gray) for the corresponding risk differences. The vertical grid lines are labeled with the value of the difference in proportion of adherent participants (P3/P3+ versus control) at month three corresponding to the particular value ofβ_1. The horizontal grid lines are labeled with the value of the difference in proportion of adherent participants at month six. From the figure, we may conclude that the study has >80% power to detect a six-month treatment effect of 20% (difference in percentage adherence) even if there is no three-month effect, or conversely a

three-month treatment effect of 20% even if there is no six-month effect. In the more realistic scenario, where there is a treatment effect at both time points, we have >80% power to detect effects if the three- and six-month treatment effects are >14%.

Though the baseline and interim participant characteristics were not predictive of adherence nor of censoring, we included these characteristics in the requisite regression models for TMLE. Thus, we expect that these power calculations will be conservative for the true power if participant characteristics are informative of adherence.

Figure 1: Power as function of 3-month and 6-month adherence



10.3 Statistical Analysis Plan

10.3.1. Usability Testing Analysis Plan

A usability report will be compiled by Drs. LeGrand and Muessig and reviewed by the full investigator team, the technology partner and the AC. The report will include: a) a list of common problems like navigation problems; and b) recommended design-improvements that will be used in the final iterative stages of app adaptation.

10.3.2 Field Testing Analysis Plan

A field testing report will be compiled by Drs. LeGrand and Hightow-Weidman and reviewed by the investigator team, the technology partner and the AC. The report will include: a) list of app functionality issues, including any issues with the texting portal; b) recommended design-improvements that will be used in the final iterative stages of app adaptation; c) recommended changes to blood and hair collection procedures; 4) any updates to the NSC procedures.

10.3.3 RCT Primary Analysis Plan

Primary Outcome: The primary analyses will assess the efficacy of the P3/P3+ intervention at 3- and 6-month follow-ups. Efficacy is defined in two ways (1) as the difference in the proportion of patients with protective levels of TFV-DP or TAF and (2) as the difference in the proportion of patients

with protective levels of FTC-TP, comparing the intervention arms to SOC. The primary tests of efficacy of the intervention (P3/P3+) will be of the following null hypotheses:

(A1) There is no difference in the proportion of patients with protective levels of TFV-DP/TAF at 3 months.
(A2) There is no difference in the proportion of patients with protective levels of FTC-TP at 3 months.
(B1) There is no difference in the proportion of patients with protective levels of TFV-DP/TAF at 6 months.
(B2) There is no difference in the proportion of patients with protective levels of FTC-TP at 6 months.

All hypotheses will be tested against the two-sided alternative of some difference in proportion. Each test will be conducted at the 0.05 level of significance and we will present corresponding 95% confidence intervals for the treatment effects.

For this analysis, we will use targeted minimum loss-based estimation (TMLE) to estimate the proportion of participants with protective levels of TFV-DP/TAF and protective levels of FTC-TP at each time and in each intervention group. TMLE is a methodology for constructing efficient and robust estimates of treatment effects and utilizes patient characteristics to account for bias due to informative participant dropout. If patient characteristics predict adherence, TMLE may also lead to greater power of tests about estimated treatment effects. Patient characteristics that will be considered in the estimation include demographic characteristics, social support, app usage and engagement, app acceptability, substance use, anxiety, and depression. We will use influence function-based variance estimators for the three- and six-month treatment effects to conduct Wald-style tests of the null hypotheses and to construct 95% confidence intervals.

10.3.4 RCT Secondary and Cost Analysis Plan

Secondary Outcomes**:** We will conduct an analysis parallel to the primary analysis exactly as above, but with the two P3 intervention arms separated (i.e., P3 vs. SOC, P3+ vs. SOC). We will also assess intervention efficacy at improving PrEP adherence by analyzing self-reported PrEP use, namely weekly PrEP use and monthly PrEP use at both 3- and 6- months follow-up. Lastly, for the secondary objective we will consider the effect of P3/P3+ on a panel of self-reported outcomes including: retention in PrEP care, PrEP persistence, sexual risk, and incident STIs. For binary outcomes, we define intervention efficacy as a difference in proportions, while for continuous outcomes, we define efficacy as a difference in means.

Compliance analyses: In addition to the ITT analyses above, we will examine methods that include covariates that quantify the degree of app usage, such as estimating the complier average causal effect of the interventions.

Table 1: Outcomes and Measures	
Primary Study Outcomes: To improve PrEP adherence	
PrEP adherence	**Whole blood specimen to assess blood plasma and intracellular concentration of TFV-DP or TAF and FTC-TP**. We will also assess self-reported PrEP adherence (number of days of last 7 PrEP was taken; % of days PrEP taken in the last month). PrEP adherence ≥57% (4 out of 7 doses/week) will be considered "high" adherence, Whereas <57% will be considered "low" adherence for the purposes of analyses.
Secondary Study Outcomes: To increase retention in PrEP clinical care, PrEP persistence, and Information, and reduce sexual risk behaviors and STI incidence	
Self-Reported Retention in PrEP Clinical Care	Self-reported adherence to PrEP medical care visits in the previous 3 months.
PrEP Persistence	Duration of PrEP use before an individual discontinues either temporarily or permanently. This will be collected via self-report at follow-up.

Sexual Risk Behaviors	Sexual Practices Assessment Schedule will be adapted to explore the number of occasions of different sexual acts (anal: receptive, insertive). with three different types of partners (romantic interest, casual partner "hookup", or transactional)..[45]
STI Incidence	Self-reported STIs (e.g., rectal and urethral gonorrhea and chlamydia, syphilis) in last 3 months
Potential Confounders and Effect Modifiers	
PrEP Self-Efficacy	We will assess PrEP adherence self-efficacy using an adapted version of The HIV Medication Taking Self-efficacy Scale.[46]
PrEP Stigma	We will assess anticipated, experienced, internalized, and perceived stigma for PrEP
HIV Risk Perception	We will assess HIV risk perception using a modified version of the Perceived Risk of HIV Scale
App Usage and Engagement	Usage and engagement data (e.g. Number of logins, time spent on the app overall, frequency and duration of use of major app components) will be collected through the app.
App Acceptability	The System Usability Scale (SUS) provides a global measure of system satisfaction and sub-scales of usability and learnability.[47]
ASSIST	An 8-item questionnaire developed in 1997 by the World Health Organization and addiction researchers. The ASSIST screens for all levels of problem or risky substance use.[48]
AUDIT-C	The AUDIT-C (a 3-item alcohol abuse scale) will be used assess problematic alcohol use. A score of 4 or more on the AUDIT is positive for hazardous drinking for men.[49,50]
GAD-7	The GAD-7 is a reliable and valid 7-item questionnaire that identifies probable cases of General Anxiety Disorder[51].
PHQ-8	The PHQ-8 is a reliable and valid 8-item questionnaire that identifies probably cases of depression[52].
PROMIS Social Support and Isolation	The PROMIS social support measures will be used to assess perceived companionship, emotional support, informational support, and instrumental support. The social isolation measure will be used to measure social isolation.[53,54]
Demographics	Items will assess demographic characteristics such as age, education, employment, arrests/incarceration, health Insurance, relationship status, housing stability, technology use.

Hair specimen TFV validation analysis: a secondary analysis, we will provide validation data on the use of hair specimens for the detection of FTC in participants at levels of 'any' and 'protective' usage. FTC response will be measured along the hair strand length, which corresponds to weeks to months of growth, and adherence classification will be assessed in a segment that is contemporaneous to collection of the blood specimen (likely the proximal 0.5cm of a hair strand). A cross-tabulated comparison between categorical assessment of adherence by dried blood spot and hair will be conducted. We will also estimate the effect of log (adherence) on log (hair level) in repeated measures linear regression models. A continuous measure of adherence will also be determined from the hair analysis over the same time period, and we will examine scatterplots and calculate Spearman correlation coefficients for the continuous adherence measure.

To augment the primary quantitative analyses, we will evaluate participants' app usage and engagement by measuring app usage (e.g. numbers of times per week participants access app, completion of daily quests, and average daily use of app), number and content of social wall posts, amount of virtual currency collected and narratives unlocked. The research team will have access to these data as they are transferred from mobile phones to the secure server, which will occur any time the participant is connected to the internet via broadband or Wi-Fi. For P3+ we will collect data on number of sessions, and content of sessions.[55]

Through our prior eHealth interventions (healthMpowerment, Epic Allies), we developed a data capture system that allows us to categorize and sort posts by user sociodemographic characteristics and intervention usage patterns. We will then use content analysis to create a categorization of user types and P3 activities, and develop a cross cutting categorization of types of posts (e.g. asking for help, sharing goals, providing encouragement). We will work with the iTech AC to 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. We will use Dedoose software to assist with theme identification, coding textual data, and describing relationships among codes (via code co-occurrence and memoing functions).[56] Coding and analytic activities will be discussed during weekly team meetings. Our study team has successfully used all of these methods in past projects with HIV+ YMSM.[20,57,58]

Cost-comparison between the two intervention study arms: Incremental cost effectiveness ratio (ICER) between the two intervention arms will be defined as ΔC/ ΔE, where ΔC denotes the estimated difference in mean costs of the intervention and ΔE reflects the estimated difference in mean effectiveness between the interventions. ICER will be calculated for outcomes in which the intervention is non-dominated. Cost was measured at the site level. We will calculate ΔC using the mean of costs for each intervention arm. Similarly, we will calculate ΔE using the mean of efficacy measurements for each intervention arm. We will also analyze individual level counseling costs with TMLE if there is substantial variation in time spent on counseling between participants.

10.4 Missing Data

Several procedures will be used to conduct data analysis when data for either outcomes or covariates are missing. The first step will be to assess the extent and pattern of missing data. If data are missing for only a few cases, then data analysis will be conducted only on study participants with complete data. However, when such a strategy would result in loss of data from a substantial proportion of participants, or if this approach would lead to biased or inaccurate results, then some form of imputation will be performed. The form of imputation used will depend on the nature of the data that are missing. For example, data that are collected repeatedly might be imputed using the “last value carried forward” method; and in some instances, mean/mode imputation or interpolation between neighboring points might also be used.

If there is missingness in a study outcome measure that will be analyzed via TMLE, imputation is not necessary. However, for high levels of missingness in the primary outcome measures (FTC-TP and TFV-DP), we will use self-report data at the follow-up time point of interest to inform our TMLE estimates. This will be done by altering the TMLE estimand to include self-reported monthly PrEP use and self-reported weekly PrEP use. When the primary endpoint is missing for other analyses, we will consider conducting the analysis using only cases with the endpoint or imputing the endpoint. Hot-deck imputation or regression imputation may also be used in this context.

11.0 HUMAN SUBJECTS

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

11.1 Participants’ Confidentiality

All laboratory specimens, questionnaires, evaluation forms, reports, transcripts, and other records will be identified by SID and participant code only, to maintain participant confidentiality. All paper records with personally-identifying information will be kept in a locked file cabinet in a limited secure access

area at each SRV site. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the 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 Internet-based studies, and we will take a variety of steps to ensure participant security, including using a dedicated server behind a firewall, encryption of data, separation of identifiers from responses, and password-protected access to data. Therefore, we believe that this risk will be minimal. All of the apps and websites included in the iTech have features to ensure app security and privacy.

For the P3/P3+ arms, participants will create a unique username that does not contain any identifying information but will be their username on the P3/P3+ apps. Intervention participants will choose an anonymous avatar (animal head) to represent themselves on the site and are told at the enrollment visit and in multiple places on the app that it is a violation of community guidelines to reveal identifying information including name, address, phone number, email address, social media handles, places of employment, or locations to meet for personal or business use. Participants will not be able to privately communicate with each other on the app - all conversations are viewable on the main feed. Trained research staff at the University of North Carolina will monitor the website daily to ensure violations to privacy, even through self-disclosure, are addressed. The P3 app is also password-protected.

11.2 Certificate of Confidentiality

This research specifically targets a vulnerable population, children – YMSM/YTWSM ages 15-17. We will take every available step to minimize the risk of identifying/linking data being subpoenaed, stolen, or inadvertently released. First, the iTech has secured a Certificate of Confidentiality from the NIH. Second, all research staff members are required to complete ethical clearance certification regarding protection of human subjects through their relevant IRBs. Third, all studies will have documented procedures to safeguard against the risk of the linking information being stolen by keeping such information in locked spaces to which only essential study personnel who have completed CITI certification for human subjects research ethics training (http://citiprogram.org) will have access.

Per Section 2012 of the 21st Century Cures Act as implemented in the 2017 NIH Certificates of Confidentiality Policy, all ongoing or new research funded by NIH as of December 13, 2016 that is collecting or using identifiable, sensitive information is automatically issued a CoC. As noted on the NIH website (http://grants.nih.gov/grants/policy/COC/faqs.htm#187), a Certificate of Confidentiality will help the research team "...avoid compelled 'involuntary disclosure' (e.g., subpoenas) of names and other identifying information about any individual who participates as a research subject (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect."

11.3 Risks and Benefits

11.3.1 Risks

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

To minimize risks to confidentiality, we will secure study data with all appropriate physical, electronic and operational protections. Data will be stored in a physically secure environment. All data files will have encryption and strong password protection. Any identifiable data will either be stored on Emory University's secure servers or will be on fully encrypted laptops. CASI assessments 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 MSM 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 an HIV- related research study, or a study that enrolls MSM/TWSM. 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 Emory 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 Analytic Core 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. 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 in A.3):

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

   All data collection will take place in secure and supervised clinical settings. All study personnel names on this protocol have completed training and received certification in Human Subjects

Research Protection (CITI Program) and HIPAA regulations. They will continue to renew this training in compliance with institutional policies. Participants will be asked to provide informed written consent to audio recording (usability testing, field testing) and medical chart abstraction and collection of whole blood and hair samples (RCT) at the time of study entry. To assure confidentiality and protection of the participants during audio recording, all files and transcripts will be stored on a password protected, encrypted computer in a locked file cabinet in a secured office. To additionally preserve confidentiality, we will only use participants' aliases and names will not be used in data analysis. Informed consent forms, audio files, and transcripts will be kept in locked files and password-protected databases in a locked office accessible only to investigators. Audio files will be destroyed within one year of study completion.

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

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

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

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

11.3.2 Benefits

The risk to individual participants is small and the potential benefit to both the individual and society is substantial. The main benefit of the proposed study to society is the development of a potentially feasible and acceptable mobile app that improves PrEP adherence, retention in PrEP clinical care, and PrEP persistence among YMSM/YTWSM that can be scaled up for use in a variety of clinical and community settings. Participants may experience improvements in their own PrEP adherence, retention in PrEP clinical care, and PrEP persistence thereby potentially reducing their risk for HIV acquisition and risks and costs to society. Therefore, the risk/benefit ratio is favorable. Study participants will be compensated for their time.

YMSM and YTWSM account for nearly two thirds of all new HIV infections in the US and YMSM are the only risk group experiencing a significant increase in HIV incidence. Phases 1 and 2 of the study (usability testing, field testing) will provide important information for intervention development to improve PrEP adherence, retention in PrEP clinical care, and PrEP persistence. If successful, our intervention will improve these outcomes in our subject population. Given this high potential impact and low potential hazards to participants, we find that a clear examination of these research questions outweighs the previously mentioned risks. The effectiveness of a novel, scalable, technology driven, intervention to address PrEP adherence, retention in PrEP clinical care, and PrEP persistence is understudied with this population. Given the significant health sequelae associated with

HIV infections, and the paucity of intervention programs for this population of young adults, the knowledge to be gained from this research is significant. The risks to participants are reasonable in relation to the importance of the knowledge to be gained.

11.4 Institutional Review Board (IRB) Review and Informed Consent

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

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

11.5 Waiver of the Requirement for Parental Permission for Special Circumstances

The site IRBs and the UNC IRB as the central IRB will be requested to grant a waiver of parental permission to participate in this research study for youth participants under (not inclusive of) the age of 18.

Under 45 CFR 46.408 (c), an IRB has the authority to waive parental permission if it determines that "a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects" and "an appropriate mechanism for protecting the children who will participate as research subjects is substituted" and "that the waiver is not inconsistent with Federal, State, or local law."

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

11.6 Waiver of the Requirement for Signed Consent Form

11.6.1 For Eligibility Screening

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

11.7 Prisoner Participation

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. Subjects enrolled who subsequently become incarcerated or are placed in detention may not continue study participation. Study visits cannot be conducted during the period of incarceration or detention.

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

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

11.9 Study Discontinuation

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

12.0 PUBLICATION OF RESEARCH FINDINGS

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

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APPENDICES

1. Schedule of Evaluations for RCT
2. Screeners
    a. Usability
    b. Field Testing
    c. RCT
3. Usability Testing Checklist
4. Usability Testing Script
5. Field Testing Checklist
6. Field Usability Testing Script
7. Field Testing Debriefing Interview Guide
8. RCT Checklist
9. RCT Scripts/onboarding documents
    a. Control Group Script
    b. P^3 Group Script (contains app onboarding instructions)
    c. P^3+ Group Script (contains app onboarding instructions)
10. Whole blood and Hair collection guidelines
11. Sample Recruitment Flyer
    a. Usability
    b. Field Testing
    c. RCT
12. Screenshots from the proposed P^3 Intervention
13. Consent/Assent
    a. Usability
    b. Field Testing
    c. RCT
14. Surveys
    a. Usability testing: demographic/prep awareness and use
    b. Field testing:
        i. Pre- demographic/prep awareness and use
        ii. Post- app satisfaction survey
    c. RCT:
        i. Baseline survey
        ii. 3-month survey
        iii. 6-month survey
15. NSC protocol
16. Control materials
17. Clinical Protocol for User Postings