Theoretically based mobile App to increase PrEP uptake among MSM

Short Title:

HealthMindr

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDA Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS AND ACRONYMS

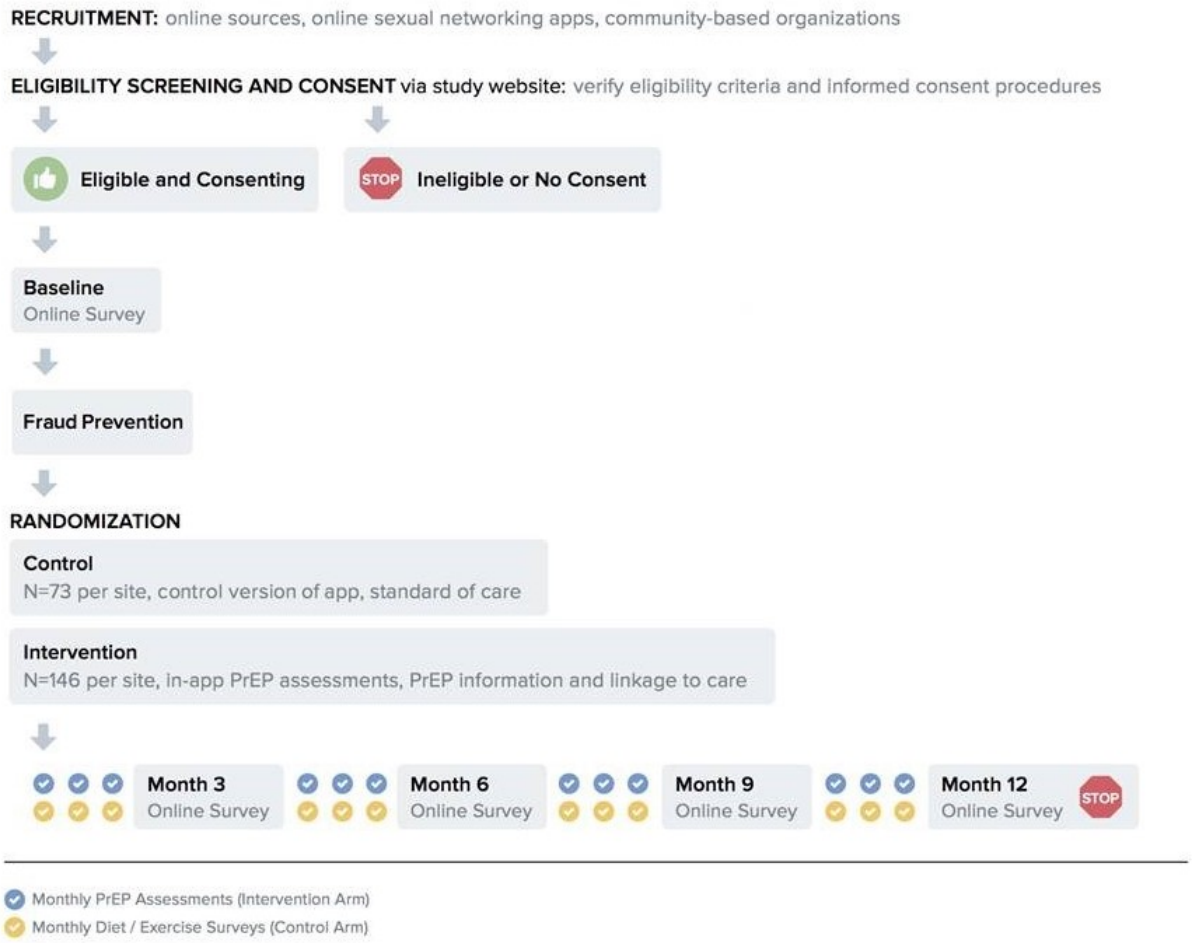
AE	Adverse Event/Adverse Experience
CDC	Centers for Disease Control and Prevention
CFR	US Code of Federal Regulations
CITI	Collaborative Institutional Training Initiative
CLIA	Clinical Laboratory Improvement Amendments
DBS	Dried Blood Spot
DHHS	Department of Health and Human Services
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HSP	Human Subjects Protection
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDI	In-depth Interview
IRB	Institutional Review Board
LGBT	Lesbian, Gay, Bisexual, Transgender
MSA	Metropolitan Statistical Area
MSM	Men who have sex with men
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OSHA	Occupational Safety and Health Administration
PEP	Post-Exposure Prophylaxis
PrEP	Pre-Exposure Prophylaxis
SAE	Serious Adverse Event/Serious Adverse Experience
SAMHSA	Substance Abuse and Mental Health Services Administration
STI	Sexually Transmitted Infection
TFV-DP	Tenofovir diphosphate
USAID	United States Agency for International Development

PROTOCOL SUMMARY

Title:	HealthMindr: Theoretically based mobile app to increase PrEP uptake among MSM
Précis:	The study is based on the premise that providing, through a mobile phone app, self-directed PrEP information; periodic PrEP eligibility screenings to identify risk and eligibility objectively; referral to PrEP providers with directions; and related prevention services will increase the uptake of PrEP among at risk, HIV-negative MSM to a greater extent than standard of care referrals to existing resources.
Objectives:	Aim 1: Test an HIV prevention mobile app versus a standard of care condition with outcome of rate of PrEP uptake among MSM. Aim 2: Quantify the behavioral, social, and clinical factors that mediate and moderate the efficacy of the HealthMindr app on the rate of PrEP uptake. Aim 3: Conduct individual in-depth interviews (IDIs) to assess how the app promoted PrEP uptake, unmet needs of men who did not start PrEP, and how repeated app interactions might further PrEP uptake.
Population:	680 MSM, aged 18-34
Sites:	Atlanta, GA; Jackson, MS; and Washington, DC
Intervention:	HIV prevention mobile app with basic prevention services including HIV test planning and test locators; risk assessment; HIV treatment locators; and condom, HIV test kit, and at-home STI specimen collection kit distribution plus monthly PrEP eligibility assessments, PrEP provider locator, enhanced information about PREP, and referrals to local PrEP navigators.
Study Duration:	60 months
Subject Participation Duration:	12 months
Estimated Time to Complete Enrollment:	18 months

Schematic of Study Design:

Figure 1. Study Schema



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

In the United States (US) HIV epidemic, MSM are disproportionately impacted in terms of HIV prevalence[1-4] and incidence.[5-7] MSM are the only US risk group for whom HIV incidence increased after 2000[6]; increases are especially alarming among young MSM[5] and MSM of color.[8] MSM aged 13-24 and 25-34 are the only MSM age groups among whom new diagnoses increased after 2009.[9] Profound health disparities exist for both MSM relative to other adult men and within the MSM community, with a burden of HIV infection that is a staggering 67 times greater than for other men in the US population.[10] There are estimated to be more than 4,700,000 MSM in the US[10] and as many as 500,000 of these men might be current candidates for pre-exposure prophylaxis (PrEP).[11]

The landscape of HIV prevention for HIV-negative MSM is changing. There is broad agreement that reducing new HIV infections will require a package of HIV prevention strategies. Multiple studies of PrEP[12-14] suggest that PrEP will be an efficacious tool in reducing HIV acquisition risk among MSM. However, other data suggest that we cannot abandon basic prevention services for MSM to focus solely on PrEP: in an agent-based modeling study of HIV incidence in MSM, Brookmeyer et al demonstrated that, even in the setting of PrEP coverage varying up to 50% of eligible men, HIV testing and condom promotion still provided 5-21% marginal benefits in terms of reductions in HIV incidence.[15] Thus, HIV testing, condom uptake, and biomedical prevention strategies must be promoted together, in a way that makes connections between negative HIV tests, screening for PrEP eligibility, and information and referrals for PrEP-interested and PrEP-eligible men. Rather than being presented with prevention alternatives, MSM need to be able to see the synergy between prevention options: to understand the need for HIV testing and to view testing as a stepping stone to their next prevention option. This must be accomplished in the setting of stagnant or shrinking Federal and local resources for HIV prevention.[16]

Models suggest that uptake of multiple prevention tools needs to be high to reduce HIV incidence in MSM, but current uptake is low. Multiple models of HIV incidence in MSM suggest that, to decrease HIV incidence in MSM, we will need to achieve 40-50% coverage of multiple prevention services and interventions (e.g., condom promotion, HIV testing, PrEP, treatment as prevention) in at-risk MSM.[15,17-19] Currently, uptake of even basic prevention services among MSM is low. HIV testing within the past 12 months, as recommended by some health jurisdictions[20] and CDC[21], is reported by 71% of men in 21 NHBS cities[22], and by 58% of respondents in American Men's Internet Survey (AMIS)[23], a national survey which includes more rural men and men from smaller cities. In Atlanta, Jackson and Washington, DC, AMIS data indicate that there are significant deficits in annual HIV testing and PrEP knowledge and uptake. Data from the 2016-2017 AMIS survey indicate substantial unmet need for PrEP: 42%, 35% and 43% of HIV-negative MSM in Atlanta, Jackson and Washington are behaviorally eligible for PrEP, but have never taken it. Accounting for the number of HIV-negative MSM per city,[24] we estimate that the unmet need for PrEP among MSM in these cities totals 62,160 MSM.

Electronic tools provide an opportunity to increase capacity for supporting certain HIV prevention services. A recent summary of electronic tools for HIV prevention in MSM noted that certain types of prevention services are most amenable to provision through new technologies. Services for which eligibility can be determined through an algorithm are good candidates to bring to scale with technologies.[25] For example, behavioral eligibility for PrEP has well-described criteria and eligibility algorithms.[26,27] Furthermore, using technology to administer PrEP eligibility screening would also eventually make services more accessible to rural MSM.[25] The need to make better use of technology to scale up PrEP is a story told in the numbers of

prevention service encounters that would be needed to bring a comprehensive package of HIV prevention tools to scale in MSM in the US. Based on CDC estimates, there are approximately 4.7 million US MSM, of whom about 4.1 million are HIV-negative.[10] Of those, approximately 500,000 are estimated by CDC to be eligible for PrEP.[28] However, men's indications for PrEP change over time[29,30], so to determine which of those 4.1 million MSM might be PrEP eligible will require periodic screening against PrEP eligibility criteria. Assuming 6-monthly PrEP eligibility screenings for HIV-negative MSM, approximately 8 million PrEP eligibility screenings would be needed annually to identify PrEP-eligible MSM. To reduce healthcare system burden, this process must be assisted by technologies that let men conduct periodic self-screenings and opt into clinical screening when indicated.

Electronically delivered or supported prevention services are effective, are acceptable to MSM, and will likely reach heavily impacted men. Across prevention disciplines, there is a substantial body of research indicating that electronically delivered prevention services are as effective as traditionally-delivered services. A meta-analysis indicated that computer-delivered HIV prevention interventions had similar efficacy to human-delivered interventions.[31] In a randomized trial, the addition of a mobile application to a standard weight loss program was found to significantly increase weight loss.[32] A systematic review documented that mobile phone and text message-based interventions to support adherence increased client satisfaction and improved biological markers of diabetes control (A1c).[33] Despite this evidence that apps can be efficacious for prevention, a 2015 inventory of all HIV-related Apple and Android apps found that less than 7% focused on MSM and none provided PrEP information[34]; a second, independent review found that <4% of HIV-related apps were tailored for MSM, and only 6 apps covered multiple key areas of HIV prevention (but not PrEP).[35]

Further, using technologies to support HIV prevention is acceptable to MSM. Before the proliferation of Smartphone apps, we asked a large geographically diverse sample of MSM about their willingness to use mobile phones as part of an HIV prevention study. About half of men were willing to use their mobile phones for HIV prevention; younger MSM and MSM of color were more likely to be willing.[36] In another study, gay and lesbian youth were much more likely than their heterosexual peers to engage in sexual health information provided using their mobile phones.[37] Smartphones are widely accessible to MSM who are most at risk: among Americans, smartphone ownership in 2015 was 85% among those 18-24 (higher than among older Americans), and was 70% among African Americans (higher than among white Americans).[38]

In 2015, we published a conceptual framework for promoting PrEP uptake among MSM taking a continuum perspective.[39] The framework is intended to facilitate categorization of interventions and conceptualization of systems-based approaches to enhance PrEP uptake and articulates several domains on the pathway to PrEP uptake: Awareness and Willingness; Access to Healthcare; Likelihood of receiving a prescription; and Adherence and Efficacy.[39] Some elements, like awareness, are necessary but not sufficient alone to lead to PrEP initiation. Further, other basic prevention services, like HIV testing, are necessary elements of PrEP uptake, both because PrEP is a serostatus-dependent intervention, and because post-test counseling sessions for HIV-negative MSM should include discussion of PrEP.[40] Access to healthcare is critical to support costs of PrEP and monitoring tests.[40] Our proposal addresses these domains through the materials and components of the HealthMindr mobile app.

2.2 Rationale

The premise is that providing, through a mobile phone app, self-directed PrEP information; periodic PrEP eligibility screenings to identify risk and eligibility objectively; referral to PrEP providers with directions; and related prevention services will increase the uptake of PrEP among at risk, HIV-negative MSM to a greater extent than standard of care referrals to existing resources.

3 OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objective

Compare the uptake of PrEP among men provided the HealthMindr app to men provided standard of care among MSM the Southern United States.

3.1.2 Secondary

Quantify the behavioral, social, and clinical factors that mediate and moderate the efficacy of the HealthMindr app on the rate of PrEP uptake.

Conduct in-depth interviews to assess how the app promoted PrEP uptake, unmet needs of men who did not start PrEP, and how repeated app interactions might further PrEP uptake.

3.2 Study Outcome Measures

3.2.1 Primary

The rate of PrEP uptake will be assessed during follow-up by self-report at months 3, 6, 9, and 12. Self-report will be confirmed by laboratory testing for the presence of tenofovir diphosphate (TFV-DP) and/or photograph of PrEP prescription or bottle.

3.2.2 Secondary

Mediation Analysis: This analysis will examine how study arm assignment may lead to intermediate effects, such as greater access to HIV testing or decreased risk behavior, which themselves are associated with the primary effect of PrEP initiation. Using the difference method for a set of Cox proportional hazards models, log coefficients for the indirect effects will be subtracted from log coefficients for the direct effect to estimate the size of the mediation.[41] Mediators will be selected on the variables known to be associated with the 4 domains of the PrEP continuum (including awareness, access, and engagement with HIV prevention services), and changes in risk behaviors resulting from app utilization.

Moderation Analysis: This analysis will examine how attitudes and beliefs about PrEP, as well as individual, social, and community characteristics can moderate the effect of the app on PrEP initiation. Examples of moderators include perceived benefits of PrEP use, self-assessed vulnerability to HIV, perceived advantages to meeting partners if currently taking PrEP, and social support for PrEP use within one's social network.

Demographic factors including age, race/ethnicity, and geographic setting will also be critical moderators. Although the distribution of these factors will be balanced across study arm with randomization, they may have effects on the level of engagement in the app (i.e., post-randomization treatment adherence) that itself will influence the rate of PrEP initiation. Given this causal model, we will use instrumental variable analyses to estimate the effect of optimal app use on PrEP initiation given measured and unmeasured moderators.[42]

In-depth Interviews (IDI): IDIs will assess the extent to which app components facilitated or inhibited PrEP uptake. Central to the IDI will be understanding the participants' use of the app. The IDI will begin by asking the participant to walk the interviewer through a "typical use session" of the app, during which the interviewer will probe around key decisions (e.g. why one function was used over other functions). The interview will examine the participant's views on the positive and negative elements of the app. The interview will focus on the use of PrEP components: participants will be asked to walk through the PrEP knowledge, screening and locating functions with the interviewer and describe why they did or did not use them. Participants who started PrEP will be asked to describe the role that the app played in their decision and which app components were most integral to their decision. They will be asked to demonstrate which components of the app were useful in adopting PrEP, and areas of the app where further support might be useful. Participants who did not start PrEP will be asked if there are additional components (e.g., better linkage to providers, other information) that could be added to the app that might lead them to change their mind about starting PrEP. Participants who did not adopt PrEP will be asked to demonstrate how they used the app and which components of the app were not used. These data will provide insight into how the app is used in PrEP decision making, and identify areas of opportunity to promote PrEP adoption for future app versions.

4 STUDY DESIGN

We will conduct a randomized controlled trial (RCT) with two arms. Participants in the intervention arm will receive access to the HealthMindr app with basic prevention services (HIV test planning and test locators; risk assessment; HIV treatment locators; and condom, HIV test kit, and at-home STI specimen collection kit distribution) plus monthly PrEP eligibility assessments, PrEP provider locator, enhanced information about PrEP, and referrals to local PrEP navigators. The app also provides links to health insurance exchanges, where men can seek health insurance (all cities) or payment assistance programs. The control arm will be standard of care (receive baseline survey, followed by referral to existing online PrEP and HIV prevention information; with a mobile-phone administered attention control survey about diet and exercise (and PrEP initiation) of the same length as the monthly PrEP assessment given to the intervention arm, to maintain the same monthly frequency of contact with control participants. Control arm participants will not have access to the active app.

Study participants are followed for 12 months with outcome measurements occurring in both arms at 3-month intervals and monthly brief surveys to assess PrEP uptake and reassess PrEP eligibility (intervention arm) or assess diet and exercise (control arm). Surveys will be distributed to all participants through the mobile app at baseline and quarterly. Participants will specify their preference for communication media in the baseline survey. Quarterly surveys will last approximately 30 minutes; to limit survey duration, some non-labile survey elements will not be assessed at each time point. Quarterly surveys are identical for men in both arms, except the final survey includes questions on acceptability only for men who used the app. Surveys are smartphone-optimized so that they may be completed on participants' phones. The survey

measures represent a comprehensive set of previously validated measures that will characterize the population, allow for assessment of adequacy of randomization, document important outcomes, and allow for exploration of possible moderating factors. A summary of measures is included in Figure 2.

Figure 2. Measures to be assessed in participant surveys.

Outcomes	**Community & Network Characteristics**
PrEP Awareness/Use/Efficacy •Participant has heard of PrEP •Current/past use of PrEP •Perceptions about partner PrEP current/past use •Attitudes about safety and utility of PrEP •Perceptions of side effects and toxicity •Perceptions of antiretroviral drug resistance	Health Care Environment •Payer source: insurance coverage, out-of-pocket •Delivery source: private provider, demonstration project, black market •Decision-Making Opportunity Scale: between patient and provider •Personal knowledge by provider, e.g., knows patient as a person •Local availability of PrEP (PrEPLocator.org) •Comfort in disclosing behaviors to provider
Perceived Benefits of PrEP Use* •Perceptions of increased sexual intimacy, pleasure	
Individual-Level Characteristics	
Demographic and Personal Characteristics •Race/ethnicity, age, education, marital/partnership status •Socioeconomic status; income, employment status •Sexual identity	Social Environment •Enacted experience of stigma and discrimination •Internalized homo-negativity •Anticipated stigma around sexuality
Vulnerability to HIV •Recent sexual behavior with main and other partners •Substance use: recent use, use during or before sex •Depression – CES-D •Recent incarceration •Perceived severity and risk of HIV infection	Media •Formal: information about sexual health, HIV prevention and PrEP from television, newspapers, radio, online media, medical journals •Social: usage, frequency, purpose (e.g., for information, to communicate) •Websites: sites that host discussions on sex and HIV Prevention
Knowledge of HIV Prevention •HIV risks: types of sexual acts, virological factors, STI co-Infection •Behavioral methods: sero-adaptation, sexual negotiation •Knowledge of emerging HIV prevention technologies	Perceptions of Local HIV Prevalence •Perceived prevalence among sex partners, friends, MSM in city of residence
Healthcare Attitudes and Values •Adherence self-efficacy: confident in ability to adhere to PrEP •PrEP stigma: e.g., perceived as promiscuous, “Truvada whore”	Social Network Composition •Proportion of social network: MSM/LGBT, using PrEP, perceived supportive of PrEP, discussed PrEP

4.1 Study Population

The study population will be men who have sex with men age 18-34 years (inclusive) who reside in one of the study MSAs - Atlanta, Georgia, Jackson, Mississippi, or Washington, DC. Additional recruitment locations may be added to meet recruitment targets, including Houston, Texas, Dallas, Texas, New Orleans, Louisiana, Nashville, TN or Miami, Florida. The total sample size will be 680, with a goal of at least 50% racial / ethnic minority participants. Full inclusion and exclusion criteria are specified below.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Eligibility Criteria

Men will be eligible to participate in the study if they: (1) are cis-gender male (male at birth and currently identify as male gender) ; (2) are 18-34 years of age (inclusive); (3) report residing in one of the study MSAs with intent to remain for the duration of the trial; (4) have an Android or iOS phone with active service and are willing to download study app; (5) are an English speaker; (6) report having anal sex with a man in the past 6 months; and (7) report being HIV-negative, or never having been tested for HIV. Men who report currently being on PrEP will be ineligible, but prior PrEP use will not be exclusionary.

5.1.1 Inclusion Criteria

- Cis-gender male
- 18-34 years of age (inclusive)
- Resides in one of the study MSAs
- Intends to remain in study area for duration of the trial
- Owns an Android or iOS smartphone and willing to download study app
- Able to read and understand English without assistance
- Reports having anal sex with a man in the past 6 months
- Reports being HIV negative or never tested for HIV

5.1.2 Exclusion Criteria

- Cisgender female, transgender male, transgender female, gender non-conforming
- Currently on PrEP
- < 18 or >34 years of age
- Reports being HIV positive
- Resides outside of the MSAs or plans to move outside study MSA within 12 months
- Current participant in an HIV prevention study
- Unable to download study app

5.2 Strategies for Recruitment and Retention

5.2.1 Recruitment

Recruitment strategies will aim to recruit MSM who are diverse in terms of race/ethnicity and to minimize recruitment biases and maintain comparability across sites. Black and Hispanic MSM will be oversampled with a goal of enrolling at least 50% of the study population in these disparately impacted groups.

Online recruiting: The primary method of recruitment will include online recruitment activities. Although online venues are constantly evolving, in the past, major categories of

recruitment have included social network sites (e.g., Facebook, Instagram, Twitter); online sexual networking apps (e.g., Grindr, Scruff); and banner advertisements on other websites frequented by MSM (e.g., Queerty, Towleroad, Adam for Adam). Examples of the online recruitment types and procedures for each type follow. We will target men at least 18 years old who live in or work near the Atlanta, GA, Jackson, MS, or Washington, D.C. MSA. Additional MSAs may be added if needed to meet recruitment targets, including New Orleans, LA; Houston, TX; Miami, FL; Dallas, TX; Nashville, TN; Austin, TX; Tampa, FL; Orlando, FL; Birmingham, AL; Memphis, TN; Louisville, KY; Baltimore, MD; Detroit, MI; Charlotte, NC; Raleigh, NC; and Columbus, OH.. When men click on a banner advertisement, they will be taken to a page containing basic study information that includes a short description of study activities. If they click on a button to advance, they will be taken to the study screening consent form, and if they consent they will be directed to a short eligibility screener to determine whether they meet the eligibility criteria.

Facebook: Targeted online recruitment will be conducted via Facebook. This involves targeting advertisements to all adults in the three study cities based on several factors, including interests expressed in profiles and through expressed "likes" of other posts or pages with gay themes. Those who click on the Facebook ads will be referred to a brief introduction script and a self-administered online screening form with questions identical to those to be administered in venues.

Grindr: Recruitment through Grindr uses banner advertisements and targeted email blasts that target MSM in the three cities. Those who click on the banner ad or who receive an email will be directed to the brief online consent and screener to determine eligibility.

Offline recruiting: Participants may be recruited through posting flyers and promoting the study through community partners (e.g., community-based organizations, drop-in centers). Those recruited through these flyers will be directed to an online web location for eligibility screening.

The data collected from screening will be stored in the secure, HIPAA-compliant servers of SurveyGizmo.

5.2.2 Retention

The study retention plan will incorporate multiple interventions to achieve a retention rate greater than 70%. Contact information will be collected from each participant, including email and mobile phone number verification. The study will allow participants to schedule their preference for when (e.g., afternoon, evening) they would like to receive prompts to complete electronic follow-up surveys. Participants are more likely to complete surveys if they are alerted about them at a time they can complete the survey. At enrollment, study staff will ask permission for several means of contacting participants and ask for updated information on each follow-up survey. Retention contacts will be customized based on participants' contact preferences (email, text, call, US mail) and organized on a database platform called Study Management and Retention Tool (SMART), a secure system accessible only to designated study staff. Participants will be asked about any changes in their contact information or plans to move during each follow-up survey, conducted at 3-month intervals.

Follow-up methods include sending electronic notification reminders to the participant up to 3 times if a survey remains uncompleted. If after the 3rd notification, the assessment has

still not been completed, then the retention activities will escalate to a staff member. Depending on the participant's preferences provided upon registration, contacts will be made initially with the preferred mode of re-contact (for example, SMS); if still unresponsive, other available modes (e.g., phone call, private social media messages) will be used. Each contact is logged in an electronic retention system developed by Emory. The system maintains electronic lists of each participant's retention status and automatically creates notification lists for retention staff to ensure that a systematic process is followed and documented for retention.

If contact with participants is lost (missed surveys or appointments and non-responsive to contact requests), we will have obtained consent to use public-use databases (e.g., Lexis-Nexis) to locate participants. Study staff will check for entry into a jail or prison in the jurisdiction from which the participant was recruited (i.e., Atlanta, GA, Jackson, MS, or Washington, D. C.). For participants who cannot be contacted, after IRB approval staff will attempt to link the identities of participants to registries of known decedents using a statewide dataset (vital records) and a nationwide dataset (National Death Index).

5.2.3 Participant Compensation

Compensation for survey completion will be graduated ($50 baseline, $40 months 3 and 6, $50 month 9, $60 month 12). Study incentives for the baseline will be sent 48-72 hours after completion of the baseline survey to allow for review of data and identification of possible fraudulent or duplicate enrollments. Incentives for IDIs and quarterly follow-up surveys will be processed electronically at the time of interview or survey completion (see Fraud Deterrence). Men in both arms will be asked monthly if they have initiated PrEP; men who report initiating PrEP in either arm will be mailed a dried blood spot collection kit with instructions and a prepaid return mailing envelope, and will be directed to collect and mail a dried blood spot specimen for tenofovir diphosphate detection. Those who return a DBS specimen will be provided with an additional compensation of $40. Participants will also be asked to take a picture of their prescription or PrEP label; those who provide a photograph will be provided with an additional compensation of $15. A maximum compensation of $295 could be provided for completing all of the study visits ($240), DBS specimen ($40), and PrEP prescription photo verification ($15).

5.3.4 Fraud deterrence and detection

Fraudulent responses in research are of concern in all settings, and there are particular vulnerabilities in online research. In order to avert fraudulent registrations details of eligibility criteria will not be reported before screening, IP addresses will be tracked to block duplicate screening attempts, and Captcha will be used to avoid bots. Payment of initial baseline incentives will be delayed for 48-72 hours to allow us to perform automated scans for duplicate IP addresses, names, duplicate email addresses, or phone numbers. In these cases, study staff will attempt to resolve concerns by contacting participants and clarifying how the situation arose. If duplicate registrations are detected, records will be inactivated and deemed to be invalid.

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

After providing informed consent, downloading the study application, and passing the fraud check, participants will be randomized to study arms in a 2:1 ratio of intervention to control arms (rationale: to allow sufficient data on app users to allow for analysis of efficacy by level of app usage), stratified by MSA to ensure balance of the study arms across the three study sites.[43] Within each city stratum, a computer program will randomly assign each participant to the next treatment allocation from a random-permuted block randomized sequence. Once participants are randomized, they will be kept in and analyzed according to their original assignment (i.e., intent-to-treat). Participants who are not verified as legitimate or are unable to download the app will not be randomized into the study.

5.4 Subject Withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. The study investigators also may withdraw participants from the study in order to protect participant or staff safety. Study staff will record the reasons for all withdrawals or holds from the study on a Study Stop Form in the participants' study records.

Participants who seroconvert will be asked to participate in in-depth interviews (IDI). All of the participants will be followed per standard protocol for linkage to care. Participant will then be withdrawn from study activities.

6 STUDY INTERVENTION

6.1 Study Product Description

HealthMindr is a mobile app with HIV prevention information and links to services developed specifically for MSM. A summary of the key features of the app is provided below.

Functions included in the HealthMindr app:

- HIV testing: learn more about testing options; make a plan to test 2-4 times in the coming year; locate possible places for those tests; and schedule reminders (goal setting).
- Behavioral risk assessment: short behavioral risk assessment (e.g., HIV risk behaviors: sex while drunk or high, condomless anal intercourse with a positive or unknown HIV status partner, total number of sex partners, recent STI diagnosis, use of methamphetamine or poppers) and protective behaviors (HIV testing, STI testing, consistent condom use; feedback/self-regulation).
- Non-occupational post-exposure prophylaxis (nPEP): information about nPEP; nPEP self-assessment[27]; nPEP locator[44]; referral to PrEP for men who evaluate multiple exposures for nPEP indication (goal setting and outcome expectation). [45]
- Product ordering: Via the app, users can order condoms, condom-compatible lubricant, and at-home STI specimen collection kits (urethral and rectal gonorrhea and chlamydia, syphilis) and at-home HIV test kits (OraQuick; goal setting). Orders are filled automatically through Amazon fulfillment services.
- Pre-exposure prophylaxis: PrEP self-assessment at first app use; monthly rescreening for PrEP eligibility; recommendation for PrEP based on CDC criteria; PrEP provider

locator; transport or driving directions to providers, and PrEP FAQ. The PrEP self-screener assesses certain key elements of behavioral eligibility (potential indicators of "ongoing, high risk for HIV acquisition"), and recommends potentially eligible MSM visit a PrEP provider for further clinical assessment, with help locating nearby providers and transport directions (self-efficacy, goal setting and outcome expectations).

- Substance Use Directory: a list of local resources available for treatment, rehab, and counselling options will be accessible through the app.

6.1.1 Acquisition

After completing the eligibility screener and informed consent (Appendix B), participants will be directed to a link to authenticate their smartphone and download the HealthMindr App from either Google Play or Apple App Store. All participants will view the same app shell and complete the baseline survey in the app. However, once randomized, the app for those marked as intervention will open up to show all HealthMindr app capabilities. The app information will cover the importance of testing, links to HIV prevention resources, resources to locate HIV testing and PrEP services, the SAMHSA substance abuse treatment resource locator, and other prevention information specific to their area. The app for the control arm will allow study staff to interact with them via the SMART system. The control-arm app will display a study event timeline but none of the HIV prevention information contained in HealthMindr app.

The HealthMindr application will prompt the intervention participants to complete a brief PrEP assessment (monthly). Any notifications directed to a phone's lock screen or to a participant's SMS/text message account can be partially viewed by unauthorized users of the phone and will be generic text (e.g., "You have a message waiting for you."). To ensure that app notifications protect the privacy and discretion of participants, all app and text notifications will be stated generally, with no reference to the content of the message, the nature of the message, the content of the app in general, the name of the study, or any reference to HIV, STI or MSM. The lock screen banner notification will indicate only that the notification is for the HealthMindr app. SMS/text message notifications will similarly alert participants that a new message is available in HealthMindr. Absolutely no content referring to sensitive topics will be exposed without directly entering the app. The same notification format will be used for both intervention and control groups.

Every three months, participants will be asked to complete a follow-up survey similar to the initial baseline survey. The follow-up survey will include questions on demographic characteristics, HIV and STI testing history and status, and condom use, PrEP use and adherence, knowledge, perceptions, beliefs, intents, communication with sex partners, substance use, mobile phone and data usage, access to internet and information, as well as psychosocial cofactors. If the participant has any questions regarding study activities, they will be connected with study staff. Study staff will handle any research related questions or issues with the participant.

7 STUDY SCHEDULE

7.1 Screening

After a potential participant is determined to be eligible and agrees to participate, they will be asked to provide their contact information including name, primary phone number and primary email address. The phone number and email address will be used as a measure against

participant fraud. If a participant does not provide valid and unique contact information, they will not be able to sign in to the app until they have provided it. If a participant provides contact information that matches that of another registrant, they will be rejected administratively.

7.2 Enrollment/Baseline

All participants will download the app, complete the Baseline survey through the app via SurveyGizmo API, and provide contact information for a friend or relative. Intervention participants will also receive access through the app to basic prevention services (HIV test planning and test locators; risk assessment; HIV treatment locators; and condom, HIV test kit, and at-home STI specimen collection kit distribution) plus monthly PrEP eligibility assessments, PrEP provider locator, enhanced information about PrEP, and referrals to local PrEP navigators. The app also provides links to health insurance exchanges, where men can seek health insurance (all cities) or payment assistance programs. The control arm will be referred to existing online PrEP and HIV prevention information (Appendix C). Participants who do not download the app or have problems downloading the app will be ineligible to participate in the study.

7.3 Follow-up Visits

All participants will be asked to complete quarterly surveys through the app for follow-up visits at Month 3, 6, 9 and 12. Participants who have indicated starting PrEP will be asked to upload a picture of their prescription and/or be asked to self-collect DBS using a home test kit.

Both groups will also receive a monthly assessment. The intervention group will receive a monthly PrEP assessment and the Control group will receive a survey about diet and exercise of similar length. All participants will also be asked questions to ascertain whether they started PrEP within the past month. Generic questions about new medication prescriptions will be used in the control arm so that PrEP is not mentioned specifically. Intervention arm participants will be asked if they have initiated PrEP prior to starting the monthly PrEP assessment. Participants reporting PrEP initiation will then complete a PrEP adherence assessment.

The intervention group will be able to use the resources in the app throughout the study, including placing orders for home test kits, condoms and lubricant.

7.4 Withdrawal Visit

Participants may withdraw at any time during the study. If they indicate they wish to withdraw, they will be asked to complete a short survey to identify reasons for wanting to withdraw.

7.5 Unscheduled Visit

Any interaction with participants between scheduled visits will be considered unscheduled visits and will be tracked in SMART.

7.6 In-depth Interviews

In-depth interviews: Up to 30 IDIs (approximately 10 per site) will be conducted within one month of PrEP initiation with men in the intervention arm who start PrEP. Up to 20 additional IDIs will be conducted within one month of study completion among men who fit the following criteria (N = maximum of 5 each): PrEP starters, PrEP non-starters, PrEP stoppers, and men that cycled on and off PrEP. IDI participants will be purposively sampled to ensure

representation of men who accessed the app at least one time during follow-up and received a PrEP recommendation. PrEP starters interviewed after one month of follow-up will not be re-interviewed at the end of study. The IDIs will be conducted by trained qualitative interviewers. We will develop semi-structured interview guides. Interviewers will receive training on the interview guides to ensure standardization across study sites. IDIs will assess the extent to which app components facilitated or inhibited PrEP uptake. Central to the IDI will be understanding the participants' use of the app. The IDI will begin by asking the participant to walk the interviewer through a "typical use session" of the app, during which the interviewer will probe around key decisions (e.g. why one function was used over other functions). The interview will examine the participant's views on the positive and negative elements of the app. The interview will focus on the use of PrEP components: participants will be asked to walk through the PrEP knowledge, screening and locating functions with the interviewer and describe why they did or did not use them. Participants who started PrEP will be asked to describe the role that the app played in their decision and which app components were most integral to their decision. They will be asked to demonstrate which components of the app were useful in adopting PrEP, and areas of the app where further support might be useful. Participants who did not start PrEP will be asked if there are additional components (e.g., better linkage to providers, other information) that could be added to the app that might lead them to change their mind about starting PrEP. Participants who did not adopt PrEP will be asked to demonstrate how they used the app and which components of the app were not used. These data will provide insight into how the app is used in PrEP decision making, and identify areas of opportunity to promote PrEP adoption for future app versions.

Additional IDIs will be conducted with any participant who seroconverts during follow-up. These IDIs will follow a structure similar to those described above. Additional questions will be added to explore factors related to PrEP and seroconversion. Participants who were not on PrEP at the time of seroconversion will be asked why they did not initiate PrEP or why they discontinued PrEP if they had previously taken it. Patients who report being on PrEP at the time of seroconversion will be asked about adherence to the dosing regimen.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Study Procedures/Evaluations

Per-Protocol and Dose-Response Analyses: The primary efficacy analysis will be an intent-to-treat analysis. Because randomization to the intervention arm will not guarantee engagement with the HealthMindr app, we will use two types of secondary analysis to estimate the potential effects of the app under conditions of optimal adherence. First, a per-protocol analysis will estimate the effect of the app on rates of PrEP initiation under assumptions of substantial adherence using principal stratification methods to estimate the causal effects given associations between measured confounders and adherence profiles.[47] Study subjects who participate in the baseline assessment and at least 3 subsequent monthly PrEP screeners during the year will be categorized as substantially adherent for this purpose. Second, level of engagement with the app, including number of times the app is opened per month or number of app features accessed per use, may vary strongly across participants. Under the hypothesis that greater engagement with the app will lead to faster initiation into PrEP, we will model the dose-response relationship between a continuous gradient of app engagement and rate of PrEP initiation among app users in the study.

8.2 Laboratory Procedures/Evaluations

HIV Testing: Participants in the intervention arm will be offered at-home HIV test kits up to 2 times during their 12 months of participation through the Emory CFAR. HIV is tested using FDA-approved OraQuick test using a mouth swab. Results can be verified through self-report.

STI Testing: Participants in the intervention arm will be offered at-home STI test kits up to two times during their 12 months of participation; through the Emory CFAR. Diagnosis of an STI is an indication for PrEP.[40] The presence of C. trachomatis (CT) and N. gonorrhea (NG) in self-collected urethral, throat, and rectal specimens will be determined by using the Aptima Combo 2 CT/NG assay or Abbott Real Time CT/NG assay, an FDA-cleared real-time polymerase chain reaction (PCR) assay for direct, qualitative detection of a region of the cryptic plasmid DNA of CT and the Opa gene of NG.[48] Syphilis screening will be conducted using the TREP-SURE EIA assay with reflexive rapid plasma reagin (RPR) test for reactive results[49]; participants with a reactive result will be referred to a local provider for treatment and follow-up. Positive STI test results will be provided to participants over the phone by a study staff member who can refer participants to treatment. Upon request, copies of results may also be sent to the study participant.

Alcohol and Substance Use Screening: Residual urine from STI testing will be screened for alcohol and substance use. This will be done as a confirmation of self-report for substance use for research purposes only and results will not be reported back to participants. Participants who wish to receive referrals for assistance with substance use will be assisted with navigation services by study staff.

Tenofovir detection: Dried blood spot specimens from men who report initiating PrEP will be analyzed for intracellular concentrations of tenofovir diphosphate (TFV-DP) in the laboratory of Dr. Angela Kashuba, who directs the University of North Carolina CFAR Clinical Pharmacology Core. DBS cards are used to obtain a 3 mm “punch” which is eluted in a micro-centrifuge tube. The eluate is analyzed by liquid chromatography/tandem mass spectrometry. Tenofovir concentration is reported as fmol/10^6 RBCs; the lower limit of quantification is 2.5 ng/mL. Intracellular TFV-DP is commonly used as method of assessing adherence to PrEP; we will consider a positive result solely to corroborate self-report of PrEP initiation and photographic evidence of prescription. This will not be used to monitor adherence and results will not be returned to participants, as disclosed in the informed consent process.

8.2.1 Specimen Shipment

Shipping CareKits to Participants

1. After the order is placed through the app, staff will place the kit order with the lab.
2. Kits will be mailed directly to the participant with instructions on how to register their kit online. This will allow staff to link the kit with the participant.

Shipping Specimen

After collecting specimen(s) for testing, participants will indicate the date of collection and place specimens collected in the provided packaging, which meets all federal regulations for shipment of Biological Substances. Participants will ship their collected specimen(s) via USPS

to the designated laboratory via the provided pre-labeled mailer. Instructions on how to mail kits are included on an instructional sheet provided within the kit.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

All adverse events reported will be assessed by the PI for the study site in which the participant was enrolled for the severity, expectedness and relatedness, using the criteria listed below.

9.1.1 Adverse Events

1. Participant report of loss of confidentiality through the app or its functions
2. Participant report of loss of confidentiality through delivery of prevention supplies or commodities
3. Participant report of access by others to protected health information through the app or study procedures.
4. Participant report of disclosure of status as a research participant due to study-related reminders (from app, phone calls, emails, or text messages).
5. Participant report of discomfort or injury due to use of provided specimen collection materials (e.g., finger stick for syphilis testing, self-administered rectal swab or pharyngeal swab).
6. Disclosure of personal information about health, sexuality or sexual practices that results in physical violence or threat of violence.
7. Disclosure of personal information about health, sexuality or sexual practices that results in adverse effects on employment

9.1.2 Serious Adverse Events

1. Suicidal behavior or intention, including but not limited to following learning the results of study-provided tests (e.g., HIV tests, STI tests)
2. Any event that results in death, is life-threatening, results in persistent or significant disability/incapacity, or requires hospitalization or prolongation of existing hospitalization

9.1.3 Relationship to Study Intervention

The potential event relationship to the study intervention and/or participation is assessed by the site investigator. A comprehensive scale in common use to categorize an event is:

- *Definitely Related*: The adverse event is clearly related to the investigational intervention – i.e. an event that follows a reasonable temporal sequence from first exposure to the app, follows as a known or expected consequence from using the intervention, and that could not be reasonably explained by the known characteristics of the subject's normal activities.
- *Possibly Related:* An adverse event that follows a reasonable temporal sequence from exposure to the app, follows a known or expected consequence from use of the app, but that also could readily have been produced by a number of other factors.

- *Not Related:* The adverse event is clearly not related to use of the app - i.e. another cause of the event is most plausible; and/or a plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered implausible.

9.1.4 Severity of Event

Severity will be classified using the following standards:

- ***Mild:*** Awareness of the issue, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Incident did not require counseling or a medical evaluation; concern on the part of the participant or physical symptoms were transient.
- ***Moderate:*** Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved within a few days (social harms) or by simple therapeutic measures (injury due to specimen collection); moderate experiences may cause some interference with usual activities for a few days.
- ***Severe:*** Events interrupt the participant's normal daily activities and require mental health assessment and treatment (social harms) or clinical treatment (injury due to specimen collection); they usually produce major disruptions in daily activities such as work, school, or family commitments.

9.2 Reporting Procedures

In all study sites, new confirmed STI infection, including HIV, is reportable to local health departments. We will complete mandatory notification of positive STI results as required by law. Participants will be informed in the informed consent process and counseled when receiving positive STI results that results will be reported to the local or state health department as required by law, and that the health department might contact them to offer treatment or to assess possible onward exposures. Abuse that comes to the attention of study staff will be required to be reported in all three jurisdictions if the abuse is perpetrated on a child (who would be ineligible to participate per the study age criteria), or if the abused person is a vulnerable adult (e.g., elderly person, person in a long-term care facility). We do not anticipate having participants who would be considered to be vulnerable, but if we become aware of abuse to a person meeting this criterion, we will report to state/district authorities as required by law.

9.2.1 Serious Adverse Event Reporting

All SAEs require expedited reporting by the Principal Investigator to the Emory IRB. An expedited report of an SAE can be submitted by telephone, fax, or email and must be reported to the IRB and the NIDA project officer within 24 hours of the event being reported to the Investigator.

The expedited report will be followed by a detailed, written SAE report of the event and its resolution as soon as possible but no longer than 72 hours after the study team learns of the event. Follow up information may be required and asked for by the IRB directly, or through the NIDA or its representative. A standardized SAE reporting form will be used.

10 STUDY OVERSIGHT

A DSMB is not planned for this study. Based on criteria included in the NIDA online guidance on safety monitoring (*https://www.drugabuse.gov/funding/clinical-research/guidelines-developing-data-safety-monitoring-plan*), monitoring will be done by the Principal Investigator and the Institutional Review Board. This level of monitoring is based on NIDA's criteria that the study is a multicenter clinical trial, but does not propose blinded or high-risk interventions. The intervention and the only medication involved is open label and is FDA approved for the indication to which we are referring men. The study does not provide medication, but rather refers men to clinical providers. Further, the centralized nature of the study data at Emory will facilitate routine monitoring.

11 CLINICAL SITE MONITORING

The principal investigator will monitor data collection throughout the study, and will ensure that interview protocols are followed, all adverse event reports are reviewed (if any), confidentiality procedures are implemented, and the Emory University IRB is alerted if unexpected concerns arise.

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

1) The rate of PrEP uptake will be higher among men provided with the HealthMindr app compared to men provided with standard of care.

2) Access to additional HIV prevention services available in the HealthMindr app will result in reductions in risk behaviors or greater access to HIV testing services, which are associated with PrEP uptake.

3) Individual, social, and community characteristics of participants will be associated with PrEP uptake among participants provided access to the HealthMindr app.

12.2 Sample Size Considerations

Power calculations were conducted for the main analysis of time to PrEP initiation comparing the intervention arm with the control condition. Current estimates of PrEP uptake in the most recent 4 quarters for which data are available are that 4,507 men started PrEP[50]. Assuming all of these men are MSM, which is an overestimate, and using as the denominator the number of MSM estimated by CDC to be eligible for PrEP22, only 4,507/492,000 = 0.9% of eligible MSM started PrEP between mid-2104 and mid-2015. Thus, our assumption that at most 2% of men in the control arm will initiate PrEP during the study period is conservative. Based on our preliminary pilot data, men using the app initiated at 9% per 4 month period; we conservatively estimate that men in the intervention period would initiate PrEP at 9% in a year. We propose a total sample size of 438 intervention arm and 219 control which will provide 91% power (α = 0.05) to detect a 4.5 fold increase in the hazard of uptake in the intervention arm compared to the control arm. If our effect were less than our conservative estimates, we would retain reasonable power (4-fold: 80% power; 3.5-fold: 74% power). These power calculations assume 20% annual attrition.

12.2.1 Efficacy Review

The primary efficacy analysis will be an intent-to-treat analysis. Participants will be analyzed based on the study arm they were assigned to regardless of the level of engagement with the HealthMindr app among intervention arm participants. Because randomization to the intervention arm will not guarantee engagement with the HealthMindr app, we will use two types of secondary analysis to estimate the potential effects of the app under conditions of optimal adherence. First, a per-protocol analysis will estimate the effect of the app on rates of PrEP initiation under assumptions of substantial adherence using principal stratification methods to estimate the causal effects given associations between measured confounders and adherence profiles.[47] Study subjects who participate in the baseline assessment and at least 3 subsequent monthly PrEP screeners during the year will be categorized as substantially adherent for this purpose. Second, level of engagement with the app, including number of times the app is opened per month or number of app features accessed per use, may vary strongly across participants. Under the hypothesis that greater engagement with the app will lead to faster initiation into PrEP, we will model the dose-response relationship between a continuous gradient of app engagement and rate of PrEP initiation among app users in the study.

12.3 Final Analysis Plan

The main analysis will use four standard survival analysis techniques to compare the rate of PrEP initiation by study arm and estimate the size and statistical significance for observed differences. This approach will account for loss-to-follow-up, study termination due to competing events (e.g., HIV seroconversion), and other forms of censoring.[51] The first analysis will use Kaplan-Meier methods to characterize the empirical survival distribution, which here is the time-dependent probability of remaining PrEP uninitiated over follow-up. This method will yield estimates of the median time to PrEP initiation and cumulative incidence with 95% confidence intervals. Second, log-rank or related (e.g., Harrington-Fleming) statistical tests will be used to test the null hypothesis of no difference in rates of PrEP initiation by study arm, with a cutoff p value of 0.05 used to determine significance.[52] Third, a Cox proportional hazards model will be used to estimate the hazard ratio associated with study arm to characterize the strength of causal effect of use of the app. The primary model will only include an independent exposure variable for the study arm as randomized (i.e., standard intent-to-treat analysis), but secondary models may include covariates (including those related to the four domains along the PrEP continuum) for which there is descriptive evidence of residual imbalance after randomization.[53] Fourth, parametric survival models (e.g., under exponential or Weibull distributional assumptions) will be used to characterize the rate of PrEP initiation overall and by study arm.

Mediation Analysis: This analysis will examine how study arm assignment may lead to intermediate effects, such as greater access to HIV testing or decreased risk behavior, which themselves are associated with the primary effect of PrEP initiation. Using the difference method for a set of Cox proportional hazards models similar to those in the Aim 2 analyses, log coefficients for the indirect effects will be subtracted from log coefficients for the direct effect to estimate the size of the mediation.[41] Mediators will be selected on the variables known to be associated with the 4 domains of the PrEP continuum (including awareness, access, and engagement with HIV prevention services), and changes in risk behaviors resulting from app utilization.

Moderation Analysis: This analysis will examine how attitudes and beliefs about PrEP, as well as individual, social, and community characteristics can moderate the effect of the app on PrEP initiation. Examples of moderators include perceived benefits of PrEP use, self-assessed

vulnerability to HIV, perceived advantages to meeting partners if currently taking PrEP, and social support for PrEP use within one's social network. Demographic factors such as age, race/ethnicity, and geographic setting will also be critical moderators. Although the distribution of these factors will be balanced across study arm with randomization, they may have effects on the level of engagement in the app (i.e., post-randomization treatment adherence) that itself will influence the rate of PrEP initiation. Given this causal model, we will use instrumental variable analyses to estimate the effect of optimal app use on PrEP initiation given measured and unmeasured moderators.[42]

In-Depth Interview Data Analysis: All IDIs will be digitally recorded, transcribed verbatim, and de-identified. Transcripts will be entered into MAXQDA, which facilitates the processes of coding, annotating, and retrieving text such that analysts may note patterns in the textual data across themes. Data analyses will be conducted using a phenomenological inquiry framework.[54,55] Phenomenology is focused on describing what a given group of people have in common as they experience a phenomenon, and is an inductive analytic approach that allows the patterns, themes, and categories of analysis to emerge from data.[54,55] Data are then presented through textual phenomena descriptions based on summaries of experiences described by respondents. Composite descriptions offer explanation of underlying structures which exist across the respondents' experiences.[54,56]

Our data analysis team will consist of lead analysts and trained analysts at Emory. Analysts will have had previous experience with thematic coding and will attend training on coding guidelines to ensure consistency. After close readings of the text, the lead analysts will create a preliminary codebook to capture emergent themes. We anticipate developing a codebook consisting of 12-15 codes representing key project themes, including explicit domains from the interview guides and from the theoretical basis of our app (deductive themes) and pervasive, unanticipated themes that were emergent across various transcripts (inductive themes). Provisional definitions will be given to each code. The preliminary codebook will be presented to other analysts (per the phenomenological approach) and a group discussion will occur. After edits are made to the codebook, all analysts will apply the preliminary codebook to a single transcript. The coded transcripts will be merged for comparison and code definitions will be revised based on an examination of coding disagreement. This process will be repeated until consistent agreement is attained among all coders. A finalized codebook will be created and the trained analysts will start coding (from scratch) all of the textual data for the project. Coders will also develop brief summaries to describe individual participants in order to help contextualize the thematic analysis across individuals. MAXQDA's search and retrieve functions will then be used to review coded data and identify patterns, including similarities and differences across study sites.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NIDA and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The main sources of possible data entry errors will lie with the matching of study ID numbers and participant identifying information and with capturing of participant information from mail in-specimens. This risk will be mitigated by identifying any mail-in specimen with a possible discrepancy in linking with study ID; such specimens will not be processed and participants will be requested to provide a new specimen. For app-based and survey-based data, the participant identifiers are associated with the electronic record automatically, so the chance of problems with attribution of responses to the incorrect participant is very small.

For study IDs, the files linking the study ID and identifying information will be generated through a SAS program that retrieves data entered by the participant at the time of enrollment.

For mailed-in specimens, all specimen tubes will be labelled with a unique ID number, which will be the same for all tubes in one specimen collection kit, i.e. the box ID. Participants will be asked to register this box ID using a unique URL linked to their study ID. This will allow linkage of specimen test results back to the correct participant.

14.1 Recontacting Past Participants

Participants who reported PrEP initiation on a monthly check-in survey but not a quarterly survey (primary study outcome) will be contacted for clarification. Only the participants who previously provided consent to be recontacted will receive a message. A $20 compensation in the form of electronic gift code will be given to those participants who respond.

Voicemail: Hi, this is [insert your name] calling from Emory with the HealthMindr study. You have reported starting PrEP during our research study, but you also reported that you have not started PrEP in surveys afterwards. I was hoping to verify some information from your time in the study. You are eligible to receive additional compensation for your response. You can call us back at [phone number]. Or feel free to text me and let me know what the best time is for a call. Thank you!

Phone Script: Hello, may I speak with [PARTICIPANT'S NAME]? My name is [insert your name]. I am with Emory working on the HealthMindr study. You have reported starting PrEP during our research study, but you also reported that you have not started PrEP in surveys afterwards. According to your survey, you reported PrEP usage in [MONTH/YEAR]. Is this correct? Did you stop taking PrEP any time after?Thank you for your clarification. Also for the compensation, we will send you a $20 gift code. Do you have a preferred store? We have gift codes from Amazon, Target and Walmart.That is all the questions I have and thank you for participating in our research study!

Text Message: Hello! This is [NAME] from the Emory HealthMindr study. We were hoping to get you on a call for a few minutes to to verify some information from your time in the study and you will be compensated for your time. What time works best for you for a short phone call?

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Potential Risks and Benefits

15.1.1 Potential Risks

The potential risks to participants are minimal.

Surveys: Some participants may be uncomfortable answering personal questions, or feel uncomfortable with the HIV prevention topics. Men will have the option for all questions to not answer.

Disclosure of participation in a research study: There is a possibility that someone participating in an online data collection could be identified as participating in research, but this is uncommon. There is some risk that those who participate in online surveys could be observed if they complete the surveys in public, or that data could be at risk during transmission. We will mitigate this risk by reminding participants at the beginning of each survey to complete the survey in a private place, where their responses cannot be observed by others. We will also encourage participants to delete any emails or text messages received as part of the study to protect them from an unauthorized individual viewing the messages.

15.1.2 Potential Benefits

There are no direct benefits for participating in this study. The potential benefits to study participants in the intervention group include access to HIV and STI testing, knowledge about serostatus, access to pre-exposure prophylaxis for HIV prevention, access to free condoms, ordered by participants through the study app and delivered through a parcel shipping service (e.g., UPS or FedEx), and access to information to promote personal health. Control arm participants might benefit from access to information about HIV prevention services.

15.2 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

15.3 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Emory University IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study. IRB authorization agreements (IAA) will be used between Emory University and each site.

15.4 Informed Consent Process

Consent will be administered through the online screening and registration portal. Because men will not be enrolled and consented at an “in person” visit, the consent process will be online.

Therefore, a video-based online consent will be used, and the participant will be provided a PDF of the complete informed consent document.

The consent will be done in two stages, for screening and study enrollment. Due to the sensitive nature of screening questions regarding participants' sexual history, all potential participants must consent to be screened before they can access the eligibility survey. The consent to screen form (Appendix A) will describe the nature of the study, the need to collect sensitive sexual health information in the screener, and what safeguards are in place to ensure the security and confidentiality of the screening data collected.

Those determined to be eligible will be directed to an electronic informed consent form (Appendix B) presented online. The electronic informed consent document will explain: (1) what is meant by consent; (2) why we need to obtain consent and (3) the purpose of the consent form. Participants will also have access to a video describing the components of the informed consent document. Participants will be required to view the informed consent document before indicating whether or not they consent; this will be enforced by requiring participants to scroll through the entire consent before they can choose to consent to participate. Consent or lack thereof will be documented in the electronic database by the stored variable indicating consent or lack of consent. A button to allow participants to print or email the consent form for their records will be located at the end of the consent form document. The consent process will take approximately 5 minutes per individual. Study staff will be available during business hours by phone or by email to answer any questions that participants have prior to consenting. The consent forms have a Flesch-Kinkaid Reading Level of <8.5.

15.5 Exclusion of Women, Minorities, and Children (Special Populations)

Women, including transgender women, are excluded from the study because (1) effective HIV preventive interventions for women are likely to differ markedly from those focusing on men (particularly men who have sex with men), both in content and presentation; (2) the individual, socio-cultural and developmental factors associated with HIV risk in MSM are different from those for women; (3) the research questions and issues of relevance for MSM are not relevant or appropriate for women; (4) several effective HIV prevention interventions for women have already been developed, evaluated, and disseminated.

People under age 18 are excluded from the study because (1) effective HIV preventive interventions for teenagers are likely to differ markedly from those focusing on young adults and adults, both in content and presentation; (2) the individual, socio-cultural and developmental factors associated with HIV risk in MSM under 18 are different from those for MSM 18 and up; and (3) the research questions and issues of relevance for MSM aged 18 and up may not be relevant or appropriate for MSM under age 18.

15.6 Subject Confidentiality

Our efforts to protect privacy and confidentiality are evident in several areas: study procedures, training, and data management practices.

<u>Study procedures</u>

We will collect multiple means of contact with participants at the study visit. For each means of permitted contact, we will leave a generic message about participation in a health research survey at that phone/email/cell phone, etc. Standardized scripts for phone and email contact will

be used (uploaded in the eIRB system for review). Participants are offered the option to receive STI testing results by email or text message; for those who so choose, the results messages will not identify the type of testing, the nature of the study, or the specific test names. Scripts for the return of results by email or text message are included in the "Miscellaneous Documents" section of the eIRB forms.

Training

All study staff will have a 1-hour training on patient privacy and confidentiality. (Section 15.7) Staff will sign a confidentiality agreement (uploaded to eIRB) before having access to any confidential data.

Data management practices

As described above, personally identifying information will be stored in a separate dataset from case report form data, test results, survey answers, and interview transcripts. Access to the identifying information will be restricted, so that persons who are responsible for scheduling can view contact information and next study visit due date, but no other study data. Similarly, persons who can view study data will only be able to see the study data and the (non-identifying) study ID.

15.7 Future Use of Stored Specimens and Other Identifiable Data

No specimens will be stored for future use. Specimens returned for STI testing or TFV-DP testing will be destroyed after laboratory analysis.

Additional data analyses beyond those described in this protocol will be performed. Study staff will continue to only have access to identifiable data only as needed.

15.8 Training

All study staff are required to complete the CITI training course modules on human subjects research, socio-behavioral science, and GCP. Annual refresher training on human subjects is required every 3 years. These requirements are tracked by the Emory IRB, and are verified for all new staff being added to the IRB protocol. Certificates will be retained by the PI and available for review on request by the IRB or NIH staff. Study staff will also receive study-specific training on delivering STI test results, and will have completed CDC's Fundamentals of HIV Prevention Counseling course before providing any test results. All staff sign a confidentiality agreement and receive annual refresher training on protecting human subject's information, PII, and protected health information (PHI).

16 DATA HANDLING AND RECORD KEEPING

16.1 Data Management

Data will be stored in password-protected, encrypted files on Rollins School of Public Health computers and on secure Rollins and SurveyGizmo servers, both HIPAA compliant. SurveyGizmo has a HIPAA Business Associate agreement with Emory University. Databases of participant identifying information (contact information such as names, emails, and phone numbers) will not be linked to databases with participant data. Participant identifying information will only be linked to whether the participant completes study procedures, needs to be re-

contacted, or refuses to participate. The name, e-mail, and phone number of screened men who decline to be scheduled for participation will be removed from the study database after we have asked them questions about why they have a lack of interest in proceeding, unless they request to be contacted for future studies. Access to the identifying information will be on a role-based system: access to identifying information will be restricted to those who need access to perform their work function. Thus, access to identifying information will be restricted to the Project Coordinator, study staff providing counseling/referral services, and 2-3 work study students charged with data entry and scheduling tasks.

16.2 Procedures for Prevention and Addressing Breaches of Confidentiality

The main approach to preventing breaches of confidentiality is to maintain identifying participant information in a single location at each site and to use a non-personally identifying study ID to store all other study data.

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

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

Admin Web Portal. The admin web portal is a web-based application developed using Microsoft .NET technologies. It uses SQL server as backend database. The application requires two servers to host: (1) Web server [Windows server with IIS] and (2) SQL server [Standard or Enterprise version]. Both these servers are to be placed behind a firewall. Web server will have a public IP to access the server using VPN. SSL certificate is to be installed on the web server. The admin website will be rendered over SSL (https). The application uses form authentication (no integrated authentication such as AD). All passwords are stored encrypted within the database. 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.

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

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

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

The HealthMindr app itself also has protections for breach of confidentiality. The app requires re-authentication through a user-selected password or proxy (e.g., fingerprint authentication) if the app has been navigated away from, or if more than 5 minutes pass without interaction. This is similar to security functions that are in place for other apps with sensitive information (such as banking or apps allowing access to medical records).

To minimize risks to confidentiality, we will provide study data with all appropriate physical and operational security protections. Paper-based data will be stored in a locked cabinet in a locked office, and all data files will have encryption and strong password protection. Access to data will be on a role-based standard; only those study staff, such as principal and co-investigators, data managers, data analysts, study staff (public health program associates and assistant or associate directors of research), and graduate research assistants, who require access to identifying data to complete their study-related roles will be allowed access. Any photographs (i.e., PrEP prescriptions or bottle labels) will be sent to study staff securely through the app. SurveyGizmo, the electronic platform for self-interview, has a HIPAA business partner agreement with Emory. All study staff will complete CITI course modules on human subjects research ethics, socio-behavioral research, and good clinical practice (GCP), will be trained in security and confidentiality procedures, and will sign a confidentiality agreement before receiving access to any participant data. Any breaches in confidentiality will immediately be reported to the PI and to the IRB. Based on the PI and IRB's recommendation, staff may be retrained or receive disciplinary action.

Study staff will follow procedures to minimize indirect disclosure that a participant is participating in an HIV-related research study, or a study that enrolls MSM. For each mode of contact information, including email, telephone, text, and voicemail, 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 to the participant 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.

16.3 Data Capture Methods

Data collected through the mobile app: Participants will use a mobile phone app to get information about HIV prevention and referrals to local services. As participants use the app, data about which features they used are entered directly by the participant in the process of interacting with the study app or control app.

Data collected through the online survey interface: Participants will also take surveys through an online survey portal. Data are collected directly on the private server as participants respond to questions. Data will be identified in the system through a Study ID. Surveys are conducted using a secure (https://) webpage, which means that data entered by participants are encrypted before they are sent through the internet, and are decrypted once received by the survey hosting site. The link between the participant and the participant contact information is held by Emory University research staff.

Data collected through mail in-specimens: Participants who request STI testing will mail in urine, rectal swab, throat swab, and blood specimens for testing. All mailed-in specimens will be labelled with a unique ID number, which will be the same for all tubes in one specimen collection kit, i.e. the box ID. Participants will be asked to register this box ID using a unique URL linked to their study ID. This will allow linkage of specimen test results back to the correct participant.

Electronic CRFs through DFexplore will be used for any data collection unable to be completed through the surveys and HealthMindr database, such as study withdrawal or adverse events. Data entry will be conducted by IRB-approved staff. Forms are double checked, and

electronically verified for possible discrepancies. Any possible discrepancies are resolved by re-review by a third, more senior data manager.

16.4 Types of Data

Data collected through interactions with the app:

Data will be recorded as participants request certain app pages or functions. Each time the participant touches a button or navigation function in the app, that piece of data is stored in the administrative portal of the app. Data are stored with a 16-digit alphanumeric string which is unique to the participant, and is not stored with identifying information for the participant. The link between the alphanumeric string and the participant contact information is held by Emory University research staff.

Management and storage:

Data within the study app: Data are stored in a secure, HIPAA compliant server in the cloud. Access to app data are password protected, and access is role-based. Access to participant data will be limited to study staff approved by IRB in each site, comprising principal and co-investigators, data managers, data analysts, study staff, and graduate research assistants. Software developers will have access to administrative aspects of the management portal, but will not routinely have access to links to Study IDs or personally identifying information (PII). In the case of a “need to know” for study related purposes (for example, duplicate or corrupted files, need to examine specific records to troubleshoot app or data functions) temporary access can be granted to developers, whose access will be limited to the specific records required to resolve the problem. Any developer who needs such access will be required to complete CITI training, complete a PRISM data confidentiality form, and be added to the IRB protocol. Access to participant-identifying information will be removed after the specific problem is resolved.

Security protections of identifying information: Identifying information will be held in a secure study database at each study site. Identifying data will be stored in the System for Management and Reporting of Trials (SMART), an IT solution provided by the Emory University CFAR and hosted on a secure cloud-based server at each of the three participating institutions. Access is role-based, and is protected through institutional firewalls and password procedures at Emory University, George Washington University, and the University of Mississippi Medical Center, respectively.

Data collection through Case Report Forms:

Collection: Data will be entered in DFexplore on electronic CRFs for enrollment, randomization, study stop, and reportable events. The records will be stored by Study ID and not include participant names.

Management and storage: Data will be stored in a cloud-based LINUX Microsoft Azure server managed by DF/net, the company of that manages DFexplore. The data will then be downloaded onto secure Emory servers. Emory has BAA with DF/net and data will only be accessible to persons who have been provided with login and passwords.

Data collection through online surveys:

Collection: Data will be recorded as participants respond to questions in an online survey portal (SurveyGizmo) from a web browser, smartphone or tablet. Data will be identified in the system through a Study ID. Surveys are conducted using a secure (https://) webpage, which means that data entered by participants are encrypted before they are sent through the internet, and are decrypted once received by the survey hosting site. The link between the participant and the participant contact information is held by Emory University research staff. For images of prescriptions or pill bottles, we will use a secure survey form to transmit the upload of the image file, and it will be treated under the same confidentiality protections as other study data (e.g., stored on a secure server). The image data will be stored on the same server as the questionnaires data, subject to the same physical and procedural security measures described for the survey data.

Management and storage: Data at SurveyGizmo are stored in a secure, HIPAA compliant server in the physical facility in Boulder, Colorado. Emory's subscription to the SurveyGizmo service includes a private server so data are not co-mingled with other study data, and a HIPAA Business Partner Agreement is in place between Emory University and SurveyGizmo. Access to participant data will be limited to study staff approved by IRB in each site. All survey and image data are maintained in a backup system. First, all data are encrypted at three levels – at the row level, at the project level, and at the disk level. Once data are encrypted, protected backups are stored in the cloud using Amazon Simple Storage Service (Amazon S3), which is designed to deliver 99.999999999% durability. In addition to this, data is backed up using Amazon Elastic Block Store (EBS) snapshots, which are used as a primary storage device for data that require frequent and granular updates. Automated encrypted snapshots (differentials) of databases are performed daily, and all data storage is redundant. Redundant databases reside in a private subnet that is only accessible via the SurveyGizmo application and web servers. Additionally, Amazon's AWS security features to further "lock down" access to these systems. Data are only able to be transmitted through secure (https://) connections.

Security protections of identifying information: Data are held on a private, physically-secured server in Boulder Colorado, and password-protected restrictions to access are in place for all study staff.

Data collected through mail-in specimens

Collection: Participants will collect a dried blood spot specimen at home, using a collection kit provided by the study. Kits will be distributed with specimen collection tubes marked with a specimen ID . Links between specimen ID and Study ID will be maintained in a password protected database. Links between specimen and Study IDs will be available only to staff who are responsible for linking study data (e.g., principal and co-investigators, data managers, data analysts, study staff , and graduate research assistants). An instructional video will be provided for participants and available through an online video facility. Participants will be provided with instructions to prepare and mail the dried blood spot through US mail to Emory University or specified laboratory.

Management and storage: Specimens received through US mail will be logged in and stored at -20 degrees. Specimens will be shipped in batches to the University of North Carolina CFAR lab, where testing for tenofovir will be conducted. Specimens will be identified by the participant study identifier and results will be reported from UNC to the Emory CFAR lab using the same specimen ID. Links between the study ID and participant identifying information will be held on a secure server .

Security protections of identifying information: Identifying information will be held with Study IDs on a private, secure server at Emory University, and password-protected restrictions to access are in place for all study staff. Dual-factor authentication is required for off-campus access.

Data collected through individual In-Depth interviews:

Collection: Interviews will be conducted through a HIPAA-compliant online platform, such as VSee or Zoom. Both platforms have end-to-end encryption to prevent 3rd party tampering. Data will be recorded as participants answer questions from a trained interviewer in a confidential space. Recorded files will be uploaded to a secure server at Emory University as mp3 files. The Study ID will be used in the file naming convention of the file, but no PII will be included in the file itself or in the naming convention.

Management and storage: Study forms and audio recorders will be kept in locked file cabinets at the project sites for the duration of the study. After each interview, the audio file will be uploaded to a secure server at Emory University and deleted from the recording device. All study data will reside in a secure SQL server file behind Emory's IT firewall. Dual-factor authentication is required for access off the University campus. Access to participant data will be limited to study staff approved by IRB in each site. Data will be transmitted via a secure (https://) web connection to a 3rd-party, licensed HIPAA-compliant transcription service. Data files will never be on a physical device, such as a flash drive, which would be lost or stolen. Data security protocols at the 3-rd party transcription service are governed by their organization policies and procedures, but must be HIPPA compliant. Transcripts will be returned to Emory via a secure, password protected file transfer protocol. The transcription service will be instructed to destroy all recordings upon completing each transcript. Upon receipt and confirmation of each transcript's quality and accuracy, the study staff will destroy all backup copies of the original recording files. Transcripts and file names will not contain any identifying information, referring to interviews by participant study ID. Links between study ID and participant identifying information will be held in separate electronic files at Emory University, consisting of a database file that contains both the Study ID and the participant name and contact information. This will allow most study data to be stored using on the Study ID, minimizing the impact of any breach of security for data files in which records are identified only by the study ID.

Security protections of identifying information: Audio recordings and transcribed data will be held on secure services with role-based access and password-protected restrictions to access. Only study staff approved by the IRB will be able to access the recordings or data. Once transcriptions are verified, audio recordings will be destroyed.

Combined data sets: Data from different modes of collection (app, lab, surveys) will be merged into a study data file which will be kept on the secure network drive at Emory. Access will be limited to the PI, Public Health Program Associates, Data managers, and Graduate Research Assistants who work in data entry or management. Backup copies are made daily and stored behind Emory's institutional firewall. Access to the combined study data file can only be gained either by being in an Emory building and accessing through an account with permission to read the data, or from off campus through a permitted account and with dual-factor authentication.

16.5 Protocol Deviations

All protocol deviations and violations will be reported to NIDA at the time of submission to the Emory IRB, and at the time of disposition from the Emory IRB. The latter reports will include any required actions specified by the IRB.

17 PUBLICATION/DATA SHARING POLICY

Any presentation, abstract or manuscript will be made available for review by the study sponsors prior to submission.

18 LITERATURE REFERENCES

1. Sullivan, P.S. and R.J. Wolitski, *HIV infection among gay and bisexual men*, in *Unequal Oppportunity: Health Disparities Affecting Gay and Bisexual Men in the United States*, R.J. Wolitski, R. Stall, and R.O. Valdiserri, Editors. 2007, Oxford University Press: New York. p. 220-247.
2. Beyrer, C., S.D. Baral, F. van Griensven, S.M. Goodreau, S. Chariyalertsak, A.L. Wirtz, and R. Brookmeyer, Global epidemiology of HIV infection in men who have sex with men. Lancet, 2012. **380**(9839): p. 367-77.
3. Beyrer, C., P. Sullivan, J. Sanchez, S.D. Baral, C. Collins, A.L. Wirtz, D. Altman, G. Trapence, and K. Mayer, The global HIV epidemics in MSM: time to act. AIDS, 2013.
4. Centers for Disease Control and Prevention. HIV Surveillance Report, 2011; vol. 23. *http://www.cdc.gov/hiv/topics/surveillance/resources/reports/*. Published February 2013. Accessed July 3, 2013.
5. Prejean, J., R. Song, A. Hernandez, R. Ziebell, T. Green, F. Walker, L.S. Lin, Q. An, J. Mermin, A. Lansky, and H.I. Hall, Estimated HIV incidence in the United States, 2006-2009. PLoS One, 2011. **6**(8): p. e17502.
6. Hall, H.I., R. Song, P. Rhodes, J. Prejean, Q. An, L.M. Lee, J. Karon, R. Brookmeyer, E.H. Kaplan, M.T. McKenna, and R.S. Janssen, Estimation of HIV incidence in the United States. JAMA, 2008. **300**(5): p. 520-9.
7. B. Koblin, K. Mayer, S. Eshleman, L. Wang, S. Shoptaw, C. Del Rio, S. Buchbinder, M. Magnus, S. Mannheimer, T-Y Liu, V. Cummings, E. Piwowar-Manning, S. Fields, S. Griffith, V. Elharrar, D. Wheeler. Correlates of HIV incidence among black men who have sex with men in 6 U.S. cities (HPTN 061). International AIDS Society Conference, Washington DC, July 20-25, 2012.
8. Centers for Disease Control and Prevention. HIV among Gay and Bisexual Men [online surveillance fact sheet]. May 2012. Available at *http://www.cdc.gov/hiv/topics/msm/pdf/msm.pdf*, last accessed September 20, 2012.
9. CDC. *Diagnosed HIV infection among adults and adolescents in Metropolitan Statistical Areas -- United States and Puerto Rico, 2011.* 2014.
10. Purcell, D.W., C.H. Johnson, A. Lansky, J. Prejean, R. Stein, P. Denning, Z. Gau, H. Weinstock, J. Su, and N. Crepaz, Estimating the population size of men who have sex with men in the United States to obtain HIV and syphilis rates. Open AIDS J, 2012. **6**: p. 98-107.
11. Smith, D.K., M. Van Handel, R.J. Wolitski, J.E. Stryker, H.I. Hall, J. Prejean, L.J. Koenig, and L.A. Valleroy, Vital Signs: Estimated Percentages and Numbers of Adults with Indications for Preexposure Prophylaxis to Prevent HIV Acquisition - United States, 2015. MMWR Morb Mortal Wkly Rep, 2015. **64**(46): p. 1291-5.
12. Molina, J.-M., C. Capitant, B. Spire, G. Pialoux, L. Cotte, I. Charreau, C. Tremblay, J.-M. Le Gall, E. Cua, and A. Pasquet, On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. New England Journal of Medicine, 2015. **373**(23): p. 2237-2246.
13. McCormack, S., D.T. Dunn, M. Desai, D.I. Dolling, M. Gafos, R. Gilson, A.K. Sullivan, A. Clarke, I. Reeves, and G. Schembri, Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. The Lancet, 2015.
14. Grant, R.M., J.R. Lama, P.L. Anderson, V. McMahan, A.Y. Liu, L. Vargas, P. Goicochea, M.n. Casap√≠a, J.V. Guanira-Carranza, M.E. Ramirez-Cardich, O. Montoya-Herrera, T. Fern√°ndez, V.G. Veloso, S.P. Buchbinder, S. Chariyalertsak, M. Schechter, L.-G. Bekker, K.H. Mayer, E.G. Kall√°s, K.R. Amico, K. Mulligan, L.R. Bushman, R.J. Hance, C. Ganoza, P. Defechereux, B. Postle, F. Wang, J.J. McConnell, J.-H. Zheng, J. Lee,

J.F. Rooney, H.S. Jaffe, A.I. Martinez, D.N. Burns, and D.V. Glidden, Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. New England Journal of Medicine, 2010. **363**(27): p. 2587-2599.
15. Brookmeyer, R., D. Boren, S.D. Baral, L.G. Bekker, N. Phaswana-Mafuya, C. Beyrer, and P.S. Sullivan, Combination HIV Prevention among MSM in South Africa: Results from Agent-based Modeling. PLoS One, 2014. **9**(11): p. e112668.
16. Holtgrave, D.R., When "heightened" means "lessened": the case of HIV prevention resources in the United States. Journal of Urban Health, 2007. **84**(5): p. 648-652.
17. Sullivan, P.S., A. Carballo-Dieguez, T. Coates, S.M. Goodreau, I. McGowan, E.J. Sanders, A. Smith, P. Goswami, and J. Sanchez, Successes and challenges of HIV prevention in men who have sex with men. Lancet, 2012. **380**(9839): p. 388-99.
18. Sullivan, P.S., J. Jones, N. Kishore, and R. Stephenson, The Roles of Technology in Primary HIV Prevention for Men Who Have Sex with Men. Curr HIV/AIDS Rep, 2015.
19. Jenness, S.M., S.M. Goodreau, E.S. Rosenberg, E. Beylerian, K. Hoover, D.K. Smith, and P.S. Sullivan, Impact of the Centers for Disease Control's HIV Pre-Exposure Prophylaxis Guidelines for Men Who Have Sex with Men in the United States. J Infect Dis, 2016 (in press).
20. Khanna, A., S.M. Goodreau, D. Wohlfeiler, E. Daar, S. Little, and P.M. Gorbach, Individualized diagnosis interventions can add significant effectiveness in reducing human immunodeficiency virus incidence among men who have sex with men: insights from Southern California. Ann Epidemiol, 2015. **25**(1): p. 1-6.
21. Oster, A.M., C.H. Johnson, B.C. Le, A.B. Balaji, T.J. Finlayson, A. Lansky, J. Mermin, L. Valleroy, D. Mackellar, S. Behel, and G. Paz-Bailey, Trends in HIV Prevalence and HIV Testing Among Young MSM: Five United States Cities, 1994-2011. AIDS Behav, 2013.
22. Centers for Disease Control and Prevention. HIV Infection Risk, Prevention, and Testing Behaviors among Men Who Have Sex With Men—National HIV Behavioral Surveillance, 20 U.S. Cities, 2014. HIV Surveillance Special Report 15. *http://www.cdc.gov/hiv/library/reports/surveillance/#panel2*. Published January 2016. Accessed January 2, 2017.
23. Sanchez, T., M. Zlotorzynska, C. Sineath, E. Kahle, and P. Sullivan, The Annual American Men's Internet Survey of Behaviors of Men Who have Sex with Men in the United States: 2014 Key Indicators Report. JMIR Public Health Surveill, 2016. **2**(1): p. e23.
24. Grey, J.A., K.T. Bernstein, P.S. Sullivan, D.W. Purcell, H.W. Chesson, T.L. Gift, and E.S. Rosenberg, Estimating the Population Sizes of Men Who Have Sex With Men in US States and Counties Using Data From the American Community Survey. JMIR Public Health Surveill, 2016. **2**(1): p. e14.
25. Sullivan, P.S., J.A. Grey, and B.R. Simon Rosser, Emerging technologies for HIV prevention for MSM: what we have learned, and ways forward. J Acquir Immune Defic Syndr, 2013. **63 Suppl 1**: p. S102-7.
26. CDC, Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex With Men. MMWR, 2011. **60**(03): p. 65-68.
27. Smith, D.K., L.A. Grhskopf, R.J. Black, J.D. Auerbach, F. Veronese, K.A. Struble, L. Cheever, M. Johnson, L.A. Paxton, I.M. Onorato, and A.E. Greenberg, Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States. MMWR, 2005. **54**(RR02): p. 1-20.
28. Smith, D.K., M. Van Handel, R.J. Wolitski, J.E. Stryker, H.I. Hall, J. Prejean, L.J. Koenig, and L.A. Valleroy, Vital signs: Estimated percentages and numbers of adults with indications for preexposure prophylaxis to prevent HIV acquisition–United States, 2015. MMWR. Morbidity and mortality weekly report, 2015. **64**(46): p. 1291.

29. Elsesser, S.A., C.E. Oldenburg, K.B. Biello, M.J. Mimiaga, S.A. Safren, J.E. Egan, D.S. Novak, D.S. Krakower, R. Stall, and K.H. Mayer, Seasons of Risk: Anticipated Behavior on Vacation and Interest in Episodic Antiretroviral Pre-exposure Prophylaxis (PrEP) Among a Large National Sample of US Men Who have Sex with Men (MSM). AIDS and Behavior, 2015: p. 1-8.
30. World Health Organization, Policy brief: pre-exposure prophylaxis (PrEP): WHO expands recommendation on oral pre-exposure prophylaxis of HIV infection (PrEP). 2015.
31. Noar, S.M., H.G. Black, and L.B. Pierce, Efficacy of computer technology-based HIV prevention interventions: a meta-analysis. AID, 2009. **23**(1): p. 107-115.
32. Spring, B., J.M. Duncan, E.A. Janke, A.T. Kozak, H.G. McFadden, A. DeMott, A. Pictor, L.H. Epstein, J. Siddique, C.A. Pellegrini, J. Buscemi, and D. Hedeker, Integrating technology into standard weight loss treatment: a randomized controlled trial. JAMA Intern Med, 2013. **173**(2): p. 105-11.
33. Krishna, S. and S.A. Boren, Diabetes self-management care via cell phone: a systematic review. J Diabetes Sci Technol, 2008. **2**(3): p. 509-17.
34. Sullivan, P.S., J. Jones, N. Kishore, and R. Stephenson, The Roles of Technology in Primary HIV Prevention for Men Who Have Sex with Men. Curr HIV/AIDS Rep, 2015. **12**(4): p. 481-8.
35. Muessig, K.E., M. Nekkanti, J. Bauermeister, S. Bull, and L.B. Hightow-Weidman, A Systematic Review of Recent Smartphone, Internet and Web 2.0 Interventions to Address the HIV Continuum of Care. Current HIV/AIDS Reports, 2015: p. 1-18.
36. Khosropour, C.M., J.G. Lake, and P.S. Sullivan, Are MSM Willing to SMS for HIV Prevention? J Health Commun, 2013.
37. Mitchell, K.J., M.L. Ybarra, J.D. Korchmaros, and J.G. Kosciw, Accessing sexual health information online: use, motivations and consequences for youth with different sexual orientations. Health Educ Res, 2013.
38. Pew Research Center. A portrait of smartphone ownership – 2015 [online research report]. 2015. Available at: *http://www.pewinternet.org/2015/04/01/chapter-one-a-portrait-of-smartphone-ownership/*. Last accessed: January 4, 2016.
39. Kelley, C.F., E. Kahle, A. Siegler, T. Sanchez, C. Del Rio, P.S. Sullivan, and E.S. Rosenberg, Applying a PrEP Continuum of Care for Men who Have Sex with Men in Atlanta, GA. Clin Infect Dis, 2015.
40. US Public Health Service, Preexposure prophylaxis for the prevention of HIV infection in the United States - 2014. 2014.
41. VanderWeele, T.J., Causal mediation analysis with survival data. Epidemiology (Cambridge, Mass.), 2011. **22**(4): p. 582.
42. Emsley, R., G. Dunn, and I.R. White, Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. Statistical Methods in Medical Research, 2010. **19**(3): p. 237-270.
43. Kernan, W., C. Viscoli, R. Makuch, L. Brass, and R. Horwitz, Stratified Randomization for Clinical Trials. Clin Epidemiol, 1999. **52**(1): p. 19-26.
44. Siegler, A. *PrEP Locator*. 2016 [cited 2016 11/22/2016]; Available from: *https://preplocator.org/*.
45. Zablotska, I.B., G. Prestage, M. Holt, M. Poynten, J. de Wit, R. Guy, L. Mao, J. McAllister, and A.E. Grulich, Australian gay men who have taken nonoccupational postexposure prophylaxis for HIV are in need of effective HIV prevention methods. CORD Conference Proceedings, 2011. **58**(4): p. 424-428.
46. Sullivan, P.S., R. Driggers, J. Stekler, A. Siegler, T. Goldenberg, S.J. McDougal, J. Caucutt, J. Jones, and R. Stepheneon, Usability and Acceptability of a Mobile

Comprehensive HIV Prevention App for Men Who Have Sex With Men – HealthMindr. J Med Internet Res, 2017 (in press).
47. Frangakis, C.E. and D.B. Rubin, Principal stratification in causal inference. Biometrics, 2002. **58**(1): p. 21-29.
48. Gaydos, C., C. Cartwright, P. Colaninno, J. Welsch, J. Holden, S. Ho, E. Webb, C. Anderson, R. Bertuzis, and L. Zhang, Performance of the Abbott RealTime CT/NG for detection of Chlamydia trachomatis and Neisseria gonorrhoeae. Journal of clinical microbiology, 2010. **48**(9): p. 3236-3243.
49. Portnoy, J., J.H. Brewer, and A. Harris, Rapid plasma reagin card test for syphilis and other treponematoses. Public health reports, 1962. **77**(8): p. 645.
50. Bush, S., L. Ng, D. Magnuson, D. Piontkowsky, and R. Mera Giler. *Significant Uptake of Truvada for Pre-exposure Prophylaxis (PrEP) Utilization in the US in Late 2014 – 1Q2015*. in *IAPAC Treatment, Prevention, and Adherence Conference*. 2015. Miami, FL.
51. Hosmer, D.W., S. Lemeshow, and S. May, *Applied survival analysis. Hoboken*. 2008, NJ, Wiley.
52. Harrington, D.P. and T.R. Fleming, A class of rank test procedures for censored survival data. Biometrika, 1982. **69**(3): p. 553-566.
53. Breslow, N.E., Analysis of survival data under the proportional hazards model. International Statistical Review/Revue Internationale de Statistique, 1975: p. 45-57.
54. Creswell, J.W., *Qualitative inquiry and research design: Choosing among five approaches*. 2012: Sage.
55. Patton, M.Q., Qualitative research and evaluation methods. California EU: Sage Publications Inc, 2002.
56. Moustakas, C., *Phenomenological research methods*. 1994: Sage Publications.

SUPPLEMENTAL MATERIALS

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

APPENDICES

APPENDIX A: Screening Informed Consent Form

APPENDIX B: Enrollment Informed Consent Form

APPENDIX C: PrEP and HIV Testing Resources

A list of existing resources that might be included on the resources page can be found below.

PrEP Resources

- Centers for Disease Control PrEP Resources, https://www.cdc.gov/actagainstaids/campaigns/starttalking/materials/prepresources.html
- The Fenway Institute: What is PrEP?, http://thefenwayinstitute.org/prepinfo/
- PrEP Locator, https://preplocator.org/
- AIDS.gov PrEP Information Page, https://www.aids.gov/hiv-aids-basics/prevention/reduce-yourrisk/pre-exposure-prophylaxis/

HIV Testing Resources

- Centers for Disease Control HIV Testing Locator, https://gettested.cdc.gov/
- Centers for Disease Control HIV Testing Information Page, https://www.cdc.gov/hiv/testing/
- AIDS.gov HIV Testing Locator, https://www.aids.gov/hiv-aids-basics/prevention/hiv-testing/hiv-testlocations/
- AIDSvu HIV Testing Locator, https://aidsvu.org/locators/testing-sites/