Making it last: A randomized, controlled trial of a home care system to promote persistence in PrEP care

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Making it last: A randomized, controlled trial of a home care system to promote persistence in PrEP care

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PrEP@Home

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS 5
PROTOCOL TEAM ROSTER 6
1. INTRODUCTION 8
2. METHODS 10
3. STUDY OVERVIEW 11
3.1 Study Design 11
3.2 **Study Schedule** 11
3.4 Study Locations 13
3.5 Study Population 13
3.5.1 Sample 13
3.5.2 Participant Eligibility 13
3.5.3 Inclusion Criteria 14
3.5.4 Exclusion Criteria 14
3.6 Recruitment Procedures 15
3.6.1 Primary recruitment methods 15
3.6.2 Secondary recruitment methods 15
3.7 Participant Retention 15
3.8 Participant Withdrawal / Early Termination 16
4. STUDY INTERVENTION 16
5. TRIAL DESIGN 17
5.1 Study Arms 17
5.2 Randomization 17
6. STUDY Procedures 17
6.1 Visit Procedures 17
6.1.1 Scheduling 17
6.1.2 Visit Reminders 18
6.2 Baseline Visit 18

6.3 **Follow-up Visits** 19
6.4 Referrals 19
6.5 Measures 20
6.5.1 Surveys 20
6.5.2 Outcome Measures 20
6.6 **Training** 20
7. LABORATORY SPECIMENS AND PROCEDURES 20
7.1 HIV Testing 20
7.2 STI Testing 21
7.3 Safety Labs 21
7.4 Dried Blood Spots 21
7.5 Biohazard Containment 21
7.6 Future Storage 21
8. SAFETY MONITORING AND ADVERSE EVENT REPORTING 21
8.1 Data Safety Monitoring Board (DSMB) 21
8.2 Adverse Events 22
9. STATISTICAL CONSIDERATIONS 22
9.1 Primary Outcome 22
9.2 **Power to detect effects in primary outcomes** 23
9.3 Exploratory analyses 23
9.4 Mathematical modeling 23
9.5 Qualitative 24
9.6 Cost-effectiveness and cost-utility analyses 25
9.6.1 Costing the intervention and standard of care arms 25
9.6.2 Determining the health effect 26
9.6.3 Cost-effectiveness and cost-utility analysis 26
10. HUMAN SUBJECTS CONSIDERATIONS 26
10.1 Informed Consent 26
10.2 Risks to participation 27
10.3 Benefits to the subject or future benefits 27
10.4 Compensation 27

10.5 Participant Privacy and Confidentiality.....27.....
10.6 Communicable Disease Reporting Requirements 28
11. ADMINISTRATIVE PROCEDURES. .....2811.1 Data Collection, Entry and Management 28
11.2 Quality Assurance 29
11.3 Regulatory Requirements 29
11.4 Institutional Review Board.....29
12. REFERENCES.....30

LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
CDC	Centers for Disease Control and Prevention
CDMS	Clinical Data Management System
CFR	U.S. Code of Federal Regulations
CITI	Collaborative Institutional Training Initiative
CLIA	Clinical Laboratory Improvement Amendments
DBS	Dried Blood Spots
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GLMM	Generalized Linear Mixed Model
GSN	Geosocial network
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISO	International Organization for Standardization
LGBT	Lesbian, Gay, Bisexual, and Transgender
MMS	Mobile messaging service
MSA	Metropolitan Statistical Area
MSM	Men who have sex with men
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PCR	Polymerase chain reaction
PEP	Post Exposure Prophylaxis

PrEP	Pre-Exposure Prophylaxis
RPR	Rapid plasma reagin
SMS	Standard messaging service
STI	Sexually Transmitted Infection
TAF/FTC	Tenofovir alafenamide/emtricitabine
TDF/FTC	Tenofovir disoproxil fumarate/emtricitabine
TFV-DP	Tenofovir diphosphate
YBMSM	Young Black Men who have sex with men
FTC-TP	Emtricitabine triphosphate

PROTOCOL TEAM ROSTER

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1. INTRODUCTION

Background and Rationale

Pre-exposure prophylaxis (PrEP) has demonstrated high effectiveness and efficacy for HIV prevention for men who have sex with men (MSM),[1-3] who are disproportionally impacted by HIV. The US Centers for Disease Control and Prevention (CDC) estimates that approximately 1.2 million US adults are eligible for PrEP, including 492,000 MSM.[4] PrEP prescriptions are growing exponentially, with over 79,000 prescriptions between 2012 and 2015 in the US,[5] yet the benefits of PrEP protection are accruing inversely to HIV acquisition risk,[6] with young and minority MSM less likely to access PrEP despite higher risk.

Studies indicate expanding PrEP access would be both cost-effective[7] and feasible for MSM, including MSM of color.[8] Modeling indicates that if PrEP were scaled to cover 40% of behaviorally eligible MSM in the United States, approximately 25% of new HIV infections among all MSM would be averted over the next ten years.[9]

Scale-up of PrEP may be limited by the burden to the healthcare system. Guidance issued by CDC[10] and by WHO[11] calls for quarterly follow-up visits for those on PrEP, to include behavioral and laboratory assessments and intervention as needed. The burden of quarterly visits for MSM, if PrEP was brought to scale at an 80% level among those eligible, would be 1,576,000 annual patient visits.[4] We estimate such visits would entail over 3 million hours of patient time, with an opportunity cost of $68 million annually, in addition to the millions spent on clinician time and clinic facilities.

In 2015, MSM continue to account for two-thirds of new HIV cases in the United States.[12] Within this elevated risk group, Black MSM (10,315/26,645, 39%) and young MSM aged 20-34 (15,381/26,645, 58%) bear disproportionate burdens,[12] and represent appropriate populations for intervention. As PrEP is being brought to scale, it has been shown to have high effectiveness: in international settings the PROUD study[1] found 86% reduction in anticipated infections, and the IPERGAY[13] study's open-label extension found 95% reduction. In domestic settings, an observational assessment of Bay Area Kaiser HMO patients found no new cases of HIV among their PrEP users, despite common bacterial STI, with 855 person years of follow-up.[3]

Implementation data from Washington D.C., San Francisco, and Miami have found that at 12months post-PrEP initiation, persistence in PrEP care was 79%, and similarly found PrEP adherence among those maintained in care at 80%.[14] Given low adherence among US MSM in the iPrEX RCT (56%),[15] higher levels of adherence can likely be attributed to patient awareness of using an active medication with documented efficacy, as opposed to the blinded RCT participants not knowing if the medication was protective, or whether they were receiving a placebo that couldn't work. Interventions that promote improved persistence in PrEP care are an essential part of optimizing the impact of PrEP.

Our theoretical model regarding a PrEP care continuum, as retrospectively applied to a cohort of young, Black MSM (YBMSM), indicates that a key to achieving high PrEP efficacy will be persistence in PrEP care,[16] yet persistence has been suboptimal in studies among YBMSM. In a cohort study of YBMSM with PrEP offered as standard of care, 38/110 participants accepted, but within 6 months of initiation 16% (n=6) ceased PrEP. Of three observed seroconversions, two were among those who had started but subsequently ceased PrEP. In ATN 113, 60% of participants had protective PrEP dosing at 4 weeks follow-up, but only 23% maintained at 36 weeks follow-up.[17] Minimizing the participant burden of PrEP while supporting persistence in care could reduce PrEP cascade drop-off.

Young persons in urban areas,[18,19] and Black persons in urban areas,[18,19] have lower access to transportation by car, and are therefore more likely to rely on transit methods requiring larger amounts of time.[18,19] This is important because urban transportation has been identified as a potential barrier to PrEP access.[20]

As effectiveness of PrEP is already established, PrEP@Home could be beneficial to bringing PrEP to scale in a variety of care settings. For large PrEP clinics, home care would enhance capacity for PrEP scale-up given limited space and personnel resources. For instance, Magnet@Strut Clinic in San Francisco has initiated over 1,900 patients on PrEP (close to 2% of total PrEP prescriptions in the United States),[21] and Callen-Lorde in New York has initiated PrEP for over 2,000 PrEP. In the past, Magnet has at times been limited in accepting new PrEP patients, attributing this problem to lack of available provider time and clinic space, the bulk of which was occupied by PrEP visits. Similarly, other common venues of PrEP provision have limited "brick and mortar" space to add substantial numbers of new patient visits, an issue that home care could address.

Electronic communication, such as that used by PrEP@Home surveys and patient portal, is now the predominant mode of communication for young people. Male adolescents send or receive over 2800 mobile messages (MMS and SMS) a month on average,[22] 96% of MSM teens use Facebook,[23] and the predominant final activity immediately prior to sleep for 69% of adolescents involves electronic media.[24] Simply put, mobile and electronic interactions are now the dominant means of communication and interaction for young men. Moreover, 75% of young MSM use geosocial network (GSN) websites, and 60% use GSN apps, with a majority reporting frequent use and reporting an intended use for "meet(ing) guys for sex."[23] Smartphone ownership is particularly high among YBMSM, with ownership higher in groups identifying as Black (70%) or under age 30 (85%) than ownership in the general US (63%).[25] Moreover, smartphone ownership is increasing as sub-$100 smartphones proliferate.

Relative to clinic-based STI tests, mail-in tests have been shown to improve rescreening rates, cost-effectiveness, and acceptability. Home-based, self-collected test kits for chlamydia increased rescreening rates by over 20% in one study.[26] Another study found home-based testing for chlamydia and gonorrhea to be more cost-effective than clinic-based testing.[27] Moreover, a majority of MSM prefer home-based HIV/STI tests to clinic-based tests, with 75% willing to undergo routine home screenings with no monetary incentive.[28,29]

A home-based PrEP support system could address some patient concerns regarding PrEP uptake. One limitation of PrEP is the heavy burden of follow-up visits borne by patients, including indirect cost (i.e. absence from paid work, need for child-care) and direct cost (i.e. transport, copayments)[30] that could lead to problems with PrEP adherence.[31,32] The home care system for PrEP is comprised of inexpensive, commonly available laboratory supplies such as finger prick devices, swabs, and microtubes. Patient self-completion surveys that simulate clinician visit typical questions may allow for clinicians to have a higher volume of patients due to time savings. Given these inputs, the home care system has the potential to be cost saving, depending in part on the level of human resources required to maintain patients in home care.

A home-based monitoring approach could facilitate PrEP prescription by non-HIV specialist doctors. Expanding access to PrEP will involve providing services to HIV-negative MSM who frequently do not visit HIV specialist providers. Provider type and current care models may pose limitations to PrEP scale-up.[31,33] A survey of providers found that generalist physicians, relative to HIV specialists, were more likely to rate time required for counseling (19% and 6%, respectively) and time for clinical monitoring (23% and 10%) as barriers to providing PrEP.[33] A qualitative study found that providers believe their current care models are poorly suited to PrEP, particularly

surrounding extensive follow-up and monitoring required. In a pilot test that replaced a regular clinician visit with a PrEP@Home visit, 55/58 participants successfully renewed their PrEP prescriptions without an in-person provider visit. Forty percent (22/55) indicated they would have a greater likelihood of remaining on PrEP if the home care system was made available and 87% (48/55) indicated they would like to use PrEP@Home again.

A home-based PrEP monitoring and support system could decrease provider and patient burden, increase patient willingness to initiate or remain on PrEP, facilitate the provision of PrEP by primary care practitioners who are less experienced in counseling to prescribe PrEP, and might be cost-saving. This study will be the first to assess the feasibility of home-based PrEP support among providers.

The purpose of this study is to assess the maintenance in PrEP care, not to study the effectiveness of PrEP medication. Adherence to follow-up visits will be assessed through several methods. PrEP will be prescribed according to standard of care practices.

2. METHODS

Aim 1. Assess protective levels of emtricitabine triphosphate (TFV-DP) for the intervention relative to the control arm.

Hypothesis: Participants randomized to PrEP@Home will have higher levels of protection against HIV infection as determined by levels of TFV-DP than standard of care controls. Drug levels are an indication of maintenance in PrEP care throughout the study.

Aim 2. Conduct additional assessments to contextualize trial results and facilitate appropriate scale-up:

> **Aim 2.1** Adjusted analyses of the primary outcome that control for potential residual confounding, and analyses of secondary outcomes including retention in PrEP care.
>
> **Aim 2.2.** Exploratory analyses of intervention effectiveness across subgroups, and analysis of potential mediators of persistence in PrEP care across both study arms, such as medication self-efficacy.
>
> **Aim 2.3.** Mathematical modeling to determine population-level impact for different scaleup scenarios.
>
> **Aim 2.4.** Interviews and survey assessments among clinicians, healthcare managers, and patients involved in PrEP care to inform roll out of home care, should the intervention demonstrate efficacy.

Aim 3. Conduct cost-effectiveness and cost-utility analyses of the PrEP@Home intervention.

3. STUDY OVERVIEW

3.1 Study Design

The study is a stratified randomized, controlled trial comparing PrEP@Home intervention care to standard of care control (i.e. patients being seen quarterly in clinic with a provider), with primary outcome of having protective levels of TFV-DP (700 fmol/ml or greater) and secondary outcome of retention in PrEP care, as measured by photo of dated prescription label.

A screening will be conducted online and involve a screening consent and questions to determine initial eligibility. This will be followed by a full consent (if eligible), a baseline survey, and the return of self-collected specimens for testing to determine clinical PrEP eligibility. Those eligible for the study will be enrolled into the trial and randomized to either intervention (PrEP@Home) or control (standard of care). Participants assigned to the PrEP@Home intervention will have a baseline teleconsultation with a site study clinician who will be responsible for prescribing PrEP as indicated. Intervention participants enrolled prior to May 2022 will be offered telemedicine consultations at 1, 3, 6, 9 and 12 months, and will complete quarterly home specimen collection for laboratory tests recommended by CDC at each time period. Individuals enrolled after May 2022 will be offered telemedicine consultations at 1, 3, and 6 months, and will complete quarterly home specimen collection for laboratory tests recommended by CDC at each time period. The study virtual visits consist of surveys, specimen collection, and telemedicine consultation. Those assigned to the control condition will be referred to a publicly available website that geolocates the nearest PrEP provider, www.PrEPLocator.org. Both conditions will have identical TFV-DP kit collection for primary outcome assessments at month 6 (and 12 months for those enrolled before May 2022) and app-based surveys for secondary outcomes assessments at baseline, 3, 6, (and 9 and 12 months for those enrolled before May 2022).

Study sites in Atlanta, GA, Boston, MA, Jackson, MS, St. Louis, MO, and Cleveland, OH, will allow for recruitment to focus on MSM known to be at highest risk of acquisition and with documented lower levels of persistence in PrEP care. The sample of 396 will be composed of at least 50% Black and 50% younger (aged 18-34) participants, including at least 25% YBMSM.

Prior to the RCT starting, a small pilot with 5-10 participants will be conducted to test and verify logistics of lab processing procedures. Included in the pilot will be shipping lab specimens, tracking the specimen samples through processing and testing the app systems shipping and lab results components.

3.2 Study Schedule

Figure 1: Study Design or Schema for 12 Months of Follow Up

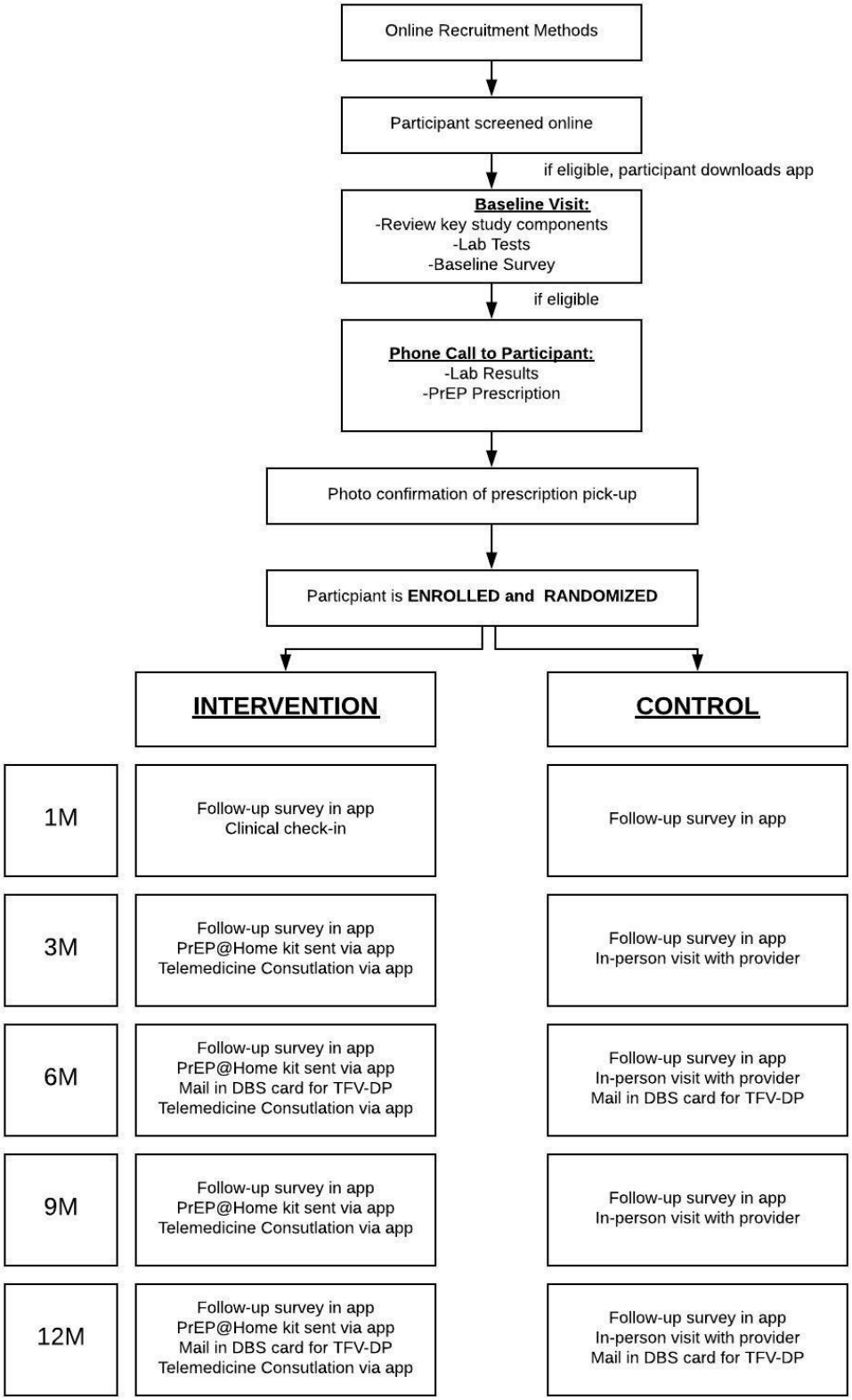
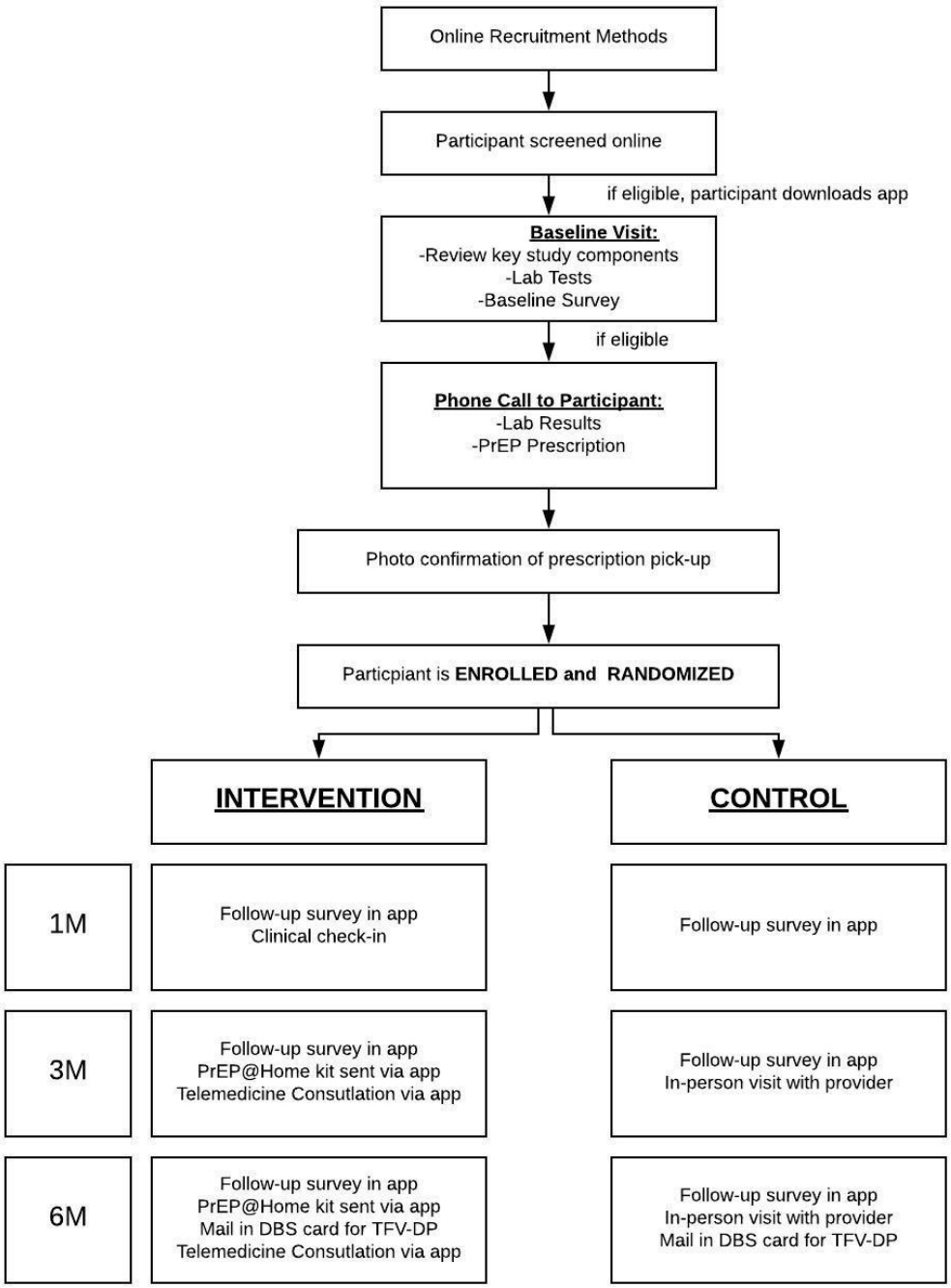


Figure 2: Study Design or Schema for 6 Months of Follow Up



3.3 Study Timeline

Study to complete target enrollment in 18 months of recruitment. Participants will be followed for 6 and/or 12 months after initiating PrEP.

3.4 Study Locations

Study procedures and data collection will take place in the metropolitan areas of Atlanta, GA, Boston MA, Jackson, MS, St. Louis, MO, and Cleveland, OH. The sites where the study will be conducted include PRISM Health Research Center (Atlanta), The Fenway Institute (Boston), UMMC with clinic space at Open Arms Health Care Center and Express Personal Health (Jackson), The Infectious Disease Clinic at Washington University (St. Louis), and MetroHealth (Cleveland). Each site will have a study clinician prescribing PrEP to site patients and site staff to support study conduct. Study participants will be completing the PrEP support kits in their homes or another private location of their selection.

3.5 Study Population

3.5.1 Sample

The study population includes born males, ages 18 to 49 years, who have sex with men. Eligible men will be residents of metropolitan areas of Atlanta, Georgia; Boston, Massachusetts; Jackson, Mississippi; St. Louis, Missouri, or Cleveland, Ohio. Total sample size will be 396, with 50% minority and 50% age 18-34.

3.5.2 Participant Eligibility

After recruitment, we will use a three-stage process to screen participants for eligibility. For Stage 1, a screener will be used to determine study visit eligibility. The screener will be conducted in Alchemer, self-completed by all participants excepting those that require a phone call, in which case the screener form will be filled by study staff. The initial eligibility criteria include (1) male at birth, (2) age 18-49, (3) live in the metro area of a study site, (4) self-report HIV negative status, (5) own a smartphone, (6) not currently taking PrEP or <3 months of PrEP use in lifetime or stopped taking PrEP >6 months ago, (7) not enrolled in an HIV prevention trial, (8) willing to use study-provided PrEP navigation services to obtain PrEP, and (9) willing to use a home test kit. Those eligible for a visit based on the screener results will be shown the full study consent to review and sign. Consented participants will be called to confirm consent and for further eligibility determination. This step may take up to two weeks.

Stage 2 of eligibility assessment will be participant visit with study staff, either conducted in clinic or via telehealth consultation over Zoom. Decision will be made depending on clinic ability to conduct in-person visits and participant preference. Participants will complete a more detailed behavioral screening (based on CDC and WHO guidelines for PrEP initiation) and screened for clinical eligibility for PrEP and other study eligibility criteria: (1) report anal sex with a man in the past 6 months, (2) provide at least 2 means of alternate contact, (3) willing to take a photo of PrEP prescription label, (4) ability to complete English-language forms, (5) willing to take and adhere to PrEP daily dosing, (6) willing to obtain PrEP for a year, even if financial assistance is not available, (7) HIV-negative rapid and laboratory test or 4th gen HIV test only, (8) no symptom(s) that could indicate acute HIV infection, (9) creatinine clearance ≥60 ml/min, (10) no contraindications to taking Tenofovir Disoproxil Fumarate/ Emtricitabine (TDF/FTC) or Tenofovir Alafenamide/ Emtricitabine (TAF/FTC), (11) no history of hemophilia and (12) successful completion of a selffinger prick at study site or home. Participants will be called by the study staff with lab results. Participants who are Stage 2 eligible for the study will be provided a prescription by the site study clinician. PrEP prescription can be called in or given to participant while waiting for 4th gen HIV

and creatinine clearance results as long as rapid HIV test is documented negative and participant meets other eligibility criteria. Participants who are ineligible will be linked to care as needed. If more than four weeks pass since initial visit, then participants will need to rescreen for PrEP eligibility, including a repeat HIV test. Participants may be able to rescreen if symptoms of acute HIV infection are no longer present and HIV infection is ruled out per local protocol.

Stage 3 screening will be verification that HIV 4th generation and creatinine clearance tests indicate eligibility and a PrEP prescription has been filled. Using our electronic software (described below) the survey will prompt participants to use their smartphone to take a photo of their prescription label that identifies their name, date of prescription, and the medication name. We anticipate this to occur within one week of receiving the prescription. Once this brief process is completed, participants will be enrolled into the trial.

3.5.3 Inclusion Criteria

- Male at birth
- Age 18-49
- Report anal sex with a man in the past 6 months
- Are able to complete survey instruments in English
- Live in the metropolitan area of a study site
- Are willing to provide at least 2 means of alternate contact
- Willing to not enroll in another HIV prevention trial
- HIV-negative (self-reported and lab confirmed)
- Own and willing to use a smart phone for the duration of the study
- Willing to download study app
- Willing to take a photo of a PrEP prescription label
- Behaviorally indicated for PrEP (per CDC guidance, Appendix 3) or if sexually active African American MSM[1] [34]
- PrEP naïve or < 3 months lifetime experience of PrEP use or stopped taking PrEP >6 months ago
- Willing to take PrEP including adherence to daily dosing
- Willing to use study-provided PrEP navigation services to obtain coverage for PrEP medication
- Able to work with study site to develop a plan to cover financial cost of PrEP if not covered through insurance or Gilead financial assistance
- Willing to use a home kit that will include self-administered collection of urine, rectal and pharyngeal swabs, and finger prick blood.

3.5.4 Exclusion Criteria

- Not male sex at birth
- Reports having genital reassignment surgery
- HIV positive
- <18 or ≥ 50 years of age
- Currently enrolled in another HIV prevention trial
- Symptoms of acute HIV infection, or being evaluated for acute infection because of recent high risk exposure
- Currently taking PEP

[1] Based on WHO Guidelines of including populations at “substantial risk”

- Creatinine clearance <60 ml/min
- Contraindications to taking tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or tenofovir alafenamide/emtricitabine (TAF/FTC)
- History of hemophilia
- Unable to conduct finger prick at study site
- Health Insurance with Kaiser Permanente (unable to prescribe PrEP through the study)
- Investigator discretion to exclude anyone whose best interest is not to participate
- Evidence of fraudulent participation, such as duplicate IP address, multiple screening attempts, duplicate emails, etc

3.6 Recruitment Procedures

For participants who meet eligibility criteria, we will ask for a first name, e-mail and phone number. For participants who do not screen eligible for the study, we will ask them if they want to provide their contact information for future studies for which they might be eligible. If they indicate interest in being contacted for future studies, we will request their contact information. These data will be stored in the secure, HIPAA-compliant servers of Alchemer.

Participants will have the opportunity to indicate that they prefer to be called by a study staff member and screened over the phone rather than completing the full study screener online. Participants will be asked to read an informed consent form and indicate consent prior to completing the online screening survey or to verbally indicate consent if being screened on the phone by a study staff.

Venue-based recruitment strategies may be used, in which staff attend known MSM venues or events to recruit for the study. Possible venues include bars, malls, clubs and events such as Gay Pride. During venue-based recruitment, study staff will obtain verbal consent and then administer screener questions using a handheld device. Flyers and similar forms of visual advertisement may also be posted in public and private venues such as clinics, bars, clubs, churches, stores, restaurants, colleges, coffee shops, public transit venues, etc.

3.6.1 Primary recruitment methods

Primary recruitment methods include targeted online recruitment strategies, venue-based recruitment, and flyers and visual advertisements reviewed by the Emory IRB. Links to the screener survey will be advertised through banners or electronic messages on social media platforms such as Facebook, Grindr, or Instagram.

3.6.2 Secondary recruitment methods

Other recruitment methods will be used if recruitment targets are not being met. These additional strategies may include recruiting individuals who have recently been prescribed PrEP but are not established in a follow-up routine. This recruitment strategy would require a change to the exclusion criteria to allow for individuals recently prescribed PrEP to enroll.

3.7 Participant Retention

Once a participant enrolls in the study, study staff will seek to retain the participant throughout the follow-up period in order to minimize possible bias associated with loss-to-follow-up. Study staff will be responsible for developing and implementing standard operating procedures to target this goal. Retention efforts include an explanation of the study and procedural requirements during the informed consent process and re-emphasis throughout the study. Detailed contact information

will be collected at the study baseline visit, with active review and updating of this information throughout the study. Reminder mechanisms will be used through the application, including notifications and messaging. Staff will use electronic messages, telephone calls, or emails to serve as reminders prior to scheduled consultation visits. Missed visits will be immediately followed up, with rescheduling. Staff will attempt to reengage participants who have been unresponsive to scheduling attempts through the duration of the study.

3.8 Participant Withdrawal / Early Termination

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. Early study termination may occur for the following reasons:

- Participants who have a confirmed HIV-positive test.
- Participants also may be withdrawn if the study is terminated prior to its planned end date.
- Participants will be withdrawn from the study if the physician determines it is in the participant's best interest to discontinue participation in the study.

4. STUDY INTERVENTION

The PrEP@Home System is a fully remote system for conducting PrEP care with the goal to serve as a virtual visit and to allow providers to renew PrEP prescriptions without an in-person visit. To allow this to happen, relevant study data will be provided to participants' PrEP-prescribing physicians. Data that would be collected as part of a standard quarterly PrEP follow-up visit[10], including all lab results and relevant participant behavioral survey results, will be shared with providers. Participants will need to sign a release form allowing us to share these test and behavioral survey results with their provider. The release form is uploaded to eIRB.

The PrEP@Home System includes the participant facing app, the clinician dashboard and the administrative system. Participants will be able to track their study schedule through an application and message study staff if needed. All participants will download the app in order to access the quarterly surveys and to be able to track the home testing kits. To manage study logistics, control participants will receive the same management system as the intervention.

PrEP@Home System: Home Care Kit

Participants will receive the home care kit as a plain box via standard mail. The box includes self-collection components and specimen return shipping. Each specimen collection component has its own bag containing instructions and materials for the specimen collection along with biohazard sealable bags for specimen return. The instructions are optimized to facilitate quality specimen collection and ease of use. The shipping is tracked through the study management system.
Laboratory results and the survey results will be collated and uploaded to an electronic interface for study clinicians, the clinician dashboard. If laboratory and behavioral survey results do not show contraindications to PrEP continuation, the study clinician will have the choice to renew the prescription without a visit by the patient. If there is a laboratory or behavioral result that the study clinician wants to discuss with the participant, then a telemedicine appointment will be scheduled. For positive laboratory results, participants will be referred to care for follow-up.

5. TRIAL DESIGN

5.1 Study Arms

The Intervention group will be assigned to using the PrEP@Home system for 6 months and/or one year of follow-up PrEP care, including telemedicine visits if needed and home test kits. Participants in the Intervention group will have full access to the application. All PrEP consultations will be conducted via telemedicine unless there is a clinical need to be seen in-clinic. Participants will have the option of coming to the clinic for in-person linkage to care at the end of study, if clinics are open.

The Control group will be actively linked to a local PrEP provider for standard of care follow-up. Participants in the Control group will see portions of the study app pertinent to their participation in the study, including electronic surveys and kit tracking for the mail DBS card for TFV-DP. Partner institutions at each site are already implementing PrEP as standard of care in their community, and participants will be referred to these institutions for PrEP care. Each study site will have designated local clinics that have agreed to provide standard PrEP care to control arm patients.

5.2 Randomization

Upon completion of stage 3 eligibility assessment (successful initiation of PrEP as determined by photo of prescription label), participants will be randomized to either intervention (PrEP@Home, n=264) or control (standard of care, n=132). Participants will be randomized using an electronic data system, DFexplore. We will implement a stratified randomization scheme using categories of age (18-34, 35-49) and study site to decreases the likelihood of Type I error due to the expected association between covariates and study outcome. An uneven allocation ratio of 2:1 (Intervention : Control) will facilitate subgroup analyses and modeling for Aims 2 and 3 by allowing for larger intervention group size.

All randomization will be accomplished within the study data management platform; within each stratum, the data system will produce a sequential block randomization list. This list, not viewable by study PI's or the study statistician, will automatically populate the appropriate study arm assignment in the electronic data system at the time each new participant is randomized at any of the four study sites.

6. STUDY PROCEDURES

Visits include screening, baseline, and follow-up for months 1, 3, 6, 9, and 12 for those enrolled prior to May 2022, and months 1, 3 and 6 for those enrolled after May 2022. Procedures outlined in Appendix 2. A cross-sectional survey will be sent out to all participants to collect information on behavior and PrEP changes due to COVID-19 pandemic and distancing regulations.

6.1 Visit Procedures

6.1.1 Scheduling

Once recruited respondents have completed the online screening, study site staff will contact the eligible participants, and schedule a baseline visit for either at the local study site or via Zoom. Participants will be seen at the research clinical space at their local study site or via Zoom telehealth consultation.

After baseline procedures are completed (Section 6.2) and participants are randomized, study staff will schedule telemedicine appointments with intervention arm participants via electronic

messages. Control arm participants will receive an active linkage to care scheduled visit to study identified standard of care clinics, or to the participant's preferred local provider, for the PrEP 1 month follow-up visit.

6.1.2 Visit Reminders

Electronic reminder mechanisms for intervention participants will be sent, including app notifications and/or electronic messages. Staff will use electronic messages, telephone calls, or emails to serve as reminders for scheduled consultation visits.

6.2 Baseline Visit

All baseline procedures are identical for both intervention and control participants and occur after participant provides consent. Participants will be directed to download the study app, P@H, and will be able to take the baseline survey through the app. Participants will be called and scheduled for a baseline visit and instructed to have materials necessary for enrollment in PrEP financial assistance programs. Study consent will be reviewed with participants at the clinic visit and eligibility will be confirmed for stage 1 and assessed for stage 2 (section 3.5.2). Participants will talk with a healthcare provider about initiating PrEP and any concerns they have regarding PrEP. The baseline survey will assess domains including demographics, healthcare, HIV/STI knowledge and testing history, PrEP knowledge and interest, sexual history including overall and detailed partner-level data, substance use history including injection drug use, and scientifically validated scales for depression, anxiety, resilience, self-efficacy, experience of racism, and stigma.

Participants will conduct self-finger prick rapid HIV test either at the clinic or from home test kit. If negative, they will proceed to have specimens collected to be tested for creatinine, HIV AbAg (4^{th} gen), Hepatitis B (HBsAg), Hepatitis C antibody (anti-HCV), syphilis (EIA with reflexive RPR), and oral, pharyngeal, and rectal gonorrhea/chlamydia (NAAT). Laboratory testing will be conducted by CLIA-certified laboratories at each site's locally contracted laboratory. If a participant has completed these labs as part of PrEP initiation at the clinic in the past 3 months, only the HIV AbAg (4^{th} gen) test will need to be repeated along with the self-finger prick. Other tests may be repeated at clinician discretion. Participants unable to come to the clinic for the baseline visit, will be sent a home test kit for self-collected specimens. The kit will contain instructions on specimen collection for urine, throat and rectal swabs, and finger prick for dried blood spot and microtainer. The participant will mail the specimens back, using pre-paid mailer, to the lab for testing.

All participants will receive a follow-up call to receive lab results. Participants with low creatinine clearance (<60 ml/min) or who are positive for HIV will be ineligible, and referred to local clinical care, independent of study participation. Participants testing positive for STI, Hepatitis B, or Hepatitis C will be referred to local clinics that can provide treatment options for those with and without insurance, with clinic referrals provided by study staff experienced in providing linkage to care services. Participants who test positive for Hepatitis B will be counselled on the need to contact study staff if they plan on stopping PrEP.

Eligible participants will have a three-month prescription for PrEP sent to the pharmacy of their choice. The study will recommend pharmacies that can send prescriptions through the mail for participants interested in receiving their prescriptions in this manner. Participants will be reminded to submit a photo of their prescription label once they have received their prescription.

To optimize external generalizability, all participants will be provided standard of care PrEP navigation services. Navigation services will be delivered by study staff experienced in PrEP navigation with the goal of assisting patients in financial access to PrEP. The navigation will use

Gilead medication assistance and co-pay access programs, in addition to state-specific programs, to facilitate access to PrEP at low or no cost to participants. All study participants will be provided with identical PrEP navigation services that will assist with covering the costs of PrEP medication.

Participants will be randomized after all Baseline Visit procedures are complete and the participant has initiated PrEP. PrEP will not be provided to the participants as part of the study. The study purpose is to evaluate maintenance in PrEP care, using standard of care PrEP guidelines.

6.3 Follow-up Visits

Follow-up visits (visits are defined as any interaction with the study data system) will be conducted at Months 1, 3, 6, 9, and 12 for those enrolled prior to May 2022 and 1, 3 and 6 Months for those enrolled after May 2022. The month 1 visit will consist of a brief survey for control participants, and a brief survey and clinical check-in for intervention participants. For intervention participants, home specimen kits for HIV and STI testing will be sent at months 3 and 6 for those enrolled after May 2022 as well as Months 9 and 12 for those enrolled prior to May 2022. Creatinine will be tested at month 3 for all participants as well as Month 9 for those enrolled prior to May 2022. Participants enrolled prior to May 2022 will complete surveys at months 3, 6, 9, and 12, and will use home specimen kit for DBS collection, TFV-DP testing, at months 6 and 12. Participants enrolled after May 2022 will complete surveys at months 3 and 6, and will use home specimen kit for DBS collection, TFV-DP testing at Month 6.

Home Care Kits:

For the intervention, the home care kits will consist of a self-collection of the following specimens: urine sample, rectal swab, pharyngeal swab, microtube blood collection, and dried blood spot collection. Instructions for self-collection of specimens will be available on the app and included in the kit. There will also be available to participants a call-in line to receive help with any unexpected problems in completing the kit during normal business hours. The kits will be tailored to the tests needed for each specific visit.

In collecting home specimens, participants will conduct 1-3 self-administered finger pricks, each one similar to the practice someone with diabetes might follow on a regular basis. The finger prick device will be spring-loaded and encased in a plastic shell, so participants will not see or manipulate the needle. Following the finger pricks, participants will collect 4-6 drops of blood by blotting their finger on collection paper, and by using a gravity-fed microtube. Participants will mail their biological specimens using pre-paid mailers included in the home kit. If an insufficient sample is collected at home, participants will be given an option to resend their sample or to take their lab tests at their provider's office.

Biological tests routinely performed at PrEP follow-up visits will be conducted on the mailed specimens from the home kit. Gonorrhea and Chlamydia tests will be performed on the urine sample and on the rectal and pharyngeal swabs. Syphilis testing and creatinine level will be performed using whole blood samples. HIV AbAg (4^{th} gen) testing will be conducted from DBS cards. These tests will be conducted at a CLIA-certified laboratory.

Communication will be sent to participants through the app to confirm kit receipt and to remind participants to return their kit in a timely fashion.

Communication of results with providers will be accomplished through the secure clinician portal dashboard. Participants will be counselled as needed during follow-up visits regarding results and PrEP adherence.

Authorization for Release of Information:

All participants, in both intervention and control arms, will be contacted during the study period to fill out an optional Authorization for Release of Information form. This form will provide study staff with permission to contact each participant's pharmacy where they fill their current PrEP prescription. Participants will be asked to sign the form and provide contact information for their pharmacy (i.e. pharmacy name and number, address, and/or phone number). Study staff and clinicians will contact pharmacies to collect information on prescription fill dates and quantities. This information will be used to better understand study outcomes, particularly the primary adherence outcome for participants who have not returned their DBS cards.

6.4 Referrals

During Study: Treatment referrals will be provided to participants for positive STI laboratory results. Staff will work with local resources to facilitate access to care at free or low cost. In the case of a positive HIV test, participants will cease PrEP dosing, be discontinued from the study, and be linked to care the next business day. For positive STI tests, participants will have PrEP prescriptions initiated or renewed, and be referred to STI treatment at a local agency. Site study staff will follow-up with participants testing positive for STI to ensure they have sought appropriate care. In cases of participant-opted discontinuation of PrEP, the participant's rationale for discontinuing PrEP will be documented.

End of Study: Participants in the intervention arm will be linked to PrEP care by study staff. Control arm participants will continue with their regular care.

6.5 Measures

6.5.1 Surveys

As part of the PrEP@Home kit, participants will also complete an electronic survey through the app hosted on Alchemer.com. These surveys will include domains that physicians usually assess at quarterly PrEP follow-up visits, including sexual risk, illicit substance use risk, self-reported PrEP adherence, and any PrEP-related side effects. This information will be marked clearly in the survey as being shared with providers. Another section of the survey will involve research assessment and will not be transmitted to providers. This will include factors relevant to PrEP experience such as length of time on PrEP, as well as assessing participant experiences with and perceptions of the home kit. An additional cross-sectional survey will be emailed to participants to complete via Alchemer as a general assessment, PrEP, and behavior changes due to COVID19 public health restrictions.

6.5.2 Outcome Measures

Measurement of TFV-DP levels will be conducted for participants in both arms using liquid chromatography/tandem mass spectrometry methods on DBS samples. The primary outcome is protective levels of PrEP, as indicated by TFV-DP levels. TFV-DP level can be translated to an interpretation that indicates mean number of days per week PrEP is ingested over a time period of approximately 1-month preceding specimen collection. The cutpoint used for the primary outcome measure will be TFV-DP levels considered to be a surrogate for substantial protection:
>700 fmol/punch, a level indicating >4 doses/wk.

6.6 Training

Recruiters and personnel staffing study data collection will complete CITI ethical conduct of research training, and also training on recruitment procedures and use of study instruments. Documentation of study staff training will be kept at each study site.

7. LABORATORY SPECIMENS AND PROCEDURES

Baseline labs will be tested at each sites local laboratory. All study lab tests will be conducted at CLIA-certified laboratories using FDA-approved tests. Testing methods are specified for each site in Appendix 5.

7.1 HIV Testing

HIV testing will be done for each study visit. All HIV testing will be conducted using a 4th generation Antibody Antigen (AbAg) test. An additional rapid HIV test may be used at the in-person baseline visit prior to determining eligibility to continue with the study. The HIV testing at follow-up visits for the intervention participants will be done using a self-finger prick collection and DBS card. Specimens with a reactive result will undergo confirmatory testing per CDC algorithm (Appendix 4) and participant will be asked to stop taking PrEP. If confirmed, results will be returned to participants by study staff experienced in HIV care linkage.

7.2 STI Testing

All participants will be tested for Hepatitis B (HBsAg), Hepatitis C (anti-HCV), syphilis (EIA and RPR), and pharyngeal, urethral, and rectal gonorrhea and chlamydia at Baseline. Intervention participants will be tested for syphilis, gonorrhea, and chlamydia (pharyngeal, urethral and rectal) at quarterly follow-up visits.

7.3 Safety Labs

Creatinine will be checked at baseline as part of eligibility and repeated at months 3 and 9 for safety. Creatinine will be tested using CLIA-certified FDA-approved tests. The creatinine clearance will be calculated using the Cockcroft and Gault equation and the participant's weight at baseline.

If creatinine clearance <60 ml/min on follow-up testing, the participant may need repeat testing and/or PrEP hold as per the prescribing physician's assessment and recommendation. Participant will be referred for further testing and management if needed.

7.4 Dried Blood Spots

DBS cards will be collected from participants at months 6 and 12 for TFV-DP testing. The CLIA-xcertified UNC Kashuba Lab will perform testing on the DBS to assess TFV-DP levels, which will allow us to gain an understanding of participant adherence to their PrEP regimen. Participants will be informed of expectations regarding specimen collection at baseline. If we find higher rates of non-return of specimen cards for those who report cessation of PrEP care, we will consider increasing incentive payments to allow for collection of outcome data.

7.5 Biohazard Containment

General (Baseline): each site has staff trained in biohazard handling who will be responsible for collecting specimens and preparing them for transport to the local laboratory for testing.

Home care: After collecting specimen(s) for testing, participants place the specimen collected in the provided packaging, which meets all federal regulations for shipment of Biological Substances, Category B (UN3373). Participants will ship their collected specimens in pre-paid mailers. Staff trained in biohazard handling will store specimens or ship them to the appropriate laboratory.

7.6 Future Storage

Participants will be asked during the consenting process if they give permission to have samples stored for future research. DBS specimens collected from participants who agree to have samples stored for future use will be stored at Emory University or contracted laboratory. Personal identifying information will not be kept with the samples. These samples could assist with other research, such as DBS validation measures. Participants who do not agree to have specimens stored will have specimens discarded after lab tests are conducted.

8. SAFETY MONITORING AND ADVERSE EVENT REPORTING

8.1 Data Safety Monitoring Board (DSMB)

A DSMB will conduct interim monitoring of accumulating study data. The DSMB will receive standard data reports on a quarterly basis, with all serious adverse events reported in real time. The chair of the DSMB will lead biannual calls to discuss study progress, and the chair will convene additional DSMB meetings as needed based on interim reporting. Although the intervention is using an FDA-approved product for an approved indication, and care will be provided in line with guidance from the US Public Health Service using a CLIA-certified laboratory, a DSMB will be to provide several areas of oversight. The DSMB will be tasked with stopping the study if the intervention proves to be significantly outperforming the standard of care, or if the inverse occurs. The DSMB will monitor a number of factors, including HIV seroconversion, behavioral disinhibition, medication adherence, persistence in PrEP care, and differential loss to follow-up. The DSMB, comprised of experts on HIV prevention and PrEP, will incorporate the most current scientific advances in the rapidly changing field of PrEP in their study oversight. Prior to study launch, the DSMB will review all study protocols and manuals of operation.

8.2 Adverse Events

Adverse events will be recorded using standardized forms and reported to the study clinician at each site; in addition, quarterly reports will be provided to the study DSMB and more as needed in the event of unexpected adverse events, such as events that are not known and commonly documented side effects of PrEP. Although no serious adverse events are anticipated, these will be reported to the IRB, the study DSMB, and NIH within 24 hours of the MPI becoming aware of them. Following NIH guidelines, adverse events will be defined as "any untoward or unfavorable medical occurrence in a human study participant." *Serious adverse events* will be adverse events that result in death, are life threatening, requires or prolongs hospitalization, causes disability, or poses other significant hazards. Severity of AEs will be classified as follows: mild, moderate, and severe. Mild AEs will be events that do not require medical attention and are easily tolerated. Moderate AEs will be events that require simple and routine medical treatment and may cause some interruption to daily life. SAEs will be defined as above. AEs will also be categorized as definitely, possibly, or not related to the study. AEs that are definitely related will follow a logical causal sequence from a study activity. Possibly related events will follow a logical causal sequence from a study activity but may also be due to non-study activities. Not related events will be events that do not follow a logical causal sequence from any study activity.

9. STATISTICAL CONSIDERATIONS

9.1 Primary Outcome

Assessment of TFV-DP will be conducted at 6 and 12-month follow-ups. Differences in the proportion of participants with protective levels of TFV-DP between the intervention arm and the control arm will be tested using two-proportion z-tests with pooled variances, based on intent-totreat assignment. The percentage of participants with protective levels of TFV-DP at months 6 and 12 will be compared using a Generalized Linear Mixed Model (GLMM) logistic regression model that accounts for within-participant correlation over time, of the form: : $logit[\quad_{ij}] = \quad + \quad_{0i} + \quad(\quad rm) + \quad(time_{ij}) + \quad(\quad rm \times time_{ij})$, where $\quad_{ij}$ represents the outcome at time *j* on participant *i*, $\quad_{0i}$ represents a random intercept for participant *i*, and fixed effect dummy variables are included for intervention arm, time, and the interaction between arm and time.[35] The statistical model will be used to estimate the proportion of participants with protective levels of TFV-DP (plus 95% confidence intervals) by intervention assignment and time on study. The statistical test for interaction between arm and time will be the primary overall test to determine whether PrEP protection changed in significantly different ways during follow-up (at α = 0.05). If a significant time*intervention interaction is detected, we will test differences between the model-based adherence estimates at each time point. If protective levels of PrEP rates are consistently different or similar (i.e., no interaction) then the main effect test for intervention assignment will be used to evaluate intervention efficacy.

9.2 Power to detect effects in primary outcomes

A total of 396 participants will be enrolled at baseline to account for a 10% expected loss to followup during 12-months of study follow-up. With this sample size and assuming α=0.5 and two-sided significance, there will be 80% power to detect absolute differences between the intervention and control arms in the proportion of subjects with protective levels of TFV-DP of > 15.8% when the average proportion in the control group is 0.50. Power calculations were performed using PASS v.13 software (NCSS, LLC. Kaysville, Utah). Hypothesis is participants randomized to PrEP@Home will have higher levels of protection against HIV infection as

determined by levels of emtricitabine triphosphate (TFV-DP) than standard of care controls.

9.2.1 Adjusted analyses

GLMM models will control for potential confounding for factors such as medication self-efficacy and motivation to take PrEP. (1) Adjusted analyses will be conducted to control for changes in PrEP eligibility over time for participants in each trial arm, per CDC guidelines, using an additional interaction term between eligibility and treatment arm. (2) Per protocol assessments will be conducted that account for potential changes in intervention as delivered; for instance, this would account for participants assigned to the intervention condition opting to instead receive standard of care PrEP from their local clinician.

A number of secondary analyses will be conducted using GLMM models. (3) Intervention impact on the secondary outcome of PrEP prescription persistence will be determined using analogous logistic regression models. (4) Secondary analysis will be conducted to model $\log_{10}$ (TFV-DP levels), using a linear mixed model. Other specific and aggregate measures of safety include: renal function, HIV incidence, and incident bacterial STI across study arms.

9.3 Exploratory analyses

Exploratory analysis of intervention effectiveness across subgroups, and analysis of potential mediators of persistence in PrEP care across both study arms

Heterogeneity of the intervention effects across subgroups, including those stratified upon (city, age), and socioeconomic indicators, using unadjusted proportion tests and subgroups*intervention arm interaction variables in GLMM models. We will examine expected mediators of primary and secondary study outcomes. Possible mediators are variables hypothesized to be on the causal pathway between the intervention and study outcomes (e.g. medication adherence self-efficacy, perceived benefits of PrEP, perceived ease of use of PrEP). For participants who seroconvert during the study, we will analyze levels of TFV-DP, PrEP persistence, and other clinically-relevant study data.

9.4 Mathematical modeling

Mathematical modeling will be used to estimate the potential impact of scaling-up PrEP@Home for MSM across the United States.[36] This will be done by using a robust model that simulates HIV transmission across dynamic sexual partnership networks,[37] which we have used to predict the impact and efficiency of CDC's PrEP guidelines for MSM.[38] Model parameters related to PrEP persistence and adherence will be based on the efficacy results in Aims 1-2.1. Sensitivity analyses will vary levels of and heterogeneity in PrEP access, PrEP@Home uptake, and time-varying PrEP adherence. The aim of these models will be to address the question of how PrEP@Home could reduce HIV incidence in the population by improving persistence above levels currently observed in clinic-based PrEP demonstration projects.[14] Modeling activities will also include extending our web-based PrEP forecasting tool for public health policymakers (https://prism.shinyapps.io/cdcprep-guidelines) to incorporate new parameter data and sensitivity analyses. Model outputs such as the cumulative number of infections averted (a measure of impact) and the number needed to treat to prevent one new infection (a measure of efficiency) will be fed into the cost-effectiveness analyses (Aim 3) as input parameters.

9.5 Qualitative

Interviews and survey assessments among clinicians, healthcare managers, and patients involved in PrEP care to inform roll out of home care, should the intervention demonstrate efficacy. Qualitative interviews will be conducted with approximately 40 participants.

To inform future research with the PrEP home care system and to contextualize study results, we will conduct in-depth interviews (IDI) and key informant interviews (KII).

IDI: Interviews will seek to explore the experiences of home care users and standard of care participants over time. We will use a timeline, activity-based approach, prompting participant memories and creating an interactive discussion between moderator and participant regarding PrEP care experiences. PrEP care visits will be plotted on the timeline, with participants adding surrounding life and PrEP care-related events. IDI topics will include: (1) barriers and facilitators to PrEP care, (2) problems with and benefits of the home care or standard of care, (3) ways to address problems and amplify success of home care or standard of care, and (4) factors that influence successful persistence in or fall-off from PrEP care. IDI will be conducted until data saturation has been reached. Purposive sampling of study participants will include up to 15 IDI with participants maintained in PrEP care (10 intervention, 5 control) and up to 15 IDI with participants not maintained in PrEP care (10 intervention, 5 control). PrEP care is a new and dynamic field, and broader healthcare system changes also may occur, so we anticipate that conducting this qualitative exploration among intervention and control participants is warranted. Participants who seroconvert during the study will also be asked to participate in IDI to assess their experience using PrEP and follow-up care, including app use, during their time on the study.

Stigma IDI: In addition to the interviews which will explore the experiences of home care users and standard of care participants over time, a second set of IDI will be conducted. In August 2020, the PrEP@Home parent grant was awarded a minority research supplement, which will allow a junior faculty-level scientist, Dr. Allysha Maragh-Bass with Family Health International (FHI 360), to conduct research as part of PrEP @Home. This supplemental qualitative research seeks to explore the relationship of stigma and resilience, and their role as potential barriers and facilitators to healthcare engagement among men who have sex with men (MSM). Interviews will be via ZOOM, given the current social distancing measures required for continuation of the study and to protect participants. Interviews will explore sexual and PrEP stigma, individual, social, and neighborhood/community level access to resilience resources, and the role of these factors as barriers and facilitators of PrEP@Home and healthcare engagement. Because some individuals may not develop resilience to sexual stigma and/or PrEP stigma, and others do even with lower levels of PrEP stigma and sexual stigma, qualitative inquiry will be critical in exploring these constructs among both White MSM and MSM of color. IDI will be conducted with participants after their 6-month visits by ZOOM, and should not take longer than 60 minutes. Participants will be paid $60 for their participation. Participants in the parent study who agreed to be contacted for future research will be recruited for interviews. Approximately six interviews will be conducted per site (i.e., four in intervention, three in control). At least two-thirds of participants will be MSM of color, and at least half will be ages 18 to 34 (informed by the parent grant's sampling frame; N=up to 25 interviews total).

Injectable PrEP IDI: In addition to the interviews which will explore the relationship of stigma and resilience in healthcare engagement, a third set of IDI will be conducted. In December 2020, the FDA approved a new injectable medication for PrEP called cabotegravir. It works for PrEP just like Truvada® or Descovy®. The difference is that it's given intramuscularly (in the buttocks) every 2 months instead of taking a daily pill. We are preparing a new project where we would integrate the administration of this medication into the PrEP@Home model. In other words, we would come to participant's homes to give them their shots every 2 months and we would also draw blood. This qualitative research seeks to explore PrEP@Home participant's opinions and preferences regarding home-based injectable PrEP to inform our future study. We are not adding the at-home injectable PrEP to this study, but only conducting interviews to assess subjects' opinions on it. Interviews will be via ZOOM, given the current social distancing measures required for continuation of the study and to protect participants. Each IDI should not take longer than 30 minutes. Participants will be paid $75 for their participation. Participants in

PrEP@Home who are currently enrolled at the Emory site and between the ages of 18 and 29 will be recruited for interviews. Approximately fourteen interviews will be conducted.

KII: Key informant interviews will be conducted with the intervention and standard of care control clinicians (n=6), as well as PrEP-prescribing clinicians and managers at institutions interested in scaling up PrEP (n=20). For the three intervention clinicians (one per site) and three comparable standard of care clinicians, KII will explore the experience of providing PrEP care to participants over the course of the clinical trial, focusing on areas for potential improvement of PrEP@Home or standard of care provision. KII with members of up to 10 institutions interested in scaling up PrEP will focus on how scale-up of PrEP@Home would influence their institution, and exploring desired/required adaptations of the system for each care setting. This set of KII will sample from PrEP care settings such as: STI/county public health clinics, Health Maintenance Organization (HMO), hospital teaching clinics, and Federally Qualified Health Centers. Depending on data saturation, we will conduct up to 20 interviews with members of these care settings, half with clinicians and half with managers at these institutions. KII will include a briefing regarding the home care system, and the results of the clinical trial. The interviews will then explore: (1) How would expanding PrEP home care impact each system of care provision, (2) What are areas of the system that would need to be adapted or developed, and (3) how home care can best be leveraged in their setting to promote their institution's goal of scaling up PrEP.

Analysis for IDI and KII: Transcriptions and interviewer notes will be entered into maxQDA qualitative software to facilitate data management and analysis. Analysis of the data will be led by MPI [redacted] and will begin with classification efforts to code data, conducted concurrently with data collection, in line with the constant comparison analysis method[39]. This method leverages the ability of qualitative research to quickly identify main themes, and then explore them in further depth among subsequent participants. To ensure consistency, coding will be verified by multiple study members trained in analysis. Final analysis will compare data within and across codes and themes, developing theoretical models based on grounded theory principles to answer study questions regarding PrEP@Home adaptation, scale-up considerations, and future research directions.

In-depth interviews will be conducted during and after the trial using either telephone or videobased systems and will be facilitated by Emory University.

9.6 Cost-effectiveness and cost-utility analyses

We will conduct an economic analysis from both the payer perspective (the cost to the party implementing the program) and societal perspective (the payer costs plus the cost to the participant for participating in the program) to estimate the cost, cost-effectiveness, and cost-utility of the intervention relative to standard of care. Including the societal perspective accounts for costs to all parties, acknowledges the value of competing uses for societies' resources, and maximizes comparability with other cost-effectiveness analyses. The cost analysis will calculate the overall cost of implementing the program, the cost per participant, and the cost per person contacted.

9.6.1 Costing the intervention and standard of care arms

Comprehensive cost analysis will be conducted to assess the cost of developing and implementing the PrEP@Home intervention. A micro-costing approach will be used along with the standard literature practice of itemizing the intervention components and attaching a dollar value to them. Two categories of costs will be defined: *developmental costs* (the initial or start-up

costs involving the time spent in developing the intervention) and *implementation costs* (on-going costs of delivering the intervention). The development costs will include costs from the first phase of the research including salaries and fringe benefits for intervention development staff, pilot testing of the intervention, study recruitment, screening, consenting, enrollment, and mailing systems; and piloting lab procedures. Implementation costs will include recruitment, salary and fringe benefits for an intervention coordinator, kit component, production and laboratory testing costs, drug costs (not paid by the study), and the as-needed cost of consultants and technical support, self-reported time participants spend adhering to the PrEP@Home intervention or standard of care, data management, and clinical costs. Participant's self-reported time spent involved in study activities will be translated into an opportunity cost, where participation incentives will be taken as a proxy of the cost of patient time and we will also use income data from study participants.

Costing analysis for the standard of care arm within the cost-effectiveness analysis will be based on secondary literature estimating the health care and societal costs associated with PrEP for MSM in the US.[7,40] To calculate personnel costs, we will multiply these hours by wage rates gathered from the Bureau of Labor Statistics and calculate an average cost per man receiving care in the standard of care arm. We will carefully track these ongoing costs during the 12 months of implementation (the time period of the analysis) using standardized data collection tools. Cost data will be collected by extraction from accounting records, budget records, external contracts, study case report forms, PrEP prescription receipt data; interviews with program implementers; and self-report from participants. Data will be entered into a standardized excel spreadsheet with embedded formulas to calculate the cost. These methods have been used by our research team for economic analyses for a variety of HIV prevention interventions including PrEP interventions. [7,40,41] Costs will be discounted at an annual rate of 3%.

9.6.2 Determining the health effect

The health effect is defined as the projected reduction in HIV incidence over time associated with adopting the intervention relative to standard of care. This will be estimated in our dynamic modeling activities and quantified by two key model outcomes: the number of infections averted per unit person-time on the intervention and the number needed to treat on PrEP@Home to prevent one new infection. The base, standard of care, model will estimate the number of infections expected in the absence of the intervention, and may vary under different assumptions of baseline, clinic-based PrEP coverage outside of the intervention.[42] Each sensitivity analysis in the epidemic model (varying levels of access, coverage, and adherence) may be tested as a unique intervention scenario for the cost-effective analysis.

9.6.3 Cost-effectiveness and cost-utility analysis

First, we will calculate the incremental cost-effectiveness ratio (ICER) for the intervention overall compared to standard of care as: [(CostIntervention – CostStandardofCare)] / [(Infections AvertedIntervention – Infections AvertedStandardofCare)]. This value will give us the cost per HIV infection averted. We will use bootstrapping to calculate the confidence interval around this ratio [43]. If we let ΔX denote the total number of infections averted by the intervention relative to standard of care, the corresponding savings in averted HIV-related treatment costs equals T*ΔX, where T is the (discounted at an annual rate of 3%) lifetime cost of medical care averted each time an incident HIV infection is averted. Thus, the net cost of the intervention can be calculated as C – T*ΔX, where C is total costs. Similarly, the total number of QALYs saved by the intervention equals Q*ΔX, where Q is the number (discounted at an annual rate of 3%) of QALYs saved by preventing a single HIV infection. Estimates of T and Q are available in the literature. We will use the most up-to-date values available for our analyses (current estimates of T are $330,000 and Q

are 5.83 [44]). The cost-utility ratio (the net cost per QALY saved) is thus (C – T*ΔX)/Q*ΔX. [45,46] The intervention will be considered "cost-saving" if the net cost per QALY saved is negative. The intervention will be considered "cost-effective" if the cost-utility ratio is less than commonly-cited U.S. thresholds (e.g., $100,000 per QALY saved).[44,47,48] One-way sensitivity analyses will be performed for all input variables to determine which inputs the cost-effectiveness and cost-utility estimates are most sensitive to. We will explore implementation scenarios including the impact of generic drug pricing, one of the major determinants of PrEP cost-effectiveness.[40]

10.HUMAN SUBJECTS CONSIDERATIONS

10.1 Informed Consent

Consent will be obtained prior to screening for study eligibility. Eligible participants will be asked to read and sign study consent online before any study procedures are initiated. All participants will be offered a copy of the informed consent form, and a study staff member will review the consent and key study components with the participant at the baseline visit. The participant will have an opportunity to ask any questions before proceeding with the visit. For those participants invited to an IDI, a separate informed consent process will be administered prior to the interview. Partial HIPAA-waiver may be used at sites with ongoing clinics to use PHI for laboratory specimens and results that have been collected for PrEP prescribing.

10.2 Risks to participation

While the purpose of the study is maintenance in care, this study will have study clinicians prescribing PrEP, in accordance with Gilead's label indications for tenofovir disoproxil fumarate/ emtricitabine or tenofovir alafenamide/emtricitabine. The prescription of PrEP in the study will also follow guidance from the US Public Health Service and US Centers for Disease Control and Prevention. However, participants may experience some side effects from taking PrEP, and these will be monitored and assessed.

This study is considered minimal risk. While there are side effects associated with PReP, those would be the same regardless of how participants access PReP We anticipate that the intervention will enhance persistence in PrEP care, based on results from the pilot phase of this research that indicated high acceptability and high levels of persistence in care. By providing remote, as opposed to in-person, clinical care for PrEP, however, it is possible that some participants may be more likely to either fail to persist in PrEP care, exhibit higher levels of behavioral disinhibition, or have lower levels of medication adherence. Other risks include performing finger pricks that can cause pain, some questions we ask may make participants feel uncomfortable, and data security risks to be addressed through careful implementation of rolebased procedures, training, and use of highly secure data systems.

Participants may feel uncomfortable answering personal questions about their sexual behavior. Electronic survey methods are used for privacy and participants will be able to refuse to answer any question that makes them feel uncomfortable. Participants may also learn that they have an STI or HIV and this may be upsetting. Participants who receive positive HIV tests will be counselled and linked to care at a local clinic of their preference. Participants who have a positive STI test will be referred for treatment at a local clinic that provides STI treatment services to MSM at either low or no cost.

10.3 Benefits to the subject or future benefits

Participants will accrue protective benefits of PrEP and of regular STI testing and referrals to care as needed. There is the potential benefit of increased knowledge about HIV, STI, PrEP and home care for PrEP in the United States. The broader community may benefit in the future, if the

information we learn results in improved HIV/STI prevention services for MSM in the United States.

10.4 Compensation

All participants will receive compensation of $125 for completing all baseline procedures ($25 for initial visit, $75 for completing labs, and $25 after completing all eligibility requirements). Participants in both the Intervention group and the Control group will receive $10 for Month 1 survey and $25 for quarterly survey completion and $75 for DBS collection for TFV-DP testing. An additional bonus compensation of $50 will be given to participants at the end of study for completing all of their study visits. In addition, participants enrolled after May 2022 will be eligible for another bonus incentive of $125 if they have completed all prior study procedures. This will allow compensation to be equal between the two groups with varied follow-up schedules. The expected total compensation is $435 for all participants. Participants who participate in an in-depth interview following completion of participation in the trial will be compensated an additional $50. For unscheduled follow-up procedures, participants will receive $20 incentive if travel is required or $10 incentive if online only. Participants will receive an additional $20 compensation for completing the COVID-19 survey.

10.5 Participant Privacy and Confidentiality

The privacy of participants and confidentiality will be protected through several means: study procedures, training, and data management practices.

Study Procedures: We will collect multiple means of contact for participants during recruitment. We will ask permission to leave a generic message on phone/email/ and cell phone numbers. Standardized scripts for phone and email contact will be used (uploaded in the eIRB system).

Training: All study staff will have completed CITI training and a 1-hour training related to recruitment, data collection and confidentiality. Staff will sign a confidentiality agreement before having access to any confidential data.

Data management practices: Personally identifying information will be stored in a separate dataset from participant data where able. 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.

The PrEP@Home System is HIPAA compliant. Data at rest and in transit are encrypted and transferred over a secure channel. The database is stored on a central SQL server that is secure and accessed via secured website that requires login and password for each user. The mobile application requires user authentication and requires login for access. The app will have an automatic logout every time the user closes the app on their mobile phone and after 15 minutes if inactive. No survey information will be stored in the mobile app. The app will be downloaded via app stores, either Google Play or Apple Store, and the user must be authenticated with a code sent to their phone and email before being able to log in.

For the telemedicine visits, the study will rely on the Zoom platform. Participants will use Zoom to communicate with their study clinician in face-to-face video chat. Zoom is HIPAA-compliant and offers the Business Associate Agreement (BAA), where Zoom agrees to be responsible for keeping all patient information secure and to immediately report any breach of personal health information. Zoom includes the following functions to protect users: End-to-End encryption and connects automatically using udp and tcp port 8801, 8802, and 8804 or HTTPS (port 443/TLS). The encryption used Advance Encryption Standard (AES) 256-bit algorithm. Session keys are

generated with device unique hardware ID to avoid data being read from other devices. This ensures that the session cannot be eavesdropped or tampered with.

The only linkage of identifying information to the study data will be a simple set of items regarding whether participant completes study procedures, needs to be re-contacted, refuses participation, or other similar recruitment information directly relevant to a participant's study involvement. This information will be stored in a secure and encrypted database. Access to that table will be limited to study staff on the role-based system described above.

10.6 Communicable Disease Reporting Requirements

All relevant local reporting procedures will be followed, as required by law, for laboratory testing for HIV and STI. Each site will be responsible for reporting positive results to the State Department of Health according to each state's guidelines.

11.ADMINISTRATIVE PROCEDURES

11.1 Data Collection, Entry and Management

Data will be stored in password-protected, encrypted files and on secure Alchemer servers. BAA between Alchemer and Emory University ensures HIPAA compliance. 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.

Paper forms will be stored in a secure filing cabinet in a locked office at each site. Electronic CRFs will be used for data capturing through DFexplore. Access to the records will be limited to study staff as necessary. CRF 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.

11.2 Quality Assurance

Site Investigators are responsible for ensuring the quality of activities conducted at their own site. Monitoring visits will be made periodically by the principal investigator during the study to ensure that all aspects of the current, approved protocol/amendment(s) are followed. The study may also be subject to a quality assurance audit by the sponsor or its designees, as well as inspection by appropriate regulatory authorities.

Site clinicians will follow CDC recommendations for PrEP guidelines.

11.3 Regulatory Requirements

Clinical trial best practice will be followed in accordance with NIH guidance, including early trial registration at clinicaltrials.gov, investigators and relevant staff completing appropriate training in Good Clinical Practice (GCP), and adherence to guidance regarding timely dissemination of

clinical trial results. We will report any protocol violations to IRB and the DSMB within three days of the principal investigator becoming aware of the violation.

The clinical trial will be registered at clinicaltrials.gov.

11.4 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the 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.

12. REFERENCES

1. McCormack S, Dunn DT, Desai M, et al. 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. *Lancet.* 2016;387(10013):53-60.
2. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *The Lancet Infectious diseases.* 2014;14(9):820-829.
3. Volk JE, Marcus JL, Phengrasamy T, et al. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2015;61(10):16011603.
4. Smith DK, Van Handel M, Wolitski RJ, et al. 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):1291-1295.
5. Mera R, McCallister S, Palmer B, Mayer G, Magnuson D, Rawlings K. Truvada (TVD) for HIV pre-exposure prophylaxis (PrEP) utilization in the United States (2013-2015). International AIDS Conference (IAS) 2016; 2016; Durban, South Africa.
6. Bush S, Magnuson D, Rawlings M, Hawkins T, McCallister S, Mera Giler R. Racial Characteristics of FTC/TDF for Pre-exposure Prophylaxis (PrEP) Users in the US. Paper presented at: ASM Microbe2016; Boston, MA.
7. Juusola JL, Brandeau ML, Owens DK, Bendavid E. The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. *Annals of internal medicine.* 2012;156(8):541-550.
8. Hosek S, Siberry G, Bell M, et al. The Acceptability and Feasibility of an HIV Pre-Exposure Prophylaxis (PrEP) Trial with Young Men who Have Sex with Men (YMSM). *J Acquir Immune Defic Syndr.* 2012.
9. Sullivan PS, Carballo-Diéguez A, Coates T, et al. Successes and challenges of HIV prevention in men who have sex with men. *The Lancet.*380(9839):388-399.
10. Centers for Disease Control and Prevention. US Public Health Service preexposure prophylaxis for the prevention of HIV infection in the United States–2014 clinical practice guideline. *http://wwwcdcgov/hiv/pdf/prepguidelines2014pdf.* 2014.
11. World Health O. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects, July 2012. 2012.
12. Centers for Disease Control and Prevention. HIV Surveillance Report, 2015. In. Vol 27: http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html; 2016.
13. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med.* 2015;373(23):2237-2246.

14. Liu AY, Cohen SE, Vittinghoff E, et al. Preexposure prophylaxis for hiv infection integrated with municipal- and community-based sexual health services. *JAMA Internal Medicine.* 2016;176(1):75-84.
15. Amico KR, Marcus JL, McMahan V, et al. Study product adherence measurement in the iPrEx placebo-controlled trial: concordance with drug detection. *Journal of acquired immune deficiency syndromes (1999).* 2014;66(5):530-537.
16. Kelley CF, Kahle E, Siegler A, et al. Applying a PrEP Continuum of Care for Men Who Have Sex With Men in Atlanta, Georgia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2015;61(10):1590-1597.
17. Hosek S, Landovitz R, Rudy B, et al. An HIV pre-exposure prophylaxis (PrEP) demonstration project and safety study for adolescent MSM ages 15-17 in the United States (ATN 113). International AIDS Conference (IAS) 2016 2016; Durban, South Africa.
18. McKenzie B, Rapino M. *Commuting in the united states: 2009.* US Department of Commerce, Economics and Statistics Administration, US Census Bureau; 2011.
19. McKenzie B. Who drives to work? Commuting by automobile in the United States: 2013. *American Community Survey Reports.* 2015.
20. Smith DK, Toledo L, Smith DJ, Adams MA, Rothenberg R. Attitudes and program preferences of African-American urban young adults about pre-exposure prophylaxis (PrEP). *AIDS education and prevention : official publication of the International Society for AIDS Education.* 2012;24(5):408-421.
21. Mera R, McCallister S, Palmer B, Mayer G, Magnuson D, Rawlings K. Truvada (TDF) for HIV pre-exposure prophylaxis (PrEP) utilization in the United States (2013-2015). International AIDS Conference; 2016; Durban, South Africa.
22. Nielson. New Mobile Obsession U.S. Teens Triple Data Usage. December 15, 2011,.
23. Lorimer K, Flowers P, Davis M, Frankis J. Young men who have sex with men's use of social and sexual media and sex-risk associations: cross-sectional, online survey across four countries. *Sex Transm Infect.* 2016.
24. Lenhart A, Smith A, Anderson M, Duggan M, Perrin A. Teens, Technology and Friendships. In: Pew Research Center; August 2015. Available at: http://www.pewinternet.org/files/2015/08/Teens-and-Friendships-FINAL2.pdf.
25. Pew Research Center. The Smartphone Difference. In:April 2015. Available at: http://www.pewinternet.org/files/2015/03/PI_Smartphones_0401151.pdf.
26. Xu F, Stoner BP, Taylor SN, et al. Use of home-obtained vaginal swabs to facilitate rescreening for Chlamydia trachomatis infections: two randomized controlled trials. *Obstetrics and gynecology.* 2011;118(2 Pt 1):231-239.
27. Smith KJ, Cook RL, Ness RB. Cost comparisons between home- and clinic-based testing for sexually transmitted diseases in high-risk young women. *Infectious diseases in obstetrics and gynecology.* 2007;2007:62467.
28. Wayal S, Llewellyn C, Smith H, Fisher M. Home sampling kits for sexually transmitted infections: preferences and concerns of men who have sex with men. *Culture, Health & Sexuality.* 2010;13(3):343-353.
29. Sharma A, Sullivan PS, Khosropour CM. Willingness to Take a Free Home HIV Test and Associated Factors among Internet-Using Men Who Have Sex with Men. *J Int Assoc Physicians AIDS Care (Chic).* 2011;10(6):357-364.
30. Eisingerich AB, Wheelock A, Gomez GB, Garnett GP, Dybul MR, Piot PK. Attitudes and acceptance of oral and parenteral HIV preexposure prophylaxis among potential user groups: a multinational study. *PLoS One.* 2012;7(1):e28238.

31. Arnold EA, Hazelton P, Lane T, et al. A Qualitative Study of Provider Thoughts on Implementing Pre-Exposure Prophylaxis (PrEP) in Clinical Settings to Prevent HIV Infection. *PLoS One.* 2012;7(7):e40603.
32. WHO. Guidance on pre-exposure oral prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: Recommendations for use in the context of demonstration projects. 2012; Geneva, Switzerland.
33. White JM, Mimiaga MJ, Krakower DS, Mayer KH. Evolution of Massachusetts physician attitudes, knowledge, and experience regarding the use of antiretrovirals for HIV prevention. *AIDS Patient Care STDS.* 2012;26(7):395-405.
34. World Health Organization. Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a Public Health Approach In. *http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1*2016.
35. Diggle P, Liang K, Zeger S. *Analysis of longitudinal data.* Oxford: Clarendon Press; 1994.
36. Cassels S, Clark SJ, Morris M. Mathematical models for HIV transmission dynamics: tools for social and behavioral science research. *Journal of acquired immune deficiency syndromes (1999).* 2008;47 Suppl 1:S34-39.
37. Goodreau SM, Carnegie NB, Vittinghoff E, et al. What drives the US and Peruvian HIV epidemics in men who have sex with men (MSM)? *PloS one.* 2012;7(11):e50522.
38. Jenness SM, Goodreau SM, Rosenberg E, et al. Impact of the Centers for Disease Control's HIV Preexposure Prophylaxis Guidelines for Men Who Have Sex With Men in the United States. *The Journal of infectious diseases.* 2016;214(12):1800-1807.
39. Strauss AL, Corbin JM. *Basics of qualitative research : techniques and procedures for developing grounded theory.* 2nd ed. Thousand Oaks: Sage Publications; 1998.
40. Paltiel AD, Freedberg KA, Scott CA, et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2009;48(6):806-815.
41. Jain KM, Maulsby C, Brantley M, et al. Cost and cost threshold analyses for 12 innovative US HIV linkage and retention in care programs. *AIDS Care.* 2016;28(9):1199-1204.
42. Jenness SM, Goodreau SM, Rosenberg E, et al. Impact of the Centers for Disease Control's HIV Preexposure Prophylaxis Guidelines for Men Who Have Sex With Men in the United States. *The Journal of infectious diseases.* 2016.
43. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes.* Oxford, England: Oxford University Press; 2005.
44. Farnham PG, Holtgrave DR, Gopalappa C, Hutchinson AB, Sansom SL. Lifetime costs and quality-adjusted life years saved from HIV prevention in the test and treat era. *Journal of acquired immune deficiency syndromes (1999).* 2013;64(2):e15-18.
45. Pinkerton SD, Holtgrave DR. A method for evaluating the economic efficiency of HIV behavioral risk reduction interventions. *AIDS and behavior.* 1998;2:189-201.
46. Pinkerton SD, Holtgrave DR. Assessing the cost-effectiveness of HIV prevention interventions: A primer. In: Holtgrave DR, ed. *Handbook of Economic Evaluation of HIV Prevention Programs.* New York: Plenum Press; 1998:33-43.
47. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. *Expert review of pharmacoeconomics & outcomes research.* 2008;8(2):165178.
48. Walensky RP, Freedberg KA, Weinstein MC, Paltiel AD. Cost-effectiveness of HIV testing and treatment in the United States. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2007;45 Suppl 4:S248-254.

Appendix 1

Example Screening Informed Consent Form

Emory University
Screening Consent Information Sheet
For Research Study Screening

Study Title: Making it last: A randomized, controlled trial of a home care system to promote persistence in PrEP care
Principal Investigators: [redacted], PhD, MHS and [redacted] MD
Epidemiology Department, Rollins School of Public Health, Emory University; Medical Director, Fenway Community Health Center, Inc.
Funding Source: National Institutes of Health, National Institute of Mental Health

Introduction and Study Overview

Thank you for your interest in this study. To see whether you may be a candidate for this study, we need to ask you for some information about yourself. But first, let me tell you about this screening consent and what we will do with your information.

1. This screening questions will take about 10 minutes.
2. You can also stop the screening interview at any time. This is completely voluntary.
3. We can send you an information sheet about this screening, along with the screening questions, if you would like. We will also give you a form you can send in later if you change your mind and want us to remove your information from our records.
4. We will ask you some demographic and sexual behavioral questions.
5. The only risk to you in this phone screening is a potential loss of privacy. However your privacy is very important to us and we will be very careful with your information.
6. The following persons or groups may use and/or disclose your PHI for this study:
    - The Principal Investigator and the research staff
    - National Institutes of Health who funds this Research, and people or companies they use to carry out the study
    - The office for Human Research Protections, the Emory Institutional Review Board and the Emory Office of Research Compliance.

Contact Information

If, at any time, you have questions about this screening process, your rights as a research participant, or if you have questions, concerns or complaints about the research you may contact study PI, [redacted] or the Emory Institutional Review Board.

[redacted] at [redacted]

Emory Institutional Review Board at [redacted] or toll-free at [redacted] or by email at [redacted]

You can also stop the screening interview at any time. This is completely voluntary.

Consent

___I consent to being screened for this study online

___I do NOT consent to being screened for this study online

Thank you for your interest. Please answer the following questions to determine if you are eligible for this study. [Go to eligibility screener.]

OR

Thank you for taking the time to complete this survey. We are sorry you are not interested in our study. If you have any concerns or questions, or would like to be considered for our study, please email us at prepathome@emory.edu or call us at 404-712-9733.

Appendix 2

Study Visits and Procedures Schedule

Study Visits and Procedures

	Online Screening	Baseline	1 Month	3 Months	6 Months	9 Months	12 Months
Screening consent	X						
Obtain demographic, risk data, and initial eligibility	X						
Study informed consent		X					
Locator information *(including 2 alternative contacts)*		X					
HIV rapid test		X					
HIV 4th gen		X		I	I	I	I
Creatinine clearance		X		I		I	
Syphilis (RPR)		X		I	I	I	I
Hepatitis B and C screening		X					
Urine for CT/NG		X		I	I	I	I

Oral & Rectal swabs for CT/NG		X		I	I	I	I
Confirm eligibility		X					
Download app		X					
Gilead financial screening		X					
Provide PrEP prescription		X					
Telemedicine visit				I*	I*	I*	I*
Electronic Survey		X	X	X	X	X	X
DBS collection for TFV-DP					X		X
Provide incentive		X	X	X	X	X	X
Provide active referral		C					I

** as needed*

Legend:	
X	All Participants
I	Intervention Only
C	Control Only

Appendix 3

CDC PrEP Guidelines

Men Who Have Sex With Men
Adult man Without acute or established HIV infection Any male sex partners in past 6 months Not in a monogamous partnership with a recently tested, HIV-negative man ***AND at least one of the following:*** Sexual partner who is HIV-positive Any STI reported or diagnosed in past 6 months Any anal sex without condoms in past 6 months

2017 PrEP Updated Clinical Practice Guideline

Appendix 4

CDC PrEP Guidelines HIV Testing Algorithm
(https://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf)