Meet me where I am: A multilevel strategy to increase PrEP uptake and persistence in rural NC ("STARR-NC")

NCT05984030

DATE: SEPTEMBER 30TH, 2024

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PHASE 1 Study

PROTOCOL NUMBER: UNC IGHID 12221

VERSION 4.0

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Table of Contents

List of Abbreviations and Acronyms

AE	Adverse Events
AIDS	Acquired Immunodeficiency Syndrome
BL	Baseline
CAB (CAB LA)	Long-Acting Injectable Cabotegravir
CASI	Computer assisted self-interview
CDC	Center for Disease Control and Prevention
CELR	Clinical and Environmental Lab Result
CRF	Case Report Form
Co-I	Co-Investigator
CQMP	Clinical Quality Monitoring Plan
DBS	Dried Blood Spots
NC DHHS	North Carolina Department of Health and Human Services
DHIs	Digital Health Interventions
EHR	Electronic Health Records
FTC	Emtricitabine
GCP	Good Clinical Practices
HD	Health Department
HCD	Human-centered design
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HMP	HealthMPowerment
HSP	Human Subjects Protection
IDI	In-Depth Interview
IGHID	Institute for Global Health and Infectious Diseases
IRB	Institutional Review Board
IT	Information Technology
MSM	Men who have Sex with Men
NC	North Carolina
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Development
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
PI	Principal Investigator
PrEP	Pre-exposure prophylaxis
OHRP	Office of Human Research Protection
QA	Quality Assurance
RCT	Randomized Control Trial

SID	Study ID Number
STI	Sexually Transmitted Infection
SOC	Standard of Care
STARR-NC	Supporting Tailored And Responsive PrEP in Rural North Carolina
TFV	Tenofovir
UNC	University of North Carolina
UNC-CH	University of North Carolina at Chapel Hill
UP	Unanticipated Problem
YGSM	Young Gender and Sexuality Minority
YAB	Youth Advisory Board
YMSM	Young Men Who Have Sex with Men

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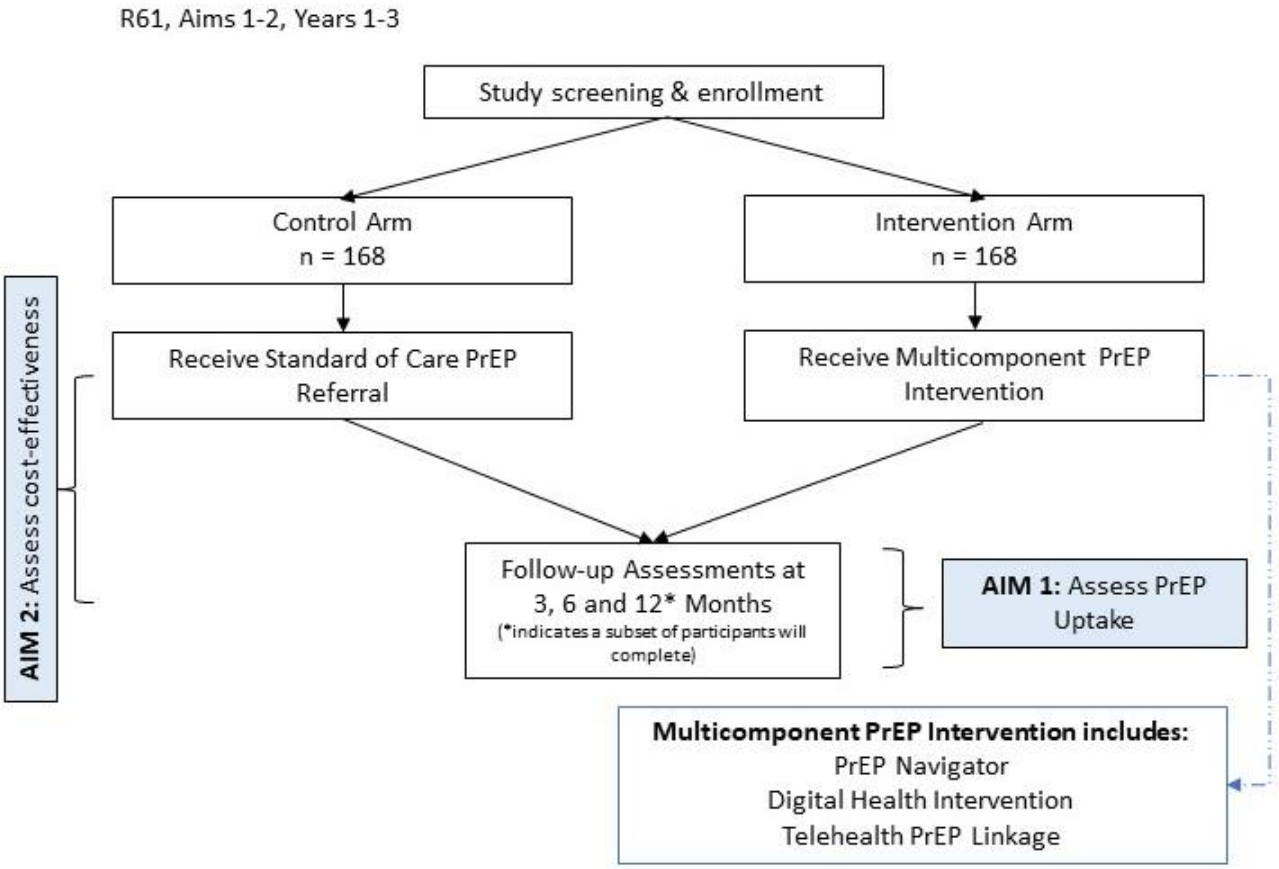
Study Synopsis

SPONSOR:	National Institute of Allergy and Infectious Diseases (NIAID)
TITLE OF STUDY:	Meet me where I am: A multilevel strategy to increase pre-exposure prophylaxis (PrEP) uptake and persistence in rural North Carolina (NC).
PROTOCOL NUMBER:	UNC IRB: 22-3058, IGHID 12221 NIH Grant: R61AI174285
STUDY DESIGN AND CONDITIONS:	This project consists of two phases to be completed over five years. Phase 1 (Aims 1 and 2) will be completed during Years 1-3 (R61). The Phase 1 study is a randomized trial of a multilevel PrEP intervention strategy in rural NC sexually transmitted infection (STI) clinics, with primary outcome of PrEP uptake within 3 months of an index STI clinic visit. Participants will be randomized 1:1 to an intervention or control condition. Participants enrolled in the intervention arm will receive a multilevel intervention with three components: a **PrEP Navigator** to facilitate linkage to PrEP services and completion of applications for health insurance/drug assistance; a **Digital Health Intervention (DHI)** platform (HealthMpowerment) – a HIPAA-compliant evidence-based DHI that provides interactive educational resources, social support, and tools for developing PrEP behavioral skills and self-efficacy; and **referral to Telehealth PrEP** services as an option for linking to PrEP care. Control arm participants will receive the standard PrEP referral services available in a given clinic setting. They will also receive linkage to a limited version of the DHI, with basic PrEP resources and information. **The current protocol is for the Phase 1 study.**
DURATION:	The navigation intervention period is 3-6 months (dependent on enrollment date), enrolled study participants are followed for **up to** 12 months.
SAMPLE SIZE:	Phase 1 Intervention trial: 336 STI clinic patients across all participating clinics. Implementation evaluation: up to 50 clinic staff, providers and other key stakeholders.
POPULATION:	Intervention trial participants enrolled who will contribute to final study outcomes will be HIV-negative individuals who were assigned male sex at birth or cisgender women, are not currently using PrEP at enrollment, have regular access to a smartphone, aged 18 to 39 years who report sexual activity with a male in the past 12 months and are presenting for STI testing or care to participating clinics and/or clinic events in North Carolina.

RECRUITMENT SITES:	Rural and peri-urban NC STI clinics.
STRATIFICATION:	Intervention trial participants will be randomized 1:1 to the control or intervention condition at enrollment using blocked randomization stratified by county, with randomly ordered blocks of sizes 4 and 6.
DATA COLLECTION:	<u>Data sources:</u> - Computer assisted self-interviewing (CASI) biobehavioral surveys - STI/HIV test results - Dried Blood Spots (DBS) to detect PrEP use - Medical records related to PrEP initiation and care - Daily app use data collected automatically by the DHI app's analytic system and as entered by participants - Process data measures collected from study implementation records - Qualitative in-depth interviews (IDI) with a subsample of up to 50 intervention trial participants and up to 50 clinic staff/providers/key stakeholders - Direct observations (time-and-motion) and relevant invoices/receipts for costing <u>Data collection points:</u> Baseline, 3-months, 6-months (subset), 12-months (subset). Participants enrolled in approximately the final quarter of enrollment will only complete baseline and 3-month data collection points. Daily app use, PrEP adherence tracking, and behavioral tracking. Costing data collection will be embedded into daily study activities.
OBJECTIVES	**Aim 1: Conduct a randomized trial of a multilevel PrEP intervention strategy in rural and peri-urban NC STI clinics.** **Primary Objective**: To use episodic STI service encounters to increase linkage to convenient, continuous PrEP care. **Primary outcome:** PrEP uptake within 3 months of an index STI clinic visit. **Secondary outcomes:** PrEP uptake within 6 months of an index STI clinic visit, PrEP care engagement, PrEP use, PrEP adherence, incident STI/HIV, and PrEP stigma. **Aim 2: Conduct cost-effectiveness analysis, including budget impact analysis** **Cost-effectiveness analysis:** Intervention effectiveness and prospectively collected cost data will be used to model cost per new PrEP initiation. Budget impact analyses will identify

	drivers of cost, informing strategy refinement for STI clinic staffing and scale-up. **Go/No-Go criteria** If pre-determined milestones are met, Phase 2 of the project will refine and scale up the intervention to all persons who enroll from a participating clinic in a subsequent implementation trial. **A revised protocol will be submitted as an amendment for Phase 2** (R33), which includes the following aims: **Aim 3:** Engage state and local stakeholders to refine PrEP intervention, tailored to unique contextual needs. **Aim 4:** Determine effectiveness and cost-effectiveness of refined PrEP implementation strategy, expanded to all participants.

Intervention Trial Study Schema



1.0 BACKGROUND AND RATIONALE

To end HIV, the United States (US) needs integrated, scalable, and cost-effective prevention strategies. Despite the high efficacy of PrEP, less than 20% of PrEP eligible people have received a prescription, with noted regional and racial disparities[1–4]. In 2018, the US South accounted for 51% of new HIV diagnoses but only 33% of PrEP users[5]. In North Carolina (NC), where 1 in 93 residents will acquire HIV in their lifetime [6,7], PrEP use is half of the US average. The PrEP-to-Need ratio, which is a metric of PrEP equity that measures PrEP uptake relative to new HIV diagnoses highlights disparities in PrEP uptake among specific demographic groups such as Black, Hispanic, Southern people, and women, indicating these groups are underserved relative to their epidemic need [8].

For newly diagnosed adolescents and adults in North Carolina in 2022, the most likely route of HIV transmission reported was male-male sex (reported by 57.8%), followed by heterosexual sex (18.7%) [9]. PrEP uptake is lowest among young sexual and gender minority populations (YSGM) who account for 63% of new HIV infections in NC [5,7]. In 2022, 17.1% of newly diagnosed HIV cases in North Carolina in were among women aged 20 – 64 [9]. Among

women, 2022 preliminary data indicated that only 15% of women in the United States who could benefit from PrEP were prescribed PrEP [10].

Among NC counties with the most HIV diagnoses in 2019, four have rural designation and nine are small or medium metropolitan areas [7,11]. The lack of robust healthcare infrastructure in these areas presents challenges for HIV prevention services. NC's HIV epidemic tracks alongside rising sexually transmitted infections (STI)[12] with disproportionately high burden among rural YSGM. **Despite behavioral risk overlap of incident STIs/HIV, in NC, PrEP is only offered at a few, primarily urban health department (HD) affiliated STI clinics[13,14].** As of November 2022, we have identified 15 HD-affiliated STI clinics in relatively high-HIV burden, rural (n=13) or peri-urban (n=2) counties across NC who are interested in participating in this study. As of January 2024, the study is expanding to additional rural and peri-urban STI clinics in NC. All patients who are seeking STI testing at the participating clinics are offered HIV testing on-site. Per NC standard of care, all patients who are diagnosed with HIV are referred to immediate ART care, which may be offered onsite or through other HIV providers. However, **linkage to PrEP services is not well-established: at the initial 15 participating HD STI clinics, as of May 2023, one clinic (Wilson County, rural) offers referral to a co-located primary care clinic that can prescribe PrEP. The remaining 14 HD clinics do not provide any PrEP services to patients beyond passive referral to services in the community (e.g. patient is provided private practice provider name(s) that may offer PrEP services. None of these 15 clinics have providers "in-house" prescribing PrEP and none have PrEP navigation services.** STI clinics are a logical entrée to PrEP, but ineffective integration in rural HDs reflects heterogeneity in clinic structure and staffing: STI clinics are designed to provide episodic care, whereas PrEP services require additional human resources and longitudinal engagement to be effective [15]. Leveraging STI clinics as an on-ramp to PrEP is a compelling opportunity to capitalize on STI service encounters and address disparities in PrEP access for YSGM[16–18]

Multilevel impediments to PrEP scale-up in NC include provider shortages, overburdened STI clinics, intersectional stigmas, and lack of PrEP knowledge among providers, rural YSGM[19–22] and cisgender women[23]. These challenges are compounded by poverty and lack of insurance. Building on collaborations with state and local partners, we will implement a multilevel intervention within county STI clinics that links PrEP and STI services, addressing barriers at policy, clinic, provider, and user levels while working within clinic operational limits and competing demands on physical and human resources. This intervention is intended to build PrEP capacity and confidence through clinic training; provides pathways to PrEP using PrEP navigators for linkage to available financial support and services; supports linkage to telehealth PrEP; and uses an evidence-based digital health platform (HealthMpowerment [HMP]) [24–27] to connect users to tailored social and informational support for PrEP initiation and persistence[28,29].

Despite behavioral risk overlap of incident STIs and HIV, incorporating PrEP services into STI clinics presents unique implementation challenges**.** Barriers at the provider (self-efficacy, scarcity of HIV practitioners), clinic (budget constraints, understaffing), and structural level (lack of billing 3rd party payers), complicate PrEP scale-up in rural HD STI clinics [30]. One of the most significant barriers to combining effective PrEP services with existing STI care is the fact that, by design, STI care is episodic: persons with recent risk, exposure, or symptoms present for diagnosis and management, and then are discharged until such need arises again. However, per CDC recommendations, screening for bacterial STIs should occur at least every 6 months for all sexually active patients and every 3 months among MSM or among patients with ongoing risk behaviors [31,32].

Effective PrEP care requires ongoing engagement, with adherence support and follow-up visits[29]. Some persons are not ready to initiate PrEP, while others may be ready but require assistance with finances and insurance[15]. One-off referrals from STI clinics to external PrEP providers rarely result in PrEP initiation [30,31], with uptake particularly poor among youth[30] and non-Hispanic Blacks[32]. Even urban programs that successfully link STI clinic patients to PrEP lack the capacity to longitudinally manage financial needs of PrEP patients without additional

individualized navigation17. The diverse needs of potential PrEP recipients likely exceed what can be reasonably provided by STI clinic staff in standalone clinics. Developing a pathway to PrEP, such as this intervention, that complements clinic resources and workflow, including linking to PrEP navigation and offering high quality STI testing services/monitoring for PrEP users, is an appealing strategy to leverage STI clinics as an on-ramp to sustained PrEP services. This study will demonstrate an effective, feasible model to co-locate STI services and PrEP access in rural and peri-urban settings and provide critical information about ways to tailor this service delivery model for differences at small vs. larger clinics and under different types of staffing scenarios (e.g., using remote PrEP navigators, telePrEP providers, onsite PrEP providers, etc.). As established, trusted service providers, STI clinics can play an important role in providing individualized services to optimize PrEP uptake and retention and ensure ongoing access to PrEP. The HMP DHI was first found effective in a North Carolina-wide RCT [23,33] which found that greater HMP engagement was significantly associated with lower condomless anal sex, stigma reduction, and greater provider communication, HIV status disclosure to partners, and HIV care outcomes (e.g., engagement in care, adherence) [23,34]. HMP is currently being employed in multiple interventional and cohort trials, including a national sample of Black and Latinx YMSM and transgender women (TGW)[33], a cohort study focusing on understanding factors associated with the risk of STI and HIV diagnosis and predictors of PrEP use among Black cis and transgender women in Alabama, and a national interventional trial aiming to improve ART and PrEP adherence over time for sexual and gender minority youth ages 13-34. HMP has also been used in RCTs in Nigeria and South Africa, focusing on medication adherence among adolescent men, and women.

This study also includes budget impact and cost-effectiveness analyses (Aim 2) which are critical for program planning and for demonstrating the feasibility and sustainability of our proposed intervention strategy for co-located service access. As payers and providers endeavor to increase PrEP uptake, understanding the comparative value of alternative strategies particularly in populations with high HIV risk and low PrEP use, is urgently needed. Successful implementation and scale-up of the proposed intervention relies on effectively focusing scarce resources and understanding the main drivers of clinic-level costs. Decision models can demonstrate and explore tradeoffs in value between upfront intervention costs, potential cost savings, and health benefits from averting future illness.

2.0 STUDY OBJECTIVES

Primary Objective: Our overarching objective is to parlay episodic STI service encounters into linkage to convenient, continuous PrEP care. Our primary effectiveness outcome of interest is PrEP uptake within 3 months of an eligible clinic visit.

In the R61, we will determine effectiveness and cost in 2 aims:

Aim 1 (R61): Conduct a randomized trial of a multilevel PrEP intervention strategy in rural and peri-urban NC STI clinics. Participants will be randomized to intervention or control conditions. Our primary outcome is PrEP uptake within 3 months of an STI clinic visit. We will also examine implementation outcomes, capturing process indicators including intervention costs, fidelity and acceptability, to inform future refinement.

Aim 2 (R61): Conduct cost-effectiveness analysis, including budget impact analysis. Using Aim 1 effectiveness and prospectively collected costs, we will model cost per new PrEP initiation. We will conduct budget impact analyses to identify drivers of cost, informing strategy refinement for clinic staffing and scale-up.

Upon meeting predefined effectiveness, implementation, and development milestones, we will pursue Phase 2 R33. An updated protocol will be submitted as an amendment for Phase 2.

Aim 3 (R33): Engage state and local stakeholders to refine PrEP intervention, tailored to unique contextual needs. We will examine individual-, structural- and organizational-level determinants of success, including assessing implementation fidelity. Using an Intervention Mapping framework, we will identify modifiable barriers and build stakeholder consensus to refine our multilevel PrEP intervention.

Aim 4 (R33): Determine effectiveness and cost-effectiveness of refined PrEP implementation strategy, expanded to all participants. We will expand implementation of the refined implementation strategy to all persons who enroll at a participating clinic. Primary effectiveness and implementation outcomes are the same as in Aim 1, comparing PrEP uptake to control condition from R61 phase (Aim 1). We will update our cost-effectiveness model using parameters generated in this final implementation phase, generating an interactive decision-support tool.

3.0 STUDY DESIGN

The Phase 1 study is a randomized trial of a multilevel intervention to increase access to, uptake of, and maintenance on PrEP for HIV prevention. Participants will be randomized to an intervention or control condition (Section 3.2). The primary outcome is PrEP uptake within 3 months of an index STI clinic visit, assessed using drug metabolite presence, chart review, and self-report. All study participants will have access to study management functions as a DHI platform (HMP). Participants randomized to the intervention condition will receive the multilevel intervention (Section 3.2.1) while those randomized to the control condition will receive the informational resources component of the DHI (Section 3.2.2). Participants will complete study measures and activities at baseline and 3- and 6-month follow-up timepoints, with a subset of participants also completing 12-month follow-up (refer to Table 2.2) Participants enrolled in approximately the last 3 months of enrollment, will be followed for 3 months (refer to Table 2.3). We will assess implementation and process outcomes and organization-level determinants of success to inform future refinement.

3.1 Collaborating STI Clinics

In coordination with North Carolina DHHS partners, we utilized county-level 2019-2021 HIV/STI data (reported to the State Laboratory of Public Health [SLPH]), to identify local Health Department STI clinics for participation. Specifically, we examined testing volume and test positivity rates by reported race/ethnicity among men <40 years of age. We also used National Center for Health Statistics urban-rural classification scheme, limiting to counties designated as small (<250,000) or medium (<1,000,000) metropolitan counties, and nonmetropolitan (rural) counties including micropolitan counties (counties associated with at least one urban cluster ≥10,000 but ≤50,000 population) and non-core counties (nonmetropolitan counties that are not in a micropolitan statistical area)[34]. Starting in 2024, additional organizations that offer STI services and which are located in urban and peri-urban designated counties in NC will be identified as part of the recruitment expansion strategy. Throughout the protocol, locations where STI services are offered are referred to as “clinics” or “STI clinics”, however these locations may also include non-traditional modes of delivering STI services, for example, mobile van clinics, services housed within community-based organizations, and clinic-affiliated health fairs or other events.

All eligible clinics are contacted with information about the study and an invitation to participate. The study team meets with clinics to assess interest and appropriate fit. Clinics that decide to participate provide signed Letters of Support indicating commitment to collaborate, as well as roles and responsibilities.

Of the 15 participating counties participating in the study as of December 2023, 13 are designated as rural[34].

3.2 Randomization and Conditions

Arms will be assigned using blocked randomization stratified by county, with randomly ordered blocks of sizes 4 and 6 to ensure that staff are not able to predict what the next randomization assignment will be.

Participants may complete baseline, 3, 6, and 12-month assessments, with the duration of follow-up predicated on the period in which they were enrolled. Participants who are enrolled into the study with sufficient follow-up time remaining in the Phase 1 R61 will be asked to complete a 12-month assessment, while those enrolled in approximately the final quarter of study enrollment will only be followed for 3 months. All participants' condition-specific HMP app access will remain the same throughout their study participation, regardless of length of participation.

After month 6, intervention arm participants will not receive additional intervention components, such as PrEP navigation.

3.2.1 Intervention Arm Condition

All intervention arm activities may be conducted virtually.

Participants randomized to the intervention arm will receive:

PrEP Navigator: PrEP navigators will connect with participants following study onboarding. Navigators will serve participants across multiple clinics, primarily operating remotely, adapting workflow to participant and clinic needs. Primary navigator responsibilities include helping participants engage in PrEP care, assisting with completing necessary paperwork for insurance, referral to PrEP care, and application for drug assistance programs, as needed. All navigators will undergo study- and navigator-specific trainings (Sections 4.1 and 4.3). Navigation services will be available to all participants randomized to the intervention for up to 6 months – participants who are only followed for 3 months will by necessity only receive 3 months of navigation services.

Digital Health Intervention: HMP is an HIV status-neutral, theory-informed DHI to support sexual health and risk reduction among YSGM[35–37]. HMP is guided by the Integrated Behavioral Model (IBM)[38] facilitating examination of the individual and structural determinants of health (e.g., stigma and discrimination, health literacy, poverty) and psychological distress (e.g., depression, anxiety, loneliness) which hinder adoption of HIV preventive behaviors. The app provides critical resources for persons regardless of readiness to initiate PrEP as well as ongoing support and resources for those who do initiate PrEP. The features of HMP are described in Table 1 and example screenshots included in Figure 1. As part of PrEP monitoring features, participants can indicate how PrEP was prescribed (i.e. daily oral, event-driven oral, or injectable), as well as indicate dates PrEP was taken or, in the case of injectable, received.

Fig 1: HMP app screenshots

Table 1: The healthMpowerment (HMP 2.0) platform

Administration Portal and mobile app (research staff-facing)	
Communication	Allows for participant management (two-way, secure, direct in-app messaging, and push notifications)
Study Management	Survey integration and incentive tracking
Calendar	View schedule of study visits and activities and send automated reminders
Analytics	Analytics dashboard to monitor app engagement and perform engagement analyses
Security	HIPAA compliant, encryption of data at rest and in transit
HMP app (participant-facing)	
Study timeline and calendar	Displays access to upcoming study-related activities and a two-way secure messaging feature for communication between participants and research staff (including PrEP navigator) and receive reminders to promote completion
Resource Center	Expansive library of multi-media content tailored for YGSM populations of varying developmental stages
Activities	Information/skills building (quizzes, self-assessments, goal setting, choose-your-own-adventure, etc.)
Newsfeed	Social component provides space for user-generated content to include peer-to-peer sharing, exchange of health information and narrative discussions on topics of interest
Ask the Expert	Allows participants to ask questions to HIV/PrEP care expert provider and receive answers
Medication Tracker	Self-monitor PrEP adherence with visual calendar and provision of user feedback
Health Tracker	Self-monitor behaviors that impact PrEP adherence with reminders and provision of tailored feedback
Gamification	Sophisticated tracking of app use to trigger behavior-specific virtual rewards (e.g. badges)

Telehealth PrEP referral: PrEP Navigators can link interested participants to telehealth PrEP via self-referral. The study facilitates referral for intervention arm participants to pre-existing telehealth PrEP services. The telehealth PrEP services participants receive are not provided, financed, or staffed by the study. Participants will receive telehealth PrEP services via the technology platform or service that the provider typically employs. PrEP clinical eligibility, visit frequency, monitoring labs, and all other PrEP management will be at the discretion of the established PrEP provider. Study staff will access records for participants who have agreed to medical record release. PrEP navigators can assist with appointment scheduling, reminders, and other provider-access issues, as requested, for the period of navigation service receipt.

3.2.2 Control Arm Condition

All control arm activities may be conducted virtually.

Participants randomized to the control arm will receive:

Digital Health Intervention Standard-of-Care: The control arm version of the HealthMPowerment DHI platform includes Study timeline and Calendar features and all educational content in the Resource Center.

4.0 TRAINING

All training will be conducted virtually or in-person.

4.1 Research Staff Trainings

Any current or future project staff having study-related contact with participants will be required to complete Good Clinical Practice (GCP) and Human Subjects Research training for the responsible conduct of research and the requirements of maintaining privacy and confidentiality. Training for all research staff includes (but is not limited to): an overview of the study; study procedures and human subjects' issues (informed consent process, confidentiality); a demonstration of all technology components (e.g., screening survey, HMP application); methods for establishing comfort with the sensitive issues that may arise; quality management; confidentiality; and reporting of adverse events. Research staff includes the project manager, PIs, and research assistants.

PrEP navigators are not involved in the assessment of study specific outcomes or patient consent. However, given that they are retained by the study and have direct participant interactions, PrEP navigators will complete all required Human Subjects Research and GCP trainings as well as PrEP Navigator Training (Section 4.3).

Clinic staff will not be responsible for assessing patient eligibility nor conducting informed consent or administering any aspect of data collection or intervention delivery. In general, clinic staff will not have access to data other than what they have previously been granted access to through their professional appointment and duties. Some clinics may opt to securely upload records from consenting participants enrolled at their clinic, rather than providing study staff direct access to these records. In this case, study staff will provide a list of consented, enrolled participants from that site to the designated clinic staff via secure, password protected files. All clinics will be asked to participate in an introduction to STARR-NC study procedures training and PrEP training (Section 4.2).

4.2 Clinic Training

Prior to study implementation, representatives from participating clinics will have completed two trainings: introduction to STARR-NC study procedures and introduction to PrEP.

STARR-NC Study Procedures Training: Clinics will select staff to attend study procedure trainings including those who interact with clinic patients who might be eligible for the study (e.g. clinical personnel, clinic leadership, laboratory, front-desk staff). Study procedure trainings will focus on building capacity to ensure that clinic staff can:

- Answer basic patient questions about study objectives and refer patients to the STARR-NC study staff.
- Understand the study timeline and the timeline for when standard of care HIV/STI testing should occur in line with current CDC clinical guidelines [31].

- Know when and how to contact STARR-NC study staff with questions or concerns related to study implementation or participant follow-up.

PrEP Training: As described in Section 1.0, there are currently no PrEP services offered at any of the participating clinics. While all participating clinics have expressed interest in expanding access to PrEP for their patients, the timing and resource capacity of each clinic to begin offering PrEP on-site is outside of the scope of this project. PrEP capacity includes everything from on-site provision of PrEP, robust PrEP referral strategies, or PrEP provider knowledge to help answering basic questions regarding PrEP effectiveness and eligibility for patients who express interest in PrEP. As a first step in building PrEP capacity at the clinic level, the North Carolina HIV Training & Education Center (NC HTEC) will provide PrEP training to all participating clinics. This standardized program will provide all participating clinics the same PrEP awareness and knowledge training regardless of each individual clinic's intention or ability to launch clinic-embedded PrEP clinics. Delivering the same training across all clinics provides clinic staff common messaging about PrEP which could help limit this potential source of site-level variation in the context of the study. PrEP training content areas will include educational and skill building to:

- Explain how PrEP protects against HIV infection.
- Distinguish among PrEP, PEP, and U=U.
- Outline criteria that would make a client eligible for PrEP.
- Describe the components of PrEP service delivery.
- Identify resources to help patients prepare for, initiate, and persist on PrEP.

4.3 PrEP Navigator Trainings

PrEP navigators will complete all trainings described in Sections 4.1 and 4.2. In addition, PrEP navigators will complete structured and hands-on training using resources developed by PrEP-focused organizations and initiatives, including:

- PleasePrEPMe
- AIDS Education & Training Center Program National Coordinating Resource Center
- Centers for Disease Control and Prevention
- National Minority AIDS Council
- U.S. National Library of Medicine
  Centers for Disease Control and Prevention National Prevention Information Network

Drawing from the above trainings, PrEP navigators will be trained to conduct the following:

- All study staff and clinic competencies as described in Sections 4.1 and 4.2 above.
- Facilitate linkage to PrEP services, including assisting participants with identifying/connecting with a PrEP provider and completing appropriate referral paperwork as needed.
- Support completion of Medicaid enrollment assistance and drug assistance programs, as appropriate.
- Recommend and discuss resources and strategies for supporting PrEP medication adherence and maintenance.
- Identify and recommend community resources that are culturally sensitive to communities at highest need for PrEP.
- Stay informed about current HIV/AIDS trends, prevention efforts, and strategies.
- Demonstrate cultural humility, understanding, awareness, and respect for diversity among study participants.

5.0 SELECTION AND ENROLLMENT OF STUDY PARTICIPANTS

5.1 Participant Inclusion Criteria

RCT eligible participants must: ; (1) report sexual activity with a male in the past 12 months; (2) received HIV testing within 90 days pre-enrollment and not known to be HIV-positive at screening/enrollment by self-report (3) age 18-39 years; (4) have daily smartphone access; (5) be English speaking; and (6) deny current PrEP use (i.e. has not taken oral PrEP or received injectable PrEP within the last 3 months).

Qualitative interview (clinic patient participants) must be enrolled in the study and complete their Baseline study visit activities and at least one follow-up study time point (3 and/or 6-month visit). We will interview up to 50 patient participants. Participants will be purposively sampled to ensure a diversity in areas such as PrEP initiation status, recruitment clinic, age, sex, and race/ethnicity.

Qualitative interviews (clinic staff/providers/relevant stakeholders): We will conduct qualitative interviews with a purposively selected sample of up to 50 clinic staff, providers and other relevant stakeholders for PrEP provision. Interviewees will be purposively sampled to ensure a diversity of clinic roles and relationship to PrEP provision services and referrals, diversity in leadership level, and representation across all participating clinics.

5.2 Participant Recruitment

The study team and clinic representatives will meet as needed to troubleshoot any clinic-specific or cross-clinic recruitment challenges, as well as share successes.

Venue-based recruitment at participating STI clinics: Ads (e.g. posters, one-pagers) and business cards/palm cards with scannable QR codes will be posted throughout the clinic waiting areas, bulletin boards, patient rooms, etc. The study will also be promoted through word of mouth via the clinic health professionals, administrative staff, and community outreach personnel. Clinic and study staff may also bring recruitment materials to community-based events they attend on behalf of the clinic (e.g. health fairs, blood drive) with information about the study and encouraging persons to seek STI services at their local STI clinic.

Primary recruitment materials: Scannable QR codes will lead to a study landing page and online screener, which allows people to learn about the study discretely if they do not wish to carry study-related materials on their person. Each county will be assigned an individualized QR code so that study staff can recognize which county each completed screener is associated with. If multiple collaborating clinics exist within one county, the participant will self-report from which clinic they engaged with recruitment materials. We will work with clinic staff and our Community Advisory Board to develop a comprehensive recruitment portfolio, reviewing messages, imagery, tone and dissemination modalities. All recruitment materials will be reviewed and approved by the IRB prior to use.

Social media promotion: In addition to clinic-based recruitment, we will also work with each clinic to establish a social media recruitment plan. To maintain consistency across clinics, the intention of the social media promotion is to increase visibility of the clinic to the target population and encourage our population of interest to seek sexual health services through the collaborating clinics.

5.3 Procedures to Minimize Fraudulent Participation

Study ads and the initial screener will not indicate full, explicit eligibility criteria and will de-emphasize incentives as to minimize fraudulent responses. UNC study staff will verify eligibility prior to full study enrollment.

5.4 Screening for Eligibility

County-specific QR codes are used to link potential participants to a study pre-screening assessment. Patients will be asked for consent to screen and then complete the pre-screening questionnaire independently of study or clinic staff. Prospective participants that complete the eligibility assessment questions will receive a small incentive valued at approximately $5. The pre-screening assessment will explain the name, sponsor, funder, and the purpose of the study and assess key eligibility criteria (Section 5.1) and collect basic demographics. Participants who are not eligible based on screening criteria, duplicate entries, or choosing not to proceed, will be thanked, and rerouted to a public webpage (e.g., Google). Prospective participants will be asked permission for study staff to contact them and to provide preferred contact information (preferred name, pronouns, phone number, email, preferred time for phone, text or email contact).

5.5 Informational Video

After providing contact information, prospective participants who are found to be eligible thus far, will be routed to a brief online video outlining the purpose of the study, participant activities, data collection, and timeline of participation. Participants may view the video immediately after pre-screening or at a time most convenient to them.

5.6 Informed Consent

Participants have the choice to complete a self-guided electronic informed consent following the informational video prior to enrollment, or to complete a staff-guided electronic informed consent (via HIPAA-compliant videoconferencing platform or phone call) prior to enrollment. All participants will be asked to complete comprehension questions to ensure they adequately understand the research, risks, and benefits prior to providing an electronic signature (Section 15.5).

5.7 HIPAA Authorization

All prospective participants who complete Informed Consent will be required to review and sign a HIPAA release form, approved by the UNC IRB, to facilitate study access to test results specific to study outcomes and PrEP eligibility and medical records related to receipt of PrEP-related services. The release form specifies the scope of results/records that will be accessed and the timeframe over which research staff would be able to access this information.

5.8 Participant Randomization

Participants will be randomized 1:1. Randomization procedures are automated through the study database. Randomization is completed after a participant has completed informed consent and their Baseline survey. Participants will be informed by study staff of their study condition assignment during their onboarding appointment. The study onboarding appointment is tailored to the study arm condition they are assigned (Figure 2).

Study staff are trained to follow similar protocol for scheduling, enrollment, and follow-up regardless of arm which includes the use of IRB-approved guides for participant communications and specified standard operating procedures for participant outreach mode, timing, and frequency. Communication attempts will be tracked in a communication log for prospective and enrolled persons. PIs and the study monitor will be able to see the records for all those who complete screening and could assess whether there is differential communication efforts or enrollment by randomization condition.

6.0 RCT STUDY PROCEDURES (AIM 1, R61)

All study activities and interactions may be completed remotely/virtually through a combination of email, phone call, SMS, study app, online assessments, and videoconference. There is no required in-person contact with study staff.

6.1 Study onboarding appointment and baseline assessment

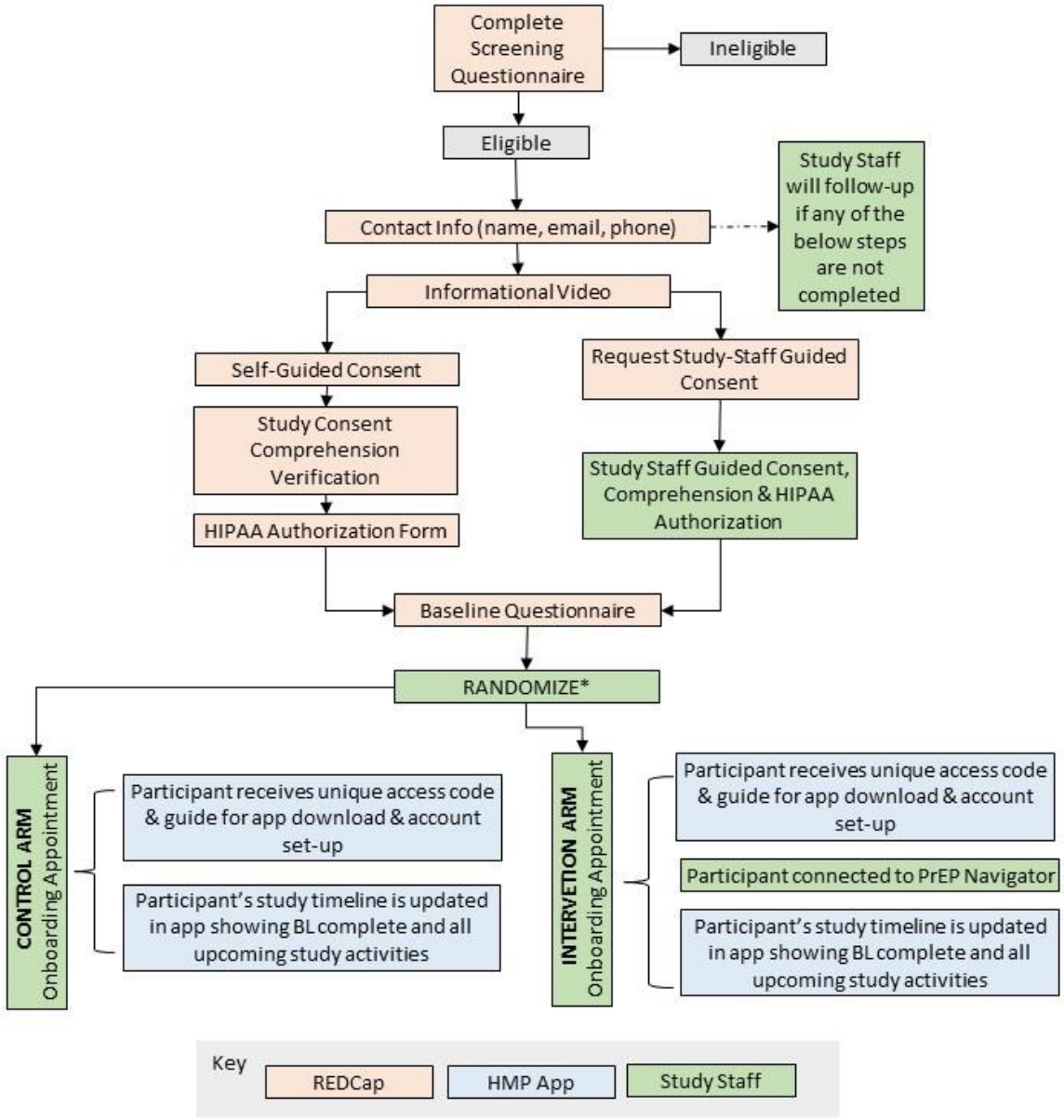
All participants will complete an onboarding appointment via phone or HIPAA-compliant videoconferencing platform. Participants will be considered enrolled and be eligible for the enrollment completion incentive once the below activities are complete:

- Informed consent and HIPAA authorization. Receipt of a unique access link to complete their Baseline CASI survey capturing PrEP use history, sexual behaviors, demographics, and determinants of PrEP use (access to care, perceived HIV risk, social support, perceived discrimination, mental health, substance use, and PrEP decision making). The CASI survey is self-administered via secure HIPAA-compliant platform (e.g. RedCap) and participants can complete the survey on their personal device with internet, wi-fi or mobile data. The survey saves after every page thus participants can return to complete the survey if their connection is disrupted or for any other reason.
- Randomized to study condition.
- Receipt of a unique access code and directions to download their free designated version (intervention or control) of the HMP study app from either the Google Play or Apple store.
- Creating their unique HMP account profile and log-in; touring the app features.

The onboarding appointment for intervention participants will also include being connected to their assigned PrEP navigator.

6.2 Participant Enrollment and Onboarding

Figure 2: Participant Enrollment Flow



* Randomization is automated within the study database. Participants are informed of the outcome of randomization as part of their onboarding appointment.

6.3 Intervention Procedures

Intervention arm participants will have access to the three primary intervention components (PrEP Navigation, Digital Health Intervention, and Telehealth PrEP Referral) for the full duration of the 6-month follow-up period, limited to 3-months for a subset of participants enrolled in approximately the final quarter of enrollment. Participants will be encouraged to use the intervention features through a combination of study staff reminders, PrEP navigator interactions, automated in-app notifications, and automated SMS and push notifications.

6.4 Follow-up study assessments

Follow-up study assessments will be conducted for all participants, including standard of care repeat HIV/STI testing [31] and repeat self-administered CASI survey assessments, with the number of follow-up assessments dictated by timing of enrollment. The baseline questionnaire is distributed after a participant completes informed consent and before they are randomized. If the participant does not complete Informed Consent, HIPAA Authorization, the baseline questionnaire and baseline HIV status verification within 45 days of completing the screening questionnaire, the participant must re-screen to assess eligibility.

The follow-up period (described as the post-randomization phase) begins once participants have been randomized to a study condition. Randomization will occur once participants have connected with study staff for their onboarding appointment. An overview of the pre and post randomization assessments conducted in each study phase are described in Tables 2.1 – 2.3.

Table 2.1: Participant Assessment Timeline

Pre-Randomization			
Study Activity	Day Open	Day Close	Study Window Duration (days)
Screening Questionnaire	0	45	45
Informed Consent + HIPAA Authorization	0	45	45

Table 2.2: Participant Assessment Timeline for Participants Followed 6 -12 Months

Post-Randomization			
Study Activity	Day Open	Day Close	Study Window Duration (days)
App Account Generation	0	0	1
Baseline STI Result Abstraction[1]	0	89	89
Baseline HIV Result Abstraction[2]	0	45	45
3M Survey	90	165	75
3M DBS	75	165	90
3M HIV/STI Result Abstraction[1]	90	165	75
6M Survey	166	196	30
6M DBS	166	211	45
6M HIV/STI Result Abstraction[1]	166	276	110
12M Survey[3]	365	440	75
Qualitative Exit Interview[3]	90	276	186

Table 2.3: Participant Assessment Timeline for Participant Followed for 3 Months

Post-Randomization			
Study Activity	Day Open	Day Close	Study Window Duration (days)
App Account Generation	0	0	1
Baseline STI Result Abstraction[1]	0	89	89
Baseline HIV Result Abstraction[2]	0	45	45
3M Survey	90	120	30
3M DBS	75	120	45
3M HIV/STI Result Abstraction[1]	90	165	75

[1] This window represents the dates in which a participant sought HIV/STI testing. The abstraction of such results can occur outside of this window.

[2] Participants initial eligibility is confirmed via their self-reported HIV negative status captured in the screening questionnaire. Participants are required to have proof of a negative HIV test within 90 days prior to completing the screening questionnaire or within 45 days of completing the screening questionnaire. The window represented in this table indicates that study staff must verify participants HIV negative status within 45 days of the participant completing the screening questionnaire.

[3] Indicates assessments done for subset of participants

A subset of participants will be asked to complete a brief CASI survey pertaining to PrEP uptake and/or persistent use and self-reported STI or HIV testing outcomes at 12-months if this follow-up interval falls within the allowable data collection timeframe based on when a person was enrolled (see Section 17.0 Timeline). The study windows for each follow-up time

point are intentionally broad to maximize data completeness and accommodate variation in HIV follow-up testing that may occur as part of standard clinical care, PrEP initiation and monitoring, and event-driven HIV testing following a potential exposure event. The target dates for follow-up assessments are at the completion of the 3-month, 6-month, and 12-month mark, with windows before and after these dates to accommodate variation in HIV/STI testing schedules.

For participants that initiate PrEP while on study, study staff will update the timeline for their HIV/STI assessments according to their PrEP initiation date. As HIV/STI testing is expected to be collected as part of their standard PrEP management, we will not ask participants to duplicate this testing at their STI clinic if they can demonstrate having been tested within the acceptable window for their expected 3- or 6-month testing interval. The timeframe in which participants are asked to complete DBS kits and CASI assessments will remain the same, defined by the date participants are randomized.

6.5 Self-collected blood sample

Dependent on their enrollment date, participants will be asked to complete one to two self-collection whole blood sample kits corresponding to a 3- and 6-month follow-up to assess for PrEP uptake by measuring for the presence and levels of tenofovir diphosphate and emtricitabine triphosphate (TFV-DP/FTC-TP) or Cabotegravir (CAB) levels. Participants may have the specimen collection kits sent to their current residence or any mailing address of their choice. Kits will contain detailed instructions for use of the blood collection device as well as all packaging materials needed to return the kit to the lab. See Section 16.1 for laboratory details.

6.6 Clinic assessments

We will conduct assessments of all participating clinics to evaluate staffing, patient volume, hours of operation, and available services. These assessments may be conducted using a combination of in-person and remote/virtual interactions and will occur within 3-months before or after initiating patient participant recruitment at each site, and again within 3-months before or after the end of the study follow-up period (see Section 17.0). Additionally, we will track how clinics are engaging with technical assistance services as offered through NC HTEC.

Alongside in-depth interviews (Section 6.7), we will also ask relevant stakeholders about intervention acceptability and organizational factors that may influence PrEP provision and integration of services, including organizational readiness for change, support climate, and intervention-values fit [39–41]. As part of anticipated biannual convening of study leadership, state policymakers, and members of our Community Advisory Board, we will monitor relevant policy changes such as those pertaining to insurance, PrEP coverage, or recommendations for use that may serve as external influences relevant to our observed outcomes. This information will be documented in study minutes and circulated to all attendees.

6.7 Qualitative in-depth interviews

A sub-set of up to 50 participants will complete an in-depth interview following their 3 or 6-month study visit to provide contextualized data about: experience with the study participation, perceived accessibility of PrEP before and after study enrollment, evaluation of the acceptability of this PrEP-access model, unmet PrEP-related health service needs/barriers, experience initiating PrEP (if relevant), experience using the study-related intervention components (app, PrEP navigator, telehealth for PrEP) (if relevant), and other emergent topics as raised by participants. Participant interviews may be conducted remotely by phone or videoconference platform.

Up to 50 relevant stakeholders, including STI clinic staff, healthcare providers, and other stakeholders relevant for PrEP services will also complete in-depth interviews covering topics such as: experiences and challenges with

being part of a participating clinic for this study, perceived accessibility of PrEP to target patient population before and after study implementation, perceived strengths and drawbacks of this PrEP-access model, suggested changes to this PrEP-access model, unmet PrEP-related health service needs/barriers among target patient population, and other emergent topics as raised by participants. Stakeholder interviews may be conducted in-person or remotely by phone or videoconference platform.

Interviews will be conducted by trained research staff experienced in qualitative research. Interviews will be guided by the use of an SOP and a semi-structured interview guide which will include open-ended questions corresponding to each qualitative endpoint. Interviewers will be allowed the flexibility to probe patient responses and pursue discussion diverging from the initial interview questions if it is relevant to the endpoints of interest. Each interview will be digitally recorded and transcribed to text for analysis.

7.0 OUTCOME MEASURES AND DATA SOURCES

For interventions that address systems-level challenges or utilize patient navigation as an intervention component, PrEP uptake is an appropriate primary outcome as it is an indication of the success of the intervention to overcome the barriers to access to the health service/treatment[42,43]. Given the current lack of PrEP availability in the proposed study settings, an intervention that can overcome the multi-level barriers to PrEP access and uptake is a critical first-step.

With PrEP uptake as the primary outcome and the primary objective to increase PrEP uptake, this study will follow a similar operational definition as another large-scale mHealth RCT intervention for PrEP uptake among MSM in the southern United States[44]: self-report taking any PrEP (oral or injection) on a follow-up survey or in the app, AND verified by at least one of the following: (1) an uploaded photo or image demonstrating a PrEP prescription; OR (2) any indication of the presence of tenofovir diphosphate or cabotegravir in DBS; OR (3) staff-abstracted electronic medical record of PrEP prescription issued or physician notation of PrEP initiated.

Table 3 presents the study Outcome Measures and their data sources.

Table 3: Study Outcome Measures and Data Sources

Name	Time Frame	Brief Description	Data sources
Primary outcome			
PrEP uptake	3-month follow-up	Verified self-reported PrEP use (first dose, oral or injectable)[1]	CASI, in-app report, EHR abstraction, self-collected lab sample
Secondary outcomes			
PrEP uptake	6-month follow-up[4]	Verified self-reported PrEP use (first dose, oral or injectable)[1]	CASI, in-app report, EHR abstraction, self-collected lab sample
PrEP care engagement	3- and 6-month[4] follow-up	Daily oral or event driven PrEP: after PrEP uptake, number and dates of any subsequent PrEP visits or new/refilled	CASI, EHR

		PrEP prescriptions Injectable PrEP: after initial injection, number and dates of any subsequent PrEP visits/injections	
PrEP use	3- and 6-month[4] follow-up	Number of consecutive months PrEP used, based on date of first and last dose[2]	CASI, EHR
PrEP adherence (self-report)	3- and 6-month[4] follow-up	Daily oral PrEP: reported PrEP use (past 30 days) Event-driven PrEP: reported PrEP use corresponding to reported sexual activity (past 30 days) Injectable PrEP: based on date of injections	CASI
PrEP adherence (injection history & drug measurement)	3- and 6-month[4] follow-up	Daily oral PrEP: PrEP concentrations detected at designated study follow-up visits, based on intraerythrocytic TFV-DP collected as DBS; Injectable PrEP: based on dates of injections	Self-collected lab sample, EHR
Incident STI/HIV	3- and 6-month[4] follow-up	Clinical test result (yes / no / indeterminate / missing) for each STI and HIV that participant is tested for.	CASI; State, clinic, commercial lab results[3]
PrEP Stigma	3- and 6-month[4] follow-up	Self-reported scored PrEP Stigma scale	CASI
Implementation measures (intervention arm and stakeholders)			
Fidelity-Engaged by PrEP navigator	First two weeks following enrollment	Proportion of Intervention Arm enrolled participants that are engaged by the PrEP navigator within two weeks of enrollment	Intervention CRF
Intervention satisfaction - Quantitative	3- and 6-month[4] follow-up	Average score on participant-completed System Usability Scale (10 item universal measure of usability and acceptability).	CASI
Intervention satisfaction – Qualitative	3- or 6-month[4] follow-up	Description of participant experiences and satisfaction, usefulness and attribution to PrEP use while on study and with each intervention component.	In-depth interviews with participants
Acceptability	Within 3-months before or after baseline and	Description of stakeholder experiences and acceptability of intervention, readiness for change, implementation	In-depth interviews and surveys with

	within 3 months before or after study close-out	climate, and intervention values	stakeholders
Clinic measures			
STI service delivery	Baseline, 3- and 6-month[4] follow-up	Proportion of enrolled participants receiving STI screening (urogenital, rectal, pharyngeal) at baseline (pre-enrollment) and follow-up timepoints	State, clinic, commercial lab results[3]
Sexual health service delivery	Within 3-months before or after baseline and within 3 months before or after study close-out	New or modified sexual health programs or offerings at participating clinic, including PrEP (on-site or integrated into clinic), point-of-care testing, and other initiatives	In-depth interviews and surveys with stakeholders
Exploratory measures			
PrEP uptake	12-month follow-up[5]	Verified self-reported PrEP use (first dose, oral or injectable)[6]	CASI, in-app report, EHR abstraction
PrEP care engagement	12-month follow-up[5]	Daily oral or event driven PrEP: after PrEP uptake, number and dates of any subsequent PrEP visits or new/refilled PrEP prescriptions Injectable PrEP: after initial injection, number and dates of any subsequent PrEP visits/injections	CASI, EHR
PrEP use	12-month follow-up[5]	Number of consecutive months PrEP used, based on date of first and last dose[2]	CASI, EHR
PrEP adherence (self-report)	12-month follow-up[5]	Daily oral PrEP: reported PrEP use (past 30 days) Event-driven PrEP: reported PrEP use corresponding to reported sexual activity (past 30 days) Injectable PrEP: based on date of injections	CASI
Incident STI/HIV	12-month follow-up[5]	Clinical test result (yes / no / indeterminate / missing) for each STI and HIV that participant is tested for.	CASI; State, clinic, commercial lab results[3]
Effective HIV protection	First 3 months of trial	Proportion of days out of the first 3 months of the trial that participant was "effectively" protected from HIV transmission based on their self-reported PrEP use and self-reported	CASI, in-app reported behaviors[7]

		sexual behavior.	
Effective HIV protection	6-month study period[4]	Proportion of total days of the trial that participant was "effectively" protected from HIV transmission based on their self-reported daily PrEP use and self-reported sexual behavior.	CASI, in-app reported behaviors[7]

[1] Persons who self-report taking any PrEP (oral or injection) during a follow-up survey OR in their app will meet this endpoint if this self-report is verified by at least one of the following: (1) an uploaded photo or image demonstrating a PrEP prescription; OR (2) any indication of the presence of tenofovir diphosphate or cabotegravir in DBS; OR (3) staff-abstracted electronic health record of PrEP prescription issued or physician notation of PrEP initiated.

[2] First dose and last dose determined based on self-report for oral PrEP and medical record (or self-report if record not available) for injectable PrEP. Respondents endorsing any PrEP dose will have uploaded current PrEP prescription as described in PrEP uptake outcome as above.

[3] State, clinic and commercial labs: We will collect HIV/STI test results directly from laboratory portals or via secure upload of results from participants or participating clinics' medical records.

[4] Participants who reach 6-months of study follow-up prior to study end will contribute to 6-month outcome measures.

[5] Participants who reach 12-months of follow-up prior to study end (see 17.0 Timeline) will complete a brief CASI survey inquiring about PrEP use, including PrEP uptake and any interruptions or discontinuations of PrEP. They will also maintain ability to self-report PrEP start within the app through month 12. Self-reported STI and HIV results will also be captured at this time point, as well as preferences for provision of extended PrEP navigation resources.

[6] Persons who self-report taking any PrEP (oral or injection) during a follow-up survey OR in their app will meet this endpoint if this self-report is verified by at least one of the following: (1) an uploaded photo or image demonstrating a PrEP prescription; OR (2) staff-abstracted electronic health record of PrEP prescription issued or physician notation of PrEP initiated. DBS samples will not be collected at month 12.

[7] All participants (intervention and control) will be asked questions on CASI about PrEP use, medication adherence and sexual behavior; CASI data will be used to calculate an estimate of effective protection for **all** participants. In-app daily medication adherence self-report and daily sexual behavior self-report are only available for intervention arm participants; in-app data will be used to calculate an app-based estimate of effective protection for any **intervention arm** participants who used the app to record these behaviors.

8.0 PARTICIPANT MANAGEMENT

8.1 Participant Retention

We will collect multiple forms of participant contact information and study-related communication preferences (e.g. email, phone/text, social media handles) as part of study enrollment. The HMP app supports participant retention through a timeline that displays upcoming study activities and a two-way secure messaging feature for participants and study staff. The study staff-facing web-based administrative portal also facilitates retention via prompts to reach out to participants who have missed specified study activities and by providing a secure platform to communicate with participants and deliver participant incentives. The study team will meet weekly

and review retention reports and proactively identify barriers to retention.

8.2 Participant Remuneration

Participants will receive remuneration throughout the course of their participation. Intervention and control arm participants are eligible to receive the same level of remuneration.

- Participant enrollment activities: $60
- Participant follow-up 3-month survey: $40
- Participant follow-up 6-month survey: $40
- Participant follow-up 12-month survey: $40
- Participant return of 3-month whole blood self-collection kit: $50
- Participant return of 6-month whole blood self-collection kit: $50
- Participant qualitative exit interview (sub-sample of participants): $50
- Clinician/Stakeholder/Staff qualitative interview and brief survey: $50

8.3 Suspected or Confirmed HIV/STI Infection at Screening, or While on Study

Individuals who self-report a prior HIV diagnosis or reactive HIV test at screening will not be eligible for the study. Once participants have completed informed consent and a HIPAA waiver, HIV status can be confirmed by study staff (access to lab results via state or clinic portals). If lab results are not available, participants/clinics may use a secure link to self-report a recent (<90 days) test result to confirm HIV negative status.

Individuals who are found to be HIV seropositive at time of eligibility verification will not complete enrollment. Participants who test positive for HIV or other STIs at any point during study follow-up will be appropriately connected to care through the North Carolina State Health Department's standard notification procedures and Disease Intervention Specialists. [45] All participants are encouraged to adhere to CDC recommended frequency of testing which includes screening for bacterial STIs every 3 months among MSM or among patients with ongoing risk behaviors [31]. Therefore, HIV/STI testing will be completed as part of patients' routine care at established STI clinics (not administered through the study). The HMP app and study staff will help facilitate participants' return to STI clinics for HIV/STI testing by providing in-app appointment reminders, text messages and phone calls, as needed. Test results will be communicated to participants by clinic staff following their standard of care and established notification procedures. Study staff will not communicate HIV/STI test results to participants directly. The conduct of HIV/STI testing at 3 & 6 months is considered routine clinical care.

For patients who initiate PrEP, quarterly HIV and STI testing will be ordered by the prescribing PrEP provider, at their clinical discretion. These participants may not require additional HIV or STI testing (see Section 6.3). Post-hoc abstraction of HIV/STI test results by research staff is considered a research activity and is covered by the HIPAA authorization form participants sign at study enrollment. Participants who initiate PrEP will have HIV/STI testing results abstracted from HD (if HD-based PrEP) or external PrEP providers' records, or, if access to such records is not feasible, participants will be asked to upload the results of said testing within the app portal. Participants who receive an HIV diagnosis while enrolled in the study will be study stopped. Following an HIV seroconversion SOP, study staff will document that the participant has been notified and received appropriate counseling as described above. Participants will have an opportunity to complete an end-of-study survey to capture any interim PrEP use and referral for or initiation of HIV treatment. A seroconversion CRF will be completed for any such participants and indication noted in the HMP study staff-facing administrative portal for study staff and PrEP navigators. Participants who test positive for other STIs will continue to be eligible for study participation.

8.4 Participant Withdrawal

Enrolled participants are free to withdraw from participation in the study at any time and for any reason upon request. A study stop CRF will be completed for participants who request withdraw from the study. No further data collection will occur following completion of the study stop CRF.

An investigator may withdraw a participant from the study for the following reasons:

a) If any clinical adverse event (AE), serious adverse event (SAE), laboratory abnormality, or other medical condition or situation – related or unrelated to the study – develops after enrollment such that continued participation in the study would not be in the best interest of the participant.
b) If a patient presents a safety risk to the research staff.
c) If their participation in the study is disruptive to the study or the clinic.
d) If the participant receives an HIV diagnosis (see section 8.3).
e) They intentionally violate study procedures, including fraudulent engagement with study screening or DHI-based survey completion.

The reason for any participant's discontinuation or withdrawal from the study will be recorded on the study stop CRF.

Furthermore, study staff may use their professional discretion not to enroll a prospective participant for reasons b through e, listed above.

9.0 STATISTICAL/ANALYTIC CONSIDERATIONS

9.1 Sample Size and Power Estimate

We expect > 7,400 patients will present for care in the 21-month enrollment period, with 20-35% study eligible. Aim 1 analysis includes eligible, consenting patients who successfully download the HMP app. The study will enroll for 21 months with a target sample size of 336. We expect approximately half of participants will be randomly assigned to the intervention arm and the remaining half to the control arm (see Randomization, Section 3.2).

We calculated statistical power for the effect of intervention upon PrEP uptake by 3-month follow-up using SAS 9.4 (Cary, NC) with a 5% type I error rate and a two-sided Chi-square test. Assuming 2.5% of eligible patients start PrEP within 3 months in the control arm, we calculated statistical power to detect a range of small to large effect sizes from 5% to 15% percentage point increases in PrEP uptake under a range of possible sample sizes and assuming 10% missing data (Table 4). At a total sample size of 336, given our design and assumptions, we will have >88% statistical power to detect medium (10%) and large (15%) effect sizes, and 80% statistical power to detect a moderate (7.5%) effect size.

Effect size rationale: As there is currently limited-to-no infrastructure or existing programing providing PrEP in rural North Carolina STI clinics, no prior studies that we are aware of have measured PrEP uptake in these settings. Overall, U.S. PrEP coverage of those assigned male sex at birth with PrEP indications was reported by CDC as 18.4% in January – March 2021, but only 5.6% among Black/African American[46], who will constitute a large portion of our sample. Among the CDC-designated End-the-Epidemic jurisdictions, recent PrEP coverage estimates of those with PrEP indications range from a low of 4.5.% in San Bernardino to a high of 42.3% in San Francisco; North Carolina's state level PrEP coverage estimate is 13.3%, which belies the wide variability from

urban to rural areas[47]. Looking to other settings with some comparable characteristics, the THRIVE national CDC demonstration project (n=9538 PrEP-eligible MSM) found a range across study sites of 10.7% to 95.9% (mean 53.8%) of eligible screened participants linked to PrEP services (defined as attending an initial PrEP appointment), with substantially fewer being prescribed PrEP (37.2%). At sites where PrEP navigation was provided, **48.5% of MSM who used navigation were linked to PrEP as compared to 2.8% being linked among those who did not use navigation** [42]**.** In a pilot RCT mHealth app **(without navigation),** overall PrEP uptake among a primarily urban MSM population was 12.8% overall (n=6/58) with no difference between intervention and control arms[48]. Among an urban sample of 2106 PrEP-priority eligible MSM attending sexual health clinics in New York City who were offered PrEP navigation services, 288 (13.6%) linked to a PrEP provider and 235 (11.2%) received a PrEP prescription[49]. Looking at these data together and considering the added barriers posed by our rural setting and PrEP stigma, we anticipate being able to see a moderate effect size and have conservatively selected a preliminary intervention efficacy milestone of an observed difference in PrEP uptake of at least 7.5% (see Table 6). This conservative, but still clinically meaningful, effect size will be used as part of the overall determination of whether the intervention approach should be explored further in Phase 2 (see 11.0 Milestones for further discussion).

Based on historical testing data, we expect <2% of all persons who are undergoing HIV screening on day of enrollment to be seropositive. Persons with unidentified HIV at time of enrollment should be randomly distributed between the intervention and control groups. Given the small proportion we anticipate may be enrolled/randomized prior to seropositive results being available, our study remains powered to detect the differences as described above.

Table 4: Statistical power as a function of the observed difference in effect (PrEP uptake) and sample size*

	TOTAL SAMPLE SIZE – R61 PHASE				
OBSERVED DIFFERENCE IN PREP UPTAKE	*n*=200	*n*=300	*n*=400	*n*=500	*n*=600
5%	33%	47%	58%	68%	76%
7.5%	59%	77%	87%	93%	96%
10%	72%	**88%**	95%	98%	99%
15%	92%	98%	99%	>99%	>99%

*Assuming PrEP uptake of 2.5% in the control arm, 10% missing data at month 3, and 5% type I error

9.2 Outcome Analysis

Eligible participants will enter the study within 45 days of screening as eligible and will be followed longitudinally for PrEP uptake for up to 12 months. Analyses will be conducted for all primary and secondary outcomes defined in Table 3 (Section 7.0) using the following general procedures for analysis.

Basic descriptive statistics will be calculated. Frequency tables will be presented for the categorical variables and means, standard deviations, and percentiles (25^{th}, 50^{th}, 75^{th}) will be given for the continuous variables. For each binary outcome, we will estimate the proportion of patients achieving the event (e.g., PrEP uptake) in each arm and a probability difference (PD) and a corresponding 95% confidence interval (CI) to compare the intervention vs. control arms at each timepoint (3-month, 6-month, and 12-month follow-up). For continuous endpoints, we will use a non-parametric Wilcoxon Rank-Sum Test to compare the intervention and control arms. For count

data variables (e.g., number of unprotected sex acts), we will use small analysis methods for count data (e.g. exact Poisson regression).

To address missing data, we will review the frequency of missing and non-missing values for all variables at baseline, 3-month, 6-month, and 12-month follow-up. We will conduct missing value analyses to determine whether persons with missing values are systematically different from those without missing values and if the probability of having missing values differs by arm. If this assessment of the frequency and imbalance of missing data suggests that bias may be introduced, we will employ inverse probability of observation weights or multiple imputation to address the missing data.

If there is chance imbalance in the measured baseline covariates, we will conduct sensitivity analyses applying stabilized inverse probability treatment weights (IPTW).

9.2.1 Primary Outcome Analyses

The primary outcome of PrEP uptake is measured at the 3-month follow-up. The effectiveness of the intervention will be estimated as the difference in proportion of participants starting PrEP within 3 months of an index STI clinic visit, comparing patients randomized to the intervention and control groups. For participants enrolled through clinic-collaborating outreach events, the date of clinic outreach serves as the index visit.

9.2.2 Secondary Outcomes Analyses

Secondary effectiveness outcomes are listed in Table 3 (Section 7.0) including PrEP uptake at 6-months, and PrEP care engagement, PrEP use, PrEP adherence, incident STI/HIV, and PrEP stigma (at both 3- and 6-months, determined by when they are enrolled in the course of study enrollment). All analyses will follow the specifications described above in 9.2.

PrEP adherence at 3 and 6 months will be assessed using PrEP metabolite levels and self-report (3-month only for persons enrolled in approximately the final quarter of enrollment). We will use standard of care quarterly STI/HIV testing results to examine differential rates of incident STIs, adjusting for testing frequency given potential increased frequency among PrEP initiators.

9.2.3 Exploratory Outcomes Analyses

As exploratory analyses, we will also report the effectiveness of the intervention as measured by PrEP uptake at the 3-month follow-up stratified by sex. The effectiveness of the intervention will be estimated as the difference in proportion of women starting PrEP within 3 months of an index STI clinic visit, comparing randomized to the intervention and control groups. For participants enrolled through clinic-collaborating outreach events, the date of clinic outreach serves as the index visit.

9.2.4 Additional Outcome Analyses

Additional analyses will compare self-reported PrEP use among patients who complete the self-administered screening questions (Section 5.4) but who do not enroll in the study (ineligible or eligible but decline). Specifically, we will examine the proportion of respondents endorsing recent or current PrEP use and trends throughout the enrollment period to evaluate “background” PrEP use in the community of patients seeking STI services at participating clinics. We will estimate the proportion reporting PrEP use in each month as the number of patients reporting current PrEP use divided by the number of patients completing the screening questionnaire. We will compute trends in PrEP use by regressing these estimated monthly proportions on time using logistic regression and interpreting the regression coefficient on time.

We will also explore effective-PrEP use, namely PrEP use that aligns with periods of HIV risk [50,51] using daily app data of tracked sexual behaviors, incident STIs, and PrEP use for persons in the intervention arm. As the daily tracking feature is only in the intervention arm app, this outcome will be exploratory for use in future work.

Additional exploratory analyses will examine PrEP uptake, persistent use, HIV or STI incidence, and intervention satisfaction/preferences at 12-months. All measures will be self-reported and captured using CASI. Only persons who reach the 12-month follow-up visit within the allowable data collection window will have these assessments completed.

We will examine whether there are subgroups (of clients and/or clinics) for which the intervention may be more or less effective (see Section 11.0).

We will also examine the proportion starting PrEP separately for patients enrolled in each calendar year quarter of the study to explore trends over time.

This assessment describes process indicators to inform intervention implementation, optimization, and scale-up. We will measure acceptability of the implementation strategies to providers and clinic directors, feasibility of the intervention, and intervention satisfaction among patients and providers.

To measure acceptability of the intervention and to explore clinic-level influences on implementation feasibility at each clinic, we will interview providers and clinic directors. We will assess factors such as provider burden of intervention, adequacy and timing of training, supervision/support structure, organizational readiness for change (quantitative scale and qualitative interviews),[39] management support (qualitative interviews), implementation climate (quantitative scale and qualitative interviews), [40] and intervention-values fit (quantitative scale and qualitative interviews) [41]. We will use facility audit data, including county population, patient panel size and demographics, number and training level of clinic staff, clinic staff-to-patient ratio, daily patient volume, open hours and local access to PrEP to contextualize determinants.

Feasibility measures will assess patient engagement with the intervention, including uptake of elements (i.e. linkage to insurance if not durably insured at enrollment, use of telehealth PrEP, interactions with PrEP navigators). We will examine the percent of enrolled participants in the intervention arm who are engaged by the PrEP navigator within two weeks of enrollment. We will also examine app-specific engagement, including successful app installation, account creation and log-in, total number of log ins, and time spent in the app.

Measurement of patient satisfaction with intervention includes qualitative (IDI data) and quantitative (e.g. System Usability Scale) assessments. We will conduct interviews with a subset of patients regarding their experiences with the intervention. This sample will include a mix of persons with variable HMP engagement and PrEP uptake. We will ask about satisfaction with clinician interactions, time and financial cost, and perceived quality of PrEP care. As a quantitative assessment, all participants will complete a satisfaction scale at quarterly follow-up visits [52].

Analysis of implementation outcome measures will include qualitative analysis. Interviews will be recorded and transcribed. Transcripts from participants and providers/clinic staff will be analyzed separately and reviewed for quality.

Interview transcripts will be thematically analyzed following a combination of deductive and inductive analytic approaches. An initial codebook will be developed based on *a priori* concepts driven by the theoretical underpinnings used to develop the interview guide. All textual data will then be read thoroughly to summarize first impressions. Emerging themes will be incorporated into the codebook. Pre-existing codes may be modified based on interview transcripts. Transcripts will be coded iteratively using qualitative analysis software. Two

researchers will code interviews separately to assess inter-coder reliability. The codebook will be revised and updated. Analysis of the coded data will include investigation of relationships between codes, coding matrices, and mapping of codes and themes. Data from qualitative interviews will be triangulated with the quantitative data to gain a more complete understanding of the factors underlying implementation. For example, if our survey data show that clinics with lower fidelity tended to score low on the implementation climate scale, we will examine our qualitative data for indications about what aspects of the leadership or climate may have contributed.

10.0 COST-EFFECTIVENESS STUDY PROCEDURES (AIM 2, R61)

10.1 Overall Approach

We will build a decision model to estimate and compare the budget impact, cost- effectiveness, and population outcomes of our multilevel PrEP intervention. We will model the value of each component (PrEP navigator, HMP app, telehealth provider) as assessed in Aim 1, separately and in combination. We will examine the impact of alternative combinations via sensitivity analyses, varying assumptions about the costs and combined effectiveness of the interventions. We will further parameterize the model and conduct sensitivity analyses using published PrEP cost and effectiveness data [53–56].

We will directly measure costs and a surrogate marker of HIV prevention effectiveness (PrEP uptake) in our RCT. Our analysis presumes that increasing uptake of PrEP is a desired outcome, focusing our assessment on incremental STI clinic related intervention costs. Following established methods, we will measure non-research related costs associated with the intervention and control arms to estimate incremental cost per additional person starting PrEP. Analyses will take the perspective of the STI clinics and public payers.

10.2 Cost Measurement

We will embed an empirical costing study into Aim 1 activities. Costs will be collected prospectively in two ways: micro costing and time-and-motion logs. **Micro-costing** involves "direct enumeration" for consumed inputs[57], an ingredients-based approach. We will quantify resources associated with the development and implementation of our intervention (Table 5).

Table 5: Cost elements and data source

Cost	***Source***
Trainings	Project receipts
HMP app updates	Project receipts
Telecommunications	Project receipts
Test supplies*	EHR
Healthcare utilization**	App paradata, EHR
Personnel	Time-and-motion, NC DHHS salary, project expenses

***HIV, STI, renal function**, **clinic visits

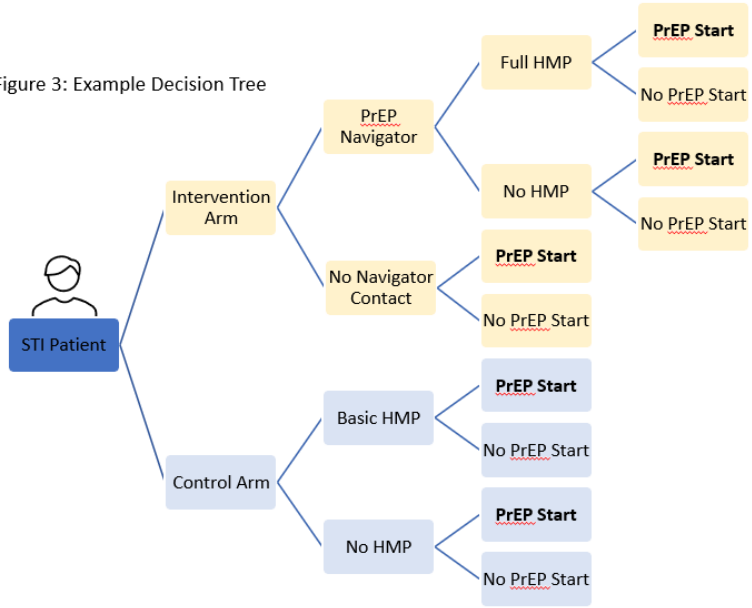
We will not assess fixed costs common to both arms (e.g., clinic operations overhead), or costs related to the conduct of the study alone (e.g., consent). Cost data will be available through contractual information with developers, clinic and project receipts, and NC DHHS supply chain partners. We will also extract data from project expenditure and management records, including purchase logs and human resource records. **Time-and-motion** assessments record how involved parties (navigators, providers, etc) divide time among PrEP-related tasks, reliably apportioning effort relevant to implementing the intervention. This includes time for: health worker trainings, PrEP navigators, and PrEP providers. Notably, PrEP provider costs will be estimated to inform clinics of the potential expenses (and possibly revenue) regardless of if a given clinic opts to implement PrEP programming during the study period. As such, costs of PrEP provision and monitoring may be extrapolated from available data even if these programs or activities are not uniformly implemented in participating STI clinics.

Costs will be calculated by multiplying total time spent with the average hourly salary of the respective roles for those who are only partially committed to PrEP services; persons whose roles are entirely PrEP-related (i.e. PrEP navigator) will be based on their 100% full time equivalent salary, with more in-depth exploration of distribution of time/tasks to examine opportunities to split service provision across multiple lower-volume health departments and other STI clinics. We will record this information in spreadsheets that document resource, category, quantity, and unit cost. We will follow international conventions for comprehensive costing (i.e. including equipment, consumables, and overhead that is not common to both arms); discounting future costs; and reporting based on accepted practices and guidelines from the Panel on Cost-Effectiveness in Health and Medicine [58]. We will conduct sensitivity analyses that consider costs related to sustainability and intervention fidelity (e.g., monitoring and evaluation), varying intervention effectiveness with fidelity changes. Incorporating downstream costs is critical to adequately estimate costs of scale-up [59].

10.3 Model Design and Analytical Perspective

We will a conduct decision analysis following best practices [57], moving a cohort through a decision tree (left-to-right), with the left-most decision node controlled by the randomized experiment in the trial (Fig 3). "Event nodes", or probabilistic events that happen by chance, will be derived from trial data. Terminal node is PrEP uptake. We will assess cost-effectiveness outcomes from two perspectives: 1) the STI clinic; and 2) Medicaid or the state, grouped together because state governments cover a larger portion of Medicaid expenses and make decisions about Medicaid administration and public health programmatic offerings. We will assume that if Medicaid launched a version of our multilevel PrEP intervention, the materials, equipment, and personnel costs would be borne by Medicaid or its care coordination entity.

Figure 3: Example Decision Tree



10.4 Outcomes and Analysis

We will conduct a budget impact analysis of the cost in dollars of the intervention overall and each of its components, answering the question of whether the intervention is *affordable* for an organization. We will also conduct a cost-effectiveness analysis estimating the incremental cost per additional person started on PrEP (the primary study outcome). We will run simulations to estimate additional costs and additional PrEP uptake compared to the status quo to assess whether the intervention provides *value* relative to the status quo. We will also assess cost per QALY gained, based on HIV infections averted, applying our estimates to accepted transmission models [56,60].

We will report incremental cost-effectiveness ratios (ICERs). Interventions that cost less and result in more PrEP starts, QALYs gained, or infections averted are cost-saving options. Interventions that cost more and result in more PrEP starts or more QALYs will be evaluated against standard willingness-to-pay thresholds ($50,000, $100,000, $150,000 per QALY gained) contextualizing willingness to absorb costs per added QALY [61,62]. For our primary outcome, for which willingness- to-pay thresholds are unavailable, we will plot outcomes on an efficiency frontier and cost-effectiveness acceptability curve to help decision makers visualize benefits gained at

different willingness-to-pay levels [63,64].

The budget impact analysis will provide decision makers with estimates of the financial feasibility of the intervention[64]. We will examine the budget impact over 1- and 3-year time horizons. Budget impact analysis results will be particularly important for decision makers in healthcare systems, as they may not see the long-term benefits modeled in cost-effectiveness analyses due to individuals moving between clinics and insurance plans over the life course. For our primary analysis (incremental cost per person started on PrEP, comparing intervention to control arms), we will use a 1-year time horizon, aligning analyses with primary RCT **effectiveness** outcome (Aim 1).

Sensitivity analyses examine the potential impact of varying cost and effectiveness assumptions. We will employ deterministic sensitivity analyses to examine model assumptions and key parameter uncertainties. We will assume that intervention effects would be additive unless cost components are redundant. We will conduct probabilistic sensitivity analyses (using Monte Carlo simulation x5000) to account for parameter uncertainty[65], capturing input uncertainty (e.g., PrEP effectiveness, intervention cost and effectiveness). Upper and lower bounds will be based on trial data, literature, and/or expert opinion. Results represent an average across simulated model runs with an estimated uncertainty range. We will depict sensitivity results graphically and with relevant descriptive statistics. We will estimate net monetary benefits over a range of willingness-to-pay thresholds[155–159], depicting the probability that each intervention is preferred given the decision maker is willing to pay at least the threshold value for each additional person started on PrEP or each QALY gained [63,64,66,67].

10.5 Dissemination

We will generate an interactive interface with data customized for each HD, to be used by decision makers to guide scale-up of the multilevel PrEP intervention. Such an interface augments conventional population health modeling data, allowing stakeholders to make informed decisions specific to their population and setting. By integrating cost-effectiveness and budget impact results from each intervention component (PrEP navigator, telehealth PrEP, and digital health platform) into a single interactive tool, decision makers will be able to access a side-by-side comparison of cost and impact estimates specific to their context. Examples of modifiable parameters include: population size, HIV incidence, budget and intervention effectiveness. Decision support tool outputs will include estimated: cost of each component of study intervention implementation (PrEP navigator, telehealth PrEP, digital health platform), cost per person starting PrEP and impact of implementation on number of people starting PrEP. We will work with local partners to make the customizable platform widely available.

11.0 MILESTONES

Milestones are summarized and defined in Table 6. Specific Go/No-Go criteria for proceeding to the R33 phase include the study meets or exceeds the two effectiveness outcome milestones (milestones #5 and 6 in Table 6), and at least four of the six R61 milestones, overall. Due to changes in the study design since initial Notice of Award, including expanding the number of involved sites and revising study design from a cluster randomized trial at the clinic level to a participant-randomized trial, some milestones have been adjusted or adapted to accommodate these differences. Revisions have been incorporated where the original wording is no longer applicable or aligned with the current design. Functionally, these still represent criteria that capture critical administrative, implementation, and effectiveness outcomes which inform decisions regarding proceeding to the next proposed phase of study (R33).

As noted in section 9.0, the study is designed to have adequate statistical power to detect an improvement in PrEP initiation at 3 months of 7.5 percentage points between the intervention arm and control arm. A statistically significant improvement would meet milestone 5. Any other scenarios would be at the discretion of NIH. For milestone 6 (see Table 6), the milestone will be met if at least 50% of those who initiate PrEP sustain

PrEP use for ≥3 months as manifest by follow-up PrEP prescription or ongoing engagement in PrEP care. Any other scenario would be at the discretion of NIH.

For milestone 5, if a statistically significant improvement is not achieved, we will explore whether the intervention is still worth pursuing at the R33 phase with further refinement and development by examining whether there are subgroups (of clients and/or clinics) for which the intervention may be effective. We propose examining the following as part of this assessment, and exploring whether there are revisions that would be worthwhile and feasible to pursue:

Race/ethnicity: U.S. HIV epidemiologic monitoring data documents continued inequities reflected in HIV risk and infection by race/ethnicity with Black/African American and Latinx individuals at higher risk as compared to White individuals. If we find that this intervention is effective for people of color, it would be worth pursuing both from an equity perspective and a cost-effectiveness perspective. For example, a recent modeling study found that PrEP use among Black MSM was substantially more cost-effective as compared to among white MSM ($33,064 vs $427,788 per QALY saved)[56,68]. In contrast, if we find differences by race/ethnicity indicating a stronger effect for white individuals, this may suggest that the intervention succeeded in overcoming some – but not all – structural-level PrEP barriers. In this case, we would explore in the R61 phase whether the barriers seem feasible to address, and if so, focus R33 refinements and intervention mapping more in these areas.

Age: U.S. HIV epidemiologic monitoring data from 2019 showed a decrease in new infections among those in the youngest and oldest age ranges, with no change for those in middle age categories. The document rates are highest among those aged 25-34 (30.1 per 100,000 people) and those aged 35-44 (16.5 per 100,000 people). Literature has also documented greater structural barriers to PrEP access among younger individuals. The components of our intervention aim to address some of these structural barriers (e.g. limited transportation, navigating health insurance, societal stigma)[68].

Intervention use: Our prior studies using technology-based interventions among MSM and transwomen (including a national sample inclusive of both and North Carolina statewide sample of MSM), have shown that those who use the digital health intervention platform experience a greater intervention benefit than those who do not (i.e. "non-compliant" participants")[27,69]. Furthermore, while results from our study using HMP among South African adolescent girls and young women are not yet published, preliminary data reflects similarly promising findings [70]. Based on results from the North Carolina study, the U.S. Centers for Disease Control and Prevention (CDC) has identified HMP as a good evidence-based intervention (EBI) for HIV risk reduction [71].

Clinic characteristics: Contextual analyses will be conducted using quantitative and qualitative measures, including intervention engagement (i.e., training attendance, participant enrollment, etc) and interview data from stakeholder interviews to identify possible characteristics and conditions that may facilitate or hinder intervention success, for example, clinic population, on-site PrEP champions, and PrEP delivery model adopted by the clinic. (See Section 6.6)

Progress on all Milestones will be tracked and reported on each annual progress report.

Table 6: Study Milestones

Year (Quarter)	Milestone	Definition
R61		
Administrative		

Y1[a] (Q2)	(1) Established data use agreement facilitating access to clinic data to assess patient PrEP eligibility and referral	Signed (by clinic-selected designee) letter of support for clinics to participate in STARR-NC; prior to clinic initiating enrollment.
Y1 (Q4)	(2) Finalized standard operating manual to cover training, study management and implementation	Written SOPs for study staff, clinic and PrEP navigator training; study specific procedures; and study implementation.
Study Implementation		
Y1 (Q4)	(3) Trial enrollment begins by month 12[a].	At least 1 clinic prepared to initiate participant screening
Y3 (end of trial)	(4) ≥50% of participants complete 6-month survey and return DBS[b]	Among participants who a) received a DBS kit and b) completed their 6-month study period, ≥50% have completed the 6-month survey; ≥50% have returned ≥1 DBS
Effectiveness Outcomes		
Y3 (end of trial)	(5) A statistically significant difference in PrEP uptake comparing intervention to control[c]	The proportion of participants who initiated PrEP[d], is at least 7.5 percentage points higher in the intervention arm than the control arm. This milestone will be met if a statistically significant increase in PrEP initiation is found at 3 months in the intervention arm compared to the control arm. Any other scenarios would be at the discretion of NIH.
Y3 (end of trial)	(6) Among intervention arm PrEP initiators, ≥50% sustain use ≥3 months	Among participants in the intervention arm who have initiated PrEP and for whom 3-months of study follow-up time has elapsed since PrEP initiation, at least 50% will sustain PrEP use for ≥3 months as indicated by engagement in PrEP care (on-time visits/refills/injections) and self-reported PrEP use. Any other scenarios would be at the discretion of NIH. We will also report the number of participants who initiate PrEP after their 3-month study visit and thus have less than 3-months of available PrEP sustainment data at their 6-month follow-up visit.
R33		
	Established relationship with HD stakeholders and letters of support	
	Refined strategy approved by key stakeholders for implementation	

	Interactive costing interface platform finalized	
	Refined strategy ≥75% effective (PrEP uptake) vs R61 intervention	

[a] Year 1 refers to the RCT pre-implementation phase aligning with the grant timeline (Budget Period 1: June 13, 2022 – May 31, 2023).

[b] Because participants for whom intended follow-up is limited to 3-month outcomes are scheduled to have only 1 DBS, criteria for these participants is as follows: ≥50% have completed the 3-month survey, and ≥50% have returned 1 DBS. Any other scenarios would be at the discretion of NIH.

[c] The original grant proposal specified this milestone as pertaining to PrEP uptake at a clinic level compared to "pre-intervention baseline". However, this is not applicable because revisions to the study now specify randomization will be at the individual (rather than clinic) level with comparison of intervention versus a concurrent control arm. This change describes the effect of the intervention above background uptake in the control arm during the same time (e.g., to control for secular trend). Power analysis suggests that this milestone will reach statistical significance at a 7.5% difference, as clarified in the definition.

[d] Persons who self-report taking any PrEP (oral or injection) during a follow-up survey OR in their app will meet this endpoint if this self-report is verified by at least one of the following: (1) an uploaded photo or image demonstrating a PrEP prescription; OR (2) any indication of the presence of tenofovir diphosphate or cabotegravir in DBS; OR (3) staff-abstracted electronic health record of PrEP prescription issued or physician notation of PrEP initiated.

12.0 REFINING INTERVENTION (AIM 3, R33)

12.1 Objectives

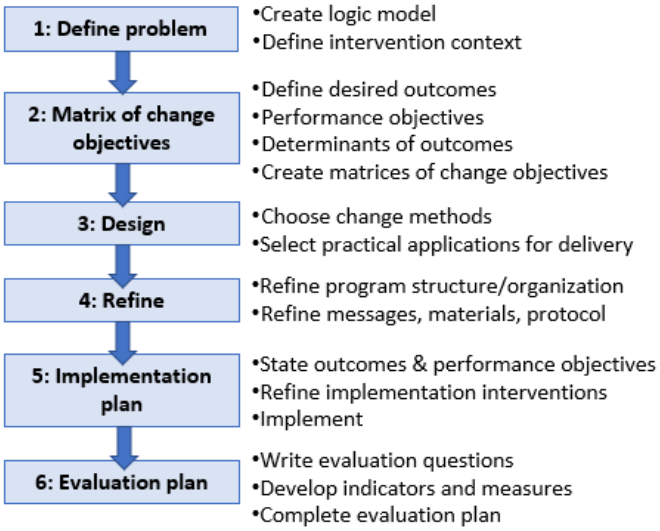
Aim 3: Engage state and local stakeholders to refine PrEP intervention, tailored to unique contextual needs using Intervention Mapping.

We will examine individual-, structural- and organizational-level determinants of success, including assessing implementation fidelity . Using an Intervention Mapping framework, we will identify modifiable barriers and build stakeholder consensus to refine our multilevel PrEP intervention.

12.2 Approach

We will use Intervention Mapping (IM) to refine our PrEP intervention. Grounded in community participatory research, IM emphasizes matching an intervention with population needs and intervention contexts[72–74]; as such, it is well-suited for translating the effectiveness, implementation, and cost-effectiveness outcomes collected in Aims 1 & 2 to the proposed expansion in Aim 4. As in Aim 1, an ecological approach will be applied to understand PrEP use from the individual (PrEP user), provider, clinic, and policy levels. We will work with providers and leaders from local HDs, NC DHHS, and additional STI clinics, being mindful of interval changes to the PrEP landscape in our intervention refinement. YSGM stakeholder engagement is a critical aspect of the process evaluation and refinement: we will engage an established Community Advisory Board overseen by mPI Muessig, which includes racially and ethnically diverse YSGM including five members recruited from participating NC counties (see **PHS**). The IM process unfolds in six major steps (Fig 4)[74]. Step 1 focuses on identifying the problem and context for intervention. We will leverage Aim 1 data (Section 6.4-6.6), contextualized by cost-effectiveness outcomes in Aim 2, to provide a comprehensive assessment of the needs and determinants of PrEP use from the critical vantage points of user, provider, and policy-influencer. In Step 2 we will state our agreed-on performance outcomes and objectives, creating matrices (how, who, result) of the change objectives and examining the determinants (barriers/facilitators) for outcomes. We will explore these determinants guided by the Consolidated Framework for Implementation Research (CFIR)[75], explicitly assessing relevant constructs (i.e., intervention complexity) in terms of their impact on implementation. In Steps 3 - 5 we move planning through design, production, and implementation – refining our multilevel PrEP intervention based on user (provider and patient) feedback. The final step is preparing the program evaluation– developing measures for assessment to be used in Aim 4. Our established collaboration and support from NC DHHS policymakers will aid progression through IM steps, returning to the Aim 1 and 2 data as a touchstone.

Fig 4: Intervention Mapping Overview



12.3 Data Collection and Analysis

Each IM step includes processes for documentation. The steps are iterative, and matrices, objectives, and outcomes are revisited, revised, and expanded as involved parties gain new knowledge about the population, determinants, and context. As such, record-keeping at each step is detailed and includes decision logs and formal reports following each step and the conclusion of the process. At the conclusion of Aim 3, the refined PrEP intervention will be ready for use in all clinics, as outlined in Aim 4 (Section 13.0).

13.0 DETERMINE EFFECTIVENESS OF REFINED INTERVENTION (AIM 4, R33)

13.1 Objectives

Aim 4: Determine effectiveness and cost-effectiveness of refined PrEP implementation strategy.

We will redeploy the refined intervention at all participating clinics from the R61- phase (sections 6.0 – 11.0). Enrollment criteria and recruitment will follow that of Aim 1 (Sections 5.1, 5.2), though some intervention adaptations may occur as part of the Aim 3 refining process. There will be no randomization in this phase. Effectiveness, as described below, will be determined via comparison to R61 control condition PrEP uptake outcomes.

13.2 Data Sources

We will use the same data sources as Aim 1 (Sections 6.4 – 6.6).

13.3 PrEP Outcome Analysis

Our primary effectiveness outcome of interest is the probability of PrEP uptake within 3 months of an eligible clinic visit or outreach encounter. For the R33 phase, we will evaluate this outcome among all participants, comparing uptake to the control condition rates observed in our R61 phase. Similar to Aim 1, we will evaluate secondary outcomes, including relevant HIV prevention cascade components, programmatic, and clinical outcomes. We will also examine the relative effectiveness of the refined vs original strategy by comparing PrEP uptake in the first 6 months of implementation for each phase. That is, the PrEP uptake in months 0-6 during the R61 among the intervention arm participants compared to the PrEP uptake in months 0-6 during the R33 using the *refined* intervention. Temporal trends and changes in PrEP awareness (both patient and provider) and prescribing capacity may influence these differences, so we will also capture the relative effectiveness by looking at differences in the PrEP uptake by time.

13.4 Power and Sample Size

Assuming stable clinic volume, we use the same assumptions for patient PrEP/study eligibility. Again, our primary analysis includes eligible patients who consent to the study and download the app, though all participants will receive the full app in this expansion phase. We anticipate enrolling 300 persons across all clinics during the R33.

We calculated statistical power for the effect of intervention upon PrEP uptake by 3-month follow-up using SAS 9.4 (Cary, NC) with a 5% type I error rate and a two-sided Chi-square test. Assuming 2.5% of eligible patients started PrEP within 3 months in the control arm during the R61 Phase 1, we calculated statistical power to detect a range of small to large effect sizes from 5% to 10% percentage point increases in PrEP uptake under a range of possible sample sizes and assuming 10% missing data (Table 4b). Given our design and assumptions, with a sample size of 300 receiving the intervention compared to 168 historic controls, we will have >84% statistical power to detect a medium effect size (7.5%) and >97% power to detect a large effect size (10%).

Table 4b: Statistical power as a function of the observed difference in effect (PrEP uptake) and sample size*

	SAMPLE SIZE IN R33 INTERVENTION ARM				
OBSERVED DIFFERENCE IN PREP UPTAKE	*n*=250	*n*=300	*n*=350	*n*=400	*n*=450
5%	54%	55%	56%	57%	59%
7.5%	83%	84%	86%	87%	88%
10%	96%	97%	98%	98%	98%

*Assuming PrEP uptake of 2.5% among the historical control arm, 10% missing data at month 3, and 5% type 1 error

13.5 Implementation Outcomes

Implementation outcomes focus on intervention fidelity at all clinics. Measures are assessed via chart review, mirroring Aim 1 (Table 3). We will also evaluate acceptability of the refined strategy, engaging clinic stakeholders in in-depth interviews (n=15) to assess provider burden of intervention, adequacy of training, support structure, and other organizational-level success determinants. Sampling, data collection and analysis for all methods will follow those of Aim 1.

13.6 Cost Analysis

We will update our cost-effectiveness (Aim 2, Section 10.0) model using parameters generated in this final implementation phase, adapting cost inputs to account for refinements in intervention components. The need for prospective costing will be determined based on the scope of intervention refinement/revision from Aim 3. If costing is pursued, we will utilize the methods previously described. Primary cost-effectiveness outcomes and methods follow those described in Aim 2, including updated budget impact analyses and sensitivity analyses, including evaluation over a range of potential effectiveness outcomes.

14.0 DATA COLLECTION, MANAGEMENT AND MONITORING

14.1 Development of Protocol and Case Report Forms

The study team is responsible for the development of this protocol as well as the Case Report Forms (CRFs) needed to collect the information required to implement this protocol.

14.2 Data Records

Participant-related study information will be identified through a study ID number (SID) and participant code on all participant CRFs, audio files, transcripts, and CASI files. Participant names or other personally identifying information will not be used on any study documents and will be redacted from interview transcripts.

14.3 Record Availability

Study PIs will ensure the availability of all study-related records for audit by NIH, UNC Regulatory, and the Study Monitor including participant records, consent forms, CRFs and supporting source documentation for the purpose of ensuring the protection of study participants, compliance with the protocol and regulatory policies, and accuracy and completeness of records.

14.4 Data Collection Across all Aims

Data collection for the purposes of each aim will occur from sources as follows (Table 7). Study screeners, assessments, and in-depth interviews may all be completed virtually/remotely via secure HIPAA-compliant platforms for survey administration, phone, or videoconferencing:

Table 7 **Data source** Collection method	**Aim 1**	**Aim 2**	**Aim 3**	**Aim 4**
CASI surveys In-clinic or online	x			x
Whole blood samples Self-collected blood sample	x			x
Qualitative notes and transcripts				

Interviews, intervention mapping	x	x	x	x
Digital Health Intervention paradata Entered in app by participants, study staff, PrEP navigators	x			x
Clinic Observations Project receipts, personnel salary		x		
HIV/STI test results Electronic Health Record data/LapCorp/Quest/CELR/participant-provided records	x			x
PrEP care history Electronic Health Record data/participant-provided records	x	x		x

14.5 Data Storage and Security

We will secure study data with all appropriate physical, electronic and operational protections. All data files will have encryption and strong password protection. Any identifiable data will either be stored on secure servers or will be on fully encrypted laptops. Participant names and their SID and participant code will be stored in separate tabs in REDCap accessible only to designated study staff, and site monitors. Original source documents for individual participants will be maintained at the UNC study site and will be accessible only to the study staff.

We use 256-bit SSL encryption for transfers of information online. UNC uses Transport Layer Security (TLS) encryption (also known as Hypertext Transfer Protocol Secure (HTTPS) for all transmitted data. Survey data are protected with passwords and HTTPS referrer checking. Secure, encrypted file transfer is also available via FTPS (FTP-ssl) for uploading and downloading data and documents. The database is hosted on secure servers at UNC which reside physically in the dedicated Institute for Global Health and Infectious Diseases (IGHID) server rooms and are maintained by UNC IGHID IT staff. The server rooms are locked, and access can only be obtained by authorized personnel. Electronically, the servers are protected by multiple layers of firewalls and the data systems use 256-bit SSL data encryption, the secure socket layer technology used for transmission of confidential information over the internet. To ensure no loss of data, an automated backup process is implemented with integrity checks and incremental backup performed daily and full back-up monthly for both the web and data servers. Encrypted copies of the monthly full back-up images are also sent to an offsite storage facility.

CASI surveys: We will use RedCap, a HIPAA-compliant web-based platform for CASI data transmission and storage.

Self-collection blood sample kits: Self-collection blood sample kit materials will be identified with a study ID number only. The kit includes return packaging and a self-addressed, pre-paid return mailer that participants will use to send completed samples directly to the study's CLIA-certified lab for storage and subsequently to UNC's lab for processing (see section 16.1). Samples will be received by the labs and logged into password-protected manifest on HIPAA-compliant secure servers using study ID only (no participant identifying information). Samples will be securely stored at the lab until processed following standard lab procedures and destroyed following testing. Test results will be added to the sample manifest. Study staff will abstract results from the sample manifest into a Blood sample CRF in RedCap. After analysis, no samples will be stored for subsequent use.

Qualitative notes and transcripts: We will use a qualitative data analysis software (e.g. Atlas.ti, Dedoose) to perform all qualitative analyses. These programs employ HIPAA-compliant data encryption and allow for password-protected, project specific access. Only approved study staff will have access to these data.

Digital Health Intervention paradata: We use 256-bit SSL encryption for transfers of information online. UNC uses Transport Layer Security (TLS) encryption (also known as Hypertext Transfer Protocol Secure (HTTPS) for all transmitted data. Secure, SSL file transfer is used for downloading of data and documents. The database is hosted on secure servers at Florida State University.

Access to data will be on a role-based standard; only those study staff who require access to each type of data to complete their study-related roles will be allowed access. Study staff will be assigned an individual login and password for use to access the system, linked to their name and e-mail address. Hierarchical permission settings are associated with each password, giving the user the level of access appropriate to their role in the study.

Medical Records: Data abstracted from medical records will be recorded by study staff on electronic CRFs stored in RedCap.

CRFs: Study monitoring data, including information about eligibility, demographic data and monitoring untoward effects, will be collected on CRFs. All CRFs for this study will be entered into REDCap. Hard copies will be made available via download from a UNC-run secure cloud management platform, to be used if needed.

14.6 Data Quality Assurance

Quality assurance checks will be implemented throughout the data collection process to quickly identify and rectify potential problems. Survey instruments will employ skip patterns and built-in checks to minimize discrepant and unrealistic answers. Standard data cleaning procedures will be used prior to analyses, including outlier detection and graphical representation of the data.

14.7 Role of Data Management

All data will be entered, managed and retained by the UNC study staff until analyses are complete and for up to three years following study closure.

14.8 Data and Safety Monitoring Plan

The purpose for study monitoring is to verify that the rights and well-being of human participants are protected; the reported trial data are accurate, complete, and verifiable from source documents; and the trial is conducted in compliance with the currently approved protocol and amendment(s), with good clinical practice (GCP), and with all applicable regulatory requirements. The Clinical Quality Monitoring Plan (CQMP) specifies the frequency and types of data that will be reviewed (CRFs, regulatory documents, study staff training records, and medical and laboratory records) to accomplish these monitoring activities. Monitoring for this study will be conducted through the North Carolina Translational and Clinical Sciences Institute monitoring service, including quality assurance and study monitoring such as regulatory file review, informed consent review, patient eligibility confirmation, protocol compliance review, assessment of safety reporting requirements, and review of training records.

Mechanisms to ensure the security and integrity of the study data are also described above in Section 14.5.

14.9 Study Monitoring Committee

A study monitoring committee (SMC) will be constituted prior to initiation of the study. This committee will include 2 HIV clinicians or research investigators not directly involved in the study, and a community representative. At least one DAIDS representative will attend the meetings. Cumulative study reports including

reports of adverse events, social harms, and unanticipated problems, as well as ad hoc reports of unanticipated problems will be shared with the SMC and reviewed on a bi-annual basis. The SMC will assess study conduct, adequate delivery of the behavioral intervention package, ascertainment of PrEP uptake outcomes, and other related data to ensure adequate collection of primary and key secondary outcome data. Recommendations from the SMC will be provided to the study investigators and DAIDS.

In addition, the University of North Carolina IRB (as prime IRB) will conduct regular reviews of the study protocol, changes in the study protocol, and adherence to the protocol during implementation The PIs are required to report any unexpected study-related adverse events following UNC IRB protocol.

15.0 HUMAN SUBJECTS CONSIDERATIONS

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

15.1 Participant Confidentiality

We will take the utmost caution to protect the confidentiality of participants' involvement in the study and all participant provided information/data throughout all research procedures and data management and analysis. Participants may be concerned about the security of their data, particularly since it is collected and stored electronically. Every effort will be made to ensure that study participants are protected from the risk of breach of confidentiality using a variety of steps to ensure participant data security across all sources (Section 14.5).

The results of the research will be disseminated but no participant names or other identifying information will be used in any dissemination materials (published or otherwise).

15.2 Risks and Benefits

15.2.1 Risks

To minimize the risk of participants feeling uncomfortable about answering personal questions, we will use CASI methods for the study's assessments. Participants will be able to decline to answer any question that makes them uncomfortable during in-depth interviews as well as on the study assessments.

To minimize risks to confidentiality, we will secure study data with all appropriate physical, electronic and operational protections (Section 14.5). Access to data will be on a role-based standard; only those study staff who require access to each type of data to complete their study-related roles will be allowed access. All study staff will be trained in security and confidentiality procedures (Section 4.1) and will sign a confidentiality agreement before receiving access to any participant data.

For each mode of participant contact information, we will ask specifically whether anyone else potentially has access to that mode of communication, and if it is acceptable to leave a non-specific message about participation in a health study. Additionally, all scripts for email, text message, and telephone contact with participants will be reviewed and approved by the IRB before being used for contact with participants.

As per NIH policy, this study is automatically issued a Certificate of Confidentiality (CoC): "Per Section 2012 of the 21st Century Cures Act as implemented in the 2017 NIH Certificates of Confidentiality Policy, all ongoing or new research funded by NIH as of December 13, 2016 that is collecting or using identifiable, sensitive information is automatically issued a CoC. Compliance requirements are outlined in the NIH Grants Policy Statement, which is a term and condition of all NIH awards."

15.2.2 Benefits

The main potential benefit of the proposed study for both Intervention and Control Arm participants is the provision of resources and referrals for PrEP among SGM men and 6/18/2025der women at risk for HIV. If the study intervention arm is shown to be effective, the potential societal benefit is an increase in affordable PrEP access, use, and maintenance among populations at heightened risk for HIV.

The risk-benefit assessment is considered acceptable given the modest level of participant risk and potential for individual and societal benefit.

15.3 Intervention Monitoring

This study involves a behavioral intervention using PrEP navigators, an interactive digital platform for information and support, and linkage of participants to PrEP providers. The PrEP providers are not part of the study. They include clinicians in the community, telehealth providers in the community, or clinicians working at STI clinics. PrEP drugs are not provided by the study. Aggregate reporting of the harms and events outlined in Sections 15.3.1 – 15.3.3 will be completed quarterly. Quarterly reports will be reviewed by representatives from the investigator team and DAIDS. Cumulative reports will be made available to the SMC for their biannual reviews (see Section 14.9).

15.3.1 Adverse Events:

As STARR is a behavioral intervention that does not include investigational product, standard adverse event (AE) reporting will not be undertaken. The study team will monitor for and track serious adverse events (SAEs) and non-serious adverse events related or possibly related to study procedures and/or to participation in the study. Such events will be reported to the NIH NIAID Division of AIDS (DAIDS) Program Officer and Medical Officer for this protocol at the same time as they are reported to IRB/ECs following the UNC IRB's reporting requirements for Promptly Reportable Information (UNC Office of Human Research Ethics SOP 1401: Promptly Reportable Information available at https://policies.unc.edu/TDClient/2833/Portal/KB/ArticleDet?ID=132230) and DAIDS Expedited Adverse Event (EAE) Manual (in the case of SAEs, as specified below). Study site staff must document in source documents all of these AEs reported or observed in STARR-NC participants, regardless of seriousness or severity. Source documentation for all AEs will minimally include the following:

- AE term/diagnosis
- Severity grade
- Onset date
- Outcome
- Outcome date
- Treatment for the AE (if any)

Study participants will be instructed how to contact the study staff to report any AEs they may experience at any time between enrollment and follow-up assessments. AEs will also be actively assessed in all follow up CASI assessments. Should a participant report experiencing an AE that they perceive to be related to their study participation, research staff will contact the participant to assess the severity and appropriate resolution action.

The most current Division of AIDS Table for Grading the Severity of Adult Adverse Events (DAIDS AE Grading Table) is used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

Serious adverse events (SAEs) are those AEs that result in one or more of the following outcomes:

- Death
- A life-threatening (i.e., an immediate threat to life) event

- Requires in-patient hospitalization or prolongation of an existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A medically important event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above

Based on the low-risk nature of the study procedures, we do not anticipate the occurrence of any SAEs.

Expedited Reporting: All SAEs will be entered into the study database, with appropriate levels of documentation (including a brief narrative description) and notification of the IRB. SAEs will be reported to the DAIDS Medical Officer within 3 reporting days of the staff becoming aware of the SAE and will include study staff assessment (per section 15.3.3) of SAE expectedness, relatedness, and whether it is an unanticipated problem. If actions are taken to address the event, these will also be reported. Reporting days are Monday through Friday, as defined in Version 2.0 of the DAIDS Expedited Adverse Event (EAE) Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance.

If additional significant information becomes available subsequently, the report will be updated. A study physician investigator or sub-investigator listed on the DAIDS Investigator of Record (IoR) Agreement must review and verify the completed expedited adverse event report for accuracy and completeness. This physician also makes the investigators' final assessment of relatedness.

The expedited AE reporting period for this study is through the end of follow-up for each participant. After this, SAEs will be reported to the DAIDS Medical Officer if the study staff become aware of the events on a passive basis (from publicly available information) until database lock.

15.3.2 Social Harms

In addition to AEs, participants may experience social harms — nonmedical adverse consequences — as a result of their participation in the study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends. They also could experience stigma or discrimination from family members and members of their community. In the event that any social harms occur, study staff will document the issues or problems and make every effort to facilitate their resolution.

The potential for social harms will be described in the informed consent form (ICF, Section 15.5) and assessed both actively and passively during study participation. At 3-, 6-and 12-month study assessment points, participants will complete a questionnaire probing for social harms that are perceived to have occurred *as a result of study participation* (For example, "Since your last visit, has anyone treated you poorly as a result of your participation in this study?"). In addition to responding to this standardized assessment at the specified visits, participants also may spontaneously passively report study-related issues and problems to study staff at any time. All reported Social Harms (actively and passively captured) will be recorded on a Social Harms CRF for aggregate reporting.

Study staff will follow all social harms to resolution (until they no longer exist) or stabilization (they exist but at a manageable level) or until study exit. Study staff will provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.

If the reported social harm is associated with an AE, the AE will be recorded on an AE Log.

15.3.3 Unanticipated Problems

An unanticipated problem is any incident, experience, or outcome that meets all of the following criteria, as defined by the OHRP[76]:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated problems will be collected by passive ascertainment. All unanticipated problems that meet the three criteria above will be reported to DAIDS (Medical Officer and Program Officer), the IRB, and to the SMC as described in Section 14.9 and in accordance with the UNC IRB's reporting requirements for Promptly Reportable Information (UNC Office of Human Research Ethics SOP 1401: Promptly Reportable Information available at https://policies.unc.edu/TDClient/2833/Portal/KB/ArticleDet?ID=132230), and may warrant consideration for alterations to the research protocol or informed consent process or documentation to more accurately reflect and communicate expected risks.

15.4 Ethical review

This protocol, the informed consent documents and any subsequent modifications will be reviewed and approved by the UNC IRB responsible for the oversight of the study. Annual IRB reporting and review is required for the duration of the study.

15.5 Informed consent

Informed consent procedures will be conducted virtually/remotely and signed electronically following the informed consent SOP.

The informed consent will follow the UNC required consent template including describing the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The consent forms will use language that is sufficiently simple for lay persons to comprehend. Patients will not be coerced into participating. Children under the age of 18 years, decisionally impaired adults and non-English speakers will not be enrolled in this study. As specified in the consent form, participants' co-enrollment in additional PrEP related studies will not be permitted.

Following initial screening (Section 5.4) participants may opt to complete a self-guided electronic informed consent process and/or to request an appointment to review the informed consent with a study staff via phone or videoconference. Study staff will review consent forms with potential participants (each in a confidential setting) and explaining all risks and benefits associated with participation of the study, soliciting questions, allowing the potential participant time to review the form, soliciting questions again, and then offering the opportunity to electronically sign the consent form. At the study enrollment/onboarding visit, the investigators will verify that informed consent has been completed for each participant before starting any study procedures according to the standards set forth in the ICH Good Clinical Practice guidelines.

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process specifically will address the following topics of importance to this study:

1. The unknown safety and unproven efficacy of the study interventions
2. The potential medical risks of study participation (and what to do if such risks are experienced)
3. The potential social harms associated with study participation (and what to do if such harms are experienced) and examples of possible adverse outcomes of these social harms.
4. The limited benefits of study participation
5. The distinction between research and clinical care
6. The right to withdraw from the study at any time

The informed consent process will include an assessment, through a series of questions, of each potential participant's understanding prior to enrollment. Patients who are not able to demonstrate adequate understanding of key concepts after exhaustive educational efforts will not be enrolled in the study.

The e-signed original consent form will be securely stored on HIPAA-compliant servers at UNC. All prospective study candidates will be offered a copy of the informed consent(s) by email and offered a hard copy sent by mail to the address of their choice. In addition, a copy of the informed consent text is available within the password protected HMP app (both intervention and control arm versions) for participants' reference.

15.6 Participant Remuneration

Participants will receive financial compensation throughout the course of their participation. See section 8.2 for specific financial compensation amounts.

16.0 LABORATORY SPECIMENS

This study is abstracting STI/HIV laboratory results from established standard-of-care HIV/STI testing done by local STI clinics specimen collection procedures. All collaborating STI clinics will be responsible for specimen collection, processing, or handling are deemed accredited by the North Carolina Local Health Department Accreditation Board (NCLHD) [77]. The NCLHD Accreditation Program provides an efficient way to ensure local STI clinics meet minimum requirements by linking basic standards to current state statutes, administrative code and the contractual and program monitoring requirements that are already in place through the N.C. Division of Public Health.

Any lab from which we are abstracting results will be appropriately licensed/certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88)[78]

16.1 Dried blood spots

Dried blood spot (DBS) kits for measuring PrEP will be sent to participants at an address of their choice at study months 3 and 6 for self-collection (See Section 6.5). Following an illustrated step-by-step instruction card, participants use a single use lancet to prick the side of their finger and collect a few drops of blood to saturate the designated areas on the DBS card. After allowing the card to dry for at least 15 minutes, participants re-package the sample as directed and return the sample using the pre-addressed, pre-paid shipping envelope.

DBS kits will be assembled, shipped out, received back, stored and processed using two laboratories: Molecular Testing Labs (MTL https://moleculartestinglabs.com/) and the UNC CFAR Clinical Pharmacology and Analytical Chemistry (CPAC) Core following previously established protocols from the NICHD-funded study protocol of the Adolescent Medicine Trials Network (ATN 142 P3 study)[79].

MTL is Clinical Laboratory Improvement Act (CLIA) certified and College of American Pathologists (CAP) accredited, and all testing is run in compliance with FDA requirements. MTL will assemble, ship, receive and store DBS kits and then batch ship samples to UNC for processing following their standard SOPs.

The UNC CFAR Clinical Pharmacology and Analytical Chemistry (CPAC) Core provides Comprehensive Study Design, Bioanalytical, and Data Analyses Support to Animal and Human Clinical Pharmacology Investigations in the HIV/AIDS arena. The CPAC Core applies the principles of Good Laboratory Practices, Good Clinical Laboratory Practices, and FDA guidelines to provide quality assurance and scientific support.

CPAC specimen collection instructions, shipping, and receipt procedures are dictated by CPAC SOP 0360 (Available upon request). Bioanalytical assays are developed and utilized according to SOPs: CPAC SOP 0342, 0343, and 0344. All Lab SOPs are available upon request. In brief, stock solutions are prepared from reference materials corrected for purity according to their respective Certificates of Analyses or supporting data, and the equivalency of two independent stock solution preparations is confirmed and should not differ by more than 5%. These reference materials are obtained from reputable commercial sources such as but not limited to the following: Aptochem, Toronto Research Chemicals, MedChemExpress, Alsachim, Moravek, and TriLink. Source, lot number, expiration date, storage conditions and certificates of analysis for all reference material is procured and documented. Calibration standards and quality control samples (QCs) are prepared from stock solutions in a matched matrix when available or surrogate matrix when not available. A calibration standard curve is generated for each analytical run to calculate the concentration of the analyte in the unknown samples. Estimation of concentration in unknown samples by extrapolation of standard curves below the lower limit of quantification (LLOQ) or above the upper limit of quantification (ULOQ) is not performed. Dilution QCs are included in the run to verify the unknown samples that are diluted due to exceeding the calibration range are accurate and precise. An analytical run generally begins with a system suitability sample, blank matrix samples to verify the lack of matrix interferences from both the analyte and internal standard, followed by a set of calibration standards, continuing with QCs and study samples intermixed. At least one blank sample is injected following the ULOQ standard to mitigate possible carryover. If two sets of calibration standards are used, the second set follows the last study sample and QCs showing minimal or no instrument fluctuation from the start to the end of the analytical run. Passing criteria for individual standards and QCs as well as the analytical run, in general, are predefined in accordance with CPAC SOP 0344.

The CPAC Core participates in domestic and international proficiency testing through the Clinical Pharmacology Quality Assurance (CPQA) and K.K.G.T. Programs to ensure the highest level of scientific rigor and reproducibility. The Laboratory employs a full time QA/QC officer who maintains and reviews SOPs on an annual basis. All data are reviewed against source to ensure accuracy of reporting and reviewed for pharmacologic plausibility before being released to investigators. Preventive Maintenance of instruments in the CPAC Core is conducted on an annual or semi-annual schedule, dependent on the instrument. Detailed descriptions of experimental procedures, including sample storage and processing, are documented electronically and in notebooks. Instruments and settings used for all experiments are detailed with the associated experiment electronically and in laboratory notebooks.

17.0 STUDY TIMELINE

The study is divided into two phases, with the Phase 2 R33 contingent on Go/No-go criteria Study Milestones (Section 11.0) which reflect critical effectiveness and implementation outcomes, indicating readiness to implement the intervention strategy on a wider scale.

Table 8: Study Timeline

	R61												R33							
	Year 1				Year 2				Year 3				Year 4				Year 5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Finalize data use agreements																				
HMP customization/SOP finalization																				
IRB Review																				
PrEP navigator training																				
Aim 1: clinic-randomized trial of multilevel intervention																				
Clinic trainings (NC ATEC)																				
Patient enrollment																				
Patient follow-up																				
Patient and provider interviews																				
Clinic surveys																				
Implementation & effectiveness outcome analysis																				
Aim 2: Cost-effectiveness																				
Prospective cost collection																				
Model construction & analysis																				
Interactive interface development																				
Submit progress report																				
Aim 3: Refine intervention																				
Stakeholder engagement & intervention mapping																				
Aim 4: Expand intervention																				
Clinic trainings/on-boarding																				
Patient enrollment																				
Patient follow-up																				
Patient and provider interviews																				
Update cost-effectiveness model/analysis & finalize interactive platform																				
Dissemination																				
Aim 1 and 2 manuscript preparation/submission																				
Aim 3 and 4 manuscript preparation/submission																				
Presentation to national Youth Advisory Board																				
Project website and social media updates																				

18.0 PROTOCOL COMPLIANCE

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s) prior to implementing the amendment.

REFERENCES

1. 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. doi:10.15585/mmwr.mm6446a4

2. Viral Suppression | HIV by Age | HIV by Group | HIV/AIDS | CDC. Accessed June 20, 2022. https://www.cdc.gov/hiv/group/age/viral-suppression.html

3. Siegler AJ, Bratcher A, Weiss KM. Geographic Access to Preexposure Prophylaxis Clinics Among Men Who Have Sex With Men in the United States. *Am J Public Health*. 2019;109(9):1216-1223. doi:10.2105/AJPH.2019.305172

4. Sharpe JD, Guest JL, Siegler AJ, Sanchez TH, Sullivan PS. The spatiotemporal distribution of pre-exposure prophylaxis accessibility in the United States, 2016-2020. *Ann Epidemiol*. 2021;64:102-110. doi:10.1016/j.annepidem.2021.09.006

5. AIDSVu. Regional Data: South. Accessed September 22, 2022. https://aidsvu.org/local-data/united-states/south/

6. Hess KL, Hu X, Lansky A, Mermin J, Hall HI. Lifetime risk of a diagnosis of HIV infection in the United States. *Ann Epidemiol*. 2017;27(4):238-243. doi:10.1016/j.annepidem.2017.02.003

7. North Carolina HIV/STD/Hepatitis Surveillance Unit. (2020). 2019 North Carolina HIV Surveillance Report. North Carolina Department of Health and Human Services, Division of Public Health, Communicable Disease Branch. Raleigh, North Carolina. 2020. Accessed November 17, 2023. https://epi.dph.ncdhhs.gov/cd/stds/figures/hiv19rpt_11302020.pdf

8. Sullivan PS, DuBose SN, Castel AD, et al. Equity of PrEP uptake by race, ethnicity, sex and region in the United States in the first decade of PrEP: a population-based analysis. *Lancet Reg Health Am*. 2024;33:100738. doi:10.1016/j.lana.2024.100738

9. NC DPH: HIV/STD Facts & Figures. Accessed August 14, 2024. https://epi.dph.ncdhhs.gov/cd/stds/annualrpts.html

10. Dear Colleague: Preliminary Data on Pre-Exposure Prophylaxis Coverage Released | Policy, Planning, and Strategic Communication | HIV | CDC. Accessed August 14, 2024. https://www.cdc.gov/hiv/policies/dear-colleague/dcl/20231017.html

11. Data Access - Urban Rural Classification Scheme for Counties. Centers for Disease Control and Prevention: National Center for Health Statistics. 2017. Accessed September 22, 2022. https://www.cdc.gov/nchs/data_access/urban_rural.htm

12. North Carolina Department of Health and Human Services. 2019 North Carolina STD Surveillance Report: Fact and Figures. March 15, 2023. Accessed February 15, 2023. https://epi.dph.ncdhhs.gov/cd/stds/annualrpts.html

13. NC Department Of Health and Human Services. NC Ending HIV: A Plan to End HIV Together Community-by-Community Hand-in-Hand. June 2021. Accessed May 9, 2023. https://epi.dph.ncdhhs.gov/cd/hiv/docs/NC-Ending-HIV-Brochure-English-Web.pdf

14. AIDS Vu. Local Data: North Carolina. 2020. Accessed May 9, 2023. https://aidsvu.org/local-data/united-states/south/north-carolina/#hiv-prevalence

15. Centers for Disease Control and Prevention. US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 Update: a clinical practice guideline. March 2018. Accessed March 8, 2023. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.

16. Tarek Mikati KJ. Immediate PrEP Initiation at New York City Sexual Health Clinics. Published online March 8, 2019. Accessed October 3, 2021. https://www.croiconference.org/abstract/immediate-prep-initiation-new-york-city-sexual-health-clinics/

17. Chan PA, Glynn TR, Oldenburg CE, et al. Implementation of preexposure prophylaxis for human immunodeficiency virus prevention among men who have sex with men at a new england sexually transmitted diseases clinic. *Sex Transm Dis*. 2016;43(11):717-723. doi:10.1097/OLQ.0000000000000514

18. Kamis KF, Marx GE, Scott KA, et al. Same-Day HIV Pre-Exposure Prophylaxis (PrEP) Initiation During Drop-in Sexually Transmitted Diseases Clinic Appointments Is a Highly Acceptable, Feasible, and Safe Model that Engages Individuals at Risk for HIV into PrEP Care. *Open Forum Infect Dis*. 2019;6(7):ofz310. doi:10.1093/ofid/ofz310

19. Hightow-Weidman L, Beagle S, Pike E, et al. “No one’s at home and they won’t pick up the phone”: using the Internet and text messaging to enhance partner services in North Carolina. *Sex Transm Dis*. 2014;41(2):143-148. doi:10.1097/OLQ.0000000000000087

20. Muessig KE. Vecchio AC, Harrison SE, Paton M, Pereira NM, Poteat T,Hanson LA, Hightow-Weidman LB. Ending the HIV Epidemic in the Carolinas:Building diverse organizational networks to design and deliverresearch-tested interventions at the community level. National LGBTQ HealthConference, May 20-21, 2021. Virtual Conference. . https://lgbtqhealthconference.org/2021-agenda

21. Vecchio AC, Muessig KE, Harrison SE, et al. Vecchio AC, Muessig KE, Harrison SE, Paton M, Mcgee D,Soberano Z, Hightow-Weidman L. Ending the HIV Epidemic: Creating a unifiedstigma-informed recruitment campaign to engage youth in HIV prevention. NationalLGBTQ Health Conference, May 20-21, 2021. Virtual Conference.https://lgbtqhealthconference.org/2021-agenda.

22. Giovenco D, Muessig KE, Horvitz C, et al. Adapting technology-based HIV prevention and care interventions for youth: lessons learned across five U.S. Adolescent Trials Network studies. *Mhealth*. 2021;7:21. doi:10.21037/mhealth-20-43

23. Teitelman AM, Tieu H-V, Flores D, et al. Individual, social and structural factors influencing PrEP uptake among cisgender women: a theory-informed elicitation study. *AIDS Care*. 2022;34(3):273-283. doi:10.1080/09540121.2021.1894319

24. Bauermeister J, Sullivan PS, Gravens L, et al. Reducing HIV Vulnerability Through a Multilevel Life Skills Intervention for Adolescent Men (The iREACH Project): Protocol for a Randomized Controlled Trial. *JMIR Res Protoc*. 2018;7(7):e10174. doi:10.2196/10174

25. Muessig KE, LeGrand S, Horvath KJ, Bauermeister JA, Hightow-Weidman LB. Recent mobile health interventions to support medication adherence among HIV-positive MSM. *Curr Opin HIV AIDS*. 2017;12(5):432-441. doi:10.1097/COH.0000000000000401

26. Hightow-Weidman LB, Muessig KE, Bauermeister J, Zhang C, LeGrand S. Youth, technology, and HIV: recent advances and future directions. *Curr HIV/AIDS Rep*. 2015;12(4):500-515. doi:10.1007/s11904-015-0280-x

27. Hightow-Weidman LB, LeGrand S, Muessig KE, et al. A randomized trial of an online risk reduction intervention for young black MSM. *AIDS Behav*. 2019;23(5):1166-1177. doi:10.1007/s10461-018-2289-9

28. Touger R, Wood BR. A Review of Telehealth Innovations for HIV Pre-Exposure Prophylaxis (PrEP). *Curr HIV/AIDS Rep*. 2019;16(1):113-119. doi:10.1007/s11904-019-00430-z

29. Siegler AJ, Mayer KH, Liu AY, et al. Developing and Assessing the Feasibility of a Home-based Preexposure Prophylaxis Monitoring and Support Program. *Clin Infect Dis*. 2019;68(3):501-504. doi:10.1093/cid/ciy529

30. Ramakrishnan A, Sales J, McCumber M, Psioda M, Powell L, Sheth AN. 852. bridging the gap in prep provider training: an implementation science study. *Open Forum Infect Dis*. 2021;8(Supplement_1):S516-S516. doi:10.1093/ofid/ofab466.1047

31. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1

32. Screening Recommendations and Considerations Referenced in Treatment Guidelines and Original Sources. Sexually Transmitted Infections Treatment Guidelines, 2021. September 6, 2022. Accessed November 17, 2022. https://www.cdc.gov/std/treatment-guidelines/screening-recommendations.htm

33. Muessig KE, Golinkoff JM, Hightow-Weidman LB, et al. Increasing HIV testing and viral suppression via stigma reduction in a social networking mobile health intervention among black and latinx young men and transgender women who have sex with men (healthmpowerment): protocol for a randomized controlled trial. *JMIR Res Protoc*. 2020;9(12):e24043. doi:10.2196/24043

34. Centers for Disease Control and Prevention. Data Access - Urban Rural Classification Scheme for Counties. December 2, 2019. Accessed September 26, 2021. https://www.cdc.gov/nchs/data_access/urban_rural.htm

35. Hightow-Weidman LB, Muessig KE, Pike EC, et al. HealthMpowerment.org: Building Community Through a Mobile-Optimized, Online Health Promotion Intervention. *Health Educ Behav*. 2015;42(4):493-499. doi:10.1177/1090198114562043

36. Hightow-Weidman LB, Fowler B, Kibe J, et al. HealthMpowerment.org: development of a theory-based HIV/STI website for young black MSM. *AIDS Educ Prev*. 2011;23(1):1-12. doi:10.1521/aeap.2011.23.1.1

37. Muessig KE, Baltierra NB, Pike EC, LeGrand S, Hightow-Weidman LB. Achieving HIV risk reduction through HealthMpowerment.org, a user-driven eHealth intervention for young Black men who have sex with men and transgender women who have sex with men. *Digit Cult Educ*. 2014;6(3):164-182.

38. Choi SK, LeGrand S, Dong W, Muessig KE, Hightow-Weidman L. Condom use intentions mediate the relationships between psychosocial constructs and HIV sexual risk behavior in young Black men who have sex with men. *AIDS Care*. 2019;31(1):53-60. doi:10.1080/09540121.2018.1492695

39. Weiner BJ. A theory of organizational readiness for change. *Implement Sci*. 2009;4:67. doi:10.1186/1748-5908-4-67

40. Weiner BJ, Belden CM, Bergmire DM, Johnston M. The meaning and measurement of implementation climate. *Implement Sci*. 2011;6:78. doi:10.1186/1748-5908-6-78

41. Teal R, Bergmire DM, Johnston M, Weiner BJ. Implementing community-based provider participation in research: an empirical study. *Implement Sci*. 2012;7:41. doi:10.1186/1748-5908-7-41

42. Kimball AA, Zhu W, Tanner MR, et al. The Effect of Navigation on Linkage to a PrEP Provider Among PrEP-Eligible Men who have Sex with Men in a U.S. Demonstration Project. *AIDS Behav*. 2023;27(6):1981-1988. doi:10.1007/s10461-022-03931-y

43. Ezennia O, Geter A, Smith DK. The PrEP Care Continuum and Black Men Who Have Sex with Men: A Scoping Review of Published Data on Awareness, Uptake, Adherence, and Retention in PrEP Care. *AIDS Behav*. 2019;23(10):2654-2673. doi:10.1007/s10461-019-02641-2

44. Jones J, Dominguez K, Stephenson R, et al. A Theoretically Based Mobile App to Increase Pre-Exposure Prophylaxis Uptake Among Men Who Have Sex With Men: Protocol for a Randomized Controlled Trial. *JMIR Res Protoc*. 2020;9(2):e16231. doi:10.2196/16231

45. North Carolina Department of Health and Human Services. Communicable Disease Programs: HIV/STD Prevention and Care. November 1, 2023. Accessed October 26, 2022. https://epi.dph.ncdhhs.gov/cd/stds/program.html

46. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention. Core indicators for monitoring the Ending the HIV Epidemic initiative (preliminary data): National HIV Surveillance System data reported through June 2021; and preexposure prophylaxis (PrEP) data reported through March 2021. HIV Surveillance Data Tables 2021;2(No. 4). Table 3a. Number of Persons Presceibed PrEP, Number of Persons with PrEP Indications, and PrEP Coverage during January 2019 through March 2021, among Persons Aged >= 16 Years, by Selected Characteristics - United States (Preliminary) . October 2021. Accessed May 4, 2023. https://www.cdc.gov/hiv/library/reports/surveillance-data-tables/vol-2-no-4/index.html

47. Centers for Disease Control and Prevention. DUPLICATE_Centers for Disease Control and Prevention. Core indicators for monitoring the Ending the HIV Epidemic initiative (preliminary data): National HIV Surveillance System data reported through June 2021; and preexposure prophylaxis (PrEP) data reported through March 2021. HIV Surveillance Data Tables 2021;2(No. 4). Table 3b. Number of Persons Prescribed PrEP, Number of Persons with PrEP Indications, and PrEP Coverage During January 2019 through March 2021, among Persons Aged ≥ 16 Years, by Area of Residence - United States and Puerto Rico (Preliminary). October 2021. Accessed May 3, 2023. https://www.cdc.gov/hiv/library/reports/surveillance-data-tables/vol-2-no-4/index.html

48. Biello KB, Daddario SR, Hill-Rorie J, et al. Uptake and acceptability of mychoices: results of a pilot RCT of a mobile app designed to increase HIV testing and prep uptake among young american MSM. *AIDS Behav*. 2022;26(12):3981-3990. doi:10.1007/s10461-022-03724-3

49. Pathela P, Jamison K, Blank S, Daskalakis D, Hedberg T, Borges C. The HIV Pre-exposure Prophylaxis (PrEP) Cascade at NYC Sexual Health Clinics: Navigation Is the Key to Uptake. *J Acquir Immune Defic Syndr*. 2020;83(4):357-364. doi:10.1097/QAI.0000000000002274

50. Haberer JE, Kidoguchi L, Heffron R, et al. Alignment of adherence and risk for HIV acquisition in a demonstration project of pre-exposure prophylaxis among HIV serodiscordant couples in Kenya and Uganda: a prospective analysis of prevention-effective adherence. *J Int AIDS Soc*. 2017;20(1):21842. doi:10.7448/IAS.20.1.21842

51. Haberer JE, Ngure K, Muwonge T, et al. Brief report: context matters: prep adherence is associated with sexual behavior among HIV serodiscordant couples in east africa. *J Acquir Immune Defic Syndr*. 2017;76(5):488-492. doi:10.1097/QAI.0000000000001548

52. Brehaut JC, Graham ID, Wood TJ, et al. Measuring acceptability of clinical decision rules: validation of the Ottawa acceptability of decision rules instrument (OADRI) in four countries. *Med Decis Making*. 2010;30(3):398-408. doi:10.1177/0272989X09344747

53. 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. *Ann Intern Med*. 2012;156(8):541-550. doi:10.7326/0003-4819-156-8-201204170-00001

54. Cambiano V, Miners A, Dunn D, et al. Cost-effectiveness of pre-exposure prophylaxis for HIV prevention in men who have sex with men in the UK: a modelling study and health economic evaluation. *Lancet Infect Dis*. 2018;18(1):85-94. doi:10.1016/S1473-3099(17)30540-6

55. Cambiano V, Miners A, Phillips A. What Do We Know About the Cost-effectiveness of HIV Preexposure Prophylaxis, and Is It Affordable? *Curr Opin HIV AIDS*. 2016;11(1):56-66. doi:10.1097/COH.0000000000000217

56. Wang LY, Hamilton DT, Rosenberg ES, et al. Cost-Effectiveness of Pre-Exposure Prophylaxis Among Adolescent Sexual Minority Males. *J Adolesc Health*. 2020;66(1):100-106. doi:10.1016/j.jadohealth.2019.07.022

57. Gold MR. *Cost-Effectiveness in Health and Medicine*. 1st ed. (Gold MR, Siegel JE, Russell LB, Weinstein MC, eds.). Oxford University Press; 1996:456.

58. Drummond MF, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programs (Oxford Medical Publications)*. 1st ed. (Drummond MF, etc., eds.). Oxford University Press; 1987:220.

59. Sohn H, Tucker A, Ferguson O, Gomes I, Dowdy D. Costing the implementation of public health interventions in resource-limited settings: a conceptual framework. *Implement Sci*. 2020;15(1):86. doi:10.1186/s13012-020-01047-2

60. Hamilton DT, Goodreau SM, Jenness SM, et al. Potential impact of HIV preexposure prophylaxis among black and white adolescent sexual minority males. *Am J Public Health*. 2018;108(S4):S284-S291. doi:10.2105/AJPH.2018.304471

61. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 2016;316(10):1093-1103. doi:10.1001/jama.2016.12195

62. Mauskopf JA, Sullivan SD, Annemans L, et al. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis. *Value Health*. 2007;10(5):336-347. doi:10.1111/j.1524-4733.2007.00187.x

63. Rutstein SE, Brown LB, Biddle AK, et al. Cost-effectiveness of provider-based HIV partner notification in urban Malawi. *Health Policy Plan*. 2014;29(1):115-126. doi:10.1093/heapol/czs140

64. Rutstein SE, Siedhoff MT, Geller EJ, et al. Cost-Effectiveness of Laparoscopic Hysterectomy With Morcellation Compared With Abdominal Hysterectomy for Presumed Myomas. *J Minim Invasive Gynecol*. 2016;23(2):223-233. doi:10.1016/j.jmig.2015.09.025

65. Briggs AH, Ades AE, Price MJ. Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. *Med Decis Making*. 2003;23(4):341-350. doi:10.1177/0272989X03255922

66. Gopalappa C, Farnham PG, Hutchinson AB, Sansom SL. Cost effectiveness of the National HIV/AIDS Strategy goal of increasing linkage to care for HIV-infected persons. *J Acquir Immune Defic Syndr*. 2012;61(1):99-105. doi:10.1097/QAI.0b013e31825bd862

67. Siedhoff MT, Rutstein SE, Wheeler SB, et al. Cost-Effectiveness of Laparoscopic Hysterectomy With Morcellation Compared to Abdominal Hysterectomy for Presumed Benign Leiomyomata. *J Minim Invasive Gynecol*. 2015;22(6S):S78. doi:10.1016/j.jmig.2015.08.209

68. HIV.gov. Data & Trends: U.S. Statistics Fast Facts . August 27, 2022. Accessed December 22, 2022. https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics

69. Hightow-Weidman L, Muessig KE, Egger JR, Vecchio A, Platt A. Epic Allies: A Gamified Mobile App to Improve Engagement in HIV Care and Antiretroviral Adherence among Young Men Who have Sex with Men. *AIDS Behav*. 2021;25(8):2599-2617. doi:10.1007/s10461-021-03222-y

70. Hanif H. Vuka+, Novel Smartphone-based PrEP Adherence Support Intervention for Adolescent Girls and Young Women, Pilot Study. Presented at the: Adherence 2023, International Association of Providers of AIDS Care (IAPAC); June 11, 2023.

71. Complete | Risk Reduction | Compendium | Intervention Research | Research | HIV/AIDS | CDC. Accessed August 14, 2024. https://www.cdc.gov/hiv/research/interventionresearch/compendium/rr/complete.html

72. L. Kay Bartholomew Eldredge CMM. *Planning Health Promotion Programs: An Intervention Mapping Approach*. Jossey-Bass; 2016.

73. Fernandez ME, Ruiter RAC, Markham CM, Kok G. Intervention Mapping: Theory- and Evidence-Based Health Promotion Program Planning: Perspective and Examples. *Front Public Health*. 2019;7:209. doi:10.3389/fpubh.2019.00209

74. Kok G, Peters LWH, Ruiter RAC. Planning theory- and evidence-based behavior change interventions: a conceptual review of the intervention mapping protocol. *Psicol Reflex Crit*. 2017;30(1):19. doi:10.1186/s41155-017-0072-x

75. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: A consolidated framework for advancing implementation science. *Implement Sci*. 2009;4:50. doi:10.1186/1748-5908-4-50

76. Unanticipated Problems Involving Risks & Adverse Events Guidance (2007) | HHS.gov. Accessed January 20, 2023. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#AA

77. FAQ | NC Local Health Department Accreditation. Accessed September 12, 2022. https://nclhdaccreditation.unc.edu/about-nclhda/faq/

78. About CLIA | CDC. Accessed September 12, 2022. https://www.cdc.gov/clia/law-regulations.html

79. LeGrand S, Knudtson K, Benkeser D, et al. Testing the Efficacy of a Social Networking Gamification App to Improve Pre-Exposure Prophylaxis Adherence (P3: Prepared, Protected, emPowered): Protocol for a Randomized Controlled Trial. *JMIR Res Protoc*. 2018;7(12):e10448. doi:10.2196/10448

Appendix

The appendix will include the following documents:

- Enrollment Informed Consent Forms