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Document:

Study Protocol and Informed Consent Form

Official Study Title:

Integrating a Combination HIV Prevention Intervention into a Widely-Used Geosocial App for Chinese MSM: Pilot Study

ClinicalTrial.gov ID: NCT06647173

Date: July, 17, 2023

INTEGRATING A COMBINATION HIV PREVENTION INTERVENTION INTO A WIDELY-USED GEOSOCIAL APP FOR CHINESE MSM

SIGNATURE PAGE

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guidelines for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.
I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about the obligations incurred by their contribution to the study.

_____
Name of Investigator of Record

_____ _____
Signature of Investigator of Record Date

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SCHEMA

Principal Investigator: Aaron Siegler, PhD

Purpose:
The overarching objective is to assess feasibility and acceptability of Blued+, a combination HIV prevention intervention that will integrate a combination package of HIV prevention services into the Blued mobile application (app) platform, for men who have sex with men (MSM) in China.

Study Design:
The pilot study will be an interrupted time series cohort of 400 MSM. In two cities, a three-month baseline standard of care (SOC) period with measurement at 0 and 3 months will be followed by a 12-month intervention period with the measurement at 6, 9, 12, and 15 months. The longitudinal design will allow for 1) assessment of feasibility and acceptability outcomes, 2) development of the logistical and operational needs to provide the app-based intervention, and 3) development of estimates for key parameters to design a future, definitive study to determine intervention efficacy.

Standard of care will consist of the existing Blued app and local health services. Blued app access currently includes health education components such as information regarding HIV testing and pre-recorded health messages from Chinese celebrities. Participants will have access to in-person no-cost services for HIV testing and condom pick-up from local non-governmental organizations (NGOs) that support MSM in both cities.

At three months, participants will be provided with educational materials in the health portal as well as theory-based HIV prevention messages, along with home HIV test kits and condoms. This intervention will have a health portal that houses all HIV prevention functionalities. The exact nature of the interventions included will be further defined by the qualitative work, as additional services may be identified as essential to an HIV prevention package in China. These may include services such as peer support or stigma reduction. Additionally, participants will receive PrEP medication, laboratory, and care costs free of charge.

In the portal, users will be able to explore health-supporting functions of the app and access offline services, including behavioral risk assessments, an HIV prevention platform, HIV testing, linkage to care for those testing positive for HIV, in-app screening and referral to HIV pre-exposure prophylaxis (PrEP) and sexually transmitted infection (STI) services, and provision of PrEP with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF).

Study Population:
The study population will be self-reported HIV-negative Blued users who are 18 years of age or greater, were assigned a male sex at birth, report having anal sex with a man in the last 6 months, are able to complete a survey in standard Mandarin Chinese, are willing to provide two forms of contact information, are willing to update the Blued app with the Blued+ portal after the baseline period, are willing to complete quarterly surveys for the 15-month study period, and reside in metropolitan Beijing or Chengdu, China.

Study Size:

The sample for the pilot study will consist of approximately 400 MSM, 200 each in Beijing and Chengdu. All 400 men will be followed for 15 months.

Study Duration:
Recruitment activities will be conducted for three months or until 200 MSM have been recruited in each intervention city. After enrollment, MSM will have a follow-up period of 15 months for each participant.

Primary Objectives:
This study has four primary objectives:

1. Conduct a review of literature on behavioral and biomedical interventions offered in online and offline settings for MSM in China.
2. Develop a mathematical model of HIV transmission in Chinese MSM, informed by annual cross-sectional surveys, that accounts for behavioral, structural, and biological factors in order to estimate the impact of different scenarios of intervention provision and inform selection of intervention components for the pilot study.
3. Assess Blued+ intervention feasibility and acceptability in China, first by collecting qualitative data to inform the development of the Blued+ app components and service delivery and then by developing and pilot testing Blued+ among MSM in Beijing and Chengdu, China. This protocol includes only the pilot study portion of the overall study.
4. Use preliminary information from the pilot study to design a larger, definitive study of the efficacy of the prevention package for Chinese MSM.

1.0 INTRODUCTION

Background and Rationale

HIV disproportionately affects the estimated 21 million men who have sex with men (MSM) who live in China.[1,2] The high impact of HIV among MSM has been recognized for nearly 2 decades, since the documentation of a high prevalence of HIV among MSM donating blood.[3] In a survey of 47,000 Chinese MSM in 61 cities, the prevalence of HIV was 4.9%; higher prevalence of HIV was reported in MSM who were non-local or met sex partners through the internet.[4] A national meta-analysis in 2014 reported a pooled 6.5% prevalence of HIV among MSM.[5] In Beijing, a cohort study of MSM documented annualized incidence of 7.8% -- a level sadly similar to intense HIV epidemics among MSM in Thailand[6], South Africa, and the United States[7]. In China, the estimated incidence of HIV was higher for MSM than for people who inject drugs (PWID), female sex workers, and male patients attending sexually transmitted infection (STI) clinics.[8] According to data from the Chinese National Sentinel Surveillance System, from 2010-2014, the HIV prevalence among MSM increased substantially, from 5.7% to 7.8%.[8] MSM in China represented 12% of new case diagnoses in 2010, and 26% of new case diagnoses in 2014.[9] Similarly, a series of cross-sectional surveys in Guangxi documented a doubling of HIV prevalence among MSM from 2008-2012.[10] To inform this proposal, our Emory/Blued team recently completed a survey of over 4,000 MSM in four cities, including the two proposed pilot cities. In this sample of Blued users, self-reported HIV prevalence among those who had tested for HIV was 12.5% (406/3256) overall, with 9.3% (162/1746) in Beijing and 19% (137/724) in Chengdu.

Despite the substantial epidemic, the use of HIV prevention services among MSM is low. In the 61-city survey, over half of the sample reported inconsistent condom use with male partners in the prior year.[4] In our four-city data, 46% (1584/3457) of sexually active MSM reported inconsistent condom use. Although sexually transmitted infection (STI) control is a priority in China's HIV prevention plan[11], less than a third of MSM in China have ever been tested for syphilis,[12] and our four-city survey found that only 30% had tested for any STI in the past year. In terms of HIV testing, a systematic review in 2014 documented an annual period prevalence of HIV testing of 38% among MSM in the most recent reporting period,[13] and our four-city survey found 52% annual testing prevalence. Taken together, these data suggest the need for improved coverage of each step of the HIV prevention continuum, including the promotion of HIV testing, increased condom uptake, and screening for STIs.

Primary reasons for low levels of HIV testing include privacy concerns and nondisclosure of sexual identity; these problems are readily addressable through home-based services. Several studies have found privacy concerns are an important barrier to HIV testing among Chinese MSM,[14-16] with one finding it the most universally agreed upon consideration.[15] Privacy concerns are likely related to the relatively low levels of sexual orientation disclosure,[17] which is also independently associated with lower likelihood of HIV testing.[15,17,18] For individuals who wish to maintain privacy, or to avoid potential disclosure of their sexual identity to clinicians or service providers, home services for HIV prevention may be a good option. One study found 57% of their sample was interested in home HIV testing,[15] and our four-city study found that 66% of Blued app users would order a home HIV test kit from the app if it were offered.

Patterns of migration are also uniquely important in China. For men who are living outside of their registered home district (hukou), access to health services might be more challenging;[19] these men were also the group with the highest HIV prevalence in China.[4] Hukou-migrating MSM often move between multiple cities, suggesting the need for a mobile system to organize reminders and to find new local health service in different cities. Stigma and discrimination are frequently anticipated and experienced by MSM, and perceived discrimination is associated with lower uptake of testing.[20] Further, MSM who reported being less engaged in gay communities have lower uptake of prevention services.[12] Thus, coordinating HIV prevention services through a mobile app might help reach critical populations of

MSM, including hukou-migrating MSM and those who may be less engaged in their communities. Men who experience stigma and who are less engaged in their communities may turn to the internet to meet partners. Delivering services online, where the highest risk men meet their partners, is responsive to the context of the Chinese epidemic among MSM and will reach MSM who would otherwise be hidden to public health efforts.

Blued is a geosocial networking (GSN) app for MSM, developed in China by a community-based organization (Danlan). The app has grown rapidly in popularity both in China and throughout the Asian Region. In 2018, Blued had 12 million active users each month, including over 480,000 in Beijing, 221,000 in Chengdu, 115,000 in Kunming, and 174,000 in Tianjin. The large user base is impressive, particularly when considering that the total population of MSM in the United States is estimated at 4.5 million.[21] Blued is a socially conscious community-based organization, providing prevention information through a team led by Dr. Mi Guodong, a Chinese physician. Previous efforts have included public health information and prevention messages through advertisements, and providing information on the locations of HIV test sites. Blued has conducted a number of large surveys of MSM,[12,17,18] including the Emory/Blued survey, illustrating the willingness of MSM to participate in data collection through the Blued app.

Modeling conducted by our previous MP3 project,[22] and other models from our work in the US and India,[23,24] have illustrated that PrEP[25] is a critical component of comprehensive prevention packages for MSM. Daily oral emtricitabine / tenofovir DF (FTC/TDF) for PrEP can provide >99% reduction in risk of HIV acquisition.[26] Yet even in the context of PrEP availability and uptake, our models have demonstrated that offering a package that includes other prevention modalities like HIV testing and condom promotion can contribute to substantial reductions in HIV incidence.[22] Despite its high efficacy, PrEP is not currently approved by China FDA. Additional data, including modeling data to demonstrate PrEP's potential impact in China and the feasibility of providing PrEP to Chinese MSM, will be important for eventual regulatory approval (see letter of support, NCAIDS).

Our scientific premise is that the HIV prevention services continuum for MSM needs to be stronger, and that integrating recommendations and direct linkages to services into a mobile app already used by Chinese MSM will be a feasible and acceptable way to increase coverage of basic prevention services. This research will be grounded in the experiences of Blued in China and the experiences of the US-based team in mHealth and app-based delivery of at-home HIV test kits and PrEP programs. We therefore propose to test the provision of a package of prevention services, optimized for Chinese MSM based on a literature review, epidemic modeling and community input that will be delivered through Blued – a GSN app that offers the potential to reach millions of Chinese MSM.

2.0 STUDY OBJECTIVES

2.1 Overarching Objective

The overarching objective of the pilot study is to evaluate the feasibility and acceptability of Blued+, a combination HIV prevention intervention that integrates a combination package of HIV prevention services into the Blued app platform.

The pilot study is Phase III of a larger project. Phase I consists of a comprehensive literature review and summary of current knowledge of HIV prevention interventions for MSM in China. The review will focus on (1) identifying successful interventions and programs related to PrEP or mobile apps, and characterizing components of the interventions that made them successful and (2) describing components of the HIV epidemic in China, including key parameters that could inform mathematical modeling. This review will also serve to provide inputs for the Phase III pilot study.

Phase II includes the development of a mathematical model of HIV transmission in Chinese MSM. This modeling will be used to estimate the potential impact of scaling up different combinations of HIV prevention packages for Chinese MSM. Further, this modeling will be used to inform the pilot study through identifying the most efficacious combinations of interventions, and by identifying leverage points for the success of key interventions that are likely to be a part of the final package.

Phase III includes both qualitative studies as well as the pilot study. Qualitative work (focus group discussions and in-depth interviews) will be used to identify acceptable and optimal HIV prevention interventions for MSM in China to include as components of the prevention package through Blued+. This qualitative work is described in a separate protocol. The pilot study will include biological and behavioral data collection to monitor the uptake of the prevention interventions by study participants. These activities are described here, though additional services may be identified as essential to an HIV prevention package in China during modeling and literature review from Aims 1 and 2, e.g. peer counseling or stigma reduction.

2.2 Specific Aims

This study will have the following four specific aims:

Aim 1. Conduct a review of literature on HIV prevention interventions offered in online and offline settings for MSM in China.

Aim 2. Develop a mathematical model of HIV transmission in Chinese MSM, informed by annual cross-sectional surveys, that accounts for behavioral, structural, and biological factors in order to estimate the impact of different scenarios of intervention provision and inform selection of intervention components for the pilot study.

Aim 3. Assess Blued+ intervention feasibility and acceptability in China.

- **Aim 3.1.** Collect qualitative data, through activity-based focus groups and user experience cognitive interviews to inform development of Blued+ app components and service delivery.
- **Aim 3.2.** Develop and pilot test Blued+ among 400 MSM in Beijing and Chengdu, China.

Aim 4. Use preliminary information from the pilot study to design a larger efficacy trial of the prevention package for Chinese MSM.

3.0 STUDY DESIGN

This study is an interrupted time series pilot study designed to assess feasibility and acceptability of several interventions to encourage uptake and adherence of PrEP. Per the NIH definition of clinical trial case studies, including 18F and 29, this study is not a clinical trial. In this study, a novel HIV combination service package, the Blued+ portal, will be delivered through a widely accessed geospatial networking app Blued. Intervention development, in terms of the selection of intervention components, the relative emphasis placed on each component, and the manner in which the components are offered will be informed by a literature review (Aim 1), mathematical modeling (Aim 2), and qualitative data collection (Aim 3.1). Blued+ will include all functionality of Blued (which attracts geosocial network users), and it will include a suite of HIV prevention services. These services may include risk screener quizzes, home

HIV test kits, and referral for PrEP provider visits and associated laboratory testing. In addition to these services, the study will include:

> Educational materials focused on PrEP as well as other sexual health topics. Educational materials will be built into the health portal. Topics of education may include an overview of PrEP and PrEP medication, the effectiveness of PrEP, PrEP payment, side effects, stigma, and where to access PrEP, among other topics related to prevention of HIV and STIs. Additionally, participants will receive theory-based sexual health and prevention messages delivered via the Blued+ app. These messages will be developed using social cognitive theory with the goal of creating a comprehensive messaging package to improve participants' self-reported sexual health and prevention behaviors, beliefs, and attitudes. Participants will also receive a screener quiz that allows them to assess whether PrEP is right for them and encourage them and link to PrEP care. Those participants who do choose to initiate PrEP will receive PrEP medication (FTC/TDF), associated laboratory testing, and clinical care free of charge. Participants will be encouraged to schedule a visit with a study provider in each intervention city in person or online, and will access PrEP free of charge through these study clinics.

A total of 400 participants will be enrolled in the intervention with quarterly follow-up with a total of six surveys for each participant comprising enrollment/baseline (two surveys) and pilot intervention (four surveys). The survey will be team translated to ensure accuracy of the text and participant understanding.

Below is a diagram of the pilot study design:

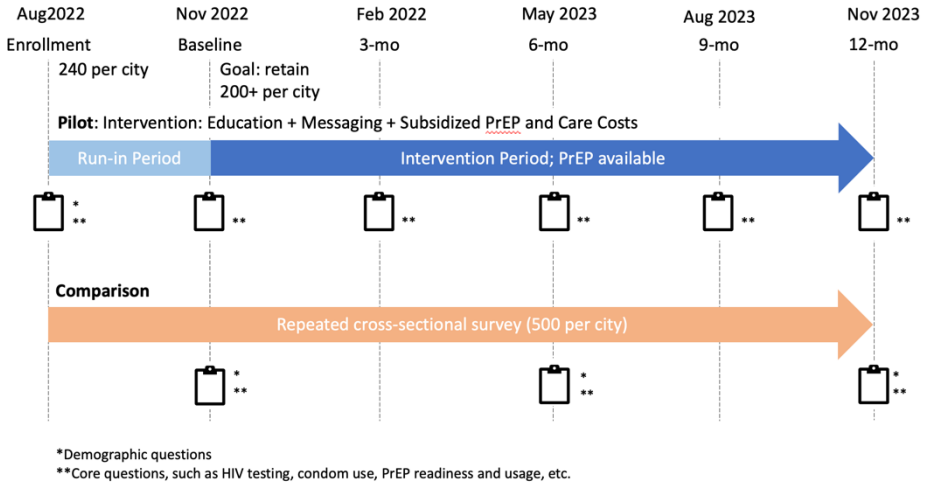

Figure 1 Pilot Study Design Overview

3.1 Study population

The study population includes registered Blued users who self-report male sex at birth, are age 18 years or older, who report anal sex with a man in the past 6 months, behaviorally eligible for PrEP, and who do not report an HIV diagnosis. Eligible men will be residents of metropolitan areas of Beijing or Chengdu, China.

3.2 Sample Size

Over the entire study period, 400 participants will be enrolled in the prospective pilot study intervention. All participants will be followed longitudinally for 15 months.

4.0 SELECTION OF STUDY PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all inclusion criteria to participate in this study. These inclusion criteria include:

1. Registered Blued app user
2. ≥18 years of age
3. Male sex at birth
4. Self-report anal sex with a man in the last 6 months
5. HIV-negative or unknown HIV status
6. Behaviorally eligible for PrEP per published China guidance
7. Able to complete study instruments in Mandarin Chinese
8. Resident of the metropolitan area of Beijing or Chengdu, China

4.2 Exclusion Criteria

Potential participants meeting any of the exclusion criteria at baseline will be excluded from participating in any part of the study. The exclusion criteria for this study include:

1. Not a registered Blued app user
2. <18 years of age
3. Not male sex at birth
4. Does not report anal sex with a man in the last 6 months
5. Has previously tested positive for HIV
6. Not eligible for PrEP per published China guidance
7. Unable to complete study instruments in Mandarin Chinese
8. Not a resident of the metropolitan area of Beijing or Chengdu, China
9. Currently enrolled in another HIV prevention study
10. Evidence of fraudulent participation, such as a duplicate IP address, multiple screening attempts, duplicate emails, etc.

4.3 Recruitment

Participants will be recruited using banner advertising and inbox messages delivered through the Blued app. We will target men at least 18 years old who live in the metropolitan area of one of the two cities where the study is being conducted. When interested men click on a banner advertisement, they will be taken to a landing page containing basic study information that includes a short description of study activities. If they click on a button to advance, they will be directed to a short eligibility screener to determine whether they meet the eligibility criteria. Men who do not meet the eligibility criteria will be taken to a screen thanking them for their interested in the study. Men who do screen preliminarily eligible will be asked to provide their contact information, including an email address, a cell phone number that can receive text messages, and a name or nickname so study staff can contact them. No identifying information will be collected from participants determined to be ineligible at screening.

5.0 PILOT STUDY PROCEDURES

Baseline procedures are identical for all study participants. These procedures include rescreening for eligibility, fraud deterrence, informed consent, and a baseline survey.

5.1 Enrollment Procedures

5.1.1 Fraud Detection and Eligibility Confirmation

To mitigate fraudulent participation, a list of Blued user accounts eligible for study participation will be developed prior to the launch of the pilot study. Accounts that are created after study initiation will not be eligible for the study. This will prevent attempts to create fraudulent additional accounts for rescreening or to collect multiple incentives.

5.1.2 Informed Consent and Enrollment

Because men will not be consented and enrolled at an "in-person" visit, the consent process will be administered via the Blued app. Participants who are eligible based on screening and fraud checks will be provided an electronic study consent on a secure electronic survey platform and will be able to download and save a copy as well. Participants will be able to contact study staff should they have any questions during this process. The consent form describes all study procedures, including confidentiality and privacy, information about potential risks, discomforts, benefits of participation, and information regarding who they can contact with further questions. It also states that participation is voluntary, that participants may decide not to take part or to withdraw from the study at any time without penalty or loss of any benefit to which they might otherwise be entitled, and that study participation is in no way related to being able to access or continue getting care or services. Participants can refuse to answer any questions, and can withdraw from the study at any time.

A brief quiz will be developed to verify understanding of key elements of the consent form. After reviewing the consent form, potential participants will be forwarded to the consent quiz. Those who do not receive a sufficient score on the quiz will be directed back to the consent form for further review before completing the quiz.

Upon successful completion of the consent quiz, potential participants will provide consent using an electronic method to document signature on the electronic consent form. Informed consent must be obtained before any study procedures are performed. The consent form will be available in Mandarin Chinese.

Upon signing of the consent form, participants will notify participants to complete the baseline survey through Blued's secure, encrypted survey platform.

5.2 Standard of Care

Assessed during the baseline study period, participants will have access to the existing Blued app and local health services. Blued app access currently includes health education components such as information regarding HIV testing and pre-recorded health messages from Chinese celebrities. Participants will have access to in-person, no cost services for HIV testing and condom pick-up from local NGOs that support MSM in both pilot cities.

5.3 Intervention Description

During the intervention period, study participants will receive the enhanced version of the Blued app with Blued+ service. Blued+ serves as the primary participant-facing component of the intervention.

5.3.1 Blued+ Service Core Components

All Blued+ intervention participants will have a health portal that houses all HIV prevention functionalities. In the portal, users will be able to explore health-supporting functions of Blued+ and access offline services such as ordering of prevention kits and supplies.

Behavioral Risk Assessment

Blued+ will use an engaging "health quiz" function that will serve to screen participants into appropriate services and to provide information relevant to the degree of protection based on current self-reported behaviors. Screening will allow users to access services most relevant to them, such as home HIV testing for users who have not recently tested or condom "choice" packages with different types of condoms for users dissatisfied with their current condoms. Information relevant to the current degree of protection will be provided through a risk dashboard. This function will inform those who receive risk screening, as well as provide clear mechanisms for individuals to mitigate their risk by accessing prevention services.

HIV Testing

Participants will have easy access in Blued+ to either order an in-home HIV test or schedule an HIV test appointment with their local provider. For the in-home option, participants will be mailed a HIV in-home test. Orders will be manually filled by study staff and mailed using the Chinese postal system. Participants preferring an in-person test will be able to select from local HIV test providers and schedule a test with that provider through an electronic calendaring system. Participants unsure of their preferred testing mode will be able to access information regarding the types of HIV testing available and their relevant benefits (e.g. in-home is saliva-based, no blood draw) and limitations (e.g. in-home has lower sensitivity for detecting HIV).

Linkage to Care for those Testing HIV Positive

Linkage to care will be available for those using home testing modalities. Those ordering home tests will be notified by Blued+ and through mailed materials accompanying the test kit that counseling and treatment are available. Brief surveys will also be sent to those ordering home test kits to query results and to refer to linkage to care services as appropriate. Experienced counselors at local HIV prevention organizations will provide linkage services through phone calls or in-person services.

In-App Screening and Referral to PrEP and STI Services

Both the baseline survey and periodic health quizzes will assess behavioral PrEP indication and STI testing frequency. Participants indicated for PrEP or STI testing will be able to schedule an appointment for PrEP or STI evaluation. For those interested in PrEP, the appointment will be in-person at a study clinic, or online with the Blued licensed PrEP clinician; those only interested in STI services will be scheduled for laboratory testing at their local NGO. Participants will also be able to access information modules describing PrEP and STIs within Blued+. A chat board or

similar communication function will allow study participants to have their questions about PrEP answered.

Provision of PrEP

Participants interested in PrEP will attend an in-person or online appointment with the study clinician at each site. The participant Blued app ID will be recorded to allow for linkage of study data and PrEP clinic visits for those who choose to access PrEP. PrEP care will follow US-CDC recommendations or Chinese recommendations if available. See the following section on PrEP with FTC/TDF for more information.

HIV Prevention Platform

An electronic platform will help participants formulate HIV prevention strategies, and monitor progress towards their prevention goals. This will allow men to create plans for HIV testing, condom use, and PrEP. The platform will feature commodity ordering offerings that provide notifications. Those who have initiated PrEP care may receive reminders regarding medication adherence and follow-up visit attendance.

5.3.2 Additional Blued+ Components

A the 3-month period, additional app components will be unlock in the health portal for each participant. These intervention components include:

Educational materials focused on PrEP as well as other sexual health topics. Topics of education may include an overview of PrEP and PrEP medication, the effectiveness of PrEP, PrEP payment, side effects, stigma, and where to access PrEP, among other topics related to prevention of HIV and STIs.
Additionally, participants will receive theory-based sexual health and prevention messages delivered via the Blued+. These messages will be developed with the goal of creating a comprehensive messaging package to improve participants' self-reported sexual health and prevention behaviors, beliefs, and attitudes. Participants will also receive a screener quiz that allows them to assess whether PrEP is right for them and encourage them and link to PrEP care. Those participants who do choose to initiate PrEP will receive the FTC/TDF, associated laboratory testing, and clinical care free of charge. Participants will be encouraged to schedule a visit with a study provider in each intervention city in-person or online, and will access PrEP free of charge through these study clinics.

5.4 PrEP

5.4.1 Additional Inclusion/Exclusion Criteria for Participants electing PrEP

In addition to the inclusion and exclusion criteria above for participants who enter the study, additional inclusion and exclusion criteria apply to participants who initiate PrEP. These criteria are based on US CDC Guidelines for PrEP or Chinese recommendations if available . All participants who choose to initiate PrEP through this study will be required to meet these guidelines, including laboratory testing.

Inclusion Criteria:

In addition to the inclusion criteria above, the inclusion criteria for PrEP are:

1. Laboratory confirmed HIV-negative
2. Behaviorally indicated for PrEP, including any of the following:
    a. History of inconsistent or no condom use with more than one partner
    b. History of inconsistent or no condom use with one partner who is not mutually monogamous
    c. Sexual partner living with HIV who is not virally suppressed
    d. History of a sexually transmitted infection by lab testing or self-report in the past six months
    e. Use of post-exposure prophylaxis
    f. Engagement in transactional sex, including sex work
    g. Requesting PrEP
    h. Other criteria as determined by future guidance from China
3. No contraindications to embtricitabine/tenofovir disoproxil fumarate (FTC/TDF)
4. Creatinine clearance of at least 60 mL/min reported by a laboratory or estimated using the Cockcroft-Gault Equation:

$$CrCL\ (mL/\text{min}\ ) = \frac{(140 - age) * body\ weight\ [kg]}{Serum\ Cr\ [mg/dL] * 72}$$

5. Willing to adhere to a PrEP dosing regimen
6. Willing to attend PrEP maintenance visits every 3 months

Exclusion Criteria
In addition to the exclusion criteria above, the exclusion criteria for PrEP are:

1. HIV-positive, either laboratory confirmed or by self-report
2. Signs or symptoms of acute HIV infection, probably recent exposure to HIV
3. Chronic hepatitis B
4. Creatinine clearance <60 mL/min
5. Symptoms of acute HIV infection within the prior 30 days
6. Contraindications to emtricitabine/tenofovir disoproxil fumarate (FTC/TDF)
7. Unwilling to attend PrEP maintenance visits every 3 months

5.4.2 Regimen (dose, schedule, route)

Pre-exposure prophylaxis for HIV will be available to participants through the study. Procedures will follow those set forth by the US CDC. The PrEP used in this study will be a combination of 200 mg emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF).

5.4.3 Study Product Formulation and Preparation

FTC/TDF tablets are capsule-shaped and usually film-coated and blue. They are available in child-resistant bottles, and including a silica gel canister or sachet. Medications will be stored by partner clinics in each intervention city at appropriate temperature and discursions based on manufacturer guidance. Containers will be kept tightly closed. Product will be dispensed in accordance with manufacturer guidance. No additional preparation will be necessary.

5.4.4 Study Product Supply and Accountability

Study Product Supply and Distribution to Participants

FTC/TDF will be purchased local in China from a manufacturer with China FDA-approved FTC/TDF pills.

Once a participant has indicated interest in PrEP, he will schedule an appointment with a clinician at partner clinics in person or online at each study site. Once deemed eligible for PrEP, he will be provided enough medication for three months and given counseling to encourage adherence. The participant will be required to attend follow-up PrEP visits every three months thereafter to check adherence, creatinine as needed, and HIV status, and thus eligibility to continue PrEP. Testing for STIs will also be completed at these visits.

PrEP eligibility will be verified before any additional pills are dispensed. The serial number or other relevant tracking information of the dispensed bottles will be recorded by the study clinician or pharmacy personnel, along with a count of pills dispensed in each bottle. At each visit, participants on PrEP will be asked to return their original prescribed FTC/TDF bottles containing any remaining tablets. Remaining tablets will be counted and used along with the information on time since the last refill to calculate pill adherence.

Study Product Accountability
All pills at partner clinics will be stored at the approved site pharmacy. These pharmacies will act in accordance with Chinese guidelines around good pharmacy practice set by these National Medical Products Administration (NMPA). All study materials will be locked and secured. The site pharmacist will track all pills received from the distributor and prescribed to or returned by study participants. The pharmacist will ensure that all PrEP participants are prescribed the correct number of pills. At the end of the study period, all unused study products will be managed in accordance with local procedures.

5.4.5 Toxicity Management on PrEP

The toxicity management described below relates only to participants on PrEP with FTC/TDF.

In general, the investigators have the discretion to hold study drug at any time if he or she feels that continued study drug use would be harmful to the participant or interfere with treatment deemed clinically necessary according to the judgement of the investigator.

5.4.5.1 Grading System

The grading system is located in the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, July 2017, which can be found on the Regulatory Support Center (RSC) website:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

5.4.5.2 Discontinuation of PrEP in the Presence of Toxicity

Grades 1 or 2

In general, participants who develop a Grade 1 or 2 AE regardless of relatedness to study drug and that is not specifically addressed below, may continue use of the study drug per protocol.

Grade 3
For participants who develop a Grade 3 AE or toxicity that is not specifically addressed below and is judged to be related to study drug by the study investigator, study drug use should be temporarily discontinued. In general, the investigator should re-evaluate the participant at least weekly for up to 2 weeks to document resolution of toxicity to less than Grade 2. The study drug should be permanently discontinued if improvement to severity ≤ Grade 2 cannot be documented within four weeks of receipt of the initial results.

Grade 4
Participants who develop a Grade 4 AE or toxicity that is not specifically addressed below (regardless of relationship to study drug) should have the study drug temporarily discontinued. The investigator should consult with the Protocol Safety Review Team (PSRT) and continue the temporary study drug hold until a recommendation is obtained from the PSRT. In general, study drug use will not be resumed if the Grade 4 AE is considered related to study drug use. If, in consultation with the PSRT, study drug use is resumed and the same Grade 4 AE recurs at Grade 4 level at any time, study drug must then be permanently discontinued.

5.4.5.3 General Criteria for PrEP Discontinuation

Participants may voluntarily discontinue the study drug for any reason at any time. Study investigators will permanently discontinue participants from study drugs per protocol for any of the specific criteria below. Site study investigators may also permanently discontinue participants for reasons not shown here.

A participant will be permanently discontinued from PrEP drug use by the study investigators for any of the following reasons:

- HIV Infection: Such participants will not resume study drug use at any time. Study drug will be held immediately upon recognition of the first reactive HIV test. The study investigator must permanently discontinue study drug if HIV infection is confirmed. A decision to resume study drug in participants who are subsequently confirmed to be HIV-uninfected requires approval of the protocol chair and PSRT.
- Viral hepatitis: Such participants will not resume study drug use at any time.

Any participant who prematurely discontinues study drug should remain in the study and will continue to be eligible for remaining interventions.

Study drug will be temporarily withheld from a participant for any of the following reasons:

- Report of prohibited concomitant medications. Study drug use may resume when the participant reports that he is no longer taking the prohibited medication, provided other reasons for temporary study drug hold or permanent discontinuation do not apply.
- The participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing study drug use, according to the judgement of the study investigator.

5.4.6 Management of Specific Toxicities on PrEP

Specific guidance related to product hold is also noted here as it pertains to the clinical management of toxicities.

- **Nausea, Vomiting, and Diarrhea**

Participants with Grade 1 or 2 nausea, vomiting, or diarrhea may be treated symptomatically with hydration, oral antiemetic therapies or antiemetic suppositories at the discretion of the study investigator. The investigator should order any clinically relevant laboratory analyses per his or her judgement.

Participants with ≥ Grade 3 nausea, vomiting, or diarrhea for which an alternative etiology is not established must discontinue the study drugs temporarily until Grade 2 or lower and be treated symptomatically. Should condition(s) not improve to Grade 2 or lower within seven days, the investigator should consult the PSRT for guidance on continuing the temporary discontinuation or progressing to permanent discontinuation of study drugs.

Repeat episodes of these events will be handled independently, and the instruction above will be followed for each event.

- **Creatinine Clearance for PrEP**

If the creatinine clearance is <60mL/min, study drug should be temporarily held and it should be confirmed within one week of the receipt of the results. If the calculated creatinine clearance is confirmed to be <60mL/min, the study drug must be permanently discontinued. If re-testing yields a result ≥60mL/min, the study investigator should consult the PSRT for further guidance on resuming study drug use, continuing the hold temporarily, or progressing to permanent discontinuation.

By which the investigator in consultation with the PSRT has determined that the case has stabilized, it may be possible to decrease the frequency of follow-up laboratory testing in addition to resumption of study drug.

- **HIV Infection**

Frequent testing for HIV acquisition during the study period will allow prompt cessation of study drug in an HIV-infected participant, minimizing the risk that resistant virus will emerge. Therefore, HIV testing will be performed at PrEP start and every three months thereafter. Any enrolled participants who acquire HIV infection while on PrEP will permanently discontinue study drug but will remain in the study.

6.0 MEASURES

A summary table of study measures, and sources for each measure, are provided in the table below. Measurement of tenofovir-diphosphate (TVF-DP) levels will be conducted using liquid chromatography/tandem mass spectrometry methods on DBS samples. TFV-DP level can be translated to an interpretation that indicates mean number of days per week PrEP is ingested over a period of approximately one month. The cutpoint used will be TFV-DP levels considered a surrogate for substantial protection: >700 fmol/punch, a level indicating >4 doses/wk.

Construct	Measure	Data source	Definition	Analysis
			PRIMARY OUTCOMES	
Feasibility	Home HIV test orders	Order fulfillment	Proportion of participants sent a home HIV test	Benchmark ≥ 30%
Feasibility	Condom orders	Order fulfillment	Proportion of participants sent 'choice' condom package	Benchmark ≥ 30%
Feasibility	PrEP initiation	Clinical site data	Proportion of participants receiving a PrEP prescription	Benchmark ≥ 20%
Acceptability	Systems Usability Scale[126, 127]	Survey	10-item scale, good score is >71	Benchmark: Good score (≥ 71 out of 100)
Acceptability	Ratings for intervention components[72]	Survey	Likert acceptability rating for each intervention component (e.g. home HIV test)	Benchmark: Acceptable ratings (≥ 3 out of 5)
			PRELIMINARY EFFICACY ASSESSMENT	
HIV testing	HIV testing[44,128]	Survey	Change in median number HIV tests	GEE model
Condom use	Condom use[44,128]	Survey	Change in proportion of participants reporting always using condoms for anal sex	GEE model
PrEP Use	PrEP use[123-125]	Laboratory data	Number participants with protective levels of TDF-DP	Descriptive report
			THEORETICAL ASSESSMENT	
Prevention cascade	PrEP cascade levels[129]	Survey and clinical site data	PrEP awareness, willingness, prescription, persistence in care, and medication adherence	Descriptive and logistic regression
Theoretical assessment	Unified Theory of Acceptance and Use of Technology (UTAUT2)[121]	Survey	Validated items for performance expectancy, effort expectancy, social influence, hedonic motivation, and habit.	Descriptive and GEE model to estimate SEM parameters
			PROCESS OUTCOMES	
Process	New HIV testers	Survey	Proportion changing from never to ever HIV test	Descriptive report
Process	New condom users	Survey	Proportion changing from none to some condom use	Descriptive report
Process	Visits to local health clinics	Survey	Proportion receiving HIV services at health departments	Descriptive report
App use	Time spent in health portal	App paradata	Hours of app health portal exposure	Descriptive report
App use	Consistency of use over time	App paradata	Number with monthly visits to health portal	Descriptive report

7.0 DATA HANDLING AND RECORD KEEPING

7.1 Data Management

Data will be stored in password-protected, encrypted files and secure Sojump servers. Databases of participant identifying information (contact information such as names, emails, and phone numbers) will not be linked to databases with participant data. Participant identifying information will only be linked to whether the participant completes study procedures, needs to be re-contacted, or refuses to participate. The name, email, and phone number of screened men who decline to be scheduled for participation will be removed from the study database after we have asked them questions about why they have a lack of interest in proceeding, unless they request to be contacted for future studies. Access to the identifying information will be on a role-based system: access to identifying information will be restricted to those who need access to perform their work function. Thus, access to identifying information will be restricted to the project coordinator, study staff, and students charged with data entry and scheduling tasks.

7.2 Procedures for Prevention and Addressing Breaches of Confidentiality

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

To minimize risks to confidentiality, we will provide study data with all appropriate physical and operational security protections. Paper-based data will be stored in a locked cabinet in a locked office, and all data files will have encryption and strong password protection. Access to data will be on a role-based standard; only those study staff, such as principal and co-investigators, data managers, data analysts, study staff, and graduate research assistants, who require access to identifying data to complete their study-related roles will be allowed access. All study staff will complete CITI course modules on human subjects research ethics, socio-behavioral research, and good clinical practice (GCP), will be trained in

security and confidentiality procedures, and will sign a confidentiality agreement before receiving access to any participant data. Any breaches in confidentiality will immediately be reported to the PI and to the IRB. Based on the PI and IRB's recommendation, staff may be retrained or receive disciplinary action. Study staff will follow procedures to minimize indirect disclosure that a participant is participating in an HIV-related research study, or a study that enrolls MSM. For each mode of contact information, including email, telephone, text, and voicemail, we will ask if it is acceptable to leave a non-specific message about participation in a health study. No study-related messages to the participant will ever mention HIV prevention or the nature of the research study. Additionally, all scripts for email, text message, and telephone contact with participants will be reviewed and approved by the IRB before being used for contact with participants.

7.3 Data Capture Methods

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

7.4 Types of Data

Data collected through interactions with the app:

Collection: Participants will use a mobile phone app to get information about HIV prevention and referrals to local services. As participants use the app, data about which they used are entered directly by the participant in the process of interacting with the study app. Data will be recorded as participants request certain app pages or functions. Each time the participant touches a button or navigation function in the app, that piece of data is stored in the administrative portal of the app. Data are stored with an alphanumeric ID that is unique to the participant, and is not stored with identifying information for the participants. The link between the alpha numeric string and the participant contact information is held by research staff at Blued.

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

Data collection through online surveys:

Collection: Data will be recorded as participants respond to questions in an online survey portal (Sojump) from a web browser, smartphone or tablet. Data will be identified in the system through a study ID.

Surveys are conducted using a secure (https://) webpage. The link between the participant and the participant contact information is held by research staff at Blued.

Management and storage: Sojump takes necessary technical measures to ensure the safety of data stored on Sojump's server, which include, but are not limited to: locked and secured server locations; enterprise firewall protection; RAID real time image preservation of data; regular data backup; and detailed data recovery mechanisms. The access level to the data stored by Sojump will be specified by Blued and Emory; only authorized users with individual password-protected accounts will be permitted to access the data. Without permission of Blued and Emory, Sojump is prohibited from changing the settings. Sojump is prohibited from intentionally or unintentionally disclosing data to any third party. The data confidentiality agreement with Sojump is valid until the Blued and Emory request that the data are destroyed. Data exported to Sojump for analysis will be stored on secure, encrypted servers at Blued in Beijing, China.

Data collected on Case Report Forms (CRFs)

Paper-based case report forms (CRFs) will be completed by site clinicians to capture PrEP-related data. CRFs will be the main data collection tool during PrEP visits. All CRFs will be completed by study clinicians or staff rather than the participants. These forms will be securely stored in participant study binders at the clinical study site, and entered electronically by staff into secure spreadsheets.

8.0 LABORATORY SPECIMENS

This study will adhere to standards of good clinical laboratory practice and local standard operating procedures for specimen management, including proper collection, processing, labeling, transport, and storage of specimens.

8.1 Laboratory Specimens

As described previously, the following types of specimens will be collected for laboratory testing throughout this study for those who initiate PrEP:

Blood Specimen: To be used for HIV testing, confirmatory HIV testing, syphilis rapid plasma reagin (RPR), serum creatinine, Hepatitis B Surface Antigen (HBsAg), dried blood spot (DBS) for measuring tenofovir diphosphate (TVF-DP) levels in plasma for PrEP adherence measure.

Dried Blood Spot: Participants who initiate PrEP will be asked at an interim visit for permission to collect blood to create a dried blood spot (DBS) for research purposes. Participants have consented to this procedure, from the consent form, "An additional blood sample may also be collected to determine how much of the PREP drug, Truvada, is present in your blood." An additional short questionnaire, contained from currently IRB-approved survey Section B: Sexual History and Section E: PrEP Intention, will be asked for the most recent information prior to blood collection. For this additional participation, we will provide an extra 300RMB ($45) incentive.

Urine Specimen: To be used for urethral chlamydia and gonorrhea testing

Rectal Swab Specimen: To be used for rectal chlamydia and gonorrhea testing

Pharyngeal Swab Specimen: To be used for pharyngeal chlamydia and gonorrhea testing

9.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

Research staff will establish a data and safety monitoring plan. The PIs and project coordinators in China and in Atlanta will monitor data collection throughout the study. They will ensure that interview protocols are followed, review all adverse event reports (if any), and ensure that confidentiality procedures are implemented. The larger project team will meet regularly via telephone to discuss progress toward study goals and objectives. At these meetings, research staff will prepare reports on data collection and any emerging issues or potential problems regarding data collection efforts. The following will be reported by site PIs in writing: all serious adverse events associated with the study procedures and/or any incidents or problems involving the conduct of the study staff or subject participation, including problems with the consent process.

9.1 Data Management, Analysis, and Quality Assurance Plan

Data sources for the intervention will include electronic surveys, case report forms tracking participant engagement in PrEP care, app paradata, and biological specimens. All data will be stored electronically, with 256-bit SSL encryption and under password protection. Further, role-based access will be implemented to limit access to sensitive data. Study staff will each have their own log-in to the electronic data platform, and will only have access to data needed to perform their study role. Back-up servers are used by all electronic study platforms. Emory will on a regular basis download all study data, and back-up these data on secure Emory servers. High levels of data quality will be assured through numerous data validation checks and post-check procedures, implemented throughout all study data collection areas. Additionally, the study data manager will create weekly reports on the progress of the study, including key areas of reporting such as accrual of participants by site, laboratory results and processing through the intervention system by site, and participant fall-off charts to facilitate retention in study processes. This weekly reporting is a procedure Drs. Siegler and Sullivan have employed to ensure high data quality and attainment of study benchmarks in terms of recruitment and retention. The data manager will also be tasked, in collaboration with study investigators, of ensuring data quality compliance that will allow for reporting consistent with Good Clinical Practice guidelines. Given that this is a pilot feasibility study, no DSMB will be used.

9.2 Specification of Safety Parameters

9.2.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a clinical research participant administered an investigational product or intervention. In this study, the study product or interventions include the HIV prevention interventions, including the study app and PrEP. Possible adverse events for study participants may include:

1. Participant report of loss of confidentiality through the app or its functions

2. Participant report of loss of confidentiality through delivery of prevention supplies or commodities

3. Participant report of access by others to protected health information through the app or study procedures

4. Participant report of disclosure of status as a research participant due to study-related reminders (from app, phone calls, emails, or text messages)

5. Participant report of discomfort or injury due to use of provided specimen collection materials

6. Disclosure of personal information about health, sexuality, or sexual practices that results in physical violence or threat of violence

7. Disclosure of personal information about health, sexuality, or sexual practices that results in adverse effects on employment

9.2.2 Serious Adverse Events

1. Suicidal behavior or intention, including but not limited to following learning the results of study-provided tests (e.g., HIV tests)

2. Any event that results in death, is life-threatening, results in persistent or significant disability/incapacity, or requires hospitalization or prolongation of existing hospitalization

9.2.3 Relationship to study intervention

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

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

- *Possibly Related*: An adverse event that follows a reasonable temporal sequence from exposure to the app, follows a known or expected consequence from use of the app, but that also could readily have been produced by a number of other factors.

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

9.2.4 Severity of Event

Severity will be classified using the following standards:

- *Mild:* Awareness of the issue, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Incident did not require counseling or a medical evaluation; concern on the part of the participant or physical symptoms were transient.

- *Moderate:* Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved within a few days (social harms) or by simple therapeutic measures (injury due to specimen collection); moderate experiences may cause some interference with usual activities for a few days.

- *Severe:* Events interrupt the participant's normal daily activities and require mental health assessment and treatment (social harms) or clinical treatment (injury due to specimen collection); they usually produce major disruptions in daily activities such as work, school, or family commitments.

9.3 Reporting Procedures

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

9.3.1 Serious Adverse Event Reporting

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

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

10.0 STATISTICAL/ANALYTIC CONSIDERATIONS

10.1 Primary Outcome

As called for by the MP3 mechanism, the primary analysis assesses the feasibility and acceptability of the pilot intervention as opposed to efficacy. This will be assessed based on a series of benchmarks. The intervention will be determined to be feasible if a minimum proportion of participants receive services for home HIV testing (benchmark ≥30%), and PrEP prescription (benchmark ≥15%). Benchmark targets were determined based on modeling in other contexts that indicates minimum levels of service uptake to substantially influence an HIV epidemic. The intervention will be considered acceptable if it reaches a systems usability scale rating benchmark score of 'good' (≥71 out of 100) and Likert component mean rating benchmark of 'acceptable' (≥3 out of 5).

10.2 Power to Detect Effects in Primary Outcome

This is a feasibility pilot and therefore is not powered to detect significant differences relative to the baseline period. The use of a non-powered pilot design is called for by the MP3 mechanism. A sample of 200 individuals per intervention city was selected based on what was determined to be achievable given budget and time constraints. It is also anticipated that this number will provide estimates of key parameters with sufficient precision. For instance, the prevalence of our binary benchmarks (home HIV

test orders, PrEP initiation) would be estimable with the following 95% confidence intervals half-width at specified prevalences: 20% ± 4%; 30% ± 5%; 50% ± 5%.

Led by the study statistician, additional analyses will be conducted to assess (1) preliminary efficacy with endpoints measuring change from baseline to intervention periods in HIV testing, condom use, and PrEP use, (2) theoretical efficacy with endpoints in the PrEP cascade and UTAUT2 constructs, and (3) process outcomes with endpoints of new HIV testers, new condom users, and app use metrics. These assessment will leverage the pilot's interrupted time series design and inform future clinical trial design.

10.3 Preliminary Efficacy Assessment

Preliminary efficacy assessments will describe differences in outcomes for the intervention, compared to the baseline period, for the median number of HIV tests and the proportion reporting all anal sex acts as condom-protected. A generalized estimating equations (GEE) repeated measures analysis will be conducted for the binary outcome of HIV testing (test/not testing). The GEE model will contain the seven time periods with primary comparisons of 0-month (first baseline) measurement to 6-month (end wash-out baseline period measurement and to 12-month (end first intervention period) measurement. Time will be considered as a fixed effect to compare proportion tested across intervals, with a random intercept for individuals. A similar GEE model will be conducted for the condom outcome (always/not always condom use). Logistic regression models will be fitted to understand PrEP cascade progressions, with the main analysis being any forward progress (yes/no) in the overall cascade between 0-month and 15-month measurements. These analyses will consider variables of progression in the PrEP cascade. Time at which cascade progress was made (e.g. 3 months) will be entered as a co-variate. A multifaceted approach to address missingness for our outcomes will be used. Primary analyses will treat values as missing at random. Sensitivity analyses will re-analyze data using both last-value-carried-forward and multiple imputation methods.

10.4 Theoretical Assessments

Theoretical assessments will include descriptive and regression models to explore PrEP cascade level and constructs of the UTAUT2. We will add UTAUT2 constructs as independent variables to the above specified GEE models. Analyzing constructs of the UTAUT2 model will allow for estimation of structural equation modeling coefficients to inform assessment of required sample size to determine theoretical components of an eventual SEM in a future RCT of the intervention (Aim 4). Analysis will also inform our understanding of whether the theoretical model is appropriate for capturing pathways of the intervention effects. Process outcomes will be reported with descriptive statistics.

11.0 HUMAN SUBJECTS CONSIDERATIONS

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

11.1 Ethical Review

This protocol will be reviewed and approved by the Emory University Institutional Review Board. The protocol will also be reviewed by the Institutional Review Board of the Danlan Beijing Media Limited in China. Revised protocols will be re-submitted to Emory's and Danlan' IRBs for final approval.

The protocol and the informed consent forms – and any subsequent modifications will be reviewed and approved by the protocol team with respect to scientific content and compliance with applicable research and human subjects regulations. The protocol, consent forms, participant education and recruitment materials, and other requested documents – and any subsequent modifications – will also be reviewed and approved by the IRB responsible for oversight of research conducted as part of this study.

Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRBs before the changes are implemented in the study.

11.2 Informed Consent

For men participating in the pilot study, participants will be asked to sign an electronic consent. Contact information for study staff will be available for participants to contact if they have any questions. The electronic consent covers all study procedures. All participants may choose to print a paper copy of the informed consent form.

An additional informed consent for participants who initiate PrEP will be written, and will be obtained before any PrEP medication is distributed. Potential participants will be given a copy of the informed consent form, and a study staff member will review the form with the participant and answer any questions the participant may have. The form will include information on the risks and benefits of FTC/TDF, and participants will be reminded that this intervention is voluntary, and if they agree to use FTC/TDF, they can withdraw from participation in this intervention at any time. Participants' signing of the informed consent form will be witnessed by a study staff member, who will also sign the form. Participants will be given a copy of the signed consent form.

All consent forms will be translated to ensure and available to participants in Mandarin Chinese.

11.3 Risks to Participation

11.3.1 Risks to Study Participation

Following are anticipated risks to participation, and procedures to reduce risk:

- *Persons may learn they have HIV or an STI, and this may be upsetting.* To minimize this risk, we will have counselors and other study staff who have been trained in HIV counseling and testing available to assist participants and provide them referrals. Referrals for STI treatment and HIV treatment and care will be made to LGBT-friendly providers.

- *Persons may be uncomfortable with some survey questions.* To minimize this risk, we will offer participants the option in the survey to not answer any question that makes them uncomfortable. Participants who find the surveys to be generally uncomfortable can choose to discontinue participation in the study.

- *Persons may have their study information compromised.* We describe procedures for data security in section 8 of this document. All study staff will sign a confidentiality agreement.

- *Persons may experience stigmatization or discrimination.* Participation in this study may lead to the participant being perceived as MSM, as living with HIV, or at risk of infection with HIV. To

minimize these risks, study-related materials and advertising will not mention the study's HIV and MSM-related goals, and inclusion/exclusion criteria and all information collected from participants – as well as their participation in the study – will be completely confidential. Study staff will not disclose participation or any participant data to non-study staff.

11.3.2 Additional Risks for Participants on PrEP

While the purpose of this study is to design and test a mobile application for MSM in China, this study will have study clinicians prescribing PrEP in-person or remotely in accordance with FTC/TDF (emtricitabine/tenofovir disoproxil fumarate) label indication. The prescription of PrEP in the study will also follow guidance from the US Public Health Service and US Centers for Disease Control and Prevention. However, persons may have additional risks and side-effects from taking FTC/TDF.

- Antiretroviral resistance can occur if participant is HIV-infected. To minimize this risk, HIV testing will occur prior to initiation of FTC/TDF and at every follow-up PrEP visit thereafter.

- Persons may have discomfort, bruising, or a local infection at the site of venipuncture. This is a typical risk of having blood drawn in any setting. The study clinicians will have experience in phlebotomy to minimize this risk.

- Gastrointestinal side-effects, including nausea, vomiting, diarrhea, and weight loss are possible on FTC/TDF.

- The use of FTC/TDF may less commonly cause severe side effects. More serious effects may include allergic reactions (rash; itching; difficulty breathing; swelling of the face, lips, throat, or tongue); bone pain; mood changes; muscle pain or weakness; severe dizziness; symptoms of kidney problems (e.g., increased or decreased urination, increased thirst) and symptoms of liver problems (e.g., yellowing of the skin or eyes; dark urine; pale stools; persistent loss of appetite). To avoid renal toxicity, creatinine clearance levels will be assessed prior to initiation of FTC/TDF, and every three months while the participant is on FTC/TDF.

- To avoid complications with hepatitis B, participants will be screened for hepatitis B prior to initiation; those who are hepatitis B surface antigen (HBsAG) negative and hepatitis B surface antibody (HBsAB) negative will be referred for hepatitis B immunization.

11.4 Benefits to Subject or Future Benefits

Possible individual benefits of participation include access to at-home HIV testing free of charge, referral to care for those who test positive for HIV, and access to PrEP for HIV prevention. Those who uptake PrEP will accrue protective benefits of PrEP and of regular STI testing and referrals to care as needed. There is also the potential benefit of increased knowledge about HIV, STIs, and PrEP for all participants. The broader community may benefit in the future in the information learned from the results of this study improve HIV/STI prevention services for MSM in China.

11.5 Compensation

Participants will be reimbursed for their time and effort in this study. For the 400 participants who receive the intervention, a ¥100 (for reference $15) reimbursement for each of the six surveys completed (0, 3,

6, 9, 12, and 15 months) will be provided. Additional ¥400 ($60) will be provided for each participant who completes all six surveys for a total of ¥1000 ($160).

11.6 Participant Privacy and Confidentiality

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

Study Procedures: We will collect multiple means of contact with participants at enrollment. For each means of permitted contact, we will leave a generic message about participation in a health research survey at that phone, email, cell phone, etc. Standardized scripts for phone and email contact will be used. Participants are offered the option to receive testing results by email or text message; for those who so choose, the results messages will not identify the type of testing, the nature of the study, or the specific test names.

Training: All study staff will have training on participant privacy and confidentiality. Staff will sign a confidentiality agreement before having access to any confidential data.

Data Management Practices: As previously described, personally identifying information will be stored in a separate dataset from case report form data, test results, survey answers, and interview scripts. Access to the identifying information will be restricted so that persons who are responsible for scheduling or participant follow-up can view contact information, but no other study data. Similarly, persons who can view study data will only be able to see the study data and the (non-identifying) study ID.

Documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the participant except as necessary for monitoring by the IRBs, the study sponsor, and the Office of Human Research Protections (OHRP).

12.0 ADMINISTRATIVE PROCEDURES

12.1 Quality Assurance

Monitoring visits will be made by the principal investigator during the study to ensure that all aspects of the current, approved protocol/amendment(s) are followed. The study may also be subject to a quality assurance audit by the sponsor or its designees, as well as inspection by appropriate regulatory authorities.

Site clinicians will follow CDC recommendations for PrEP guidelines.

12.2 Regulatory Requirements

Clinical trial best practice will be followed in accordance with NIH guidance, including early trial registration at clinicaltrials.gov, investigators and relevant staff completing appropriate training in Good Clinical Practice (GCP), and adherence to guidance regarding timely dissemination of clinical trial results. We will report any protocol violations to IRB and the DSMB within three days of the principal investigator becoming aware of the violation.

13.0 REFERENCES

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Emory University
Consent to be a Research Subject

Title: Integrating a Combination HIV Prevention Intervention into a Widely-Used Geosocial App for Chinese MSM

Principal Investigator: Aaron Siegler, PhD, MHS; Department of Behavioral Sciences and Health Education, Emory University

Funding Source: National Institutes of Health

Introduction
You are being asked to be in a public health research study. This study is being done by Dr. Mi Guodong at Blued and Dr. Aaron Siegler from Emory University's Rollins School of Public Health. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study. You can skip any questions that you do not wish to answer.** The decision to join or not join the research study will not cause you to lose any medical benefits.

Before making your decision:
- Please carefully read this form or have it read to you
- Please ask questions about anything that is not clear

You can save a copy of this consent form to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form, you will not give up any legal rights.

What is the purpose of this study?
The purpose of this study is to test a smartphone app designed to promote healthy behaviors in men who have sex with men. This will be done through information, health messaging, periodic screenings, and prevention resources. We will ask participants to tell us about their thoughts on the app and its use. We will also ask participants about their sexual health and history in order to determine whether using the app has an effect on sexual health outcomes.

What will I be asked to do?
If you choose to be in this study, we will ask you to participate in a series of activities over the course of 15 months. These activities will include filling out surveys about your sexual health and behavior, and interacting with a smartphone app Blued+. The study activities are described individually below:

Six 45-minute surveys

If you choose to be in this study, we will ask you to complete a baseline survey through the Blued app on your own electronic device (i.e. smartphone) to establish some basic facts about you for our study. These facts include your sexual history, medical history, behaviors, and attitudes. We will also ask you to complete a series of follow-up surveys for our study. These will be delivered to you through the Blued app every three months (i.e. 3, 6, 9, and 12 months) after today. These follow-up surveys will repeat many of the questions from the baseline survey to determine whether your behaviors, beliefs, and attitudes have changed.

App Interactions

Three months from today, you will also be asked to interact with a version of the Blued app with additional health resources. You will receive a version of the Blued app with health education, health messaging, and

health quizzes delivered through the app. You will be able to order health HIV prevention materials such as condoms, lubricants, and HIV tests through the App. All HIV prevention materials will be provided at no cost to you. You will be expected to interact with the app regularly. As you use the app, it will collect data about that use.

Pre-Exposure Prophylaxis Sub-study

You will be asked to participate in a sub-study of Blued. This sub-study offers pre-exposure prophylaxis (PrEP), also known as Truvada or FTC/TDF. PrEP is a type of antiretroviral tablet that is taken to lower the rate of new HIV infections when used with other HIV prevention tools. Truvada has been shown to be >99% effective in preventing HIV in MSM who take the medication as directed. Used this way, PrEP is not meant to treat any illnesses that you may have, but rather to help keep you from getting HIV. You are not required to take PrEP if you join this larger Blued study. However, if you are interested, we can help you to schedule an online or in-person interview with the study doctor for PrEP initiation, and if you meet the requirements, we will help you schedule a visit with a study doctor or nurse who prescribes PrEP. They will use your blood sample to check if you are eligible. This will make sure your kidneys function by testing your creatinine levels in your blood. You will also be tested for HIV. You will have additional regular study visits if you choose to start PrEP. All participants in this study will have the option of receiving PrEP free of charge. There will be no cost to you for these services.

The purpose of this sub-study is to study the attitudes and behaviors of local men who are eligible to start taking PrEP, as offered as part of an HIV prevention package through the Blued app. If you join this sub-study today, you will be told about PrEP. If you are eligible, you will be scheduling online or in-person PrEP appointment through Blued App and the study doctor will give you a prescription for Truvada (FTC/TDF). We will then provide you with a prescription and mail PrEP drug to your address .

To ensure your safety, you will be asked to come back to the test site every 3 months after starting PrEP for HIV testing, STI testing, and other testing. This is the standard for men who take PrEP. This means that you may expect to come to the site for about 4 extra visits over the course of the year. During your visits, you will meet with the study staff and/or study doctor who will talk to you about how you have been feeling since starting the medication. The study doctor will review your medical history and we will collect some blood from you. Each blood draw will be about 15mls (1 tablespoon full). The blood sample will be used to assess your HIV status and measure creatinine levels to ensure your kidneys are healthy. An additional blood sample may also be collected to determine how much of the PREP drug, Truvada, is present in your blood. During your regular study surveys, you will be asked questions about your experiences taking PrEP. This may also involve a more detailed in person interview with one of the study doctors.

In order for the doctor to be able to renew your prescription for PrEP, it is important to come to your visits every 3 months. The information about your health learned at these visits will be used by the doctor to renew your prescription. At the end of the 12-month period of Blued, the study will stop providing prescriptions for PrEP and will stop PrEP-related testing.

There may be minor discomfort from blood draws. The blood draws may cause bruising. There is a slight risk of an infection where the blood was drawn.

There may be side effects from the study drug. There is a chance that you could have nausea, vomiting, and diarrhea when taking the drug. You may also have some weight loss. The use of the drug may less commonly cause severe side effects. More serious effects may include allergic reactions (rash; itching; difficulty breathing; swelling of your face, lips, throat, or tongue). They may also include bone pain; mood changes; muscle pain or weakness; severe dizziness; symptoms of kidney problems (e.g., increased or decreased urination, increased thirst) and symptoms of liver problems (e.g., yellowing of the skin or eyes; dark urine; pale stools; persistent loss of appetite).

Please call the study staff if you are having any concerns. If needed, we will have the study doctor call you back. If you are having a medical emergency, please seek immediate medical attention.

If you become HIV infected while taking Truvada, there is a chance that the HIV virus could develop resistance to Truvada. The best way to avoid this is to take your medication strictly following the prescription.

Please keep the study drug out of the reach of children or anyone else who may not be able to read or understand the label. Do not let anyone else take the study drug besides you.

There will be no additional compensation for participating in this sub-study.

There will be no costs to you for participating in this study, other than basic expenses like transportation.

This section of consent is designed to tell you everything you need to think about before you decide if you want to take PrEP or not. **It is entirely your choice. If you begin taking PrEP now, you can change your mind later on and stop taking it.** Either way, you will remain enrolled in the larger Blued Study.

Risks and Discomforts

There are minor risks associated with this study. Some of the questions in the survey are personal, and may make you uncomfortable. We hope you will answer all questions to the best of your ability. You can choose not to answer any question that makes you uncomfortable. We will keep information about your HIV and STI testing, and your responses to the survey questions. Although we will take steps to reduce the chance, there is a small chance that someone other than study staff might see your study information. More information about how we will protect your confidentiality is below.

There is a possibility that someone may see the mobile app on your device. Because this app provides information about STIs, HIV, and sexuality, there is a risk of breach of privacy. To prevent this, we recommend closing out of the app and/or locking your mobile phone when you are not interacting with the app.

New Information

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Benefits

This study is not designed to benefit you directly. However, you may benefit from participating because the mobile app will provide information and HIV prevention resources.

This study may also indirectly benefit you because we may learn about how to promote prevention services that can help reduce the health burden of HIV and STIs among men who have sex with men.

Compensation

You will get ¥100 ($15) for each of the six study survey you complete (at 0, 3, 6, 9, 12, and 15 months). If you do not finish the study, you will be paid for the surveys you have completed. If you complete all six study surveys, you will receive an extra ¥400 ($60), for a total of ¥ 1000 ($160).

What are my other options?

If you decide not to enter this study, there is care available to you outside of this research. You should discuss this with the researchers if you have concerns or want to know about other options.

How will you protect my private information that you collect in this study?

All information about you obtained from this research study will be kept as confidential as possible. Your personal information may be disclosed if required by law. Any publication of this study's results will not use your name or identify you personally in any way. The study staff may use your personal information to verify that you are not in any other research studies.

Certain offices and people other than the researchers may look at study records. Government agencies and Emory University employees overseeing proper study conduct may look at your study records. These offices include the Office for Human Research Protections, the Emory Institutional Review Board, the Institutional Review Board of the National Center for HIV/STD Control and Prevention (NCAIDS), and the Emory Office of Compliance. Study funders may also look at your study records. Emory will keep any research records we create private to the extent we are required to do so by law. A study number rather than your name will be used on study records wherever possible. Your name and other facts that might point to you will not appear when we present this study or publish its results.

Withdrawal from the Study

You have the right to leave this study at any time without penalty. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done. The researchers also have the right to stop your participation in this study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

Contact Information

Contact the China study coordinator: Yu Fei at +86 18980952400 or yufei@blued.com

- if you have any questions about this study or your part in it,
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at +1 404-712-0720 or irb@emory.edu or the IRB of NCAIDS, Ms. Liu Mengchi at mengchi@chinaaids.cn:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the Emory University IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75.

Consent

Being in this study is entirely your choice. You have the right to refuse to participate or to stop at any time. Please print a copy of this form for your records.

If you agree to the above information and would like to be in the study, please sign your name using mouse or touch pad, and then type in your name below. *

Signature of

I understand that checking this box constitutes a legal signature confirming that I have read the consent form, and agree to participate in the Blued study. *

- ○ Legally sign document
- ○ Do NOT legally sign document