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TITLE PAGE

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A community-engaged mHealth intervention to increase uptake of HIV Pre-Exposure Prophylaxis (PrEP) among gay, bisexual and other men who have sex with men in China: Study protocol for a pilot randomized controlled trial

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ABSTRACT

Introduction: The large number of key populations in China who would benefit from HIV pre-exposure prophylaxis (PrEP) in the context of limited health system capacity and public awareness will pose challenges for timely PrEP scale-up, suggesting an urgent need for innovative and accessible interventions. This study aims to develop and pilot test a theory-informed, tailored mobile phone intervention that was co-developed by young gay men, HIV clinicians and public health researchers to increase engagement in PrEP education and initiation among Chinese gay, bisexual, and other men who have sex with men (GBMSM), who bear a disproportionate burden of HIV infections and remain underserved in the healthcare system.

Methods and analysis: This two-phase study includes a formative assessment using in-depth interviews (N=31) and a 12-week experimental pilot study using a two-arm randomized controlled trial design (N=70). The primary intervention is delivered through a WeChat-based mini-app (a program built into a Chinese multi-purpose social media application) developed by young GBMSM from a 2019 crowdsourcing hackathon. Using mixed-methods, we will further investigate the specific needs and concerns among GBMSM in terms of using PrEP as an HIV

prevention strategy, how their concerns and PrEP use behaviors may change with exposure to the mini-app intervention during the study period, and how we can further refine this intervention tool to better meet GBMSM's needs for broader implementation.

Ethics and dissemination: This study and its protocols have been reviewed and approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill, USA (19-3481), the Guangdong Provincial Dermatology Hospital, China (2020031), and the Guangzhou Eighth People's Hospital, China (202022155). Study staff will work with local GBMSM community-based organizations to disseminate the study results to participants and the community via social media, workshops, and journal publications.

Trial Registration: The study was registered on clinicaltrials.gov (NCT04426656) on June 11, 2020. Prospectively registered.

Keywords: HIV, pre-exposure prophylaxis, mHealth, intervention, men who have sex with men, China, mini-app

Article Summary

1. The intervention app prototype was co-created by the GBMSM community, HIV clinicians and public health researchers through a gay-friendly doctor finder hackathon - a crowdsourcing strategy that solicits innovative public health solutions directly from the end-user community, increasing the intervention's acceptability and potential impact among target communities.
2. The intervention content development was guided by the Information, Motivation, and Behavioral Skills Model, a theoretical model of behavioral change that has been widely applied in HIV-related behavioral intervention studies among different populations including Chinese GBMSM.
3. Mobile health (mHealth) interventions for HIV prevention and sexual health promotion are feasible and highly acceptable among Chinese GBMSM due to their privacy, portability, and convenience, facing the broad spread of HIV- and gay-related stigma in Chinese society.
4. The study design follows the best practice of intervention development that includes a formative assessment of unmet needs, co-creation with the community, pilot testing for preliminary evidence of efficacy, providing preliminary data for a future larger-scale intervention study.
5. The intervention allows participants to make online PrEP appointments at the only local HIV hospital in the study city, and an initial in-person clinical visit is still required for PrEP prescription. It is also a timely response to China's recent approval of TDF-FTC as PrEP in 2020, which we believe could facilitate a rapid scale-up of PrEP among populations at risk of HIV infection in China.

INTRODUCTION

HIV prevalence among gay, bisexual, and other men who have sex with men (GBMSM) in China has steadily increased over the past five years (1,2). In Guangzhou, a major economic center in Southern China, the HIV prevalence among sexually active GBMSM increased from 3.9% in 2009 (3) to 11% in 2017 (4). Individual and contextual risk factors associated with HIV acquisition among Chinese GBMSM include condomless sex, high rates of ulcerative sexually transmitted infections (e.g. syphilis), use of recreational drugs during sex, gay entertainment venues (e.g., public bathhouse), and social and sexual networking mobile phone applications (5–11). Taken together, these risk factors suggest that Chinese GBMSM could benefit from additional HIV prevention strategies such as pre-exposure prophylaxis (PrEP).

However, the overall awareness of PrEP among Chinese GBMSM remains relatively low - only 22.4% of a national survey sample of GBMSM in 2017 had ever heard of PrEP (12). By July 2021, there was an estimated number of 6000-6500 PrEP users reported from official demonstration projects in this country (13). Cross-sectional surveys (12,14–22) and PrEP clinical trials (23–25) have reported perceived barriers to PrEP uptake among Chinese GBMSM including concerns about side effects, financial cost, and low HIV risk perception. Yet little is known about multi-level barriers to PrEP uptake and maintenance in China. Further, there is widespread HIV- and gay-related stigma and discrimination in clinical settings (26–28) that may inhibit the effective delivery of PrEP drugs and related services for GBMSM (29).

The China National Medical Products Administration approved Tenofovir-Emtricitabine (TDF-FTC) as HIV PrEP in China on August 11, 2020. However, the aforementioned gaps highlight the need for innovative, culturally appropriate, and GBMSM-friendly tools that prepare GBMSM for PrEP uptake, to pave the way for a rapid scale-up. Facing the broad spread of HIV- and gay-related stigma in Chinese society, mobile health (mHealth) interventions for HIV prevention and sexual health promotion are feasible and highly acceptable among Chinese GBMSM due to their privacy, portability, and convenience (30–32). Health hackathons as a crowdsourcing approach are an effective and convenient way to mobilize GBMSM communities in generating innovative mHealth solutions to meet their own health needs (39), which could further potentially contribute to reductions in internalized stigma and an increase in community resilience among sexual minority populations (40,41).

Globally, limited data exist on the efficacy of app-based interventions aimed to increase PrEP uptake among GBMSM. Among the few published mHealth PrEP intervention efficacy studies, text messaging has been effective in improving PrEP adherence in GBMSM via reducing missed doses (33,34). More mHealth PrEP uptake intervention studies are underway, however, all are in high-income countries (35–38). To date, little is known about the optimal design and efficacy of using mHealth-enabled interventions for PrEP promotion in Chinese populations, especially among GBMSM.

Aims and objectives

This study focuses on developing and testing a tailored mobile app-based intervention built on our previous work from a gay-friendly doctor finder hackathon in China (42), aiming to increase engagement in PrEP education and initiation, and generate hypotheses that explain potential behavioral pathways to PrEP uptake among Chinese GBMSM. The study site is Guangzhou, a major economic center of southern China. To this end, the study has two phases: Phase 1 collects formative data using in-depth interviews to assess unmet needs in HIV prevention (PrEP in particular) and sexual health among HIV-negative GBMSM, and test and refine the usability of the mini-app. Phase 2 will implement a two-arm RCT to access the feasibility and preliminary evidence of the efficacy of the refined mini-app in increasing intention to use PrEP and PrEP initiation among HIV-negative GBMSM. Specific aims include:

Aim 1: Generate hypotheses around behavioral pathways explaining PrEP uptake among Chinese GBMSM by analyzing qualitative data from in-depth interviews of the formative assessment (Phase 1, n=31) and the process evaluation interviews during the RCT (Phase 2, n=15-20).

Aim 2: Assess the feasibility and preliminary efficacy evidence of a mobile phone-based PrEP education intervention tool (the mini-app) compared to the standard of HIV prevention care in increasing individual intentions to use PrEP and actual PrEP initiation rate through a two-arm pilot RCT (Phase 2) with 70 HIV-negative GBMSM (18 years old and above) in Guangzhou, China.

METHODS AND ANALYSIS

Theoretical foundation for intervention

Figure 1 presents the study's conceptual model. The intervention content development is informed by the Information, Motivation and Behavioral Skills Model (the IMB model). The IMB model proposes a mediational framework that hypothesizes that the performance of many health-related behaviors is determined by three core constructs: *information*, *motivation,* and *behavioral skills* (43). With years of application in HIV research, the IMB model has been widely applied in intervention studies and adapted to promote specific HIV-related behaviors, including PrEP care-related behaviors (44–46). Among Chinese GBMSM, the IMB model was also found useful in explaining HIV preventive behavior such as condom use (47). We also use the Transtheoretical Model of Behavioral Change (TTM) to inform the measurement of the several stages of behavioral change culminating in PrEP initiation. The TTM outlines stages of readiness to make a behavioral change, including pre-contemplation, contemplation, preparation, action, and maintenance of the change (48). Given variable awareness about PrEP and the wide range of age of the target population, measuring the stages of change toward PrEP initiation will help us better tailor and refine the intervention.

Figure 1 *The conceptual model of the WeChat mini-app PrEP intervention*

Patient and Public Involvement: Development of the Intervention Tool – PrEP Education WeChat Mini-app

The intervention is delivered via a WeChat-based mini-app (a program built within an existing commercial application) that was developed by a team of young GBMSM from a GBMSM-friendly Doctor Finder Hackathon contest (42). This hackathon contest was part of a series of crowdsourcing events that aimed to engage the GBMSM community in generating public health innovations in HIV and sexual health promotion in China. From February 2018 to March 2018, the Shenzhen University College of Mass Communication, the non-profit organization Social Entrepreneurship to Spur Health (SESH), and Blued (the largest gay social networking app in China) held a crowdsourcing contest for designing concepts of a mobile phone-based, GBMSM-friendly doctor mobile app. In July 2018, four focus group discussions with 38 GBMSM in Guangzhou and Shenzhen were subsequently conducted to solicit participants' feedback on refining the app design (51).

From December 2018-April 2019, UNC Project China with support from SESH and Blued hosted a GBMSM-friendly Doctor Finder Hackathon in Guangzhou, during which the participants were asked to develop a mobile phone-based doctor finder prototype based on the work from previous events. A total of 38 participants grouped into eight teams attended the final hackathon contest and developed eight prototypes after a 72-hour hacking. Four prototypes adopted the mode of a mini-app embedded within WeChat, and three prototypes were designed as stand-alone apps, and one was designed as a tool that can be adjusted to multiple platforms. One of the WeChat mini-app prototypes was adapted for use in the current study. WeChat (Android and iOS) is a social platform in China with over one billion active users (52) that has been widely used for public health education by Chinese health administrations and private

organizations (53). The WeChat app allows developers to build new app programs (i.e. the mini-app) within the platform that are accessible without additional download or installation.

Before testing and evaluating the mini-app in the current study, we invited a group of key community stakeholders including gay men, sex educators, and local HIV-related CBO workers to test the mini-app prototype and provide valuable feedback in user-interface design and choice of educational materials. The main features of the version of the interventional mini-app for the current study include: (1) the Mini-classroom, educational materials which cover topics of HIV and STI, PrEP and PEP, and mental health, designed to change participant's information, motivation, and behavioral skills to initiate PrEP; (2) an at-home HIV/syphilis dual testing kit ordering system; (3) chat-based online counseling, and (4) a user profile center (their account in the mini-ap is automatically linked to their WeChat account with the user's permission). The overall structure of the mini-app is illustrated in Figure 2, and a detailed description of the main features is presented in the Supplemental File.

Figure 2 *Wireframe of the mini-app PrEP intervention*

Phase 1: Formative Research—Needs Assessment and Mini-app Testing

Study design

In Phase 1 we conduct in-depth interviews among Chinese GBMSM to understand the key barriers and facilitators of using PrEP. We also assess participants' perceived usability of the intervention mini-app during the interview. Interviews are conducted one-on-one via

videoconference (audio-recorded with participants' permission) and last 60-90 minutes. We use a semi-structured interview guide with tailored questions for participants with and without PrEP experience. Interview topics cover knowledge, attitudes, and willingness to use PrEP and/or PrEP use history, and past pathways, barriers, and facilitators to HIV testing and PrEP services. During the interview, participants are introduced to the mini-app design and features, use the mini-app for 5 minutes, complete a 10-item app usability scale, and discuss the app's design, contents, and ease of use. Following the interview, each participant completes a brief demographic survey via Wenjuanxing, an online survey tool in China. All interviews will be transcribed in Chinese and analyzed using the online qualitative analysis platform, Dedoose. (49) A thematic analysis-based approach (50) will be applied for identifying, analyzing, and reporting patterns within the data. This will be conducted in Chinese with the translation of exemplary content for English-language publications.

Participants

To represent the variety of experience GBMSM has had with PrEP, we will conduct in-depth interviews with 31 Chinese GBMSM at different stages of the PrEP care continuum, including approximately 20 PrEP naïve individuals, five prior or intermittent PrEP users, and five current PrEP users. This sample size is generally considered sufficient for thematic analysis to reach information saturation among a relatively homogenous group. While the mini-app is primarily designed for PrEP-naïve GBMSM, including the perspectives of past and current PrEP users is intended to gain feedback on the intervention design and content based on experiences across the

stages of change in PrEP adoption. Participants will be recruited through research advertising on Chinese social media and referral by local GBMSM-related organizations.

Eligibility criteria for Phase 1 are: Chinese citizen and current resident, assigned male sex at birth, age 18 and above, any lifetime anal sex with another man, and willingness to sign (or e-sign) informed consent. Exclusion criteria include self-reported HIV-positive status or reporting or demonstrating mental health issues which may compromise participant safety, including memory loss, cognitive impairment, intellectual disability, or communication disorders.

Mini-app Refinement

Before starting Phase 2, we will refine the mini-app based on participants' feedback on the app design from Phase 1 formative assessment. Potential adjustments to the mini-app may be feasible in changing content, and graphic and text appearance, but not functionality or structure of the app. All requests regarding functionality and app structure will be recorded and considered for future iterations of the app.

Phase 2: Pilot Randomized Controlled Trial

Study Design

Phase 2 will evaluate the feasibility and preliminary evidence of the efficacy of the mini-app in increasing intention to use PrEP and PrEP uptake through a two-arm pilot RCT comparing the

mini-app to the standard of HIV prevention care (Figure 3). The study is estimated to last up to 12 weeks, where the first eight weeks is the active intervention period and the last 4 weeks is post-intervention observation.

Figure 3 *Phase 2 study design, a two-arm RCT*

Note: Participants can purchase PrEP medicines (TDF-FTC) from the study clinic. Participants pay for the medicine out-of-pocket and are reimbursed 50% of the cost at each monthly follow-up visit.

Participants

A convenience sample will be recruited in Guangzhou, China from a post-exposure prophylaxis (PEP) clinic, and GBMSM/HIV-related community-based organizations (CBOs). The generally recommended sample size of pilot trials ranges from 24 to 100 (54,55). In this pilot test, we plan to enroll 70 participants to assess preliminary evidence of efficacy and feasibility for a future main trial. Those interested in the study will complete a verbal eligibility screening (Textbox 1). Those screened eligible will be scheduled for an initial in-person clinic visit or a virtual enrollment via videoconferencing. During this visit, they will complete informed consent and a baseline survey, and be randomized to one of two study arms.

Textbox 1. PrEP mini-app Phase 2 Pilot RCT inclusion and exclusion criteria

Inclusion criteria: Individuals must self-report:

- Having a smartphone with WeChat installed.

- Assigned male sex at birth, HIV-negative, age 18 and above, ever having had anal sex with another man, currently residing in Guangzhou, identifying as a Chinese citizen, able to sign written informed consent and participate in the study procedures as required. AND
- At least one characteristic associated with the risk of HIV infection in the previous 6 months:
    - Unprotected (condomless) receptive anal intercourse with a male partner(s)
    - More than two male partners (regardless of condom use and HIV serostatus)
    - Reported STI, such as syphilis, HSV-2, gonorrhea, chlamydia, chancroid, or lymphogranuloma venereum.
    - Reported use of post-exposure prophylaxis (PEP)
    - Have a sexual partner living with HIV

Exclusion Criteria:

- People living with HIV
- Currently taking oral PrEP based on self-report before enrollment
- Symptoms of acute HIV infection in the previous 30 days (e.g. fever, flu-like symptoms)
- Suspected exposure to HIV in the previous 72 hours
- Contraindications for taking oral PrEP
- Personal diagnosis or family history of hemophilia or Chronic Hepatitis B (self-report)
- Participating in another research intervention study related to HIV or PrEP

- Having serious chronic disease, including metabolic diseases (such as diabetes), neurological, or psychiatric disorders
- Mental health issues may compromise adherence or safety, including memory loss, cognitive impairment, intellectual disability, or communication disorders.

Randomization

We will conduct a permuted block randomization that assigns the 70 participants to either the mini-app arm or the control arm in a 2:1 ratio. Randomization sequence will be created using Microsoft Excel (Microsoft, Redmond, WA, USA) with block sizes of three and six. The 2:1 allocation will be used to ensure the capture of the range of users' reactions to the mini-app and its content. The randomization process will be conducted by a research assistant after the full consent process.

Study arms

Intervention Condition: The PrEP education mini-app

The PrEP education mini-app (Figure 4 presents the screenshots) serves as the primary participant-facing component of the intervention. Usage of the mini-app will be at participants' discretion or preference. Weekly reminders that encourage participants to use the mini-app will be sent out through WeChat messages. At this stage of development, the mini-app will not be able to track individual user information or activity. Self-reported app usage will be assessed in

bi-weekly follow-up surveys and in-depth interviews at the 4th and 8th weeks. After Week 8, participants in the intervention arm will no longer receive reminder messages but may continue using the mini-app throughout the whole study period – up to 12 weeks from the time of enrollment, or continue using to the end of their first two months of PrEP use.

Figure 4 *Screenshot of the mini-app from left to right: (1) Homepage 1: at-home test kit, (2) Homepage 2: PrEP appointment, (3) the Mini-classroom, (4) User profile center*

Standard of HIV prevention care

Participants in both study arms will receive standard HIV prevention care during the initial and final study visits, including printed or electronic HIV prevention materials about PrEP and HIV/STI testing, referrals to local prevention services, and a description of the standard procedure to access PrEP through the study clinic.

PrEP Initiation

Participants in both arms can choose to initiate PrEP through the research study at any time point from enrollment through the end of Week 8. Participants who decide to start PrEP after Week 8 will still be able to receive standard PrEP care at the study clinic, but they will not be eligible to receive complimentary physical examinations that are covered by this research project (Please see details in *Incentives*). Participants can contact the study team via phone call, text messages, or via the chat function in the mini-app (intervention arm only) to communicate their interest in PrEP initiation. Interested participants will be referred to the Department of Infectious Diseases

at the study hospital to consult a clinician regarding HIV risks and PrEP eligibility. As per protocols in the study hospital, participants starting PrEP will undergo standard of care comprehensive physical examinations including routine blood and urine examinations, hepatic and renal function tests, and HIV/syphilis/HBV/HCV tests.

During this clinical encounter, participants who are confirmed to be HIV-negative and without any relative contraindications for PrEP initiation will be prescribed a 30-day supply of TDF-FTC. Once starting PrEP, participants will be required to complete two monthly clinic visits during their first two months of PrEP use to monitor their medication adherence, HIV/STI tests, and overall physical health status, and receive another 30-day supply of TDF-FTC. Participants may follow the daily oral regimen or event-driven regimen based on their discretion, and they will be given education on the two PrEP regimens during their initial PrEP counseling and through the Mini-classroom in the mini-app. PrEP prescriptions may be filled at the study clinic's pharmacy or a private pharmacy.

Study assessments and evaluation

Behavioral assessments

Baseline assessments will be conducted at enrollment, with follow-up surveys conducted at weeks 4, 8 (end of active intervention), and 12 (post-intervention) via self-administrated Web-based surveys on Wenjuanxing. Participants will be asked to complete follow-up surveys within one week; reminders through WeChat message will be sent on days 7 and 10 of the survey

window, as needed. The time points of assessment are presented in Table 1. The full list of study measures is included in the Supplemental File. To track app use activities, two questions will be sent via the mini-apps chat box during the active intervention period at the end of weeks 2, 4, 6, and 8.

Table 1 Phase 2 pilot RCT study assessment timepoints

			Week					
			(Day 1)	2	4	6	8	12
Assessments								
Enrollment			X					
Informed consent			X					
Randomization			X					
Baseline assessment			X					
Interventions								
	Mini-app	Weekly reminder messages to use the mini-app	←	—	—	—	→	
		Mini-app access	←	—	—	—	—	→
	Control	Standard HIV prevention care	←	—	—	—	—	→
Follow-up survey (Long)					X		X	X
App-use survey (short)*				X		X		
In-depth interviews **					X		X	

*Only performed in participants in the intervention arm;

** Only performed in a subgroup of participants.

Qualitative progress evaluation

When close to the fourth week of intervention, a subgroup of 15 participants (10 intervention, 5 control) will be purposively sampled prioritizing those who have initiated PrEP to complete two in-depth interviews at weeks 4 and 8. Another group of participants (up to 5) who started PrEP between week 4 and week 8, regardless of the study arm, will receive a one-time in-depth interview at week 8. Interviews will focus on participants' experiences using the app and any changes in their perceptions and/or behaviors related to PrEP and HIV prevention practices

during the study period. Interviews will be conducted one-on-one in private spaces – or via videoconferencing software (e.g. Zoom or Tencent Meeting), the last 60-90 minutes, and will be audio recorded with participants' permission.

Primary Outcome in

The primary outcomes for Phase 2 pilot RCT include the intention to use PrEP, progression along the stages of change to PrEP initiation, and PrEP initiation. PrEP use intention will be constructed as a continuous variable (range -3 to 3, from Very unlikely to Very likely) according to the participant's response to the question "How likely are you to start using PrEP?" PrEP initiation will be a binary variable, such that participants who successfully started PrEP (either through the study clinic or other PrEP providers) during the study period (Weeks 0 - 8) will be recorded as "1", otherwise as "0". Individual progression along the stages of change to PrEP initiation will be measured by a set of eight questions evaluating their contemplation, preparation, and actions to start PrEP and maintenance of using PrEP (56). This will be constructed as a discrete variable ranging 0-4 (0=precontemplation, 1=contemplation, 2=preparation, 3= action, 4= maintenance).

Secondary Outcome Measures

Secondary outcomes include: (1) feasibility variables, including the length of time for recruitment and enrollment, participants' retention rate (staying in the study) throughout the study course, and self-reported mini-app usage; (2) PrEP knowledge (5-item quiz, response

options: true/false, total score: 0 – 5); (3) Number of HIV/syphilis tests (>=0, continuous) ordered through the mini-app, tracked by the backend data; (4) PrEP adherence, measured by self-reported missed doses in the past week (a continuous variable, ranging from 0-7); (5) PrEP stigma (5-item scale, five-point Likert response scale from strongly disagree to strongly agree, total averaged score ranging from 1 – 5 with higher scores indicating higher perceived PrEP stigma; (6) PrEP attitudes, an averaged score of the participant's responses to a five-item PrEP attitudes scale with a five-point Likert response scale from strongly disagree to strongly agree, with higher scores indicating more positive attitudes toward PrEP (a continuous variable, ranging from 1-5); (7) PrEP self-efficacy, an averaged score of the participant's responses to a seven-item PrEP self-efficacy scale with a five-point Likert response scale from very difficult to very easy, with higher scores indicating higher self-efficacy to use PrEP (a continuous variable, ranging from 1-5).

Referrals

In the case of an initial positive HIV test done through the study, participants who have initiated PrEP will be instructed to discontinue PrEP dosing. Participants testing positive will be referred to the Guangzhou Eighth People's Hospital for confirmation tests or other testing places if needed. The Guangzhou Center for Diseases Prevention and Control will be notified of confirmed positive results following China's public health reporting laws, a procedure that will be explained to participants at consent. For positive syphilis testing results, participants will be referred to as STI treatment at the Guangzhou Eighth People's Hospital. The study team will follow-up with participants testing positive for HIV or STI to encourage participants to seek appropriate care.

Data management

In-depth interviews will be audiotaped, transcribed verbatim (in Chinese), summarized in English, and organized and managed using Dedoose cloud-based qualitative data analysis software (www.dedoose.com). The web-based survey will be collected through a Chinese professional secure electronic survey platform Wenjuanxing (www.wjx.cn). Survey data will be downloaded from Wenjuanxing and will be stored on password-protected encrypted study computers along with other electronic study files. All study files will have a back-up copy stored on UNC secure server space that only study personnel will have access to.

Statistical Analysis plan

All data will be All statistical data analyses will be conducted in SAS 9.4 (SAS Institute, Cary, NC). An intention-to-treat analysis approach will be utilized (57).

Descriptive analysis

Descriptive statistical analyses will be first conducted to report baseline characteristics of participants, actual PrEP initiation rates, distribution of outcome variables, and other control variables at different time points throughout the study period. For continuous outcome variables, we will first examine the mean changes from baseline to follow-up for the entire sample using paired t-tests, and then estimate whether there are differences in net gains between the mini-app

group and the control group, and between frequent mini-app users (use the mini-app once a week or more) and less frequent users. Observed effect sizes will be reported, to inform future study designs.

Bivariate analyses

Bivariate correlation analyses will be conducted to assess variables (including predictor and control variables) relating to PrEP use intention and PrEP initiation rate at Week 4 and Week 8. For the binary dependent variable "PrEP initiation" in particular, we will use the Chi-Square test to compare the difference in PrEP initiation between the intervention group and the control group. Unadjusted *Odds Ratios (OR)* will be calculated and reported.

Multivariable analyses

Common confounder variables (e.g., age, education, in, come and other socio-demographic characteristics) and theoretical construct variables (i.e. PrEP knowledge, self-efficacy, stigma, and attitudes) will be adjusted for in multivariable analyses for each outcome of interest.

Given that the data collected in the pilot RCT is a longitudinal dataset with repeated measures at three time points, we will apply multilevel linear regression models to assess the association between continuous outcome variables and predictor variables. Missing data will be replaced with predicted values by multiple imputations, and sensitivity analyses will be conducted to compare the multiple imputation approach with analysis with complete cases only. If we have

less than 50 participants retained at Week 8, or the multilevel model does not converge, we will run regression models and control for change over time.

Phase 2 Qualitative Analysis

The analytic approach for qualitative interviews from participants in Phase 2 will be similar to that applied in Phase 1. Besides, we will conduct a trajectory analysis (58) to understand participants' experience throughout the intervention period, including user experience of the mini-app, study engagement, evolving PrEP-related perceptions, and PrEP use behaviors. As we will purposively sample participants who have initiated PrEP during the study and those who show less engagement for the interview, this approach will allow us better to understand the changing or non-changing process of individual PrEP use intention and initiation.

Incentives

Participants in Phase 1 will be provided remuneration at the end of each completed interview in the form of a 75-CNY (~ 10 USD) gift card or equivalent. Participants in Phase 1 will not be eligible for Phase 2.

Participants in Phase 2 will receive a 50-CNY (~ 7 USD) gift card for the in-person initial visit or baseline assessment and another 20-CNY (~3 USD) gift card for completing each Web-based follow-up survey via Wenjuanxing at Weeks 4, 8, and 12. Participants who complete all required study activities in Phase 2 will receive a bonus of 50-CNY (~ 7 USD) at the end of the study.

Phase 2 participants who are sampled for in-depth interviews will receive 75-CNY (~10 USD) for completing each interview (up to two interviews for each participant). For participants who initiated PrEP through this research study, the cost of physical examinations (including required lab tests) and PrEP prescription will be covered by the study team. Participants will need to pay for PrEP medications out-of-pocket first and get 50% of the cost reimbursed at the monthly follow-up clinic visits. After reimbursement, the total estimated cost to a participant in Phase 2 who starts PrEP is from 1000 CNY (about 143 USD, for one-month PrEP supply or 30 pills) to 2000 CNY (about 286 USD, for two-month PrEP supply or 60 pills).

ETHICS AND DISSEMINATION

This study was reviewed and approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill, USA (IRB#19-3481), the Guangdong Provincial Dermatology Hospital, China (IRB#2020031), and the Guangzhou Eighth People's Hospital, China (IRB#202022155). All participants will be provided online consent and sign it electronically before taking part in the study. Our study team will work with local GBMSM CBOs to disseminate the study results to participants and the community via social media, journal publication, and offline workshops at local CBOs. This research addresses a critical need as GBMSM bear a disproportionate burden of China's HIV infections and remain underserved in the healthcare system.

DISCUSSION

Despite the high prevalence of HIV infection and risk factors among Chinese GBMSM, PrEP use is quite limited (59). A theory-informed, GBMSM-friendly, and innovative behavioral intervention to facilitate PrEP uptake among Chinese GBMSM may help to increase the awareness of PrEP among this population through timely information and strengthened motivation and skills. It may also help to link individuals to providers and clinics where they can receive PrEP. While PrEP campaigns in China have to-date failed to engage relevant communities (60), initiatives in other settings have successfully used GBMSM-tailored approaches to promote PrEP (35–38), including using mHealth technologies to approach GBMSM "where they are". In an online survey of 1,035 Chinese GBMSM in 2017, about 75% of the participants mainly met their sex partners online (61), and Chinese GBMSM have been using the Internet frequently to search for HIV-related information, counseling, or testing services (32).

A large body of evidence has suggested that HIV-related and sexual health interventions delivered through Internet-enabled platforms are feasible and acceptable in Chinese settings (62), including interventions through websites, text message, and mobile apps that have shown effectiveness in reducing HIV-related risk behaviors, increasing linkage to care, and improving medication adherence (3,63,64). Thus, an mHealth-enabled intervention, like this PrEP education mini-app, which leverages the platform of a popular Chinese social media app could facilitate the rapid scale-up of PrEP use in China. In contrast to the traditionally top-down health mandates or researcher-led intervention projects, the PrEP mini-app tested in our study was co-created by a team of young gay men, HIV clinicians and public health researchers through a crowdsourcing hackathon. This not only helps to generate innovative approaches to address their own social and

health needs, but also increases the acceptability and potential impact of the intervention in target populations.

Developing and testing theory-driven interventions around HIV prevention and care is challenged by rapid developments in the field, which can influence the pertinence or timeliness of interventions – a case in point concerns PrEP in China. The Chinese government has taken several crucial steps in introducing PrEP to China, including launching large-scale PrEP studies in multiple provinces and cities in 2018, developing implementation guidelines for PrEP in China (60), and officially approving TDF-FTC for HIV PrEP in August 2020 (65). Nevertheless, the large population of GBMSM who would benefit from PrEP will encounter significant challenges for timely scale-up. The PrEP education mini-app developed by this study aims to meet the pressing need for innovative, easily accessible, and broadly acceptable modes of promoting and supporting PrEP among Chinese populations (66).

We also expect some challenges in the study implementation given the rapidly evolving conditions of the global COVID-19 pandemic and its impact on human activities and interpersonal interactions. The fieldwork is expected to take place between summer 2020 to summer 2021, while international travel of our research team members will be significantly delayed or restricted because of the global mitigation strategies to control COVID-19. In order not to bring significant delay to the study progression as well as encourage participants' engagement, our research team has been working remotely with local collaborators regarding MSM recruitment and enrollment. All data collection activities including in-depth interviews and surveys will be conducted electronically via videoconferencing systems or web-based survey

tools, to ensure participants' and the research team's safety. The mHealth-based feature of the proposed intervention does not require in-person interaction between the participants and the research team; though study enrollment currently includes clinic-based lab tests and follow-up visits among PrEP users.

Whether globally or in China, limited data exist on the efficacy of app-based interventions aimed to increase PrEP uptake and adherence among GBMSM. If successful, this research study may help guide the PrEP/HIV prevention cascade in China by examining whether an mHealth intervention can promote HIV prevention services. Promoting such services among GBMSM is of great importance as this population bears a disproportionate burden of China's HIV infections and remains underserved in the healthcare system.

DECLARATIONS

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Author Contributions

KM, JT, and CL conceived the study and drafted the manuscript. EF, DM, WT, RS, AH, LLH, XY, HJH, and JL participated in designing and implementing the study and assisted in drafting the manuscript. JT and WT obtained funding for the study. TS, KXT, MY, and ZM developed the prototype of the mini-app and assisted in drafting the manuscript. All authors have read the final manuscripts, and approve for it to be published.

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Data Availability Statement

Deidentified individual data that supports the results will be shared beginning 9 to 36 months following publication provided the investigator who proposes to use the data has approval from an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Research Ethics Board (REB), as applicable, and executes a data use/sharing agreement with the University of North Carolina at Chapel Hill.

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Figure 1

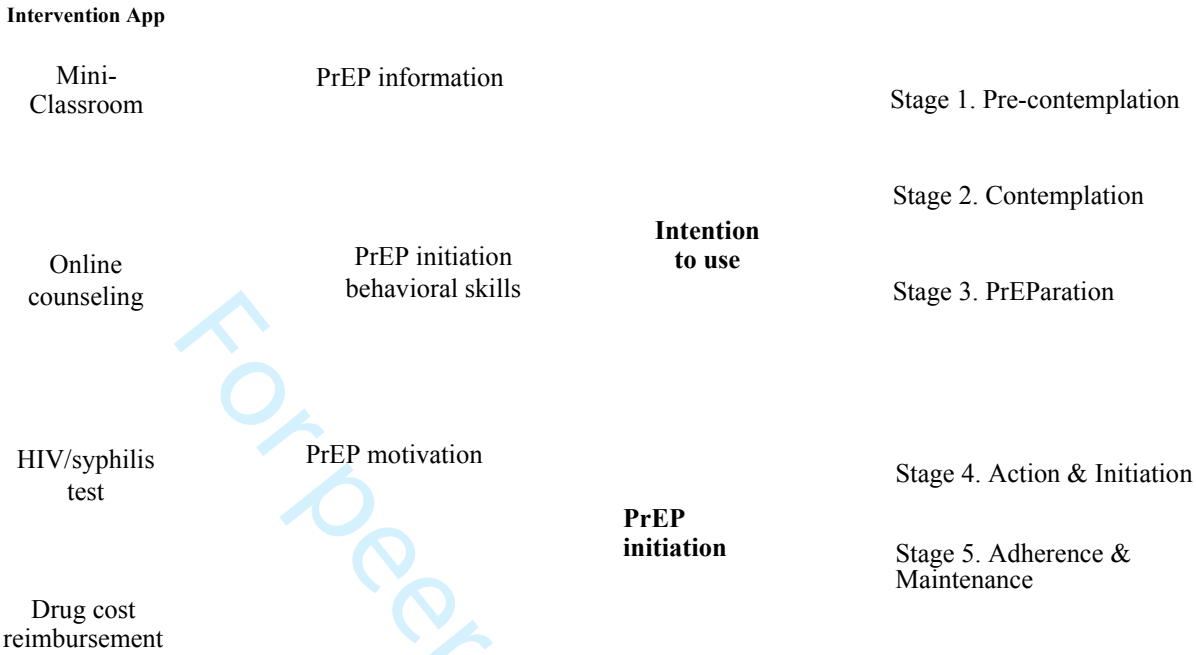


Figure 2

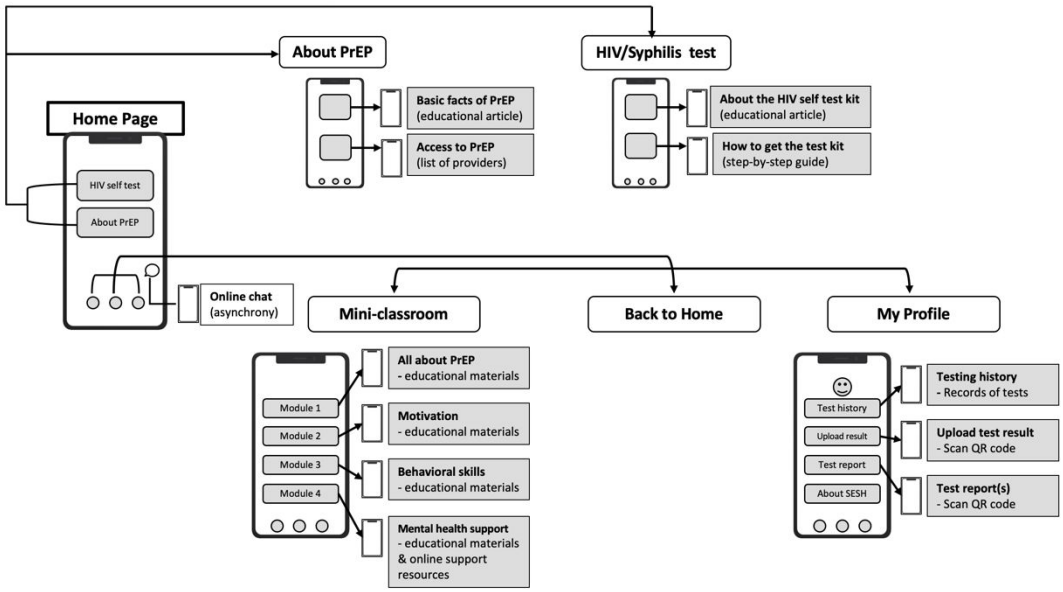


Figure 3

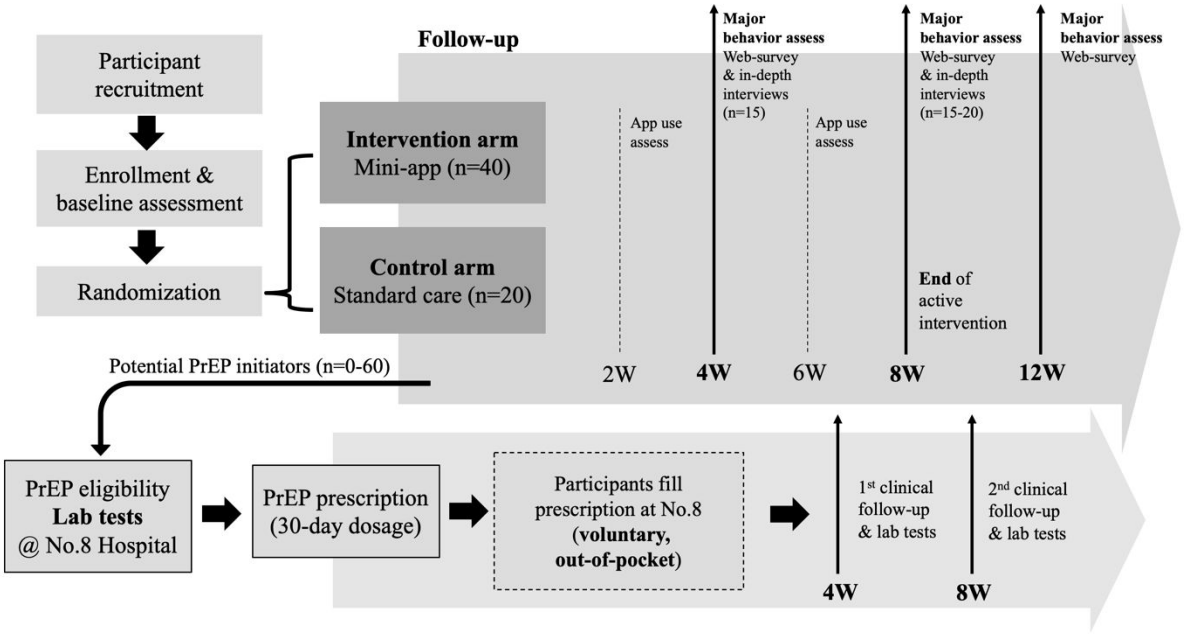
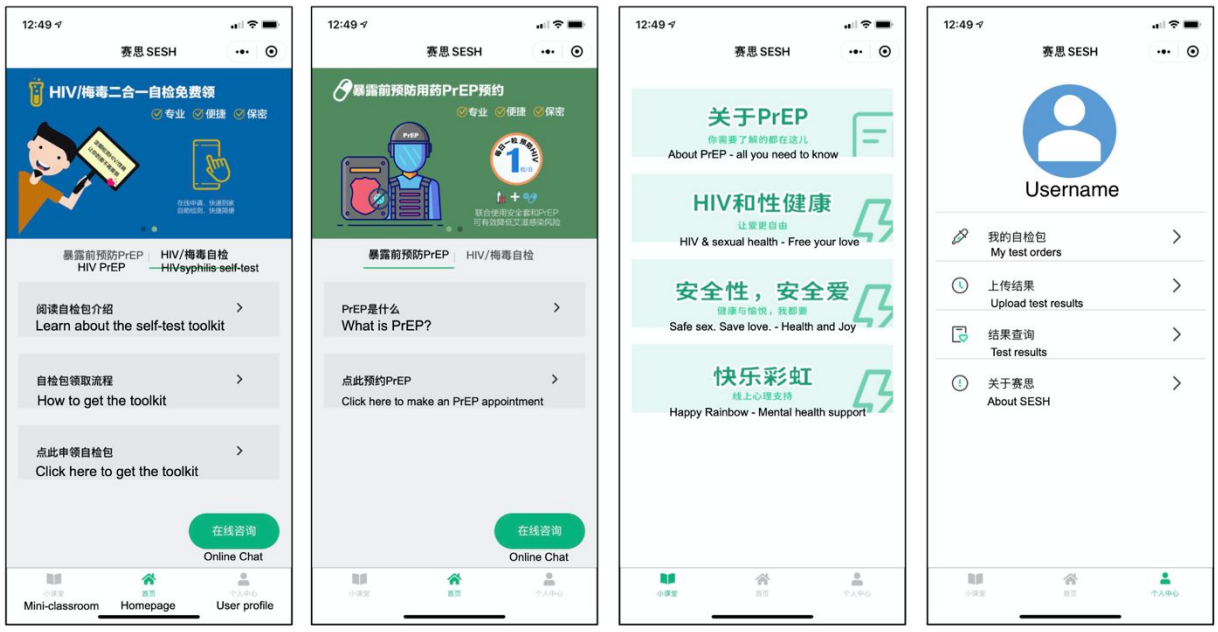
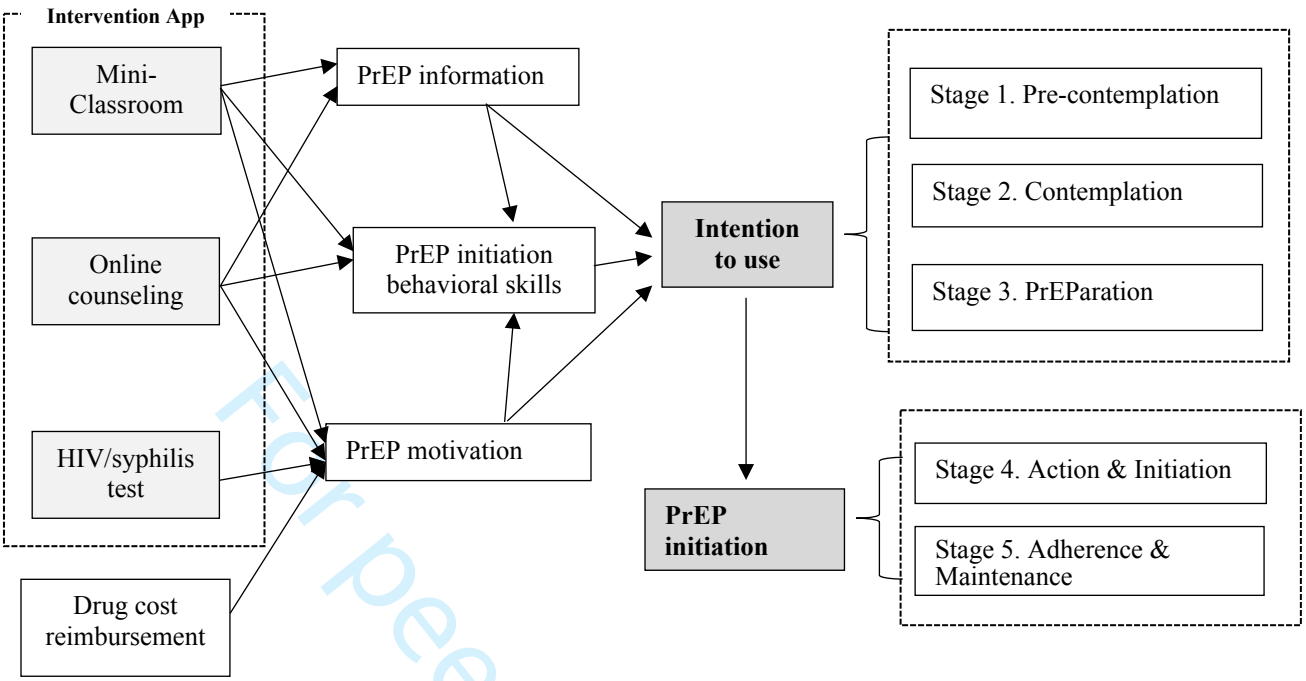


Figure 4





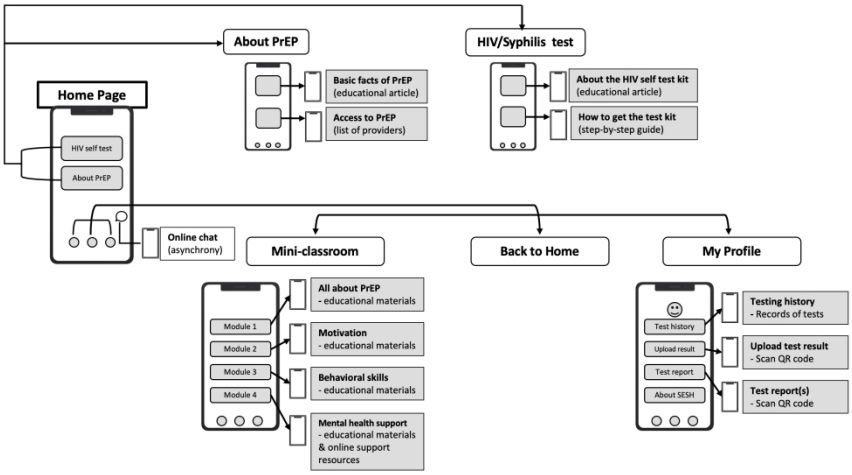


Figure 2. Wireframe of the mini-app PrEP intervention

505x284mm (144 x 144 DPI)

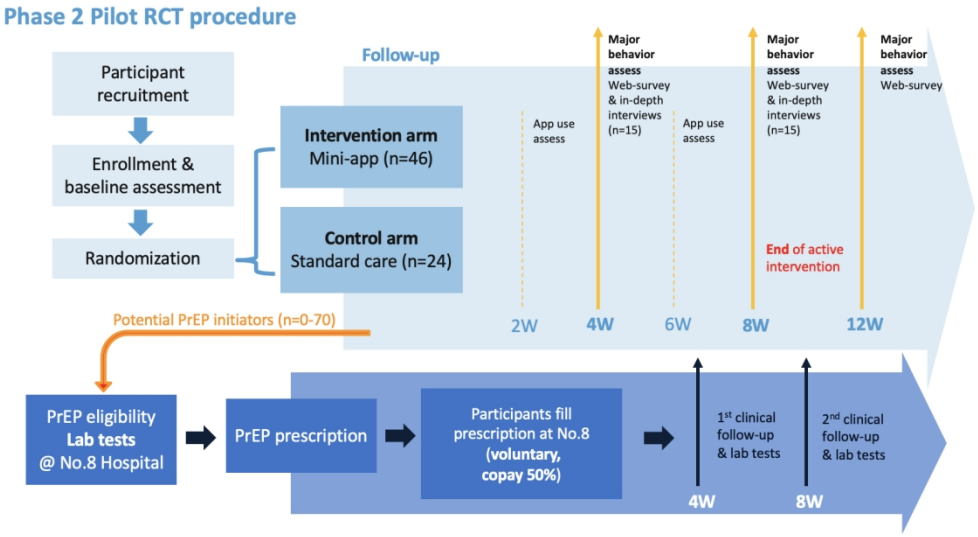


Figure 3. Phase 2 RCT procedure

307x173mm (144 x 144 DPI)

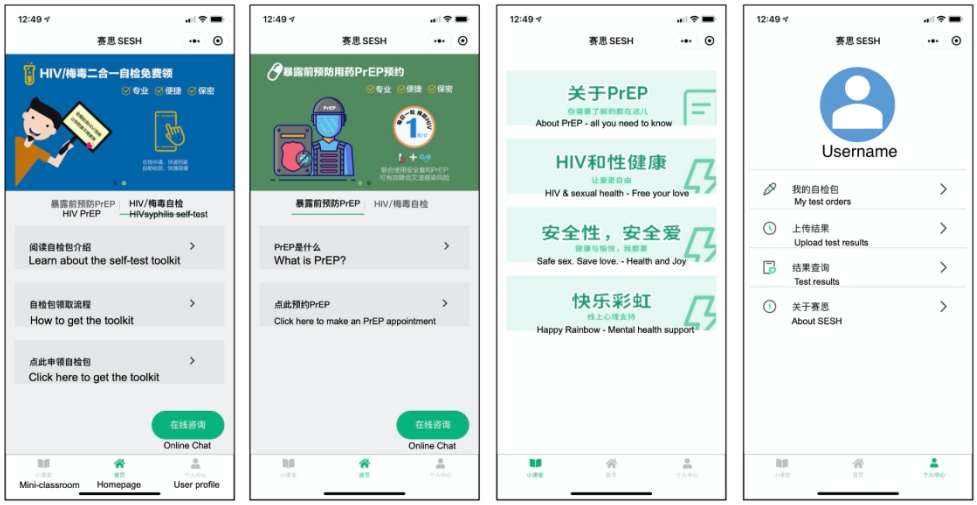


Figure 4 Screenshot of the mini-app from left to right: (1) Homepage 1: at-home test kit, (2) Homepage 2: PrEP appointment, (3) the Mini-classroom, (4) User profile center

338x190mm (150 x 150 DPI)

Supplementary file

Table 1 Summary of key functions of the mini-app prototype

Key functions	Intervention objectives	Intervention strategies			
		Information	Motivation	Behavioral Skills	Mental Health
Mini-classroom	Build knowledge and navigation skills around local HIV care system, enhance interest and motivation to use PrEP, and increase self-efficacy in HIV/STI prevention strategies; Improve mental health management skills.	Educational materials in multimedia forms, including text, videos, and graphics.	Real stories of PrEP users; Positive meanings of using PrEP and HIV/STI testing.	List local PrEP and other HIV/STI care providers and contact information; Tips for safe sex, condom use, and PrEP initiation, adherence, and management.	Links to local support groups and mental health care resources. Self-management for mental health. Coping with stigma and discrimination against LGBTQ community.
Online counseling	Enable MSM to describe their feelings or concerns related to HIV, sexual health or this intervention study, and help them make healthy decisions.	Answer questions about HIV, STI, PrEP, and/or other health topics, and provide additional information if needed.	Tailored health advice regarding PrEP use.	Referral to the HIV/PrEP clinic at the study hospital, or other healthcare providers based on individual needs.	Listen to their needs, and refer to local support groups or mental health care resources, if necessary.
Home-based HIV/syphilis test ordering	Establish individual habit of routine testing for HIV and syphilis.	Information about how to complete the home-based test kit.	Provides a cue to action and removes barrier of in-person testing and stigma.	An HIV/syphilis home-based test kit ordering system.	
User profile center	Allow participants to monitor their HIV/syphilis testing behaviors.			A profile page to manage orders of HIV/syphilis test kits and keep a record of test results.	

Table 2 Phase 2 pilot RCT study measures and timepoints of data collection

		Week					
		Day 1	**2**	**4**	**6**	**8**	**12**
Primary outcomes							
PrEP use intention	3-item scale with 5-point rating (1 to 5) (45)	X		X		X	X
PrEP stages of change	10-item scale with 5 stages of progression (1 to 5)	X		X		X	X
PrEP initiation	Yes/No (study record)			X		X	X
Secondary outcomes							
PrEP knowledge	5-item True/False quiz	X		X		X	X
Test behavior	Frequency of at-home HIV/syphilis tests (≥0)			X		X	X
Willingness to pay	Percentage of monthly income to pay for PrEP	X		X		X	X
Self-report PrEP adherence***	Daily PrEP: missed doses in past 7 days (0 to 7) PrEP on-demand: missed doses in a single sex event (0 to 4)			X		X	X
PrEP self-efficacy	8-item scale with 5-point rating (1 to 5)(45)	X		X		X	X
PrEP stigma	5-item scale with 5-point rating (1 to 5) (45)	X		X		X	X
PrEP attitudes	5-item scale with 5-point rating (0 to 5) (45)	X		X		X	X
Predictor variables							
Intervention exposure	Yes/No	X					
Mini-app Engagement*	Self-reported frequency of app use		X	X	X	X	X
	Perceived app usefulness		X	X	X	X	X
Covariates							
Demographics & socio-economic indicators	Age, education, gender, sexual orientation, relationship status, private or shared bedroom, employment, income	X				X	
Drug use	Ever used recreational drugs (Yes/No)	X					
	Drug use in the past 4 weeks	X		X		X	X
Alcohol use	Ever consumed alcohol (Yes/No)	X					
	Average weekly alcohol consumption, past 30 days	X		X		X	X
Tobacco use	Ever consumed tobacco products (Yes/No)	X					
	Average weekly tobacco consumption, past 30 days	X		X		X	X
Prior HIV test history	Self-report HIV test history before the study (Yes/No)	X					
HIV knowledge	2-item HIV quiz	X		X		X	X
HIV risk perception	2 questions of perceived risk of HIV infection	X		X		X	X
HIV-related anxiety	3-item scale with 5-point rating(67)	X		X		X	X
Perceived stress	4-item Cohen Perceived Stress Scale(67) (overall stress)	X		X		X	X
HIV-social support	10-item scale with bipolar scale (-2 to 2)(68)	X		X		X	X
Condomless sex	Occurrence of condomless sex in the past 4 weeks	X		X		X	X
Number of sex partners	Self-reported number of sex partners, past 4 weeks	X		X		X	X

*Only performed in participants in the intervention arm;

** Only performed in a subgroup of participants;

***Only performed in participants who have started using PrEP.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Page 1
Funding	4	Sources and types of financial, material, and other support	Page 27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 26-27
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 27
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4-6
	6b	Explanation for choice of comparators	Page 4-6
Objectives	7	Specific objectives or hypotheses	Page 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Phase 1: "Participant" section on Page 10; Phase 2: the "Participant" section on Page 12.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Phase 1: "Participant" on Page 10 Phase 2: Textbox 1 on Page 12.
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	"Study arms" on Page 14-16. Table 1, Figure 2-4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	"Referrals" on Page 19.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	"Qualitative progress evaluation" on Page 17. "Incentives" on Page 22-23.

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Exclusion criteria in Textbox1 on Pages 12-14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pages 18-19, Table 2 in supplementary file
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1 Figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Phase 1: “Participant” on Page 10 Phase 2:
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Phase 1: last paragraph on Page 10 Phase 2: first paragraph under “Participants” on Page 12.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	“Randomization” on Page 14.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	“Randomization” on Page 14.

Implement ation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	"Randomizatio n" on Page 14.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Phase 1: "Study design" on Pages 9-10 Phase 2: "study assessments" on Pages 16-18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Description of sending weekly reminder messages to participants in the last paragraph on Page 14. "Qualitative progress evaluation" on Page 17. "Incentive" section on Page 22
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Phase 1: first paragraph on Page 10. Phase 2: Page 20

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pages 20-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 21
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	"Referrals" on Page 19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 23
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Pages 16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 27
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 27
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary materials.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT

BMJ Open

A community-engaged mHealth intervention to increase uptake of HIV Pre-Exposure Prophylaxis (PrEP) among gay, bisexual and other men who have sex with men in China: Study protocol for a pilot randomized controlled trial

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TITLE PAGE

A community-engaged mHealth intervention to increase uptake of HIV Pre-Exposure Prophylaxis (PrEP) among gay, bisexual and other men who have sex with men in China: Study protocol for a pilot randomized controlled trial

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A community-engaged mHealth intervention to increase uptake of HIV Pre-Exposure Prophylaxis (PrEP) among gay, bisexual and other men who have sex with men in China: Study protocol for a pilot randomized controlled trial

Protocol date and version: 2020-09-02, Version 3.

ABSTRACT

Introduction: The large number of key populations in China who would benefit from HIV pre-exposure prophylaxis (PrEP) in the context of limited health system capacity and public awareness will pose challenges for timely PrEP scale-up, suggesting an urgent need for innovative and accessible interventions. This study aims to develop and pilot test a theory-informed, tailored mobile phone intervention that was co-developed by young gay men, HIV clinicians and public health researchers to increase engagement in PrEP education and initiation among Chinese gay, bisexual, and other men who have sex with men (GBMSM), who bear a disproportionate burden of HIV infections and remain underserved in the healthcare system.

Methods and analysis: This two-phase study includes a formative assessment using in-depth interviews (N=30) and a 12-week experimental pilot study using a two-arm randomized controlled trial design (N=70). The primary intervention is delivered through a WeChat-based mini-app (a program built into a Chinese multi-purpose social media application) developed by young GBMSM from a 2019 crowdsourcing hackathon. Using mixed-methods, we will further investigate the specific needs and concerns among GBMSM in terms of using PrEP as an HIV

prevention strategy, how their concerns and PrEP use behaviors may change with exposure to the mini-app intervention during the study period, and how we can further refine this intervention tool to better meet GBMSM's needs for broader implementation.

Ethics and dissemination: This study and its protocols have been reviewed and approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill, USA (19-3481), the Guangdong Provincial Dermatology Hospital, China (2020031), and the Guangzhou Eighth People's Hospital, China (202022155). Study staff will work with local GBMSM community-based organizations to disseminate the study results to participants and the community via social media, workshops, and journal publications.

Trial Registration: The study was registered on clinicaltrials.gov (NCT04426656) on June 11, 2020. Prospectively registered.

Keywords: HIV, pre-exposure prophylaxis, mHealth, intervention, men who have sex with men, China, mini-app

Article Summary

1. The intervention app prototype was co-created by the GBMSM community, HIV clinicians and public health researchers through a gay-friendly doctor finder hackathon - a crowdsourcing strategy that solicits innovative public health solutions directly from the end-user community, increasing the intervention's acceptability and potential impact among target communities.
2. The intervention content development was guided by the Information, Motivation, and Behavioral Skills Model, a theoretical model of behavioral change that has been widely applied in HIV-related behavioral intervention studies among different populations including Chinese GBMSM.
3. Mobile health (mHealth) interventions for HIV prevention and sexual health promotion are feasible and highly acceptable among Chinese GBMSM due to their privacy, portability, and convenience, facing the broad spread of HIV- and gay-related stigma in Chinese society.
4. The study design follows the best practice of intervention development that includes a formative assessment of unmet needs, co-creation with the community, pilot testing for preliminary evidence of efficacy, providing preliminary data for a future larger-scale intervention study.
5. The intervention allows participants to make online PrEP appointments at the only local HIV hospital in the study city, and an initial in-person clinical visit is still required for PrEP prescription. It is also a timely response to China's recent approval of TDF-FTC as PrEP in 2020, which we believe could facilitate a rapid scale-up of PrEP among populations at risk of HIV infection in China.

INTRODUCTION

HIV prevalence among gay, bisexual, and other men who have sex with men (GBMSM) in China has steadily increased over the past five years (1–3). In Guangzhou, a major economic center in Southern China, the HIV prevalence among sexually active GBMSM increased from 3.9% in 2009 (4) to 11% in 2017 (5). Individual and contextual risk factors associated with HIV acquisition among Chinese GBMSM include condomless sex, high rates of ulcerative sexually transmitted infections (e.g. syphilis), use of recreational drugs during sex, gay entertainment venues (e.g., public bathhouse), and social and sexual networking mobile phone applications (1,6–11). Taken together, these risk factors suggest that Chinese GBMSM could benefit from additional HIV prevention strategies such as pre-exposure prophylaxis (PrEP).

However, the overall awareness of PrEP among Chinese GBMSM remains relatively low and varies across samples. Generally 20 % - 75% of GBMSM respondents reported having heard of PrEP in China-based studies. (12–14) By July 2021, there was an estimated number of 6000-6500 PrEP users reported from official demonstration projects in this country (15). Cross-sectional surveys (12,16–24) and PrEP clinical trials (25–27) and in-depth interviews with HIV-negative GBMSM (26,28) have reported perceived barriers to PrEP uptake among Chinese GBMSM including concerns about side effects, financial cost, and low HIV risk perception. Yet little is known about multi-level barriers to PrEP uptake and maintenance in China, especially from those with PrEP using experience. Further, there is widespread HIV- and gay-related stigma and discrimination in clinical settings (29–31) that may inhibit the effective delivery of PrEP drugs and related services for GBMSM (32).

The China National Medical Products Administration approved Tenofovir-Emtricitabine (TDF-FTC) as HIV PrEP in China on August 11, 2020. However, the aforementioned gaps highlight the need for innovative, culturally appropriate, and GBMSM-friendly tools that prepare GBMSM for PrEP uptake, to pave the way for a rapid scale-up. Facing the broad spread of HIV- and gay-related stigma in Chinese society, mobile health (mHealth) interventions for HIV prevention and sexual health promotion are feasible and highly acceptable among Chinese GBMSM due to their privacy, portability, and convenience (33–35). Health hackathons as a crowdsourcing approach are an effective and convenient way to mobilize GBMSM communities in generating innovative mHealth solutions to meet their own health needs (36), which could further potentially contribute to reductions in internalized stigma and an increase in community resilience among sexual minority populations (37,38).

Globally, limited data exist on the efficacy of app-based interventions aimed to increase PrEP uptake among GBMSM. Among the few published mHealth PrEP intervention efficacy studies, text messaging has been effective in improving PrEP adherence in GBMSM via reducing missed doses (39,40). More mHealth PrEP uptake intervention studies are underway, however, all are in high-income countries (41–44). To date, little is known about the optimal design and efficacy of using mHealth-enabled interventions for PrEP promotion in Chinese populations, especially among GBMSM.

Aims and objectives

This study focuses on developing and testing a tailored mobile app-based intervention built on our previous work from a gay-friendly doctor finder hackathon in China (45), aiming to increase engagement in PrEP education and initiation, and generate hypotheses that explain potential behavioral pathways to PrEP uptake among Chinese GBMSM. The study site is Guangzhou, a major economic center of southern China. To this end, the study has two phases: Phase 1 collects formative data using in-depth interviews to assess unmet needs in HIV prevention (PrEP in particular) and sexual health among HIV-negative GBMSM, and test and refine the usability of the mini-app. Phase 2 will implement a two-arm RCT to assess the feasibility and preliminary evidence of the efficacy of the refined mini-app in increasing intention to use PrEP and PrEP initiation among HIV-negative GBMSM. Specific aims include:

Aim 1: Generate hypotheses around behavioral pathways explaining PrEP uptake among Chinese GBMSM with different PrEP using experience (e.g., PrEP-naïve, former and current PrEP users) by analyzing qualitative data from in-depth interviews of the formative assessment (Phase 1, n=30).

Aim 2: Assess the feasibility and preliminary efficacy evidence of a mobile phone-based PrEP education intervention tool (the mini-app) compared to the standard of HIV prevention care in increasing individual intentions to use PrEP and actual PrEP initiation rate through a two-arm pilot RCT (Phase 2) with 70 HIV-negative GBMSM (18 years old and above) in Guangzhou, China.

METHODS AND ANALYSIS

Theoretical foundation for intervention

Figure 1 presents the study's conceptual model. The intervention content development is informed by the Information, Motivation and Behavioral Skills Model (the IMB model). The IMB model proposes a mediational framework that hypothesizes that the performance of many health-related behaviors is determined by three core constructs: *information*, *motivation,* and *behavioral skills* (46). With years of application in HIV research, the IMB model has been widely applied in intervention studies and adapted to promote specific HIV-related behaviors, including PrEP care-related behaviors (47–49). Among Chinese GBMSM, the IMB model was also found useful in explaining HIV preventive behavior such as condom use (50). We also use the Motivational PrEP Cascade (MPC), (51) originally proposed by Dr. Jeffrey Parsons and colleagues who combined the concept of PrEP care cascade (52) and the Transtheoretical Model of Behavioral Change, to inform the measurement of the several stages of behavioral change culminating in PrEP initiation. The MPC outlines stages of readiness to make a behavioral change, including pre-contemplation, contemplation, preparation, action, and maintenance of the change. (53) A 2018 survey study based on the MPC among a sample of 708 HIV-negative GBMSM from multiple major cities in China showed that 53% of the respondents who were PrEP eligible were in the pre-contemplation stage, 36% in contemplation, 9% in PrEParation, 2% in PrEP action and initiation, and none in adherence and maintenance.(17) Given variable awareness about PrEP and the wide range of age of the target population, measuring the stages of change toward PrEP initiation will help us better tailor and refine the intervention.

Figure 1 *The conceptual model of the WeChat mini-app PrEP intervention*

Patient and Public Involvement: Development of the Intervention Tool – PrEP Education WeChat Mini-app

The intervention is delivered via a WeChat-based mini-app (a program built within an existing commercial application) that was developed by a team of young GBMSM from a GBMSM-friendly Doctor Finder Hackathon contest (45). This hackathon contest was part of a series of crowdsourcing events that aimed to engage the GBMSM community in generating public health innovations in HIV and sexual health promotion in China. From February 2018 to March 2018, the Shenzhen University College of Mass Communication, the non-profit organization Social Entrepreneurship to Spur Health (SESH), and Blued (the largest gay social networking app in China) held a crowdsourcing contest for designing concepts of a mobile phone-based, GBMSM-friendly doctor mobile app. In July 2018, four focus group discussions with 38 GBMSM in Guangzhou and Shenzhen were subsequently conducted to solicit participants' feedback on refining the app design (54).

From December 2018-April 2019, UNC Project China with support from SESH and Blued hosted a GBMSM-friendly Doctor Finder Hackathon in Guangzhou, during which the participants were asked to develop a mobile phone-based doctor finder prototype based on the work from previous events. A total of 38 participants grouped into eight teams attended the final hackathon contest and developed eight prototypes after a 72-hour hacking. Four prototypes adopted the mode of a mini-app embedded within WeChat, and three prototypes were designed as stand-alone apps, and one was designed as a tool that can be adjusted to multiple platforms.

One of the WeChat mini-app prototypes was adapted for use in the current study. WeChat (Android and iOS) is a social platform in China with over one billion active users (55) that has been widely used for public health education by Chinese health administrations and private organizations (56). The WeChat app allows developers to build new app programs (i.e. the mini-app) within the platform that are accessible without additional download or installation.

Before testing and evaluating the mini-app in the current study, we invited a group of key community stakeholders including gay men, sex educators, and local HIV-related CBO workers to test the mini-app prototype and provide valuable feedback in user-interface design and choice of educational materials. The main features of the version of the interventional mini-app for the current study include: (1) the Mini-classroom, educational materials which cover topics of HIV and STI, PrEP and PEP, and mental health, aiming to change participant's information, motivation, and behavioral skills to initiate PrEP; (2) an at-home HIV/syphilis dual testing kit ordering system; (3) chat-based online counseling, and (4) a user profile center (their account in the mini-ap is automatically linked to their WeChat account with the user's permission). The overall structure of the mini-app is illustrated in Figure 2, and a detailed description of the main features is presented in Table 1 in the Supplementary File1.

Figure 2 *Wireframe of the mini-app PrEP intervention*

Phase 1: Formative Research—Needs Assessment and Mini-app Testing

Study design

In Phase 1 we conduct in-depth interviews among Chinese GBMSM to understand the key barriers and facilitators of using PrEP. We also assess participants' perceived usability of the intervention mini-app during the interview. All one-on-one interviews are conducted by the principal investigator via videoconference (audio-recorded with participants' permission) and last 60-90 minutes. The principal investigator (CL) is a PhD candidate in Health Behavior with over 10 years training in public health and 5 years research experience in HIV prevention and LGBTQ health among Chinese populations in particular. We use a semi-structured interview guide (Table 2 in Supplementary File1) with tailored questions for participants with and without PrEP experience. Interview topics cover knowledge, attitudes, and willingness to use PrEP and/or PrEP use history, preference over PrEP regimens (daily vs. event-driven dosing, oral vs long-term active injectable PrEP) and delivery modes, and past pathways, barriers, and facilitators to HIV testing and PrEP services. During the interview, participants are introduced to the mini-app design and features, use the mini-app for 5-10 minutes, complete a 10-item app usability scale (System Usability Scale(57,58)), and discuss the app's design, contents, and ease of use. Following the interview, each participant completes a brief demographic survey via Wenjuanxing, an online survey tool in China. All interviews will be transcribed in Chinese and analyzed using the qualitative analysis platform, Dedoose. (59) A thematic analysis-based approach (60) will be applied for identifying, analyzing, and reporting patterns within the data. This will be conducted in Chinese with the translation of exemplary content for English-language publications.

Participants

To represent the variety of experience GBMSM has had with PrEP, we will conduct in-depth interviews with 30 Chinese GBMSM at different stages of the PrEP care continuum, including approximately 20 PrEP naïve individuals, five prior PrEP users who are not currently on PrEP, and five current PrEP users. This sample size is generally considered sufficient for thematic analysis to reach information saturation among a relatively homogenous group. (61) While the mini-app is primarily designed for PrEP-naïve GBMSM, including the perspectives of past and current PrEP users is intended to gain feedback on the intervention design and content based on experiences across the stages of change in PrEP adoption. Participants will be recruited through research advertising on Chinese social media and referral by local GBMSM-related organizations.

Eligibility criteria for Phase 1 are: Chinese citizen and current resident, assigned male sex at birth, age 18 and above, any lifetime anal sex with another man, and willingness to sign (or e-sign) informed consent. Exclusion criteria include self-reported HIV-positive status or reporting or demonstrating mental health issues which may compromise participant safety, including memory loss, cognitive impairment, intellectual disability, or communication disorders.

Mini-app Refinement

Before starting Phase 2, we will refine the mini-app based on participants' feedback on the app design from Phase 1 formative assessment. Potential adjustments to the mini-app may be feasible in changing content, and graphic and text appearance, but not functionality or structure of the

app. All requests regarding functionality and app structure will be recorded and considered for future iterations of the app.

Phase 2: Pilot Randomized Controlled Trial

Study Design

Phase 2 will evaluate the feasibility and preliminary evidence of the efficacy of the mini-app in increasing intention to use PrEP and PrEP uptake through a two-arm pilot RCT comparing the mini-app to the standard of HIV prevention care (Figure 3). The study is estimated to last up to 12 weeks, where the first eight weeks is the active intervention period and the last 4 weeks is post-intervention observation.

Figure 3 *Phase 2 study design, a two-arm RCT*

Note: Participants can purchase PrEP medicines (TDF-FTC) from the study hospital. Participants pay for the medicine out-of-pocket and are reimbursed 50% of the cost at each monthly follow-up visit.

Study setting

A convenience sample will be recruited in Guangzhou, China via SESH and local LGBTQ-related community-based organizations (CBOs). Our partners –SESH, CBOs and the study hospital (the Guangzhou Eighth People's Hospital) have extensive experience in providing research support on GBMSM- and HIV-related studies in Chinese settings. The study physicians

at Guangzhou hospital have years of experience in both clinical practice and research with GBMSM patients. All study team members have completed the CITI training in Good Clinical Practice before the study starts.

Participants

A convenience sample will be recruited via partner CBOs and online advertising on Chinese major social medias, including WeChat and Sina Weibo. The generally recommended sample size of pilot trials ranges from 24 to 100 (62,63). In this pilot test, we plan to enroll 70 participants to assess preliminary evidence of efficacy and feasibility for a future main trial. Those interested in the study will complete a verbal eligibility screening by the principal investigator (Textbox 1). Those screened eligible will be scheduled for an initial in-person clinic visit or a virtual enrollment via videoconferencing. During this visit, they will complete informed consent and a baseline survey, and be randomized to one of two study arms.

Textbox 1. PrEP mini-app Phase 2 Pilot RCT inclusion and exclusion criteria

Inclusion criteria: Individuals must self-report:

- Having a smartphone with WeChat installed.
- Assigned male sex at birth, HIV-negative, age 18 and above, ever having had anal sex with another man, currently residing in Guangzhou, identifying as a Chinese citizen, able to sign written informed consent and participate in the study procedures as required. AND

- At least one characteristic associated with the risk of HIV infection in the previous 6 months:
    - Unprotected (condomless) receptive anal intercourse with a male partner(s)
    - More than two male partners (regardless of condom use and HIV serostatus)
    - Reported STI, such as syphilis, HSV-2, gonorrhea, chlamydia, chancroid, or lymphogranuloma venereum.
    - Reported use of post-exposure prophylaxis (PEP)
    - Have a sexual partner living with HIV

Exclusion Criteria:

- People living with HIV
- Currently taking oral PrEP based on self-report before enrollment
- Symptoms of acute HIV infection in the previous 30 days (e.g. fever, flu-like symptoms)
- Suspected exposure to HIV in the previous 72 hours
- Contraindications for taking oral PrEP
- Personal diagnosis or family history of hemophilia (self-report)
- Participating in another research intervention study related to HIV or PrEP
- Having serious chronic disease, including metabolic diseases (such as diabetes), neurological, or psychiatric disorders
- Mental health issues may compromise adherence or safety, including memory loss, cognitive impairment, intellectual disability, or communication disorders.

1

Randomization

We will conduct a permuted block randomization that assigns the 70 participants to either the mini-app arm or the control arm in a 2:1 ratio. Randomization sequence will be created using Stata 16.0 (StataCorp LLC. College Station, TX) with block size of six. The 2:1 allocation will be used to ensure the capture of the range of users' reactions to the mini-app and its content. The randomization process will be conducted by a research assistant after the full consent process.

Study arms

Intervention Condition: The PrEP education mini-app

The PrEP education mini-app (Figure 4 presents the screenshots) serves as the primary participant-facing component of the intervention. Usage of the mini-app will be at participants' discretion or preference. Weekly reminders that encourage participants to use the mini-app will be sent out through WeChat messages. At this stage of development, the mini-app will not be able to track individual user information or activity. Self-reported app usage will be assessed in bi-weekly follow-up surveys and in-depth interviews at the 4th and 8th weeks. After Week 8, participants in the intervention arm will no longer receive reminder messages but may continue using the mini-app throughout the whole study period – up to 12 weeks from the time of enrollment, or continue using to the end of their first two months of PrEP use.

Figure 4 *Screenshot of the mini-app from left to right: (1) Homepage 1: at-home test kit, (2) Homepage 2: PrEP appointment, (3) the Mini-classroom, (4) User profile center*

Standard of HIV prevention care

Participants in both study arms will receive standard HIV prevention care during the initial and final study visits, including printed or electronic HIV prevention materials about PrEP and HIV/STI testing, referrals to local prevention services, and a description of the standard procedure to access PrEP through the study clinic.

PrEP Initiation

Participants in both arms can choose to initiate PrEP through the research study at any time point from enrollment through the end of Week 8. Participants who decide to start PrEP after Week 8 will still be able to receive standard PrEP care at the study clinic, but they will not be eligible to receive complimentary physical examinations that are covered by this research project (Please see details in *Incentives*). Participants can contact the study team via phone call, text messages, or via the chat function in the mini-app (intervention arm only) to communicate their interest in PrEP initiation. Interested participants will be referred to the Department of Infectious Diseases at the study hospital to consult a clinician regarding HIV risks and PrEP eligibility. As per protocols in the study hospital, participants starting PrEP will undergo standard of care comprehensive physical examinations including routine blood and urine examinations, hepatic and renal function tests, and HIV/syphilis/HBV/HCV tests.

During this clinical encounter, participants who are confirmed to be HIV-negative and without any relative contraindications for PrEP initiation will be prescribed a 30-day supply of TDF-FTC. Participants can choose from two PrEP medicines that is available for prescription at the study clinic during the study period: Truvada (before reimbursement: 1980 CNY/ 30 pills) or the generic Keaike (1180 CNY/ 30 pills). Once starting PrEP, participants will be required to complete two monthly clinic visits during their first two months of PrEP use to monitor their medication adherence, HIV/STI tests, and overall physical health status, and receive another 30-day supply of TDF-FTC. Participants may follow the daily oral regimen or event-driven regimen based on their discretion, and they will be given education on the two PrEP regimens during their initial PrEP counseling and through the Mini-classroom in the mini-app. PrEP prescriptions may be filled at the study clinic's pharmacy or a private pharmacy.

Study assessments and evaluation

Behavioral assessments

Baseline assessments will be conducted at enrollment, with follow-up surveys conducted at weeks 4, 8 (end of active intervention), and 12 (post-intervention) via self-administrated Web-based surveys on Wenjuanxing. Participants will be asked to complete follow-up surveys within one week; reminders through WeChat message will be sent on days 7 and 10 of the survey window, as needed. The time points of assessment are presented in Table 1. The full list of study measures is included in Table 3 in the Supplementary File1. To track app use activities, two

questions will be sent via the mini-apps chat box during the active intervention period at the end of weeks 2, 4, 6, and 8.

Table 1 Phase 2 pilot RCT study assessment timepoints

			Week					
			(Day 1)	2	4	6	8	12
Assessments								
Enrollment			X					
Informed consent			X					
Randomization			X					
Baseline assessment			X					
Interventions								
	Mini-app	Weekly reminder messages to use the mini-app	←	—	—	—	→	
		Mini-app access	←	—	—	—	—	→
	Control	Standard HIV prevention care	←	—	—	—	—	→
Follow-up survey (Long)					X		X	X
App-use survey (short)*				X		X		
In-depth interviews **					X		X	

*Only performed in participants in the intervention arm;

** Only performed in a subgroup of participants.

Qualitative progress evaluation

When close to the fourth week of intervention, a subgroup of 15 participants (10 intervention, 5 control) will be purposively sampled prioritizing those who have initiated PrEP to complete two in-depth interviews at weeks 4 and 8. Another group of participants (up to 5) who started PrEP between week 4 and week 8, regardless of the study arm, will receive a one-time in-depth interview at week 8. Interviews will focus on participants' experiences using the app and any changes in their perceptions and/or behaviors related to PrEP and HIV prevention practices during the study period (Table 4 in the Supplementary File1). Interviews will be conducted one-

on-one in private spaces – or via videoconferencing software (e.g. Zoom or Tencent Meeting), the last 60-90 minutes, and will be audio recorded with participants' permission.

Primary Outcome Measures

The primary outcomes for Phase 2 pilot RCT include the intention to use PrEP, progression along the stages of change to PrEP initiation, and PrEP initiation. PrEP use intention will be constructed as a continuous variable (range -3 to 3, from Very unlikely to Very likely) according to the participant's response to the question "How likely are you to start using PrEP?" PrEP initiation will be a binary variable, such that participants who successfully started PrEP (either through the study clinic or other PrEP providers) during the study period (Weeks 0 - 8) will be recorded as "1", otherwise as "0". Individual progression along the stages of change to PrEP initiation will be measured by a set of eight questions evaluating their contemplation, preparation, and actions to start PrEP and maintenance of using PrEP (64). This will be constructed as a discrete variable ranging 0-4 (0=precontemplation, 1=contemplation, 2=preparation, 3= action, 4= maintenance).

Secondary Outcome Measures

Secondary outcomes include: (1) feasibility variables, including the length of time for recruitment and enrollment, participants' retention rate (staying in the study) throughout the study course, and self-reported mini-app usage; (2) PrEP knowledge (5-item quiz, response options: true/false, total score: 0 – 5); (3) Number of HIV/syphilis tests (>=0, continuous)

ordered through the mini-app, tracked by the backend data; (4) PrEP adherence, measured by self-reported missed doses in the past week (a continuous variable, ranging from 0-7); (5) PrEP stigma (5-item scale, five-point Likert response scale from strongly disagree to strongly agree, total averaged score ranging from 1 – 5 with higher scores indicating higher perceived PrEP stigma; (6) PrEP attitudes, an averaged score of the participant's responses to a five-item PrEP attitudes scale with a five-point Likert response scale from strongly disagree to strongly agree, with higher scores indicating more positive attitudes toward PrEP (a continuous variable, ranging from 1-5); (7) PrEP self-efficacy, an averaged score of the participant's responses to a seven-item PrEP self-efficacy scale with a five-point Likert response scale from very difficult to very easy, with higher scores indicating higher self-efficacy to use PrEP (a continuous variable, ranging from 1-5).

Risks and Referrals

As HIV remains a stigmatized disease in many places in the world, including China. Same-sex sexual behaviors can also be associated with stigma and lack of social acceptance. The potential social harm that may cause to the participants by participation in our study may include emotional distress, embarrassment, and breach of confidentiality. During the study implementation, every effort will be made to ensure that study participants are protected from these risks, and to maintain confidentiality and discretion throughout all research procedures and data management and analysis. If at any time during the study, a participant divulges that he is at risk for harm, measures will be taken to ensure their safety. Reporting will be done as

appropriate to the situation and the legal statutes, and referrals will be provided to appropriate support, counseling or treatment resources.

In the case of an initial positive HIV test done through the study, participants who have initiated PrEP will be instructed to discontinue PrEP dosing. Participants testing positive will be referred to the study hospital – the Guangzhou Eighth People's Hospital for confirmation tests or other testing places if needed. The Guangzhou Center for Diseases Prevention and Control will be notified of confirmed positive results following China's public health reporting laws, a procedure that will be explained to participants at consent. For positive syphilis testing results, participants will be referred to as STI treatment at the Guangzhou Eighth People's Hospital. The study team will follow-up with participants testing positive for HIV or STI to encourage participants to seek appropriate care. For participants who want to continue using PrEP after the study ends, they can contact the study team and a list of local PrEP providers will be provided.

Data management

In-depth interviews will be audiotaped, transcribed verbatim (in Chinese), summarized in English based on the interview guide, and organized and managed using Dedoose cloud-based qualitative data analysis software (www.dedoose.com). The web-based survey will be collected through a Chinese professional secure electronic survey platform Wenjuanxing (www.wjx.cn). Survey data will be downloaded from Wenjuanxing and will be stored on password-protected encrypted study computers along with other electronic study files. All study files will have a back-up copy stored on UNC secure server space that only study personnel will have access to.

Statistical Analysis plan

All statistical data analyses will be conducted in Stata 16.0. An intention-to-treat analysis approach will be utilized (65).

Descriptive analysis

Descriptive statistical analyses will be first conducted to report baseline characteristics of participants, actual PrEP initiation rates, distribution of outcome variables, and other control variables at different time points throughout the study period (A full list of control variables please see Table 2 in the Supplementary File1. Examples include demographic characteristics, behavioral history of recreational drugs, alcohol and tobacco products, HIV risk perception, general stress, etc). For continuous outcome variables, we will first examine the mean changes from baseline to follow-up for the entire sample using statistical tests, and then estimate whether there are differences in net gains between the mini-app group and the control group, and between frequent mini-app users (use the mini-app once a week or more) and less frequent users. Observed effect sizes will be reported, to inform future study designs.

Bivariate analyses

Bivariate correlation analyses will be conducted to assess variables (including predictor and control variables) relating to PrEP use intention and PrEP initiation rate at Week 4 and Week 8. For the binary dependent variable "PrEP initiation" in particular, we will use the Chi-Square test

to compare the difference in PrEP initiation between the intervention group and the control group. Unadjusted *Odds Ratios (OR)* will be calculated and reported.

Multivariable analyses

Common confounder variables (e.g., age, education, in, come and other socio-demographic characteristics) and theoretical construct variables (i.e. PrEP knowledge, self-efficacy, stigma, and attitudes) will be adjusted for in multivariable analyses for each outcome of interest.

Given that the data collected in the pilot RCT is a longitudinal dataset with repeated measures at three time points, we will apply multilevel linear regression models to assess the association between continuous outcome variables and predictor variables. Missing data will be replaced with predicted values by multiple imputations, and sensitivity analyses will be conducted to compare the multiple imputation approach with analysis with complete cases only. If we have less than 50 participants retained at Week 8, or the multilevel model does not converge, we will run regression models and control for change over time.

Phase 2 Qualitative Analysis

The analytic approach for qualitative interviews from participants in Phase 2 will be similar to that applied in Phase 1. Besides, we will conduct a trajectory analysis (66) to understand participants' experience throughout the intervention period, including user experience of the mini-app, study engagement, evolving PrEP-related perceptions, and PrEP use behaviors. As we

will purposively sample participants who have initiated PrEP during the study and those who show less engagement for the interview, this approach will allow us better to understand the changing or non-changing process of individual PrEP use intention and initiation.

Incentives

Participants in Phase 1 will be provided remuneration at the end of each completed interview in the form of a 75-CNY (~ 10 USD) gift card or equivalent. Participants in Phase 1 will not be eligible for Phase 2 as they will have been exposed to the intervention before randomization.

Participants in Phase 2 will receive a 50-CNY (~ 7 USD) gift card for the in-person initial visit or baseline assessment and another 20-CNY (~3 USD) gift card for completing each Web-based follow-up survey via Wenjuanxing at Weeks 4, 8, and 12. Participants who complete all required study activities in Phase 2 will receive a bonus of 50-CNY (~ 7 USD) at the end of the study. Phase 2 participants who are sampled for in-depth interviews will receive 75-CNY (~10 USD) for completing each interview (up to two interviews for each participant). For participants who initiated PrEP through this research study, the cost of physical examinations (including required lab tests) and PrEP prescription will be covered by the study team. Participants will need to pay for PrEP medications out-of-pocket first and get 50% of the cost reimbursed at the monthly follow-up clinic visits, only if they fill the prescription at the study clinic or designated private pharmacies. After reimbursement, the total estimated cost to a participant in Phase 2 who starts PrEP is from 590 CNY (about 85 USD, for one-month generic PrEP supply or 30 pills) to 2000 CNY (about 286 USD, for two-month Truvada supply or 60 pills).

ETHICS AND DISSEMINATION

This study was reviewed and approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill, USA (IRB#19-3481), the Guangdong Provincial Dermatology Hospital, China (IRB#2020031), and the Guangzhou Eighth People's Hospital, China (IRB#202022155). All participants will be provided online consent and sign it electronically before taking part in the study. Our study team will work with local GBMSM CBOs to disseminate the study results to participants and the community via social media, journal publication, and offline workshops at local CBOs. This research addresses a critical need as GBMSM bear a disproportionate burden of China's HIV infections and remain underserved in the healthcare system.

DISCUSSION

Despite the high prevalence of HIV infection and risk factors among Chinese GBMSM, PrEP use is quite limited (67). A theory-informed, GBMSM-friendly, and innovative behavioral intervention to facilitate PrEP uptake among Chinese GBMSM may help to increase the awareness of PrEP among this population through timely information and strengthened motivation and skills. It may also help to link individuals to providers and clinics where they can receive PrEP. While PrEP campaigns in China have to-date failed to engage relevant communities (68), initiatives in other settings have successfully used GBMSM-tailored approaches to promote PrEP (41–44), including using mHealth technologies to approach

GBMSM "where they are". In an online survey of 1,035 Chinese GBMSM in 2017, about 75% of the participants mainly met their sex partners online (69), and Chinese GBMSM have been using the Internet frequently to search for HIV-related information, counseling, or testing services (35).

A large body of evidence has suggested that HIV-related and sexual health interventions delivered through Internet-enabled platforms are feasible and acceptable in Chinese settings (70), including interventions through websites, text message, and mobile apps that have shown effectiveness in reducing HIV-related risk behaviors, increasing linkage to care, and improving medication adherence (4,71,72). Thus, an mHealth-enabled intervention, like this PrEP education mini-app, which leverages the platform of a popular Chinese social media app could facilitate the rapid scale-up of PrEP use in China. In contrast to the traditionally top-down health mandates or researcher-led intervention projects, the PrEP mini-app tested in our study was co-created by a team of young gay men, HIV clinicians and public health researchers through a crowdsourcing hackathon. This not only helps to generate innovative approaches to address their own social and health needs, but also increases the acceptability and potential impact of the intervention in target populations.

Developing and testing theory-driven interventions around HIV prevention and care is challenged by rapid developments in the field, which can influence the pertinence or timeliness of interventions – a case in point concerns PrEP in China. The Chinese government has taken several crucial steps in introducing PrEP to China, including launching large-scale PrEP studies in multiple provinces and cities in 2018, developing implementation guidelines for PrEP in

China (68), and officially approving TDF-FTC for HIV PrEP in August 2020 (73). Nevertheless, the large population of GBMSM who would benefit from PrEP will encounter significant challenges for timely scale-up. The PrEP education mini-app developed by this study aims to meet the pressing need for innovative, easily accessible, and broadly acceptable modes of promoting and supporting PrEP among Chinese populations (74).

We also expect some challenges in the study implementation given the rapidly evolving conditions of the global COVID-19 pandemic and its impact on human activities and interpersonal interactions. The fieldwork is expected to take place between summer 2020 to summer 2021, while international travel of our research team members will be significantly delayed or restricted because of the global mitigation strategies to control COVID-19. In order not to bring significant delay to the study progression as well as encourage participants' engagement, our research team has been working remotely with local collaborators regarding GBMSM recruitment and enrollment. All data collection activities including in-depth interviews and surveys will be conducted electronically via videoconferencing systems or web-based survey tools, to ensure participants' and the research team's safety. The mHealth-based feature of the proposed intervention does not require in-person interaction between the participants and the research team; though study enrollment currently includes clinic-based lab tests and follow-up visits among PrEP users.

Whether globally or in China, limited data exist on the efficacy of app-based interventions aimed to increase PrEP uptake and adherence among GBMSM. If successful, this research study may help inform the implementation design of a rapid PrEP roll-out in China by examining whether

an mHealth intervention can promote PrEP uptake and other HIV prevention services. Promoting such services among GBMSM is of great importance as this population bears a disproportionate burden of China's HIV infections and remains underserved in the healthcare system.

DECLARATIONS

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Author Contributions

KM, JT, and CL conceived the study and drafted the manuscript. EF, DM, WT, RS, AH, LLH, XY, HJH, and JL participated in designing and implementing the study and assisted in drafting the manuscript. JT and WT obtained funding for the study. TS, KXT, MY, and ZM developed the prototype of the mini-app and assisted in drafting the manuscript. All authors have read the final manuscripts, and approve for it to be published.

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Data Availability Statement

Deidentified individual data that supports the results will be shared beginning 9 to 36 months following publication provided the investigator who proposes to use the data has approval from an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Research Ethics Board (REB), as applicable, and executes a data use/sharing agreement with the University of North Carolina at Chapel Hill.

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1

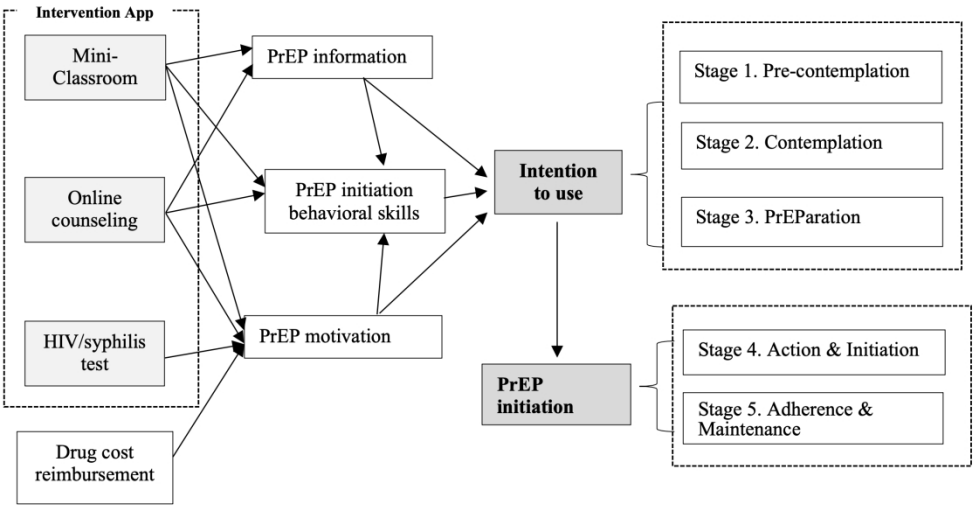

Figure 1 The conceptual model of the WeChat mini-app PrEP intervention

443x238mm (144 x 144 DPI)

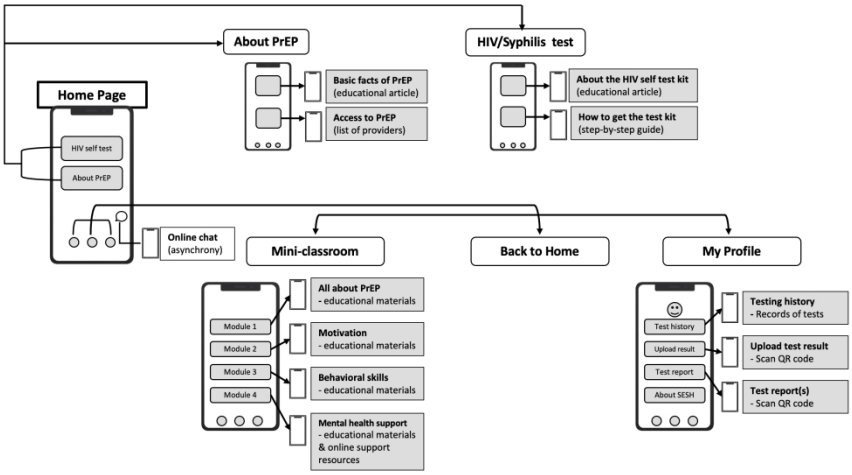

Figure 2 Wireframe of the mini-app PrEP intervention

505x284mm (144 x 144 DPI)

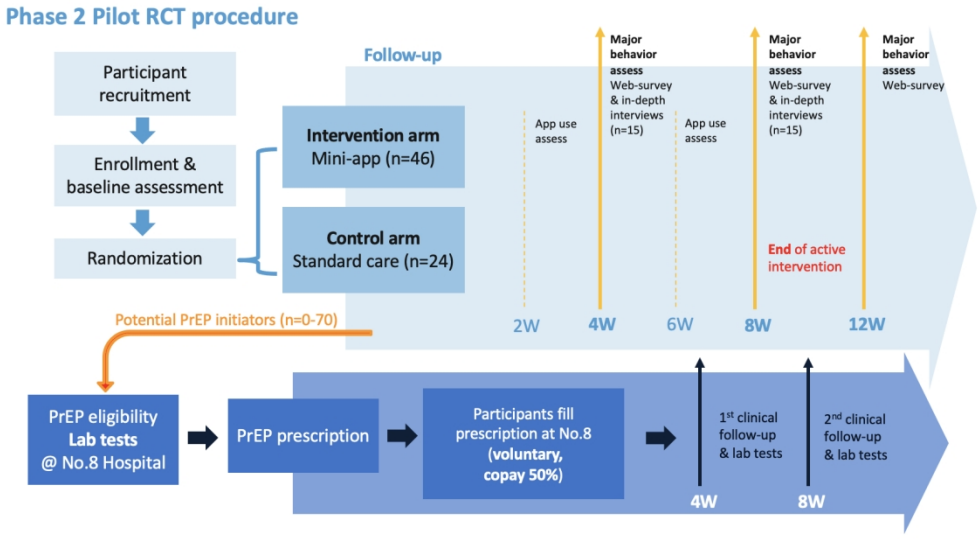

Figure 3 Phase 2 study design, a two-arm RCT

307x173mm (144 x 144 DPI)

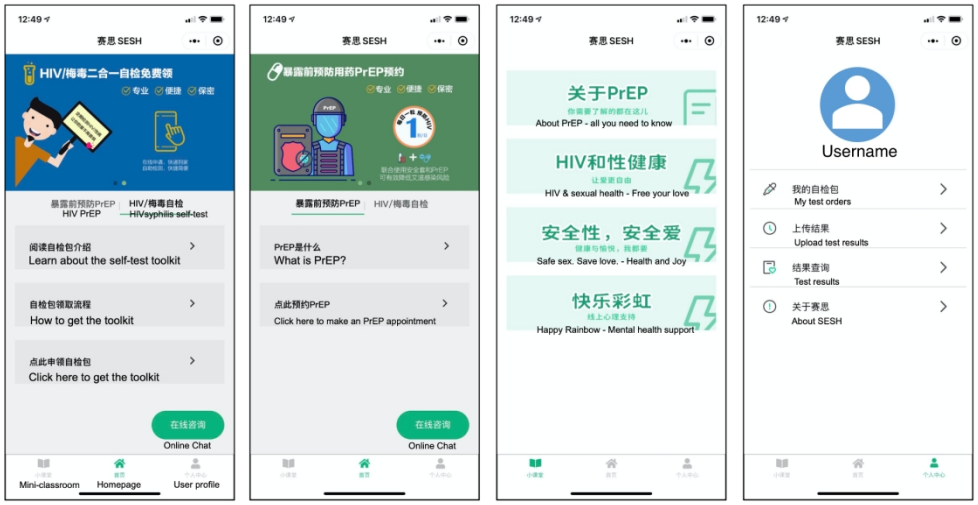

Figure 4 Screenshot of the mini-app from left to right: (1) Homepage 1: at-home test kit, (2) Homepage 2: PrEP appointment, (3) the Mini-classroom, (4) User profile center

338x190mm (150 x 150 DPI)

Supplementary file

Table 1 Summary of key functions of the mini-app prototype

Key functions	Intervention objectives	Intervention strategies			
		Information	Motivation	Behavioral Skills	Mental Health
Mini-classroom	Build knowledge and navigation skills around local HIV care system, enhance interest and motivation to use PrEP, and increase self-efficacy in HIV/STI prevention strategies; Improve mental health management skills.	Educational materials in multimedia forms, including text, videos, and graphics.	Real stories of PrEP users; Positive meanings of using PrEP and HIV/STI testing.	List local PrEP and other HIV/STI care providers and contact information; Tips for safe sex, condom use, and PrEP initiation, adherence, and management.	Links to local support groups and mental health care resources. Self-management for mental health. Coping with stigma and discrimination against LGBTQ community.
Online counseling	Enable MSM to describe their feelings or concerns related to HIV, sexual health or this intervention study, and help them make healthy decisions.	Answer questions about HIV, STI, PrEP, and/or other health topics, and provide additional information if needed.	Tailored health advice regarding PrEP use.	Referral to the HIV/PrEP clinic at the study hospital, or other healthcare providers based on individual needs.	Listen to their needs, and refer to local support groups or mental health care resources, if necessary.
Home-based HIV/syphilis test ordering	Establish individual habit of routine testing for HIV and syphilis.	Information about how to complete the home-based test kit.	Provides a cue to action and removes barrier of in-person testing and stigma.	An HIV/syphilis home-based test kit ordering system.	
User profile center	Allow participants to monitor their HIV/syphilis testing behaviors.			A profile page to manage orders of HIV/syphilis test kits and keep a record of test results.	

Table 2 Main topics in the in-depth interview guide in Phase 1

Topic	Description	Sample probes
HIV/STI knowledge & experience	Understanding or knowledge of HIV/STI, HIV/STI testing experience, experience with the local HIV/STI prevention & care system.	What do you know about HIV/STI? What do you think about the local HIV prevention and care system? What do you know about PEP and your experience with it, if any?
PrEP knowledge and attitudes	Understanding of PrEP, and attitudes, including acceptability and willingness of using PrEP to prevent HIV, pre- and post- PrEP attitudes for PrEP-experienced individuals.	What do you know about Pre-Exposure Prophylaxis (PrEP)? Have you ever heard any people you know are taking PrEP? How do you think PrEP have or could have an impact on your sexual health?
PrEP experience *(for current & intermittent users only)*	Narrative of PrEP using experience	What do you think about your PrEP using experience? (probe for motivations to start PrEP, experience with PrEP refilling, cost, side effects, adherence/discontinuation, others' attitudes and/or support)
Barriers to PrEP use/continued use	Perceived barriers to access, use, and manage PrEP care, and suggestions for PrEP-scale in China	Have you ever considered using PrEP? (If Yes) How would you think that will help you? (If not) would you please tell me about your concerns?
Biomedical prevention strategies	Experience or perceptions of using biomedical strategies to prevent diseases.	What do you think about taking medicines for preventive purpose, like using PrEP to prevent HIV?
Health beliefs and stress due to COVID-19	Experience of the COVID-19 pandemic and how it has influenced health beliefs, views on preventive medicine, and mental health	What do you think about the COVID-19 pandemic has changed your thoughts of health, if any? How have you been since the outbreak of COVID-19?
Mini-app usability test	Feedback on the mini-app design, contents and ease of use.	How was your overall experience with the mini app? How did you think the app meet your needs/expectations?
	Suggestions on app refinement based on the current structure.	If you were able to redesign this feature, what changes would you make? What other contents could be added to make the app more useful or engaging to you?

Note: for people who have never heard of PrEP before, a standard brief description of PrEP will be given before asking further questions: *The HIV prevention pill (known as 'PrEP') is a pill taken to prevent HIV. It is safe and more than 90% effective when taken every day. People who decide to use the oral HIV prevention pill need to return to their doctor every 3 months for HIV/STI testing, bloodwork, and a new prescription for the next 3 months*". [2]

Table 3 Phase 2 pilot RCT study measures and timepoints of data collection

		Week					
		Day 1	**2**	**4**	**6**	**8**	**12**
Primary outcomes							
PrEP use intention	3-item scale with 5-point rating (1 to 5) [1]	X		X		X	X
PrEP stages of change	10-item scale with 5 stages of progression (1 to 5) [2]	X		X		X	X
PrEP initiation	Yes/No (study record)			X		X	X
Secondary outcomes							
PrEP knowledge	5-item True/False quiz	X		X		X	X
Test behavior	Frequency of at-home HIV/syphilis tests (≥0)			X		X	X
Willingness to pay	Percentage of monthly income to pay for PrEP	X		X		X	X
Self-report PrEP adherence***	Daily PrEP: missed doses in past 7 days (0 to 7) PrEP on-demand: occurrence of missing any dose in a single sex event and number of sex events without any PrEP coverage in the past month			X		X	X
PrEP self-efficacy	8-item scale with 5-point rating (1 to 5)[1]	X		X		X	X
PrEP stigma	5-item scale with 5-point rating (1 to 5) [1]	X		X		X	X
PrEP attitudes	5-item scale with 5-point rating (0 to 5) [1]	X		X		X	X
Predictor variables							
Intervention exposure	Yes/No	X					
Mini-app Engagement*	Self-reported frequency of app use		X	X	X	X	X
	Perceived app usefulness		X	X	X	X	X
Covariates							
Demographics & socio-economic indicators	Age, education, gender, sexual orientation, relationship status, private or shared bedroom, employment, income	X				X	
Drug use	Ever used recreational drugs (Yes/No)	X					
	Drug use in the past 4 weeks	X		X		X	X
Alcohol use	Ever consumed alcohol (Yes/No)	X					
	Average weekly alcohol consumption, past 30 days	X		X		X	X
Tobacco use	Ever consumed tobacco products (Yes/No)	X					
	Average weekly tobacco consumption, past 30 days	X		X		X	X
Prior HIV test history	Self-report HIV test history before the study (Yes/No)	X					
HIV knowledge	2-item HIV quiz	X		X		X	X
HIV risk perception	2 questions of perceived risk of HIV infection	X		X		X	X
HIV-related anxiety	3-item scale with 5-point rating[3]	X		X		X	X
Perceived stress	4-item Cohen Perceived Stress Scale[3] (overall stress)	X		X		X	X
HIV-social support	10-item scale with bipolar scale (-2 to 2)[4]	X		X		X	X
Condomless sex	Occurrence of condomless sex in the past 4 weeks	X		X		X	X
Number of sex partners	Self-reported number of sex partners, past 4 weeks	X		X		X	X

*Only performed in participants in the intervention arm;
** Only performed in a subgroup of participants;
***Only performed in participants who have started using PrEP.

Table 4 Main topics in the in-depth interview guides in Phase 2

Topic	Description	Sample probes
HIV/STI knowledge & experience	Understanding or knowledge of HIV/STI, HIV/STI testing experience, experience with the local HIV/STI prevention & care system.	What do you know about HIV/STI? What do you think about the local HIV prevention and care system? What do you know about PEP and your experience with it, if any?
Health beliefs and stress due to COVID-19	Experience of the COVID-19 pandemic and how it has influenced health beliefs and mental health	What do you think about the COVID-19 pandemic has changed your thoughts of health, if any? How have you been since the outbreak of COVID-19?
PrEP knowledge and attitudes	Understanding of PrEP, and attitudes, including acceptability and willingness of using PrEP to prevent HIV	How has your participation in this study changed your thoughts on PrEP? In general, what do you think about taking medicines for health purposes? How about take medicines to prevent HIV?
PrEP experience *(for participants who started PrEP)*	Narrative of PrEP using experience in this study, including perceived barriers to access, use, and manage PrEP care	What you think are the main reasons that motivate you to initiate PrEP? What is your experience of getting and refilling PrEP through this study?
PrEP intention *(for participants who haven't started PrEP)*	Perceived barriers or concerns of starting PrEP Readiness to start PrEP	Would you please tell me about your concerns or things that you think are barring you from accessing PrEP? How likely are you going to start PrEP in next week, next month or in near future?
Mini-app using experience	Feedback on the mini-app design, contents and ease of use, technical problems encountered.	How was your overall experience with the mini app? How did you think the app meet your needs/expectations?
	Using experience on each of the main functions: HIV/syphilis testing, the Knowledge Center, & online counseling	How would you describe your experience of using this feature? How did you think by reading these articles have changed your health beliefs or behaviors? Overall, how useful do you think this online counseling is for supporting your health, PrEP use or HIV/STI prevention?
	Long-term sustainability	How could you see yourself using this app in the future? Would you recommend this app to your friends?

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Page 1
Funding	4	Sources and types of financial, material, and other support	Page 27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 26-27
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 27
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4-6
	6b	Explanation for choice of comparators	Page 4-6
Objectives	7	Specific objectives or hypotheses	Page 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Phase 1: "Participant" section on Page 10; Phase 2: the "Participant" section on Page 12.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Phase 1: "Participant" on Page 10 Phase 2: Textbox 1 on Page 12.
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	"Study arms" on Page 14-16. Table 1, Figure 2-4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	"Referrals" on Page 19.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	"Qualitative progress evaluation" on Page 17. "Incentives" on Page 22-23.

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Exclusion criteria in Textbox1 on Pages 12-14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pages 18-19, Table 2 in supplementary file
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1 Figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Phase 1: “Participant” on Page 10 Phase 2:
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Phase 1: last paragraph on Page 10 Phase 2: first paragraph under “Participants” on Page 12.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	“Randomization” on Page 14.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	“Randomization” on Page 14.

Implement ation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	"Randomizatio n" on Page 14.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Phase 1: "Study design" on Pages 9-10 Phase 2: "study assessments" on Pages 16-18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Description of sending weekly reminder messages to participants in the last paragraph on Page 14. "Qualitative progress evaluation" on Page 17. "Incentive" section on Page 22
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Phase 1: first paragraph on Page 10. Phase 2: Page 20

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pages 20-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 21
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	"Referrals" on Page 19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 23
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Pages 16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 27
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 27
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary materials.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT

BMJ Open

A community-engaged mHealth intervention to increase uptake of HIV Pre-Exposure Prophylaxis (PrEP) among gay, bisexual and other men who have sex with men in China: Study protocol for a pilot randomized controlled trial

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Manuscript ID	bmjopen-2021-055899.R2
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Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	HIV/AIDS, Infectious diseases, Public health, Sexual health
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, PUBLIC HEALTH, SOCIAL MEDICINE, QUALITATIVE RESEARCH

TITLE PAGE

A community-engaged mHealth intervention to increase uptake of HIV Pre-Exposure Prophylaxis (PrEP) among gay, bisexual and other men who have sex with men in China: Study protocol for a pilot randomized controlled trial

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A community-engaged mHealth intervention to increase uptake of HIV Pre-Exposure Prophylaxis (PrEP) among gay, bisexual and other men who have sex with men in China: Study protocol for a pilot randomized controlled trial

Protocol date and version: 2020-09-02, Version 3.

ABSTRACT

Introduction: The large number of key populations in China who would benefit from HIV pre-exposure prophylaxis (PrEP) in the context of limited health system capacity and public awareness will pose challenges for timely PrEP scale-up, suggesting an urgent need for innovative and accessible interventions. This study aims to develop and pilot test a theory-informed, tailored mobile phone intervention that was co-developed by young gay men, HIV clinicians and public health researchers to increase engagement in PrEP education and initiation among Chinese gay, bisexual, and other men who have sex with men (GBMSM), who bear a disproportionate burden of HIV infections and remain underserved in the healthcare system.

Methods and analysis: This two-phase study includes a formative assessment using in-depth interviews (N=30) and a 12-week experimental pilot study using a two-arm randomized controlled trial design (N=70). The primary intervention is delivered through a WeChat-based mini-app (a program built into a Chinese multi-purpose social media application) developed by young GBMSM from a 2019 crowdsourcing hackathon. Using mixed-methods, we will further investigate the specific needs and concerns among GBMSM in terms of using PrEP as an HIV

prevention strategy, how their concerns and PrEP use behaviors may change with exposure to the mini-app intervention during the study period, and how we can further refine this intervention tool to better meet GBMSM's needs for broader implementation.

Ethics and dissemination: This study and its protocols have been reviewed and approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill, USA (19-3481), the Guangdong Provincial Dermatology Hospital, China (2020031), and the Guangzhou Eighth People's Hospital, China (202022155). Study staff will work with local GBMSM community-based organizations to disseminate the study results to participants and the community via social media, workshops, and journal publications.

Trial Registration: The study was registered on clinicaltrials.gov (NCT04426656) on June 11, 2020. Prospectively registered.

Keywords: HIV, pre-exposure prophylaxis, mHealth, intervention, men who have sex with men, China, mini-app

Article Summary

1. The intervention app prototype was co-created by the GBMSM community, HIV clinicians and public health researchers through a gay-friendly doctor finder hackathon - a crowdsourcing strategy that solicits innovative public health solutions directly from the end-user community, increasing the intervention's acceptability and potential impact among target communities.
2. The intervention content development was guided by the Information, Motivation, and Behavioral Skills Model, a theoretical model of behavioral change that has been widely applied in HIV-related behavioral intervention studies among different populations including Chinese GBMSM.
3. Mobile health (mHealth) interventions for HIV prevention and sexual health promotion are feasible and highly acceptable among Chinese GBMSM due to their privacy, portability, and convenience, facing the broad spread of HIV- and gay-related stigma in Chinese society.
4. The study design follows the best practice of intervention development that includes a formative assessment of unmet needs, co-creation with the community, pilot testing for preliminary evidence of efficacy, providing preliminary data for a future larger-scale intervention study.
5. The intervention allows participants to make online PrEP appointments at the only local HIV hospital in the study city, and an initial in-person clinical visit is still required for PrEP prescription. It is also a timely response to China's recent approval of TDF-FTC as PrEP in 2020, which we believe could facilitate a rapid scale-up of PrEP among populations at risk of HIV infection in China.

INTRODUCTION

HIV prevalence among gay, bisexual, and other men who have sex with men (GBMSM) in China has steadily increased over the past five years (1–3). In Guangzhou, a major economic center in Southern China, the HIV prevalence among sexually active GBMSM increased from 3.9% in 2009 (4) to 11% in 2017 (5). Individual and contextual risk factors associated with HIV acquisition among Chinese GBMSM include condomless sex, high rates of ulcerative sexually transmitted infections (e.g. syphilis), use of recreational drugs during sex, gay entertainment venues (e.g., public bathhouse), and social and sexual networking mobile phone applications (1,6–11). Taken together, these risk factors suggest that Chinese GBMSM could benefit from additional HIV prevention strategies such as pre-exposure prophylaxis (PrEP).

However, the overall awareness of PrEP among Chinese GBMSM remains relatively low and varies across samples. Generally 20 % - 75% of GBMSM respondents reported having heard of PrEP in China-based studies. (12–14) By July 2021, there was an estimated number of 6000-6500 PrEP users reported from official demonstration projects in this country (15). Cross-sectional surveys (12,16–24) and PrEP clinical trials (25–27) and in-depth interviews with HIV-negative GBMSM (26,28) have reported perceived barriers to PrEP uptake among Chinese GBMSM including concerns about side effects, financial cost, and low HIV risk perception. Yet little is known about multi-level barriers to PrEP uptake and maintenance in China, especially from those with PrEP using experience. Further, there is widespread HIV- and gay-related stigma and discrimination in clinical settings (29–31) that may inhibit the effective delivery of PrEP drugs and related services for GBMSM (32).

The China National Medical Products Administration approved Tenofovir-Emtricitabine (TDF-FTC) as HIV PrEP in China on August 11, 2020. However, the aforementioned gaps highlight the need for innovative, culturally appropriate, and GBMSM-friendly tools that prepare GBMSM for PrEP uptake, to pave the way for a rapid scale-up. Facing the broad spread of HIV- and gay-related stigma in Chinese society, mobile health (mHealth) interventions for HIV prevention and sexual health promotion are feasible and highly acceptable among Chinese GBMSM due to their privacy, portability, and convenience (33–35). Health hackathons as a crowdsourcing approach are an effective and convenient way to mobilize GBMSM communities in generating innovative mHealth solutions to meet their own health needs (36), which could further potentially contribute to reductions in internalized stigma and an increase in community resilience among sexual minority populations (37,38).

Globally, limited data exist on the efficacy of app-based interventions aimed to increase PrEP uptake among GBMSM. Among the few published mHealth PrEP intervention efficacy studies, text messaging has been effective in improving PrEP adherence in GBMSM via reducing missed doses (39,40). More mHealth PrEP uptake intervention studies are underway, however, all are in high-income countries (41–44). To date, little is known about the optimal design and efficacy of using mHealth-enabled interventions for PrEP promotion in Chinese populations, especially among GBMSM.

Aims and objectives

This study focuses on developing and testing a tailored mobile app-based intervention built on our previous work from a gay-friendly doctor finder hackathon in China (45), aiming to increase engagement in PrEP education and initiation, and generate hypotheses that explain potential behavioral pathways to PrEP uptake among Chinese GBMSM. The study site is Guangzhou, a major economic center of southern China. To this end, the study has two phases: Phase 1 collects formative data using in-depth interviews to assess unmet needs in HIV prevention (PrEP in particular) and sexual health among HIV-negative GBMSM, and test and refine the usability of the mini-app. Phase 2 will implement a two-arm RCT to assess the feasibility and preliminary evidence of the efficacy of the refined mini-app in increasing intention to use PrEP and PrEP initiation among HIV-negative GBMSM. Specific aims include:

Aim 1: Generate hypotheses around behavioral pathways explaining PrEP uptake among Chinese GBMSM with different PrEP using experience (e.g., PrEP-naïve, former and current PrEP users) by analyzing qualitative data from in-depth interviews of the formative assessment (Phase 1, n=30).

Aim 2: Assess the feasibility and preliminary efficacy evidence of a mobile phone-based PrEP education intervention tool (the mini-app) compared to the standard of HIV prevention care in increasing individual intentions to use PrEP and actual PrEP initiation rate through a two-arm pilot RCT (Phase 2) with 70 HIV-negative GBMSM (18 years old and above) in Guangzhou, China.

METHODS AND ANALYSIS

Theoretical foundation for intervention

Figure 1 presents the study's conceptual model. The intervention content development is informed by the Information, Motivation and Behavioral Skills Model (the IMB model). The IMB model proposes a mediational framework that hypothesizes that the performance of many health-related behaviors is determined by three core constructs: *information*, *motivation,* and *behavioral skills* (46). With years of application in HIV research, the IMB model has been widely applied in intervention studies and adapted to promote specific HIV-related behaviors, including PrEP care-related behaviors (47–49). Among Chinese GBMSM, the IMB model was also found useful in explaining HIV preventive behavior such as condom use (50). We also use the Motivational PrEP Cascade (MPC), (51) originally proposed by Dr. Jeffrey Parsons and colleagues who combined the concept of PrEP care cascade (52) and the Transtheoretical Model of Behavioral Change, to inform the measurement of the several stages of behavioral change culminating in PrEP initiation. The MPC outlines stages of readiness to make a behavioral change, including pre-contemplation, contemplation, preparation, action, and maintenance of the change. (53) A 2018 survey study based on the MPC among a sample of 708 HIV-negative GBMSM from multiple major cities in China showed that 53% of the respondents who were PrEP eligible were in the pre-contemplation stage, 36% in contemplation, 9% in PrEParation, 2% in PrEP action and initiation, and none in adherence and maintenance.(17) Given variable awareness about PrEP and the wide range of age of the target population, measuring the stages of change toward PrEP initiation will help us better tailor and refine the intervention.

Figure 1 *The conceptual model of the WeChat mini-app PrEP intervention*

Patient and Public Involvement: Development of the Intervention Tool – PrEP Education WeChat Mini-app

The intervention is delivered via a WeChat-based mini-app (a program built within an existing commercial application) that was developed by a team of young GBMSM from a GBMSM-friendly Doctor Finder Hackathon contest (45). This hackathon contest was part of a series of crowdsourcing events that aimed to engage the GBMSM community in generating public health innovations in HIV and sexual health promotion in China. From February 2018 to March 2018, the Shenzhen University College of Mass Communication, the non-profit organization Social Entrepreneurship to Spur Health (SESH), and Blued (the largest gay social networking app in China) held a crowdsourcing contest for designing concepts of a mobile phone-based, GBMSM-friendly doctor mobile app. In July 2018, four focus group discussions with 38 GBMSM in Guangzhou and Shenzhen were subsequently conducted to solicit participants' feedback on refining the app design (54).

From December 2018-April 2019, UNC Project China with support from SESH and Blued hosted a GBMSM-friendly Doctor Finder Hackathon in Guangzhou, during which the participants were asked to develop a mobile phone-based doctor finder prototype based on the work from previous events. A total of 38 participants grouped into eight teams attended the final hackathon contest and developed eight prototypes after a 72-hour hacking. Four prototypes adopted the mode of a mini-app embedded within WeChat, and three prototypes were designed as stand-alone apps, and one was designed as a tool that can be adjusted to multiple platforms.

One of the WeChat mini-app prototypes was adapted for use in the current study. WeChat (Android and iOS) is a social platform in China with over one billion active users (55) that has been widely used for public health education by Chinese health administrations and private organizations (56). The WeChat app allows developers to build new app programs (i.e. the mini-app) within the platform that are accessible without additional download or installation.

Before testing and evaluating the mini-app in the current study, we invited a group of key community stakeholders including gay men, sex educators, and local HIV-related CBO workers to test the mini-app prototype and provide valuable feedback in user-interface design and choice of educational materials. The main features of the version of the interventional mini-app for the current study include: (1) the Mini-classroom, educational materials which cover topics of HIV and STI, PrEP and PEP, and mental health, aiming to change participant's information, motivation, and behavioral skills to initiate PrEP; (2) an at-home HIV/syphilis dual testing kit ordering system; (3) chat-based online counseling, and (4) a user profile center (their account in the mini-ap is automatically linked to their WeChat account with the user's permission). The overall structure of the mini-app is illustrated in Figure 2, and a detailed description of the main features is presented in Table 1 in the Supplementary File1.

Figure 2 *Wireframe of the mini-app PrEP intervention*

Phase 1: Formative Research—Needs Assessment and Mini-app Testing

Study design

In Phase 1 we conduct in-depth interviews among Chinese GBMSM to understand the key barriers and facilitators of using PrEP. We also assess participants' perceived usability of the intervention mini-app during the interview. All one-on-one interviews are conducted by the principal investigator via videoconference (audio-recorded with participants' permission) and last 60-90 minutes. The principal investigator (CL) is a PhD candidate in Health Behavior with over 10 years training in public health and 5 years research experience in HIV prevention and LGBTQ health among Chinese populations in particular. We use a semi-structured interview guide (Table 2 in Supplementary File1) with tailored questions for participants with and without PrEP experience. Interview topics cover knowledge, attitudes, and willingness to use PrEP and/or PrEP use history, preference over PrEP regimens (daily vs. event-driven dosing, oral vs long-term active injectable PrEP) and delivery modes, and past pathways, barriers, and facilitators to HIV testing and PrEP services. During the interview, participants are introduced to the mini-app design and features, use the mini-app for 5-10 minutes, complete a 10-item app usability scale (System Usability Scale(57,58)), and discuss the app's design, contents, and ease of use. Following the interview, each participant completes a brief demographic survey via Wenjuanxing, an online survey tool in China. All interviews will be transcribed in Chinese and analyzed using the qualitative analysis platform, Dedoose. (59) The qualitative analysis will be conducted in Chinese with the translation of exemplary content for English-language publications. The PI (CL) will take the lead role in applying a thematic analysis-based approach (60) for identifying, analyzing, and reporting patterns within the data. The other research team members will be actively engaged in the monitoring of data collection process, and proving continuous feedback on data analysis and interpretation via regular meetings with CL.

Participants

To represent the variety of experience GBMSM has had with PrEP, we will conduct in-depth interviews with 30 Chinese GBMSM at different stages of the PrEP care continuum, including approximately 20 PrEP naïve individuals, five prior PrEP users who are not currently on PrEP, and five current PrEP users. This sample size is generally considered sufficient for thematic analysis to reach information saturation among a relatively homogenous group. (61) While the mini-app is primarily designed for PrEP-naïve GBMSM, including the perspectives of past and current PrEP users is intended to gain feedback on the intervention design and content based on experiences across the stages of change in PrEP adoption. Participants will be recruited through research advertising on Chinese social media and referral by local GBMSM-related organizations.

Eligibility criteria for Phase 1 are: Chinese citizen and current resident, assigned male sex at birth, age 18 and above, any lifetime anal sex with another man, and willingness to sign (or e-sign) informed consent. Exclusion criteria include self-reported HIV-positive status or reporting or demonstrating mental health issues which may compromise participant safety, including memory loss, cognitive impairment, intellectual disability, or communication disorders.

Mini-app Refinement

Before starting Phase 2, we will refine the mini-app based on participants' feedback on the app design from Phase 1 formative assessment. Potential adjustments to the mini-app may be feasible

in changing content, and graphic and text appearance, but not functionality or structure of the app. All requests regarding functionality and app structure will be recorded and considered for future iterations of the app.

Phase 2: Pilot Randomized Controlled Trial

Study Design

Phase 2 will evaluate the feasibility and preliminary evidence of the efficacy of the mini-app in increasing intention to use PrEP and PrEP uptake through a two-arm pilot RCT comparing the mini-app to the standard of HIV prevention care (Figure 3). The study is estimated to last up to 12 weeks, where the first eight weeks is the active intervention period and the last 4 weeks is post-intervention observation.

Figure 3 *Phase 2 study design, a two-arm RCT*

Note: Participants can purchase PrEP medicines (TDF-FTC) from the study hospital. Participants pay for the medicine out-of-pocket and are reimbursed 50% of the cost at each monthly follow-up visit.

Study setting

A convenience sample will be recruited in Guangzhou, China via SESH and local LGBTQ-related community-based organizations (CBOs). Our partners –SESH, CBOs and the study hospital (the Guangzhou Eighth People's Hospital) have extensive experience in providing

research support on GBMSM- and HIV-related studies in Chinese settings. The study physicians at Guangzhou hospital have years of experience in both clinical practice and research with GBMSM patients. All study team members have completed the CITI training in Good Clinical Practice before the study starts.

Participants

A convenience sample will be recruited via partner CBOs and online advertising on Chinese major social medias, including WeChat and Sina Weibo. The generally recommended sample size of pilot trials ranges from 24 to 100 (62,63). In this pilot test, we plan to enroll 70 participants to assess preliminary evidence of efficacy and feasibility for a future main trial. Those interested in the study will complete a verbal eligibility screening by the principal investigator (Textbox 1). Those screened eligible will be scheduled for an initial in-person clinic visit or a virtual enrollment via videoconferencing. During this visit, they will complete informed consent and a baseline survey, and be randomized to one of two study arms.

Textbox 1. PrEP mini-app Phase 2 Pilot RCT inclusion and exclusion criteria

Inclusion criteria: Individuals must self-report:

- Having a smartphone with WeChat installed.
- Assigned male sex at birth, HIV-negative, age 18 and above, ever having had anal sex with another man, currently residing in Guangzhou, identifying as a Chinese citizen, able to sign written informed consent and participate in the study procedures as required. AND

- At least one characteristic associated with the risk of HIV infection in the previous 6 months:
    - Unprotected (condomless) receptive anal intercourse with a male partner(s)
    - More than two male partners (regardless of condom use and HIV serostatus)
    - Reported STI, such as syphilis, HSV-2, gonorrhea, chlamydia, chancroid, or lymphogranuloma venereum.
    - Reported use of post-exposure prophylaxis (PEP)
    - Have a sexual partner living with HIV

Exclusion Criteria:

- People living with HIV
- Currently taking oral PrEP based on self-report before enrollment
- Symptoms of acute HIV infection in the previous 30 days (e.g. fever, flu-like symptoms)
- Suspected exposure to HIV in the previous 72 hours
- Contraindications for taking oral PrEP
- Personal diagnosis or family history of hemophilia (self-report)
- Participating in another research intervention study related to HIV or PrEP
- Having serious chronic disease, including metabolic diseases (such as diabetes), neurological, or psychiatric disorders
- Mental health issues may compromise adherence or safety, including memory loss, cognitive impairment, intellectual disability, or communication disorders.

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Randomization

We will conduct a permuted block randomization that assigns the 70 participants to either the mini-app arm or the control arm in a 2:1 ratio. Randomization sequence will be created using Stata 16.0 (StataCorp LLC. College Station, TX) with block size of six. The 2:1 allocation will be used to ensure the capture of the range of users' reactions to the mini-app and its content. The randomization process will be conducted by a research assistant after the full consent process.

Study arms

Intervention Condition: The PrEP education mini-app

The PrEP education mini-app (Figure 4 presents the screenshots) serves as the primary participant-facing component of the intervention. Usage of the mini-app will be at participants' discretion or preference. Weekly reminders that encourage participants to use the mini-app will be sent out through WeChat messages. At this stage of development, the mini-app will not be able to track individual user information or activity. Self-reported app usage will be assessed in bi-weekly follow-up surveys and in-depth interviews at the 4th and 8th weeks. After Week 8, participants in the intervention arm will no longer receive reminder messages but may continue using the mini-app throughout the whole study period – up to 12 weeks from the time of enrollment, or continue using to the end of their first two months of PrEP use.

Figure 4 *Screenshot of the mini-app from left to right: (1) Homepage 1: at-home test kit, (2) Homepage 2: PrEP appointment, (3) the Mini-classroom, (4) User profile center*

Standard of HIV prevention care

Participants in both study arms will receive standard HIV prevention care during the initial and final study visits, including printed or electronic HIV prevention materials about PrEP and HIV/STI testing, referrals to local prevention services, and a description of the standard procedure to access PrEP through the study clinic.

PrEP Initiation

Participants in both arms can choose to initiate PrEP through the research study at any time point from enrollment through the end of Week 8. Participants who decide to start PrEP after Week 8 will still be able to receive standard PrEP care at the study clinic, but they will not be eligible to receive complimentary physical examinations that are covered by this research project (Please see details in *Incentives*). Participants can contact the study team via phone call, text messages, or via the chat function in the mini-app (intervention arm only) to communicate their interest in PrEP initiation. Interested participants will be referred to the Department of Infectious Diseases at the study hospital to consult a clinician regarding HIV risks and PrEP eligibility. As per protocols in the study hospital, participants starting PrEP will undergo standard of care comprehensive physical examinations including routine blood and urine examinations, hepatic and renal function tests, and HIV/syphilis/HBV/HCV tests.

During this clinical encounter, participants who are confirmed to be HIV-negative and without any relative contraindications for PrEP initiation will be prescribed a 30-day supply of TDF-FTC. Participants can choose from two PrEP medicines that is available for prescription at the study clinic during the study period: Truvada (before reimbursement: 1980 CNY/ 30 pills) or the generic Keaike (1180 CNY/ 30 pills). Once starting PrEP, participants will be required to complete two monthly clinic visits during their first two months of PrEP use to monitor their medication adherence, HIV/STI tests, and overall physical health status, and receive another 30-day supply of TDF-FTC. Participants may follow the daily oral regimen or event-driven regimen based on their discretion, and they will be given education on the two PrEP regimens during their initial PrEP counseling and through the Mini-classroom in the mini-app. PrEP prescriptions may be filled at the study clinic's pharmacy or a private pharmacy.

Study assessments and evaluation

Behavioral assessments

Baseline assessments will be conducted at enrollment, with follow-up surveys conducted at weeks 4, 8 (end of active intervention), and 12 (post-intervention) via self-administrated Web-based surveys on Wenjuanxing. Participants will be asked to complete follow-up surveys within one week; reminders through WeChat message will be sent on days 7 and 10 of the survey window, as needed. The time points of assessment are presented in Table 1. The full list of study measures is included in Table 3 in the Supplementary File1. To track app use activities, two

questions will be sent via the mini-apps chat box during the active intervention period at the end of weeks 2, 4, 6, and 8.

Table 1 Phase 2 pilot RCT study assessment timepoints

			Week					
			(Day 1)	2	4	6	8	12
Assessments								
Enrollment			X					
Informed consent			X					
Randomization			X					
Baseline assessment			X					
Interventions								
	Mini-app	Weekly reminder messages to use the mini-app	←	—	—	—	→	
		Mini-app access	←	—	—	—	—	→
	Control	Standard HIV prevention care	←	—	—	—	—	→
Follow-up survey (Long)					X		X	X
App-use survey (short)*				X		X		
In-depth interviews **					X		X	

*Only performed in participants in the intervention arm;

** Only performed in a subgroup of participants.

Qualitative progress evaluation

When close to the fourth week of intervention, a subgroup of 15 participants (10 intervention, 5 control) will be purposively sampled prioritizing those who have initiated PrEP to complete two in-depth interviews at weeks 4 and 8. Another group of participants (up to 5) who started PrEP between week 4 and week 8, regardless of the study arm, will receive a one-time in-depth interview at week 8. Interviews will focus on participants' experiences using the app and any changes in their perceptions and/or behaviors related to PrEP and HIV prevention practices during the study period (Table 4 in the Supplementary File1). Interviews will be conducted one-

on-one in private spaces – or via videoconferencing software (e.g. Zoom or Tencent Meeting), the last 60-90 minutes, and will be audio recorded with participants' permission.

Primary Outcome Measures

The primary outcomes for Phase 2 pilot RCT include the intention to use PrEP, progression along the stages of change to PrEP initiation, and PrEP initiation. PrEP use intention will be constructed as a continuous variable (range -3 to 3, from Very unlikely to Very likely) according to the participant's response to the question "How likely are you to start using PrEP?" PrEP initiation will be a binary variable, such that participants who successfully started PrEP (either through the study clinic or other PrEP providers) during the study period (Weeks 0 - 8) will be recorded as "1", otherwise as "0". Individual progression along the stages of change to PrEP initiation will be measured by a set of eight questions evaluating their contemplation, preparation, and actions to start PrEP and maintenance of using PrEP (64). This will be constructed as a discrete variable ranging 0-4 (0=precontemplation, 1=contemplation, 2=preparation, 3= action, 4= maintenance).

Secondary Outcome Measures

Secondary outcomes include: (1) feasibility variables, including the length of time for recruitment and enrollment, participants' retention rate (staying in the study) throughout the study course, and self-reported mini-app usage; (2) PrEP knowledge (5-item quiz(48), response options: true/false, total score: 0 – 5); (3) Number of HIV/syphilis tests (>=0, continuous)

ordered through the mini-app, tracked by the backend data; (4) PrEP adherence, measured by self-reported missed doses in the past week (a continuous variable, ranging from 0-7); (5) PrEP stigma (5-item scale (48), five-point Likert response scale from strongly disagree to strongly agree, total averaged score ranging from 1 – 5 with higher scores indicating higher perceived PrEP stigma; (6) PrEP attitudes, an averaged score of the participant's responses to a five-item PrEP attitudes scale (48) with a five-point Likert response scale from strongly disagree to strongly agree, with higher scores indicating more positive attitudes toward PrEP (a continuous variable, ranging from 1-5); (7) PrEP self-efficacy, an averaged score of the participant's responses to a eight-item PrEP self-efficacy scale (48) with a five-point Likert response scale from very difficult to very easy, with higher scores indicating higher self-efficacy to use PrEP (a continuous variable, ranging from 1-5).

Risks and Referrals

As HIV remains a stigmatized disease in many places in the world, including China. Same-sex sexual behaviors can also be associated with stigma and lack of social acceptance. The potential social harm that may cause to the participants by participation in our study may include emotional distress, embarrassment, and breach of confidentiality. During the study implementation, every effort will be made to ensure that study participants are protected from these risks, and to maintain confidentiality and discretion throughout all research procedures and data management and analysis. If at any time during the study, a participant divulges that he is at risk for harm, measures will be taken to ensure their safety. Reporting will be done as

appropriate to the situation and the legal statutes, and referrals will be provided to appropriate support, counseling or treatment resources.

In the case of an initial positive HIV test done through the study, participants who have initiated PrEP will be instructed to discontinue PrEP dosing. Participants testing positive will be referred to the study hospital – the Guangzhou Eighth People's Hospital for confirmation tests or other testing places if needed. The Guangzhou Center for Diseases Prevention and Control will be notified of confirmed positive results following China's public health reporting laws, a procedure that will be explained to participants at consent. For positive syphilis testing results, participants will be referred to as STI treatment at the Guangzhou Eighth People's Hospital. The study team will follow-up with participants testing positive for HIV or STI to encourage participants to seek appropriate care. For participants who want to continue using PrEP after the study ends, they can contact the study team and a list of local PrEP providers will be provided.

Data management

In-depth interviews will be audiotaped, transcribed verbatim (in Chinese), summarized in English based on the interview guide, and organized and managed using Dedoose cloud-based qualitative data analysis software (www.dedoose.com). The web-based survey will be collected through a Chinese professional secure electronic survey platform Wenjuanxing (www.wjx.cn). Survey data will be downloaded from Wenjuanxing and will be stored on password-protected encrypted study computers along with other electronic study files. All study files will have a back-up copy stored on UNC secure server space that only study personnel will have access to.

Statistical Analysis plan

All statistical data analyses will be conducted in Stata 16.0. An intention-to-treat analysis approach will be utilized (65).

Descriptive analysis

Descriptive statistical analyses will be first conducted to report baseline characteristics of participants, actual PrEP initiation rates, distribution of outcome variables, and other control variables at different time points throughout the study period (A full list of control variables please see Table 2 in the Supplementary File1. Examples include demographic characteristics, behavioral history of recreational drugs, alcohol and tobacco products, HIV risk perception, general stress, etc). For continuous outcome variables, we will first examine the mean changes from baseline to follow-up for the entire sample using statistical tests, and then estimate whether there are differences in net gains between the mini-app group and the control group, and between frequent mini-app users (use the mini-app once a week or more) and less frequent users. Observed effect sizes will be reported, to inform future study designs.

Bivariate analyses

Bivariate correlation analyses will be conducted to assess variables (including predictor and control variables) relating to PrEP use intention and PrEP initiation rate at Week 4 and Week 8. For the binary dependent variable "PrEP initiation" in particular, we will use the Chi-Square test

to compare the difference in PrEP initiation between the intervention group and the control group. Unadjusted *Odds Ratios (OR)* will be calculated and reported.

Multivariate analyses

Common confounder variables (e.g., age, education, in, come and other socio-demographic characteristics) and theoretical construct variables (i.e. PrEP knowledge, self-efficacy, stigma, and attitudes) will be adjusted for in multivariate analyses for each outcome of interest.

Given that the data collected in the pilot RCT is a longitudinal dataset with repeated measures at three time points, we will apply multilevel linear regression models to assess the association between continuous outcome variables and predictor variables. Missing data will be replaced with predicted values by multiple imputations, and sensitivity analyses will be conducted to compare the multiple imputation approach with analysis with complete cases only. If we have less than 50 participants retained at Week 8, or the multilevel model does not converge, we will run regression models and control for change over time.

Phase 2 Qualitative Analysis

The analytic approach for qualitative interviews from participants in Phase 2 will be similar to that applied in Phase 1. Besides, we will conduct a trajectory analysis (66) to understand participants' experience throughout the intervention period, including user experience of the mini-app, study engagement, evolving PrEP-related perceptions, and PrEP use behaviors. As we

will purposively sample participants who have initiated PrEP during the study and those who show less engagement for the interview, this approach will allow us better to understand the changing or non-changing process of individual PrEP use intention and initiation.

Incentives

Participants in Phase 1 will be provided remuneration at the end of each completed interview in the form of a 75-CNY (~ 10 USD) gift card or equivalent. Participants in Phase 1 will not be eligible for Phase 2 as they will have been exposed to the intervention before randomization.

Participants in Phase 2 will receive a 50-CNY (~ 7 USD) gift card for the in-person initial visit or baseline assessment and another 20-CNY (~3 USD) gift card for completing each Web-based follow-up survey via Wenjuanxing at Weeks 4, 8, and 12. Participants who complete all required study activities in Phase 2 will receive a bonus of 50-CNY (~ 7 USD) at the end of the study. Phase 2 participants who are sampled for in-depth interviews will receive 75-CNY (~10 USD) for completing each interview (up to two interviews for each participant). For participants who initiated PrEP through this research study, the cost of physical examinations (including required lab tests) and PrEP prescription will be covered by the study team. Participants will need to pay for PrEP medications out-of-pocket first and get 50% of the cost reimbursed at the monthly follow-up clinic visits, only if they fill the prescription at the study clinic or designated private pharmacies. After reimbursement, the total estimated cost to a participant in Phase 2 who starts PrEP is from 590 CNY (about 85 USD, for one-month generic PrEP supply or 30 pills) to 2000 CNY (about 286 USD, for two-month Truvada supply or 60 pills).

ETHICS AND DISSEMINATION

This study was reviewed and approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill, USA (IRB#19-3481), the Guangdong Provincial Dermatology Hospital, China (IRB#2020031), and the Guangzhou Eighth People's Hospital, China (IRB#202022155). All participants will be provided online consent and sign it electronically before taking part in the study. Our study team will work with local GBMSM CBOs to disseminate the study results to participants and the community via social media, journal publication, and offline workshops at local CBOs. This research addresses a critical need as GBMSM bear a disproportionate burden of China's HIV infections and remain underserved in the healthcare system.

DISCUSSION

Despite the high prevalence of HIV infection and risk factors among Chinese GBMSM, PrEP use is quite limited (67). A theory-informed, GBMSM-friendly, and innovative behavioral intervention to facilitate PrEP uptake among Chinese GBMSM may help to increase the awareness of PrEP among this population through timely information and strengthened motivation and skills. It may also help to link individuals to providers and clinics where they can receive PrEP. While PrEP campaigns in China have to-date failed to engage relevant communities (68), initiatives in other settings have successfully used GBMSM-tailored approaches to promote PrEP (41–44), including using mHealth technologies to approach

GBMSM "where they are". In an online survey of 1,035 Chinese GBMSM in 2017, about 75% of the participants mainly met their sex partners online (69), and Chinese GBMSM have been using the Internet frequently to search for HIV-related information, counseling, or testing services (35).

A large body of evidence has suggested that HIV-related and sexual health interventions delivered through Internet-enabled platforms are feasible and acceptable in Chinese settings (70), including interventions through websites, text message, and mobile apps that have shown effectiveness in reducing HIV-related risk behaviors, increasing linkage to care, and improving medication adherence (4,71,72). Thus, an mHealth-enabled intervention, like this PrEP education mini-app, which leverages the platform of a popular Chinese social media app could facilitate the rapid scale-up of PrEP use in China. In contrast to the traditionally top-down health mandates or researcher-led intervention projects, the PrEP mini-app tested in our study was co-created by a team of young gay men, HIV clinicians and public health researchers through a crowdsourcing hackathon. This not only helps to generate innovative approaches to address their own social and health needs, but also increases the acceptability and potential impact of the intervention in target populations.

Developing and testing theory-driven interventions around HIV prevention and care is challenged by rapid developments in the field, which can influence the pertinence or timeliness of interventions – a case in point concerns PrEP in China. The Chinese government has taken several crucial steps in introducing PrEP to China, including launching large-scale PrEP studies in multiple provinces and cities in 2018, developing implementation guidelines for PrEP in

China (68), and officially approving TDF-FTC for HIV PrEP in August 2020 (73). Nevertheless, the large population of GBMSM who would benefit from PrEP will encounter significant challenges for timely scale-up. The PrEP education mini-app developed by this study aims to meet the pressing need for innovative, easily accessible, and broadly acceptable modes of promoting and supporting PrEP among Chinese populations (74).

We also expect some challenges in the study implementation given the rapidly evolving conditions of the global COVID-19 pandemic and its impact on human activities and interpersonal interactions. The fieldwork is expected to take place between summer 2020 to summer 2021, while international travel of our research team members will be significantly delayed or restricted because of the global mitigation strategies to control COVID-19. In order not to bring significant delay to the study progression as well as encourage participants' engagement, our research team has been working remotely with local collaborators regarding GBMSM recruitment and enrollment. All data collection activities including in-depth interviews and surveys will be conducted electronically via videoconferencing systems or web-based survey tools, to ensure participants' and the research team's safety. The mHealth-based feature of the proposed intervention does not require in-person interaction between the participants and the research team; though study enrollment currently includes clinic-based lab tests and follow-up visits among PrEP users.

Whether globally or in China, limited data exist on the efficacy of app-based interventions aimed to increase PrEP uptake and adherence among GBMSM. If successful, this research study may help inform the implementation design of a rapid PrEP roll-out in China by examining whether

an mHealth intervention can promote PrEP uptake and other HIV prevention services. Promoting such services among GBMSM is of great importance as this population bears a disproportionate burden of China's HIV infections and remains underserved in the healthcare system.

DECLARATIONS

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Author Contributions

KM, JT, and CL conceived the study and drafted the manuscript. CL, EF, DM, WT, RS, AH, LLH, XY, HJH, and JL participated in designing and implementing the study and assisted in drafting the manuscript. JT and WT obtained funding for the study. XKT, JXY, ZYY, and TM developed the prototype of the mini-app and assisted in drafting the manuscript. All authors have read the final manuscript and approved for it to be published.

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Data Availability Statement

Deidentified individual data that supports the results will be shared beginning 9 to 36 months following publication provided the investigator who proposes to use the data has approval from an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Research Ethics Board (REB), as applicable, and executes a data use/sharing agreement with the University of North Carolina at Chapel Hill.

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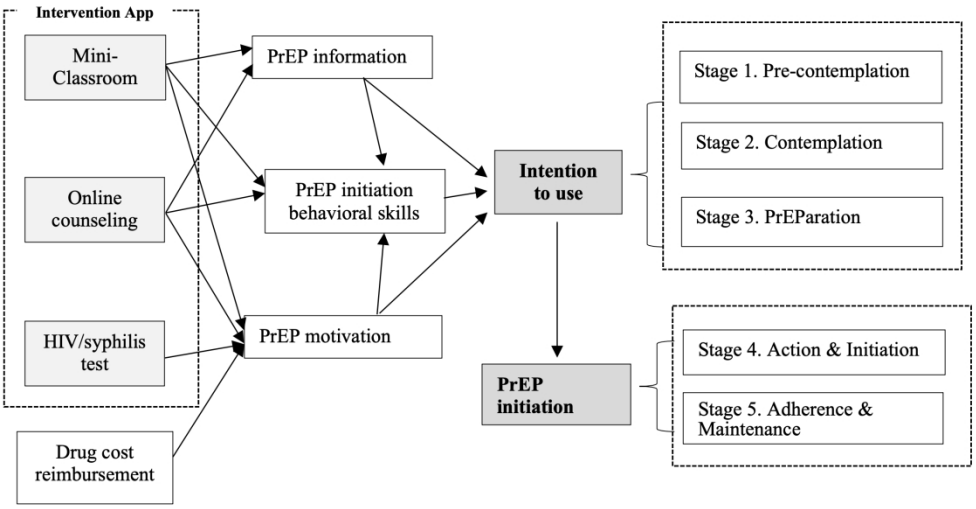

Figure 1 The conceptual model of the WeChat mini-app PrEP intervention

443x238mm (144 x 144 DPI)

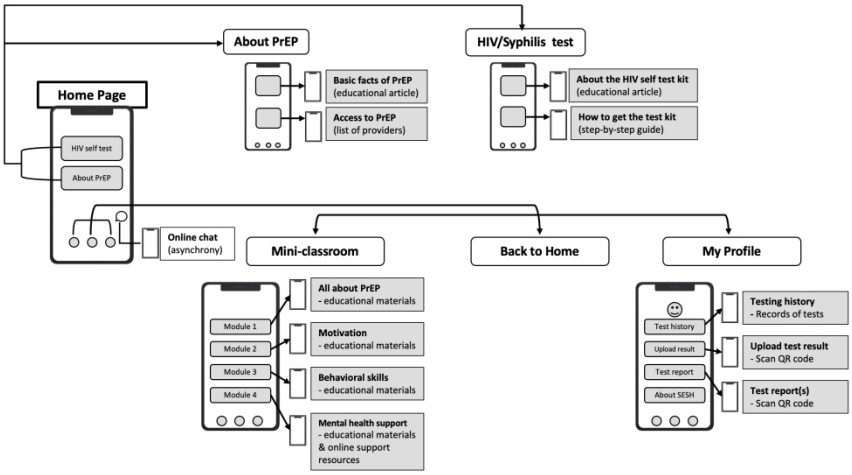

Figure 2 Wireframe of the mini-app PrEP intervention

505x284mm (144 x 144 DPI)

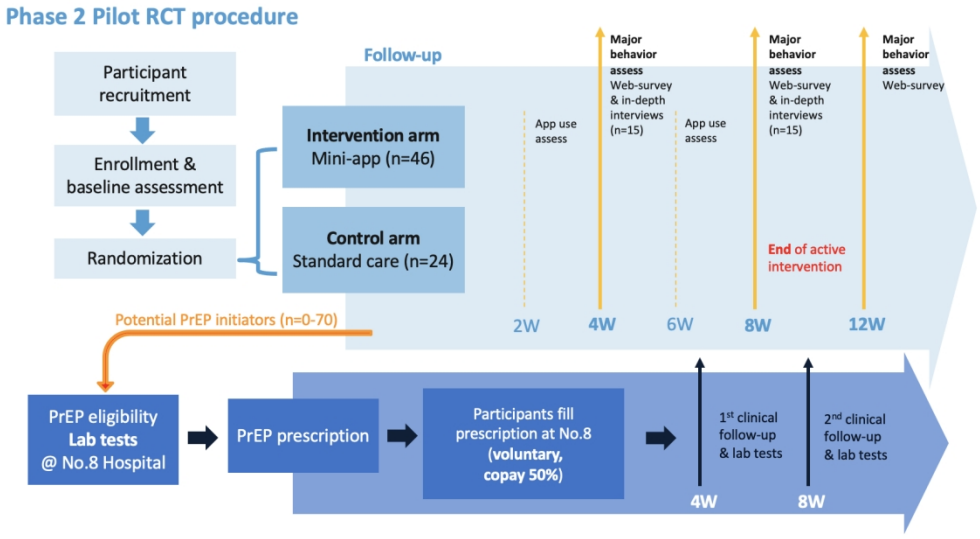

Figure 3 Phase 2 study design, a two-arm RCT

307x173mm (144 x 144 DPI)

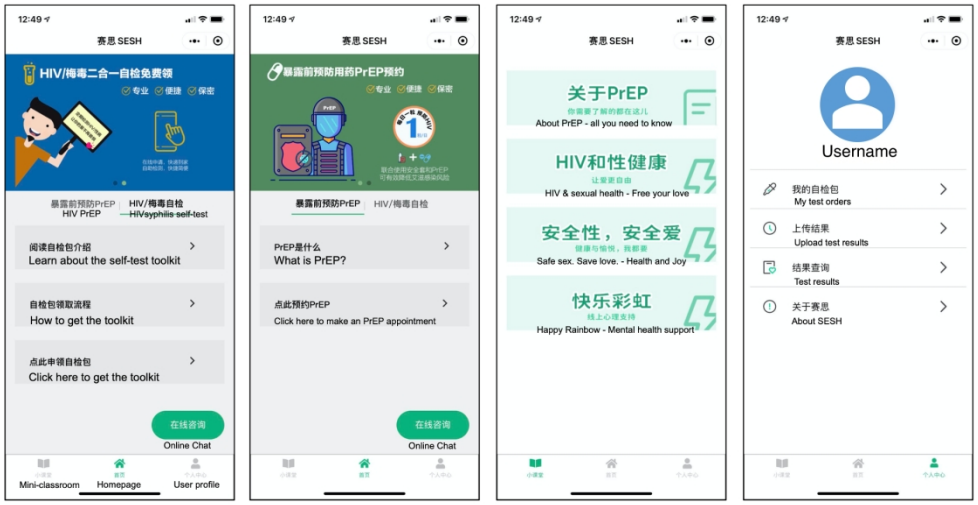

Figure 4 Screenshot of the mini-app from left to right: (1) Homepage 1: at-home test kit, (2) Homepage 2: PrEP appointment, (3) the Mini-classroom, (4) User profile center

338x190mm (150 x 150 DPI)

Supplementary file

Table 1 Summary of key functions of the mini-app prototype

Key functions	Intervention objectives	Intervention strategies			
		Information	Motivation	Behavioral Skills	Mental Health
Mini-classroom	Build knowledge and navigation skills around local HIV care system, enhance interest and motivation to use PrEP, and increase self-efficacy in HIV/STI prevention strategies; Improve mental health management skills.	Educational materials in multimedia forms, including text, videos, and graphics.	Real stories of PrEP users; Positive meanings of using PrEP and HIV/STI testing.	List local PrEP and other HIV/STI care providers and contact information; Tips for safe sex, condom use, and PrEP initiation, adherence, and management.	Links to local support groups and mental health care resources. Self-management for mental health. Coping with stigma and discrimination against LGBTQ community.
Online counseling	Enable MSM to describe their feelings or concerns related to HIV, sexual health or this intervention study, and help them make healthy decisions.	Answer questions about HIV, STI, PrEP, and/or other health topics, and provide additional information if needed.	Tailored health advice regarding PrEP use.	Referral to the HIV/PrEP clinic at the study hospital, or other healthcare providers based on individual needs.	Listen to their needs, and refer to local support groups or mental health care resources, if necessary.
Home-based HIV/syphilis test ordering	Establish individual habit of routine testing for HIV and syphilis.	Information about how to complete the home-based test kit.	Provides a cue to action and removes barrier of in-person testing and stigma.	An HIV/syphilis home-based test kit ordering system.	
User profile center	Allow participants to monitor their HIV/syphilis testing behaviors.			A profile page to manage orders of HIV/syphilis test kits and keep a record of test results.	

Table 2 Main topics in the in-depth interview guide in Phase 1

Topic	Description	Sample probes
HIV/STI knowledge & experience	Understanding or knowledge of HIV/STI, HIV/STI testing experience, experience with the local HIV/STI prevention & care system.	What do you know about HIV/STI? What do you think about the local HIV prevention and care system? What do you know about PEP and your experience with it, if any?
PrEP knowledge and attitudes	Understanding of PrEP, and attitudes, including acceptability and willingness of using PrEP to prevent HIV, pre- and post- PrEP attitudes for PrEP-experienced individuals.	What do you know about Pre-Exposure Prophylaxis (PrEP)? Have you ever heard any people you know are taking PrEP? How do you think PrEP have or could have an impact on your sexual health?
PrEP experience *(for current & intermittent users only)*	Narrative of PrEP using experience	What do you think about your PrEP using experience? (probe for motivations to start PrEP, experience with PrEP refilling, cost, side effects, adherence/discontinuation, others' attitudes and/or support)
Barriers to PrEP use/continued use	Perceived barriers to access, use, and manage PrEP care, and suggestions for PrEP-scale in China	Have you ever considered using PrEP? (If Yes) How would you think that will help you? (If not) would you please tell me about your concerns?
Biomedical prevention strategies	Experience or perceptions of using biomedical strategies to prevent diseases.	What do you think about taking medicines for preventive purpose, like using PrEP to prevent HIV?
Health beliefs and stress due to COVID-19	Experience of the COVID-19 pandemic and how it has influenced health beliefs, views on preventive medicine, and mental health	What do you think about the COVID-19 pandemic has changed your thoughts of health, if any? How have you been since the outbreak of COVID-19?
Mini-app usability test	Feedback on the mini-app design, contents and ease of use.	How was your overall experience with the mini app? How did you think the app meet your needs/expectations?
	Suggestions on app refinement based on the current structure.	If you were able to redesign this feature, what changes would you make? What other contents could be added to make the app more useful or engaging to you?

Note: for people who have never heard of PrEP before, a standard brief description of PrEP will be given before asking further questions: *The HIV prevention pill (known as 'PrEP') is a pill taken to prevent HIV. It is safe and more than 90% effective when taken every day. People who decide to use the oral HIV prevention pill need to return to their doctor every 3 months for HIV/STI testing, bloodwork, and a new prescription for the next 3 months*". [1]

Table 3 Phase 2 pilot RCT study measures and timepoints of data collection

		Week					
		Day 1	**2**	**4**	**6**	**8**	**12**
Primary outcomes							
PrEP use intention	A single bipolar scale with 7-point rating (-3 to 3)	X		X		X	X
PrEP stages of change	5 stages informed by the Transtheoretical Model of Behavioral Change (pre-contemplation, contemplation, preparation, action, & maintenance)	X		X		X	X
PrEP initiation	Yes/No (study record)			X		X	X
Secondary outcomes							
PrEP knowledge	5-item True/False quiz[2]	X		X		X	X
Test behavior	Frequency of at-home HIV/syphilis tests (≥0)			X		X	X
Willingness to pay	Percentage of monthly income to pay for PrEP	X		X		X	X
Self-report PrEP adherence***	Daily PrEP: missed doses in past 7 days (0 to 7) PrEP on-demand: occurrence of missing any dose in a single sex event and number of sex events without any PrEP coverage in the past month			X		X	X
PrEP self-efficacy	8-item scale with 5-point rating (1 to 5)[2]	X		X		X	X
PrEP stigma	5-item scale with 5-point rating (1 to 5) [2]	X		X		X	X
PrEP attitudes	5-item scale with 5-point rating (0 to 5) [2]	X		X		X	X
Predictor variables							
Intervention exposure	Yes/No	X					
Mini-app Engagement*	Self-reported frequency of app use		X	X	X	X	X
	Perceived app usefulness		X	X	X	X	X
Covariates							
Demographics & socio-economic indicators	Age, education, gender, sexual orientation, relationship status, private or shared bedroom, employment, income	X				X	
Drug use	Ever used recreational drugs (Yes/No)	X					
	Drug use in the past 4 weeks	X		X		X	X
Alcohol use	Ever consumed alcohol (Yes/No)	X					
	Average weekly alcohol consumption, past 30 days	X		X		X	X
Tobacco use	Ever consumed tobacco products (Yes/No)	X					
	Average weekly tobacco consumption, past 30 days	X		X		X	X
Prior HIV test history	Self-report HIV test history before the study (Yes/No)	X					
HIV knowledge	2-item HIV quiz	X		X		X	X
HIV risk perception	2 questions of perceived risk of HIV infection	X		X		X	X
HIV-related anxiety	3-item scale with 5-point rating[3]	X		X		X	X
Perceived stress	4-item Cohen Perceived Stress Scale[3] (overall stress)	X		X		X	X
HIV-social support	10-item scale with bipolar scale (-2 to 2)[4]	X		X		X	X
Condomless sex	Occurrence of condomless sex in the past 4 weeks	X		X		X	X
Number of sex partners	Self-reported number of sex partners, past 4 weeks	X		X		X	X

*Only performed in participants in the intervention arm;
** Only performed in a subgroup of participants;

***Only performed in participants who have started using PrEP.

Table 4 Main topics in the in-depth interview guides in Phase 2

Topic	Description	Sample probes
HIV/STI knowledge & experience	Understanding or knowledge of HIV/STI, HIV/STI testing experience, experience with the local HIV/STI prevention & care system.	What do you know about HIV/STI? What do you think about the local HIV prevention and care system? What do you know about PEP and your experience with it, if any?
Health beliefs and stress due to COVID-19	Experience of the COVID-19 pandemic and how it has influenced health beliefs and mental health	What do you think about the COVID-19 pandemic has changed your thoughts of health, if any? How have you been since the outbreak of COVID-19?
PrEP knowledge and attitudes	Understanding of PrEP, and attitudes, including acceptability and willingness of using PrEP to prevent HIV	How has your participation in this study changed your thoughts on PrEP? In general, what do you think about taking medicines for health purposes? How about take medicines to prevent HIV?
PrEP experience *(for participants who started PrEP)*	Narrative of PrEP using experience in this study, including perceived barriers to access, use, and manage PrEP care	What you think are the main reasons that motivate you to initiate PrEP? What is your experience of getting and refilling PrEP through this study?
PrEP intention *(for participants who haven't started PrEP)*	Perceived barriers or concerns of starting PrEP Readiness to start PrEP	Would you please tell me about your concerns or things that you think are barring you from accessing PrEP? How likely are you going to start PrEP in next week, next month or in near future?
Mini-app using experience	Feedback on the mini-app design, contents and ease of use, technical problems encountered.	How was your overall experience with the mini app? How did you think the app meet your needs/expectations?
	Using experience on each of the main functions: HIV/syphilis testing, the Knowledge Center, & online counseling	How would you describe your experience of using this feature? How did you think by reading these articles have changed your health beliefs or behaviors? Overall, how useful do you think this online counseling is for supporting your health, PrEP use or HIV/STI prevention?
	Long-term sustainability	How could you see yourself using this app in the future? Would you recommend this app to your friends?

References:

1. Wu Y, Xie L, Meng S, et al. Mapping Potential Pre-Exposure Prophylaxis Users onto a Motivational Cascade: Identifying Targets to Prepare for Implementation in China. *LGBT Heal*. 2019;6(5):250-260. doi:10.1089/lgbt.2018.0256
2. Walsh JL. Applying the Information–Motivation–Behavioral Skills Model to Understand PrEP Intentions and Use Among Men Who Have Sex with Men. *AIDS Behav*. 2019;23(7):1904-1916. doi:10.1007/s10461-018-2371-3
3. Nemeroff CJ, Hoyt MA, Huebner DM, Proescholdbell RJ. The Cognitive Escape Scale: measuring HIV-related thought avoidance. *AIDS Behav*. 2008;12(2):305-320. doi:10.1007/s10461-007-9345-1
4. Peterson JL, Coates TJ, Catania JA, Middleton L, Hilliard B, Hearst N. High-risk sexual behavior and condom use among gay and bisexual African- American men. *Am J Public Health*. 1992;82(11):1490-1494. doi:10.2105/AJPH.82.11.1490

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Page 1
Funding	4	Sources and types of financial, material, and other support	Page 27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 26-27
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 27
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4-6
	6b	Explanation for choice of comparators	Page 4-6
Objectives	7	Specific objectives or hypotheses	Page 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Phase 1: "Participant" section on Page 10; Phase 2: the "Participant" section on Page 12.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Phase 1: "Participant" on Page 10 Phase 2: Textbox 1 on Page 12.
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	"Study arms" on Page 14-16. Table 1, Figure 2-4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	"Referrals" on Page 19.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	"Qualitative progress evaluation" on Page 17. "Incentives" on Page 22-23.

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Exclusion criteria in Textbox1 on Pages 12-14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pages 18-19, Table 2 in supplementary file
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1 Figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Phase 1: “Participant” on Page 10 Phase 2:
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Phase 1: last paragraph on Page 10 Phase 2: first paragraph under “Participants” on Page 12.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	“Randomization” on Page 14.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	“Randomization” on Page 14.

Implement ation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	"Randomizatio n" on Page 14.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Phase 1: "Study design" on Pages 9-10 Phase 2: "study assessments" on Pages 16-18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Description of sending weekly reminder messages to participants in the last paragraph on Page 14. "Qualitative progress evaluation" on Page 17. "Incentive" section on Page 22
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Phase 1: first paragraph on Page 10. Phase 2: Page 20

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pages 20-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 21
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	"Referrals" on Page 19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 23
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Pages 16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 27
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 27
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary materials.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT