Study Protocol and Statistical Analysis Plan for Research Project: "Design and Development of a Mobile App to Improve Adherence to Pre-exposure Prophylaxis in Men Who Have Sex with Men?" clinicaltrials.gov #NCT04248790 December, 28, 2020

Study design: This study is an open label, single group assignment, interventional study, aiming to examine the preliminary effectiveness of the app in monitoring adherence to PrEP. The study expects to enroll participants since May, 2020 and follow-up for 4 months.

Participants:

Inclusion criteria:

- Male.
- Aged 20 or above.
- Resides in Taiwan and able to understand, read, and speak Mandarin Chinese.
- Remains HIV negative prior to and during the study period.
- The results of the laboratory tests are eligible to initiate PrEP.
- Currently taking PrEP or willing to initiate PrEP.
- Reports having 4 times or above anal sex with men in the past month.
- Owns an Android or Apple operating system (iOS) smartphone and willing to download the study app.
- Willing to wear the device we provided during the study period.

Exclusion criteria:

- With abnormal kidney function (creatinine clearance rate $\leqq$ 60 mL/minute).
- Currently on medication that might interact with PrEP, such as drugs contain lamivudine in the pre-PrEP assessment.

Sample size: above 30 participants and 70 participants at maximum. The sample size calculation is based on central limit theorem (CLT), which states that the distribution of sample means approximates a normal distribution as the sample size gets larger. CLT refers to that sample sizes equal to or greater than 30 are considered sufficient for the CLT to hold.

Interventions: The UPrEPU app is a self-monitoring tool to improve PrEP adherence regardless of the MSM user's choice of dosing regimen and lifestyle. All of participants will receive access to all the app capabilities. The app features include information on HIV testing locations, sex and PrEP diary and reminder of taking PrEP.

Data Collection:

Recruitment: Participants from two medical centers in two major cities of Taiwan. Potential study participants will be referred by physicians and case navigators from the clinics.

Screening: Their eligibility will be assessed by a screening tool available online. Screening questionnaire shown in Table 1. The participants' answers have to meet "Answers to enroll" in each question to enroll this study.

Table 1. Screening questionnaire

Questions	Options	Answers to enroll
What is your gender	☐ Male □Female	Male
Are you able to understand, read, and speak Mandarin Chinese	☐ Yes □ No	Yes
Are you living in Taiwan	☐ Yes □ No	Yes
HIV status	☐ Positive □ Negative	Negative
Do you assess the pre-PrEP assessment and eligible to use PrEP	☐ Yes □ No	Yes
Birth Year	Open question	<=1999
Currently or willing to use PrEP	☐ Yes □ No	Yes
Do you ever have anal intercourse with men	☐ Yes □ No	Yes
How many episodes of anal intercourse with men in the past month	Open question	>=4
What is your cell phone brands and models	Open question	Only smart phone is available

Afterward, trained research assistants will inform those who are eligible about the purposes of the study and the information that will be collected in the study. Individuals who express interest in this study will be required to provide signed informed consent. For those who do not consent to participate, the reasons for declining participation will be documented.

Baseline visit: Eligible participants will download the UPrEPU app on their phone and answer a baseline questionnaire in the app regarding sociodemographics, mental health scales, sexual behaviors, and PrEP use at the baseline visit at the study site. Participants will also receive a wearable device that collects physiological sensor data. Participants will be encouraged to use all app components over the next four months and wear the wearable devices at all times.

Follow-up visit: Participants will be followed up monthly for the four months at the two medical centers where they were recruited. Each monthly visit will include rapid testing for HIV antigen and antibodies, measuring TDF/FTC concentration, and complete a follow-up questionnaire on their mental health scales, sexual behaviors, and PrEP use. Depression and anxiety will be assessed by Patient Health

Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7). We collect these two mental health indicators since studies have shown that mental health status may be associated with adherence to medications.

Kidney function and sexually transmitted infections will be assessed at the end of follow-up. The system usability scale (SUS) for the UPrEPU app will be assessed during the first follow-up visit and at the end of the study. A face-to-face, semi-structured qualitative interview will be conducted at each visit to assess the feasibility of the app. It will focus on any technical challenges participants may have encountered, recommendations for app improvement, and their satisfaction and comfort in using this app. All interviews will take around 30 minutes and will be audio-recorded for transcription and analysis. Data collection Items and Schedule shown in Table 2.

Table 2. Data collection Items and Schedule

	Screening	Baseline	F-up -1	F-up -2	F-up -3	F-up -4
1. Eligibility/Interest	●					
2. Informed Consent	●					
3. Blood sample		●	●	●	●	●
A. Drug concertation ◎Can be collected either F-up-2, F-up-3, or F-up-4				◎	◎	◎
B. HIV test		●	●	●	●	●
C. Liver and kidney function		●				●
D. Syphilis screening		●				●
4. Installing UPrEPU app		●				
5. Set up smart device		●				
6. Receive data in smart device			●	●	●	●
7. Baseline questionnaire		●				

8. Follow-up questionnaire			●	●	●	●
9. SUS questionnaire			●			
10. APP feasibility interview			●	●	●	●
11. Incentive			$20	$20	$20	$20 OR $53

Incentives: Participants will receive incentives for completing each follow-up visit and in-depth interview. This includes US $20 cash for each follow-up visit and US $33 cash for twice completing the in-depth interviews. Participants whose cumulative frequency of log-in and use of features reached 90% will receive an additional US $33 at the end of the study.

Statistical analysis plan: Usability of the app will be measured by the System Usability Scale (SUS), a 10-item, 5-point Likert scale, which gives a global view of subjective assessment of usability [1]. A score above 50 out of 100 indicates acceptable [2].The primary feasibility outcomes include frequency of app log-in, use of app components such as PrEP-taking and sexual behavior reports, and the length of time of the app use based on the app analytics. Descriptive statistics will be used and confidence intervals will be calculated to evaluate the primary feasibility outcomes. Secondary feasibility outcomes of this app will be analyzing data from qualitative interviews focusing on technical challenges and satisfaction of the app during the follow-up with thematic analysis methods.

We will examine the app users' effectiveness of adherence monitoring for this app by comparing the pill-taking reports in the PrEP-taking diary component in the app with the Tenofovir (TDF) and Emtricitabine (FTC) drug concentration in dried blood spot (DBS) samples in the previous seven days before the follow-up day. We will use correlation analysis to examine the consistency between the drug concentration in the DBS samples and self-reported PrEP diary in the app. Higher correlation reflects higher effectiveness of adherence monitoring.

Reference

1. Brooke J, *SUS-A quick and dirty usability scale*. Usability evaluation in industry. Vol. 189. 1996. 4-7.
2. Bangor A, Kortum PT, and Miller JT, An empirical evaluation of the system usability scale. Intl. Journal of Human–Computer Interaction, 2008. 24(6): 574-594.