Study Protocol:

Development of Ingestible Biosensors to Enhance PrEP Adherence in Substance Users (PrEPSteps)

NCT03512418

Detailed Protocol for Development of Ingestible Biosensors to Enhance PrEP Adherence in Substance Users (PrEPsteps)
IRB Protocol: 1162312
Version 21.0, September 8, 2023
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I. Background and Significance

Digital pills provide real-time verification of medication ingestion events and can be used to monitor medication adherence; previous studies have demonstrated their acceptability in real-world patient populations.[1-3] Digital pills comprise a radiofrequency emitter combined with a standard gelatin capsule that is compounded with a study medication.[4] Upon ingestion of the digital pill, the chloride ion gradient in the stomach energizes the radiofrequency emitter, transmitting a unique signal of medication ingestion that is captured by a wearable Reader. The Reader acts as a relay, storing and transmitting ingestion data to a smartphone and cloud based server. Ingestion data is then available for real time interpretation by clinicians. Digital pill technology has been previously applied to opioid ingestion, diabetes management, and as a surrogate for directly observe therapy in schizophrenics.[1-3]

Direct measures of medication adherence are an important advance in the study of medication adherence, especially among patients with poor adherence linked to non-alcohol substance abuse. Although recent studies have demonstrated pre-exposure prophylaxis (PrEP) with once daily Truvada is efficacious in preventing HIV infection, protection is highly dependent on adherence. There is a clear dose response relationship between PrEP adherence and prevention of HIV transmission.[2] Post-hoc analyses of the iPrEX data (corroborated by the PROUD and iPERGAY studies) found that individuals whose drug levels were consistent with taking 4 or more doses of TDF/FTC (e.g., Truvada) a week had a greater than 90% level of protection from HIV; but only 50% of MSM in iPrEX achieved consistent adherence.[2,4-6] Substance use, especially stimulant use, among MSM occurs syndemically in the context of other mental health vulnerabilities (most notably depression, sexual trauma, and intimate partner violence[7] that increase their risk for condomless anal sex and HIV infection. Similarly, among HIV-infected MSM, the impact of substance use on ART adherence and HIV treatment outcomes is also well established[8,9] and recent studies have already identified substance use as a significant barrier to optimal PrEP adherence among MSM.[10,11]

In this study, we plan to develop and deploy a novel smartphone based intervention, PrEPsteps. PrEPsteps, a smartphone-based intervention that addresses real-time PrEP nonadherence among MSM with non-alcohol substance use (MSM+S). PrEPsteps is a brief Cognitive Behavioral Therapy intervention to improve PrEP adherence among MSM+S. It is comprises an established, empirically supported adherence intervention (LifeSteps[12-14]) augmented for this population by the inclusion of A) app-delivered booster sessions; B) contingent reinforcement/corrective feedback[15-17]; and C) evidence based Screening, Brief Intervention and Referral to Treatment (SBIRT) addressing non-alcohol substance use.[18,19] Innovatively, PrEPsteps responds to objective, real-time PrEP adherence data obtained from a digital pill that directly measures TDF/FTC ingestion. I will conduct focus groups among HIV negative MSM+S to inform the specification, presentation and design of PrEPsteps, and test the usability and sustainability of PrEPsteps and the digital pill in a pilot randomized controlled trial (N=60) of MSM+S using PrEP. Finally, we will conduct qualitative interviews to assess the response to PrEPsteps and digital pill in order to further optimize PrEPsteps.

II. Specific Aims

Aim 1: *To inform the specification of the PrEPsteps adherence intervention with participant-generated content solicited through five focus groups. We will solicit feedback from the focus group participants on all the components of the PrEPsteps intervention delivery content and platform.*

Aim 2: *To test, through a pilot randomized controlled trial (N=30x2), the feasibility, acceptability and potential for an effect of PrEPsteps on PrEP adherence, compared to treatment as usual (TAU) in HIV seronegative MSM with non-alcohol substance use who are initiating or continuing PrEP.*

Aim 3: *To assess the acceptability of the PrEPsteps intervention components (and the digital pill) through qualitative exit interviews with those randomized to the PrEPsteps condition.*

III. Recruitment

Eligible participants are HIV-negative cis-gender MSM who have non-alcohol substance use (identified in medical record) and are currently taking PrEP. We will use recruitment techniques previously employed in Fenway studies, including venue outreach (bar, club, cruising areas), community outreach, word of mouth from past or present participants in FCH studies, and advertising (print, clinic flyers and electronic media). Potential participants will also be screened during clinical appointments at Fenway Health by study staff. New patients at Fenway Health are given a Notice of Privacy Practices which informs them that their protected health information may be utilized for research when the research proposal is IRB-approved and conducted in accordance with HIPAA privacy and confidentiality rules. Further, under HIPAA, as employees of the covered entity (Fenway Health), the study staff may utilize medical records to identify potential participants. Potentially eligible patients will be identified using electronic reports from the data team. A study staff member will then work with medical assistants and/or providers before approaching patients to assess interest. After entering the room and prior to screening, the study staff member will explain the study before asking permission to complete the screening questionnaire. Those who appear to be eligible will be invited to participate in the study after their appointment, or set up an appointment in the future.

During periods of remote work (i.e., when in-person recruitment on Fenway Health medical floors is not feasible due to COVID-19-related restrictions), we will additionally run a Tableau report (after securing a HIPAA waiver from Fenway Health IRB), to identify patients who meet basic eligibility criteria. For patients that meet initial eligibility criteria, we will reach out via phone and/or patient portal to those who gave permission to be contacted directly by TFI for research opportunities. For individuals who have not yet opted-in, we will reach out to their provider for permission to contact them. If a provider does not respond to emails, we will attempt to call them or connect with their support staff via email or phone. We will document patients' permission or providers' permission to contact their patients in a password-protected file, which will be saved on Dropbox. Upon receiving permission from providers to contact their patients directly, we will reach out to patients via the patient portal. The initial message will not contain any sensitive information (e.g. mention of PrEP status, HIV status, etc.), and will use the subject line, "Paid Research Study Opportunity." We will respond to general questions about the study (e.g., related to eligibility criteria) directly in the patient portal for the patient's convenience; however, we will not respond to non-study-related questions and will ask participants to contact us directly should they require more information. The portal message will allow patients the option of opting out of future communications from the PrEPsteps study team. If a patient opts out, we will not contact

them again, unless they decide to opt back in. If a patient does not opt out within 7 days, we will reach out either via phone or via email with a provider letter. We will abide by patients' stated contact preferences. The provider letter sent via email will not include any sensitive information, and will use the subject line, "Paid Research Study Opportunity." After 7 days or more of no response, we will send an additional communication. We will additionally use Tableau reports to identify HIV-negative individuals who are currently receiving Truvada for PrEP from the Fenway Pharmacy. We will include study flyers in the mailed Truvada prescriptions for these patients, which will contain details about the study, as well as contact information for those interested.

The PrEPsteps study team will also utilize the recruitment database established from the TechPrEP study to recruit potential participants. The recruitment database was created from TechPrEP participants who gave permission to be contacted for future studies, and elected to provide their email address, cell phone number, and/or zip code. The recruitment database is saved as a password-protected Excel file on Dropbox, which the study staff will access to recruit potential participants for PrEPsteps. The staff will contact potential participants who provided a zip code located in or near Boston, MA either via phone or via email. We will abide by potential participants' stated contact preferences.

Our recruitment efforts, in line with our previous recruitment initiatives, will include targeted recruitment of men of color, by adapting our recruitment materials, and conducting recruitment drives in minority communities. Initially, a potential participant will contact study staff, express interest in the study, and provide the staff person with their name and telephone number for future contact. Also, staff will use a study screener on Fenway medical floors that cover inclusion criteria for PrEPsteps (as well as a screener for an investigation recruiting a similar study population, the IMPACT study). The staff will briefly describe the study requirements and procedures for IMPACT and PrEPsteps, and if the prospective participant is interested, an eligibility screening will be conducted for both studies. This recruitment method has been utilized by the recruitment team at Fenway Health for biomedical studies with similar inclusion criteria. Contact information for individuals who were ineligible for or have completed IMPACT, and are interested in enrolling in PrEPsteps, will be stored in a password-protected spreadsheet on a shared folder in the Fenway server accessible only to members of the PrEPsteps study team.

We will advertise aim 2 of the study on social media (e.g., Grindr, Growlr, Facebook, Twitter, Reddit, Instagram, Craigslist) in coordination with the recruitment team at the Fenway Institute. We will also receive referrals for potentially eligible participants through the use of a centralized pre-screener facilitated by the recruitment team and BSRP. Finally, BIDMC will be used as a site for passive recruitment, in which a PowerPoint slide advertising the study will be shared/presented at regular HIV conference meetings attended by BIDMC faculty.

IV. Subject Selection

Inclusion Criteria	Exclusion Criteria
Aim 1: 1) Cis-gender MSM with problematic stimulant use (identified in medical record as stimulant dependence or recurrent stimulant use that interferes with daily life: ICD 304, 305 and 292) or self-report (e.g. reported stimulant use in the past 6 months) 2) HIV-negative 3) On PrEP or qualifies for PrEP 4) Age 18 or older	**Aim 1:** Does not speak English
Aim 2: 1) Cis-gender MSM with moderate to severe non-alcohol substance use disorder (via MINI assessment) 2) HIV-negative 3) On PrEP or initiating PrEP 4) Has qualifying laboratory testing: Cr clearance, HBV, liver function tests 5) Owns a smartphone with Android or iOS 6) Age 18 or older	**Aim 2:** 1) Does not speak English 2) HIV positive 3) History of Crohn's disease or ulcerative colitis 4) History of gastric bypass, bowel stricture 5) History of GI malignancy or radiation to abdomen 6) Unable/unwilling to ingest digital pill 7) Allergy to gelatin, silver or zinc (components of the digital pill) 8) Does not qualify for PrEP (abnormal liver function, or Cr Clearance <60)
Aim 3: Participants in Aim 2 will be enrolled in Aim 3	**Aim 3:** Did not participate in Aim 2

Justification for Inclusion Criteria
MSM represent the largest risk group for new HIV infection nationally (Centers for Disease Control and Prevention, 2015). We did not include women or heterosexual men in the current study because the intervention approach may vary in different communities. Moreover, Fenway's extensive experience working with MSM makes this site most appropriate for the development of an intervention that focuses on MSM. This study proposes to recruit biological MSM. The decision not to recruit transgender men or women is based upon the following considerations. The priority for this treatment development study is to develop a treatment that will identify important relationships between non-alcohol substance use and PrEP nonadherence so that we can modify these experiences to improve adherence in this population. If we are successful in developing PrEPsteps in the MSM population, we will expand our study to explore if the intervention can be translated towards transgender individuals who may have different barriers to PrEP adherence.

Justification for Substance Use Disorder
Among MSM enrolled in the iPrEX study, individuals who experience suboptimal and eventual nonadherence had concomitant substance use disorders. While the majority of MSM with PrEP nonadherence in iPrEX were stimulant users, substance use in general has been a predictor of PrEP nonadherence, especially after the end of

a structured clinical trial (Hoenigl JAIDS 2019). Additionally, all substance use has been associated with increased incidence of sexually transmitted infections, suggesting that risky sexual activity occurs in the context of substance use (Hoenigl Emerg Infect Dis 2018). MSM who use substances also experience other concurrent risk factors for nonadherence including missed appointments and disengagement with care (Zucker JAIDS 2019). These concurrent risk factors for nonadherence are increasingly exaggerated in individuals with moderate to severe substance use disorder who have increasingly disorganized lives. The aim of this investigation is to develop the PrEPSteps intervention to address personalized barriers to adherence in these individuals for whom substance use disorder impacts their PrEP adherence.

Justification for Exclusion Criteria
We are excluding individuals with bowel strictures, Crohn's disease, ulcerative colitis, bowel neoplasm or radiation to the abdomen in order to minimize the risk of retention of digital pill components. Despite safety data that has demonstrated no risk of retained components of the digital pill in individuals, potential participants that are at risk of developing bowel stricture or obstruction would be at the highest risk of experiencing adverse events related to the digital pill.

V. Subject Enrollment

For all aims, we will publicize the study at Fenway Health primary care provider (PCP) meetings. We will additionally distribute flyers and palm cards at Fenway Health and at local sites including local bars and clubs in coordination with our recruitment team. For recruitment from the medical floors at Fenway, we will utilize CPS/Centricity to access the patient scheduler in conjunction with electronic reports (HIPAA waiver) in order to know if potential participants are scheduled for appointments at Fenway locations, their providers (so that we can approach them or nursing staff on the appropriate floor and time), and whether or not potential participants have confirmed their appointment or cancelled them. If Fenway PCPs have eligible participants we will ask the PCP if they are willing to refer them to us. We will also screen participants at scheduled Fenway Health appointments using electronic reports generated from the data team under our HIPAA waiver.

Participants who consent and are recruited for aim 1 and also meet eligibility criteria for aims 2/3 will be additionally approached regarding aims 2/3 if they are interested. Potential participants will contact the study team through the study email, call the BSRP team phone line, or meet with study staff in person to confirm eligibility. If participants meet eligibility criteria, we will then schedule them for the first study visit.

Finally, we will also advertise on social media, and flyering through clubs and other venues in the Greater Boston area. We will also advertise through local electronic billboards in the greater Boston area.

VI. Study Procedures

Aim 1: In this aim, we will conduct a series of 8 focus groups that will inform the specification of PrEPSteps, a smartphone-based adherence intervention that responds to feedback from a digital pill. We will schedule focus groups based on availability of participants. Participants in all focus groups will be verbally consented. On the day of the scheduled focus group, we will have participants complete a quantitative assessment (PrEPsteps_quantatitveassessment_v1). In the first two exploratory focus groups, we will discuss the digital pill and PrEPsteps as a whole. We will explore themes of the interconnection between digital pills, adherence data, and interventions based on nonadherence. We will also explore the hardware relationships between digital pills,

the Readers and smartphone app. Additionally, we will solicit methods to prepare potential participants for using digital pills in PrEP adherence monitoring.

Next, we will conduct five focus groups that will explore the structure of PrEPsteps. The focus groups will start with a general description of PrEPsteps. Next we will discuss each component of PrEPsteps: the LifeSteps framework, contingent reinforcement/corrective feedback (CR/CF) and SBIRT interventions. Iterative refinements to the structure of PrEPsteps, the wording of messages in CR/CF and content within SBIRT interventions. We will additionally inform the design features that improve the acceptability of each component of PrEPsteps: the timing of delivered interventions, how many messages are delivered daily, and the design and appropriate display of messages on the smartphone interface.

We will compile important themes in digital pill presentation, preparing participants for digital pill investigations, the structure and delivery of PrEPsteps and content of PrEPsteps into a final product package of digital pill hardware, smartphone app interface and interventions that comprise PrEPsteps. We will present this package to one final focus group (N=10) to ensure that all components are acceptable and understandable by potential study participants. Once this final focus group is complete, we will program PrEPsteps with our industry partner, etectRx, into the smartphone app and conduct a series of pilot tests in response to mock episodes of adherence and nonadherence to ensure the technology functions and correct components of PrEPsteps are displayed in response to detected ingestion patterns.

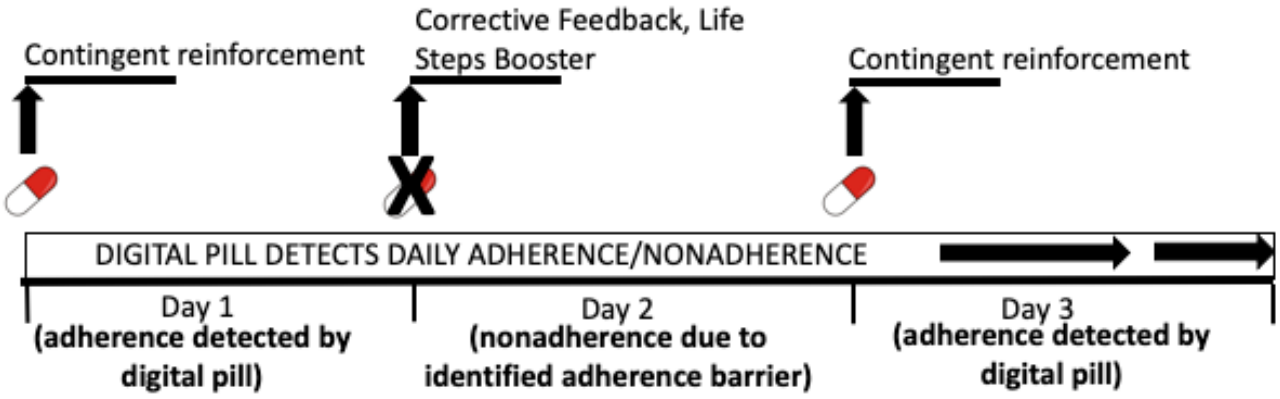
Aim 2 and 3: In Aims 2 and 3, we will deploy PrEPsteps in a pilot randomized controlled trial in MSM with non-alcohol substance use who are on PrEP. This portion of the study will involve 7 study visits (most of them remote) over the course of 6 months where participant ingest digital pill PrEP daily. Details of the PrEPSteps intervention, delivery of intervention and all study visits are described below:

Intervention Condition (PrEPsteps): The PrEPSteps intervention integrates feedback from focus groups completed in aim 1 to specify the content of this intervention. At the core of PrEPSteps are text messages that are housed in the etectRx app that respond to adherence and nonadherence events detected by the digital pill. Daily messaging is triggered based on detection of adherence. There are three major parts to PrEPSteps:

1) Contingent reinforcement: These are neutral positive feedback messages (e.g. “ingestion detected”) that are delivered to the participant confirming that their digital pill ingestion was recorded. These messages are delivered each time the participant ingests a digital pill and successfully uses the technology.
2) Corrective feedback: In the setting of detected nonadherence, participants will receive a message of corrective feedback, reminding participants that they did not take their PrEP. This message will be linked to the third component of PrEPSteps, a LifeSteps booster.
3) Life Steps booster sessions: As part of study visit 3, we will conduct an initial session of LifeSteps with the study participant. We will use this session to identify major perceived barriers to adherence and solutions to these barriers. We will focus specifically on substance use (Non-alcohol) as a potential barrier to adherence given our study population. These barriers and solutions are displayed in concert with corrective feedback messages after every nonadherence event detected by the digital pill. Participants are prompted to select the barrier that they may have encountered. They will also have the option to select “other,” which will generate a free text field to describe the barrier they faced. If they select one of the barriers they previously identified during LifeSteps in study visit 3, they will also receive their previously identified solution to that barrier.

Timing of Message Delivery: Contingent reinforcement messages are delivered immediately upon collection of digital pill ingestion events. Corrective feedback tied to Life Steps booster messages are delivered 1-2 hours after digital pill nonadherence is detected outside of the participant's self-defined dosing window (e.g., participant-identified regular PrEP ingestion time). For example, if a participant defines their dosing window as 9-11am, they will receive corrective feedback in the context of not taking their digital pill between 12pm-1pm.

See below for a figure of PrEPSteps algorithm:



Components of PrEPSteps Intervention
(see attached, *PrEPsteps_Study Messages_Participants Only)*:

Intervention Component	Message Content	Timing of Delivery
Contingent Reinforcement	Standardized "Ingestion detected" message and weekly summary of adherence metrics	Immediately after every digital pill ingestion; once weekly
Corrective Feedback	Standardized "It looks like you missed your medication today. What happened?"	2 hours after dosing window has closed without ingestion event
LifeSteps Booster	Participant-generated interventions during study visit 3, linked to corrective feedback content	Linked with corrective feedback message

Control Condition: The control condition will receive the digital pill as a medication adherence monitoring device. Participants will be trained on the digital pill device, operation of the reader and the accompanying app. For individuals in the control arm, they will receive confirmation messages surrounding digital pill ingestion. If participants want to see if they ingested a digital pill, they will be able to query this in the app. Participants will receive weekly adherence metrics (please see attached list of PrEPSteps messaging for both conditions).

Study Visits:

Screening Visit: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. If this visit is conducted entirely onsite, individuals will be roomed in the 8th floor consult rooms. We will conduct the informed consent process and answer questions about the study. If they consent, we will ask participants to sign the Fenway Institute Medical Release Form, Fenway Locator Form, and the Informed Consent Form. Once we verify consent is signed, we will ask participants to either show us their most recent screening lab work, or send results via secure email. If participants do not have qualifying lab work, or are initiating PrEP, we will draw labs specimens (Chem 7, Hepatitis B status, liver function tests). All lab tests will be processed by Quest Diagnostics. Next, after the consent process, a trained member of the study team will walk the participant through the substance use screener (*MINI 7.0 Substance Use Disorder Subscale)* via Zoom. Once the substance use screener is complete, participants will complete the acute HIV screener (*PrEPsteps_Screening Visit_Acute HIV Screener*). If their responses indicate potential for acute HIV, they will receive HIV viral load testing or be referred to their PCP. We will also ask for permission to contact the participant's PCP via Mimecast secure email to inform them that the participant has enrolled in the study. All participants will then receive a 3rd generation rapid HIV test. If participants test positive, we will refer to them to Fenway Health for confirmatory testing. If participants do not wish to continue care at Fenway, we will refer them to the infectious disease clinic at Brigham and Women's Hospital. If participants are eligible, and have all qualifying laboratory work, we will contact them to schedule Study Visit 1.

In the event that the Screening Visit is conducted in a partially remote format, we will email participants the Fenway Institute Medical Release Form, Fenway Locator Form, and the Informed Consent Form prior to the virtual (Zoom) portion of the visit. We will conduct the informed consent process via Zoom and answer questions about the study. If they consent, we will ask participants to electronically sign all three of these forms while study staff remain on the Zoom line. Also during the virtual portion of this visit, we will review recent lab work, walk the participant through the substance use screener, and ask participants to complete the acute HIV screener. During the onsite portion of this visit, we will conduct the rapid HIV test, and any required lab work.

Study Visit 1: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. If this visit is conducted entirely onsite, participants will complete the baseline quantitative assessment (*PrEPsteps_Quantative Assessment_Visit 1*) via REDCap. We will show participants optional training videos on how to operate the digital pill system (see *PrEPsteps_etectRx Training Videos Link*). We will then conduct a short training of operation of the components of the digital pill and Reader. We will instruct participants on basic troubleshooting of the technology. We will also identify a 2-4 hour dosing window (e.g., period of time during which the participant usually takes their PrEP) and program this window into the online interface. This dosing window will be used to time the corrective feedback and LifeSteps booster components of PrEPSteps at Study Visit 3 if the participants are randomized to the intervention arm. Participants will then ingest their first digital pill PrEP under the observation of a study team member, to demonstrate their understanding of how to operate digital pills and to ensure that the technology is functioning properly. Finally, participants will electronically sign an acknowledgement of receipt of privacy practices from ARx Pharmacy (*ARx_Receipt of Notice of Privacy Practices*) via a link provided by ARx Pharmacy. A copy of this receipt will be emailed to the study team and filed in the participant's study file. Participants will be scheduled for a 2-week follow-up (Study Visit 2), and provided with 21 days of Truvada digital pills (14 pills to cover the 2-week period, plus 7 additional pills to serve as a buffer if scheduling issues arise). We will contact study participants via text message on days 2, 5, and 7 to ensure the technology is functioning.

In the event that Study Visit 1 is conducted in a partially remote format, we will send participants the baseline quantitative assessment (*PrEPsteps_Quantative Assessment_Visit1*) via email or REDCap survey link, and ask them to complete it prior to the onsite portion of this visit. We will also send participants optional training videos on how to operate the digital pill system (see *PrEPsteps_etectRx Training Videos Link*). During the onsite portion of this visit, we will conduct all training on the use of the digital pill and Reader, and observe the participant ingest their first digital pill PrEP. Participants will also sign the receipt of privacy practices from ARx Pharmacy during the onsite portion.

As part of the PrEPsteps supplement (3K23DA044874-05S1, funded in September 2022), additional questions were added to the baseline quantitative assessment at Study Visit 1 (*PrEPsteps_Quantative Assessment_Visit 1*). Participants who enrolled after the start of the supplement project completed the updated baseline quantitative assessment with the additional questions integrated. The study team will seek to contact participants via phone who enrolled prior to the start of the supplement, and therefore did not complete the additional questions. If interested in completing the additional quantitative questions, participants may complete the PrEPsteps supplement baseline questions via REDCap, or over the phone with a study team member. If participants complete these questions verbally via phone, their answers will be recorded in REDCap by a study team member. Participants who elect to complete the additional questions will be remunerated.

Study Visit 2: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. This visit will take place 2 weeks after Study Visit 1. We will contact participants on day 7 to remind participants of their appointment. Participants will be randomized into the control arm (treatment as usual with digital pills to measure adherence) or the intervention arm (PrEPsteps). Randomization will occur via a predetermined schema using REDCap. We will review the previous 2 weeks of adherence data and reconcile discordant or nonadherent events with participants. At this study visit and subsequent study visits, participants will have the option of viewing the original digital pill training videos used in Study Visit 1 as a refresher course for technology training if they desire. Participants will return any unused digital pills from the prior 14-day period (to be counted by study staff), and will additionally undergo a blood draw for dried blood spot (DBS) testing for tenofovir diphosphate (to measure adherence and compare DBS against the digital pill). For all participants, a 30-day supply of Truvada digital pills will be dispensed at this study visit. We will contact participants via text message on days 16, 19, 21 to ensure technology is functioning. *This contact schema (i.e., reminder messages for study visit) will remain the same for each subsequent visit.*

In the event that Study Visit 2 is conducted in a partially remote format, we will randomize the participant, review the previous 2 weeks of adherence data, and provide the link to the digital pill training videos during the virtual (Zoom) portion of this visit. All remaining study visit procedures will be conducted during the onsite portion of this visit. If necessary, the 30-day supply of digital pills may be mailed to participants if they are unable to attend the in-person portion of the visit due to COVID-19.

Arm	**Study Visit 2 Procedures**

PrEPsteps	• Life Steps counseling (remote) • Responses to Life Steps programmed into PrEPsteps (remote or onsite) • Substance use counseling (remote) • Dispense digital pills, technology training, digital pill ingestion (onsite) • Return unused digital pills from prior 14-day period (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite)
Treatment as usual	• Life Steps counseling (remote) • Substance use counseling (remote) • Dispense digital pills, technology training, digital pill ingestion (onsite) • Return unused digital pills from prior 14-day period (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite)

Study Visit 3: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. This visit will take place 30 days post-randomization. We will contact participants prior to their appointment via text or phone call to remind them of their visit. We will review the previous 30 days of adherence data over and reconcile discordant or nonadherent events with participants in both study arms. Participants will return any unused digital pills from the prior 30-day period (to be counted by study staff). Participants will additionally undergo a blood draw for dried blood spot (DBS) testing for tenofovir diphosphate (to measure adherence and compare DBS against the digital pill), and a urine drugs of abuse immunoassay assessing non-alcohol substance use. Upon participant request, we will inform them of the results of the urine drugs of abuse screen via phone or in-person. A 60-day supply of Truvada digital pills will be dispensed to participants in both study arms at this visit.

In the event that Study Visit 3 is conducted in a partially remote format, we will review the previous 30 days of adherence data during the virtual (Zoom) portion of this visit. During the onsite portion of this visit, participants will return any unused digital pills, and a 60-day supply of Truvada digital pills will be dispensed. If necessary, the 60-day supply of digital pills may be mailed to participants if they are unable to attend the in-person portion of the visit due to COVID-19. The blood draw for DBS, and a urine drugs of abuse immunoassay will also be completed during the onsite portion.

Arm	**Study Visit 3 Procedures**
PrEPsteps	• Return unused digital pills from prior 30-day period (onsite) • DBS testing to confirm PrEP adherence (onsite) • Urine drugs of abuse screen (onsite) • Digital pill refill, technology refresher, digital pill ingestion (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite)
Treatment as usual	• Return unused digital pills from prior 30-day period (onsite) • DBS testing to confirm PrEP adherence (onsite) • Urine drugs of abuse screen (onsite) • Digital pill refill, technology refresher, digital pill ingestion (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite)

Study Visit 4: Procedures for this visit will be conducted entirely remotely. We will check in with the participant via Zoom 60 days post-randomization. We will review the previous 30 days of adherence data over Zoom and reconcile discordant or nonadherent events with participants in both study arms. We will also ask participants via Zoom to conduct a pill count of any unused digital pills from the prior 30-day period. Participants will be asked to hold onto any unused digital pills and return them the following month, during the in-person portion of Study Visit 5.

Arm	**Study Visit 4 Procedures**
PrEPsteps	• Pill counts of remaining digital pills (remote) • Review of adherence data, discussion surrounding nonadherent events (remote) • Technology refresher, digital pill ingestion (remote)
Treatment as usual	• Pill counts of remaining digital pills (remote) • Review of adherence data, discussion surrounding nonadherent events (remote) • Technology refresher, digital pill ingestion (remote)

Study Visit 5: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. We will contact participants on day 83 to remind participants of this study visit. We will remind participants to bring all PrEPsteps equipment with them to be returned to the study team. Participants will have DBS testing for adherence onsite at Fenway Health, a urine drugs of abuse screen, and will also return all remaining unused digital pills from the prior 60-day period (to be counted by the study team). Upon participant request, we will inform them of the results of the urine drugs of abuse screen via phone or in-person. For participants who are in the PrEPSteps arm, we will conduct a 20 minute semi-structured qualitative interview (*Aim 3 Exit Interview*) to assess the user experience working with PrEPsteps. Participants in both study arms will also complete a brief quantitative assessment via REDCap (see attached *PrEPsteps_Quantitative Assessment_Visits 5+6)*.

In the event that Study Visit 5 is conducted in a partially remote format, the participants in both study arms will complete the brief quantitative assessment virtually, which will be sent via email or REDCap survey link during the virtual (Zoom) portion of this visit. Participants in the PrEPsteps arm will so complete the 20 minute semi-structured interview via Zoom. All remaining study visit procedures will be conducted during the onsite portion of this visit.

Arm	**Study Visit 5 Procedures**
PrEPsteps	• Return unused digital pills from prior 60-day period (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite) • DBS testing to confirm PrEP adherence (onsite) • Urine drugs of abuse screen (onsite) • Audio-recorded review of adherence data from digital pill with focus on nonadherence episodes or PrEPsteps-triggered corrective feedback to describe episodes of nonadherence (remote or onsite)

Treatment as usual	• Return unused digital pills from prior 60-day period (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite) • DBS testing to confirm PrEP adherence (onsite) • Urine drugs of abuse screen (onsite)

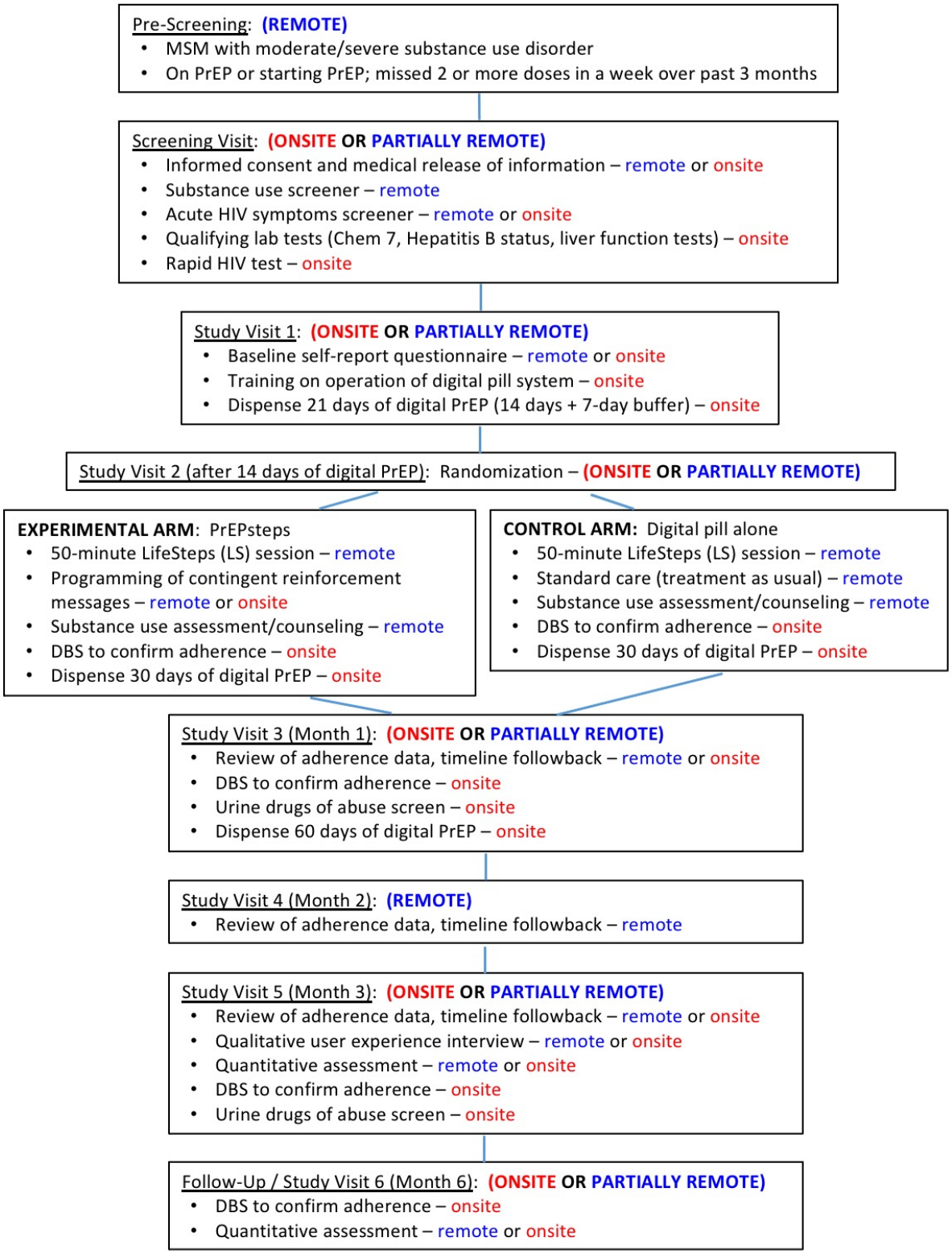
Study Visit 6: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. This visit will take place 3 months after study visit 5 (6 months post randomization). We will conduct a DBS to assess PrEP adherence. We will ask participants to complete a brief quantitative assessment (see attached *PrEPsteps_Quantitative Assessment_Visits 5+6)*, via REDCap.

In the event that Study Visit 6 is conducted in a partially remote format, we will connect with participants via Zoom and ask them to complete a brief quantitative assessment (see attached *PrEPsteps_Quantitative Assessment_Visits 5+6)*, which will be sent via email or REDCap survey link. For the onsite portion of this visit, we will conduct a DBS to assess PrEP adherence.

See study schematic below for a breakdown of Aims 2 and 3 study procedures:

PrEPsteps Aim 2 Study Flow

Onsite & Remote Procedures



At the conclusion of this study, we will provide the following avenues in which study participants can continue to access PrEP outside of the study: First, participants can return to their primary care provider and ask them to prescribe PrEP, second, we can refer participants to a provider at Fenway Health to prescribe PrEP and finally, participants can access PrEP through the Brigham and Women's Infectious Disease Clinic.

Remuneration: Participants will be remunerated via ClinCards using the following schedule. Participants will only receive compensation for completed study visits. Participants who enrolled prior to the start of the PrEPsteps supplement in September 2022, and who elect to complete the additional questions added to the baseline quantitative assessment, will be compensated an additional $20.

Study Visit	Compensation
Screening Visit	$20
Study Visit 1	$20
Study Visit 2	$30
Study Visit 3	$30
Study Visit 4	$30
Study Visit 5	$40
Study Visit 6	$50
Additional Supplement Questions (if applicable)	$20
Total	**$240**

Participant Contact: We will contact participants via text message at described times after study visits (see *PrEPSteps Study Messages_Participant Only*). Additionally, if participants do not respond to text messages (e.g., technology check-ins at days 2, 5, 7, 16, 19, 21), we will contact them via phone, and/or email. We will also contact participants to remind them of upcoming study visits via phone, Nomi text message, patient portal, and/or email. Upon participant request, we will inform them of the results of the urine drugs of abuse screen at study visits 3 and 5 via phone or in-person. As part of the PrEPsteps supplement, questions were added to the baseline quantitative assessment (*PrEPsteps_Quantitative Assessment_Visit 1*). The study team will contact participants via phone who completed the Study Visit 1 baseline quantitative assessment prior to the addition of the PrEPsteps supplement questions (in September 2022) to inquire about their interest in completing the additional supplement questions.

Standard Operating Procedures for Nonadherence: The digital pill technology has the potential to report real time PrEP adherence data during the course of this study. Recognizing standard medical care does not include daily reminders around PrEP adherence, we have developed a standard operating procedure to surround nonadherence/non-detection of digital pill ingestion during the study. Communication surrounding nonadherence is detailed in a separate document (SOP_nonadherence).

Drug Procurement: Digital pills are procured from ARx Pharmacy (our collaborating pharmacy). Once participants sign informed consent during the Screening Visit, and we have confirmed qualifying laboratory work and eligibility, we will fax a Patient Prescription and Enrollment Form to ARx. This order form will contain the following information, as required by ARx per drug dispensing requirements: (1) participant's name; (2) participant's date of birth; (3) participant's study ID number; (4) participant's phone number; (5) participant's mailing address; (6) participant's drug allergies and current medications (if applicable); (7)

participant's anticipated start date; (8) target drug delivery date; and (9) delivery information for pharmacist at Fenway Pharmacy. Following receipt of the Patient Prescription and Enrollment Form, ARx will mail 21 digital Truvada pills to cover the 14-day run in period (including 7 digital pills for any operational delays). Upon determination that the participant is eligible to continue in the study, the study team will fax a second Patient Prescription and Enrollment Form to ARx (same order form as for initial run-in period). ARx will then mail 90 digital pills (three 30-day supplies) to the Fenway Pharmacy. Confirmation of all shipment receipt will be documented in the PrEPSteps Pharmacy SOP binder. At Study Visits 1, 2, and 3, we will complete a Prescription Card that study staff will bring to the Fenway Pharmacy, who will sign out drug to us. If participants no-show during their study visit, we will return and sign back in drug to the Fenway Pharmacy. Leftover drug (during study visits, or in the case of lost to follow up) will be kept at Fenway. Pharmacy labels will be scratched off and destroyed to protect participant privacy prior to return to our industry collaborators at a time to be determined.

Study Visit Scheduling: We will schedule study visits as close to 30 days apart as possible. Recognizing that participants may have scheduling conflicts, we will seek to schedule participants for study visits within 7 days prior to the 30-day mark in order to prevent participants from running out of digital PrEP pills. For participants who have completed the screening visits (Study Visits 1 and 2), we will continue to contact them if they are eligible for the study in order to progress to Study Visit 3. We will review participants who are lost to follow up at this stage to determine if continued attempts to contact them are warranted. All remote portions of study visits (via Zoom) will be scheduled as close in proximity as possible to the in-person portions of those visits.

Risk Assessments: A licensed clinician will be onsite during all study visits where the quantitative assessment component is completed in-person. If a participant answers "nearly every day" to question #9 on the PHQ9, indicating suicidality, this will trigger a safety evaluation by a licensed clinician (e.g., Dr. Peter Chai) before the participant is released. The clinician will review the results of the assessment with the participant, evaluate their safety and risk of harm, and make clinical referrals to Brigham and Women's Hospital if needed. In the unlikely event that the PI cannot be reached, another licensed clinician will conduct the safety evaluation. The participant's primary treating physician will be notified of the any clinical referrals made as a result of this evaluation.

VII. Biostatistical Analysis

Aim 1: We will conduct qualitative analysis on individual interviews in aim 1 to elucidate themes of technology acceptance, design, and optimal timing and delivery of messaging.

Aim 2: We will calculate descriptive statistics regarding the degree of adherence collected from the digital pill. We will also calculate the accuracy of the digital pill in comparison to pill counts and validate ingestion data compared to DBS. We additionally will report overall percent adherence and measure the association between percent adherence and PrEPSteps. Additionally we will report weeks of adherence (>4 doses a week) and measure the association between weeks of adherence and the use of PrEPSteps. Because this is a pilot, proof-of-concept study, we will not be powered to determine the degree of adherence the use of a digital pill alone confers upon study participants.

Aim 3: We will conduct an applied thematic analysis on all recorded interviews using NVivo 12.

VIII. Risks and Discomforts

We anticipate the major risks due to PrEPsteps are the potential for exposure to metal components in the digital pill, retention of the radiofrequency emitter portion of the digital pill, and allergic reaction to the silver and zinc components of the radiofrequency transmitter and to the gelatin pill capsule. Participants may also experience psychological discomfort in working with study staff to program PrEPsteps, and a risk of discoverability of their involvement in the study from PrEPsteps. Major psychological discomforts could occur during study interviews when participants are asked about their adherence patterns. We have addressed each of these risks below:

Exposure to Metal Components in Digital Pill: The Digital Pill is manufactured from the same basic components as other ingestible medical devices. The radiofrequency tags contain minimal amounts of silver, zinc and magnesium that are significantly less than the recommended daily intake of these metals. In order to prevent absorption of these metals, the radiofrequency tag is coated with an epoxy and ethylcellulose coating in a technique that is used for other ingestible medical devices.[20,21] Extensive experience in the use of ingestible small bowel endoscopy cameras has not reported adverse events related to the exposure of electronic components.[22,23]

Digital Pill Radiofrequency Emitter Retention: Study participants may experience retention of the radiofrequency emitting portion of the digital pill. A study assessing the efficacy of the capsule portion of PrEPsteps among healthy volunteers documented 560 successful ingestion events without any adverse effects. Dr. Chai has completed a pilot study that recorded 96 ingestions with the digital pill containing oxycodone without any adverse events.[2] Additional pilot data from Novartis of over 100 participants who ingested radiofrequency tagged gelatin capsules revealed no reports of sensor retention (Personal communication from Joris VanDam, Novartis). An additional investigation to determine the safety of digital pills demonstrated no retention of any of the components of the digital pill by abdominal imaging.[21] The best comparison to the digital pill are capsule endoscopy pills which are over twice the size of digital pills. Over a decade of experience of capsule endoscopy has revealed a capsule retention rate of less than 2%.[22,24] In the case of a retained endoscopy pill, patients were mostly asymptomatic, and treatment consisted only of oral fluid administration. Patients who elected to have the capsule removed successfully underwent elective partial small bowel resection with pathologic findings including mild bowel stricture or intimal ulceration from capsule retention.[25] Complication rates among patients with Crohn's disease, bowel neoplasm, radiation enteritis, or stricture were higher.[26,27] In high-risk patients, standard therapy for retained endoscopy pills included aggressive oral hydration with successful removal of the retained pill.[28] We believe that the risk of retention of a PrEPsteps capsule will be less than that of a capsule endoscopy pill given the smaller dimensions of the digital pill. Unlike a capsule endoscopy pill, PrEPsteps is dissolvable with only the radiofrequency emitting portion of the capsule passing through the gastrointestinal tract. In order to minimize the risk of PrEPsteps capsule retention, we plan to exclude patients with underlying bowel disease or surgical intervention to the bowel.

Allergic Reaction: There is a risk of allergic reaction to the silver and zinc components of the radiofrequency transmitter, and to the gelatin pill capsule used to encase the radiofrequency transmitter and PrEP inside the capsule. In order to minimize the risk of a potential allergic reaction, we plan to exclude patients with a known allergy to silver, zinc or gelatin.

Risk of Discoverability from PrEPsteps: There is a risk of discoverability of PrEP use or participation in the study in the case when a study participant's messages from the PrEPsteps app is discovered by a bystander, or if PrEPsteps messages are discovered by individuals outside of the study. We will take 4 major steps to ensure that we maximally protect participants from the risk of discoverability.

- *Password protection on participants' cellphones:* We will ensure that participants' cellphones are enabled with password protection (or Touch ID, for iPhones). Participants will be the only individuals who have access to their personal cellphones.
- *Messaging that does not directly reveal PrEP ingestion:* During focus groups in aim 1, we will craft messages from PrEPsteps that avoid inadvertent disclosure that participants are on PrEP to protect against individuals who are uninvolved in the study reading messages from PrEPsteps. Although messages are password protected, we will take the additional step of ensuring the text of messaging protects participants against PrEP discoverability.
- *Masking the icon of the PrEPsteps app to prevent discoverability:* We will mask the icon of the PrEPsteps app as a generic "ID Cap" app to avoid discoverability of PrEP ingestion or participation in PrEPsteps.
- *Opaque digital pill capsules:* The digital pill gelatin capsule is opaque, prevent discoverability of PrEP ingestion by recognition of the color of TDF/FTC.

Psychological Discomfort of Disclosing Adherence Patterns: Participants may experience psychological discomfort in disclosing and learning of their adherence data during study visits.

IX. Potential Benefits

Participants may indirectly benefit from participation in the study by improving their adherence to PrEP. Interacting and using PrEPsteps may confer some increased adherence among study participants.

X. Data Transmission from Digital Pills

It is important to note that no protected health information flows through ingestion events recorded by the digital pill. There is no medication data that identifies study drug as Truvada, nor personal identifiers within the digital pill system. Ingestion of the digital pill activates a generic radiofrequency signal that is collected by the Reader. The Reader then transmits ingestion data via low energy Bluetooth to the participant's cellular phone. This data is collected by an app housed on the participant's smartphone. Within the app, data is converted to Java Script notation that describes the presence of an ingested medication. This data is transferred to servers at our collaborating industry partner, etectRx. This data is then stored on a secure server. Access is limited to etectRx maintenance technicians and the study team. For PrEPSteps interventions and text messages, receipt of digital pill ingestion data is sent to the NOMI dashboard- this dashboard automates the PrEPSteps intervention and pushes messages via SMS text messaging to the participant's phone in response to their ingestion patterns. Study participants are identified on the etectRx and NOMI dashboard only as study numbers. Their PHI is kept within secure Fenway computers. A secure excel spreadsheet that links study numbers to participant names is kept on desktop computers at Fenway accessible to the PI and study team.

XI. Data Monitoring and Quality Assurance

We will review and monitor data from PrEPsteps for each study participant. At each study visit, participants will undergo pill counts to correlate adherence data from PrEPsteps, and calculate the accuracy of the digital pill to measure PrEP adherence. Any discrepancies between the digital pill and pill counts will be addressed in real time at each study visit with the participant. For each participant, we will also review signaling from the digital pill to the Reader with our industry collaborator (etectRx) to ensure there are no errors in data transmission contribution to missed adherence events. If errors occur as a result of data transmission, we will correct the participant's adherence data, and convey these changes to participants' PCP via Mimecast secure email. We will additionally obtain dried blood spot testing at study visits 3 and 4 to confirm adherence (see section V. study procedures)

Recorded interviews: Audio-recorded interviews (Aim 1 and 3) will be transcribed using a HIPAA compliant transcription service (Landmark transcription), and scrubbed of identifiers

Aim 2 QA review: Study investigators will conduct QA review of baseline adherence data after the first 10 participants are enrolled. Additionally, we will review adherence data and interactions with PrEPsteps after the first 10 participants randomize to PrEPsteps. We will similarly conduct QA review after the first 10 participants randomize to treatment as usual. We will continue to conduct subsequent QA reviews in increments of 10 participants enrolled in each arm to ensure fidelity of the study data.

Data Safety Monitoring Board (DSMB): Three investigators who are external to the study and external to Dr. Chai's mentoring team as defined by his NIH K23 award with expertise in PrEP, non-alcohol substance use disorder, technology security and behavioral interventions, will comprise a DSMB for Aim 2 (pilot randomized controlled trial) of the research plan. The DSMB will convene annually during Aim 2. Additionally, the DSMB will meet when N=30 study participants are enrolled in Aim 2. They will review the data, and any potential study related adverse events prior to approving the continuation of recruitment. The responsibilities of the DSMB will include:

- Reviewing the research protocol, consent form, and plans for DSMB.
- Evaluating the progress of the pilot randomized controlled trial: recruitment, retention, data quality, site performance, adverse events.
- Protection of participant safety
- Making recommendations to Dr. Chai and the Fenway Institute IRB regarding continuation, termination or modification of the study depending on benefits or adverse events.
- Ensuring the confidentiality of study data.
- Reviewing adverse events.
- Providing annual written reports to Dr. Chai, and NIH regarding safety concerns, continuation or modification of the research plan.

We will additionally comply with all Fenway regulations regarding reporting of adverse events and ensuring data quality.

Data Tracking: Ingestion data will be automatically logged into the web interface hosted by etectRx with a date/time stamp to ensure accurate record keeping of all data and linking to the results. All data will be securely accessed at Fenway Health.

Data Entry Process: Protected health information, including study participant demographics, non-alcohol substance use disorder history, and HIV risk factors will be collected by Dr. Chai and the research assistant and entered into REDCap, a secure web application being used for data storage and management. A separate spreadsheet of study participant contact information and a technology log including participant mobile phone number, electronic mail (email) address, identifiers of the Receiver, study smartphone and a log of dispensed digital pills will also be maintained by Dr. Chai and the RA. All logs will be stored behind TFI firewall and password protected. Each variable with missing data (such as an interruption between smartphone and sensor) will be identified and a placeholder ("<<-99>>") entered to connote a missing value. Data from the digital pill is recorded on the etectRx interface and automatically transferred via a HIPAA-compliant secure link to the adherence interface (NOMI). Ingestion data may potentially require editing if there are transmission failures, errors from the reader device, or manually recorded data from study participants. All of these potential edits will be identified by etectRx in collaboration with the study team. Edits to data will be agreed upon by both parties and approved by the PI. An audit trail of all potential edits will be maintained. We will additionally comply with Fenway regulations regarding reporting of adverse events and ensuring data quality. Landmark Associates Inc, an external company, will be contracted to transcribe audio-taped exit interviews.

Data Storage: Raw ingestion data, transcripts from this study and self-report questionnaires will not be made publicly available. De-identified data may be shared with NIH who is funding the study, as well as industry collaborators etectRx and NOMI. For future investigations that use de-identified participant data, we will submit IRB protocols detailing the use of this data. Mass General Brigham Dropbox is being used for file storage in the study.

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Detailed Protocol for Development of Ingestible Biosensors to Enhance PrEP Adherence in Substance Users (PrEPsteps)
IRB Protocol: 1162312
Version 21.0, September 8, 2023
Principal Investigator: Peter R Chai MD MMS

I. Background and Significance

Digital pills provide real-time verification of medication ingestion events and can be used to monitor medication adherence; previous studies have demonstrated their acceptability in real-world patient populations.[1-3] Digital pills comprise a radiofrequency emitter combined with a standard gelatin capsule that is compounded with a study medication.[4] Upon ingestion of the digital pill, the chloride ion gradient in the stomach energizes the radiofrequency emitter, transmitting a unique signal of medication ingestion that is captured by a wearable Reader. The Reader acts as a relay, storing and transmitting ingestion data to a smartphone and cloud based server. Ingestion data is then available for real time interpretation by clinicians. Digital pill technology has been previously applied to opioid ingestion, diabetes management, and as a surrogate for directly observe therapy in schizophrenics.[1-3]

Direct measures of medication adherence are an important advance in the study of medication adherence, especially among patients with poor adherence linked to non-alcohol substance abuse. Although recent studies have demonstrated pre-exposure prophylaxis (PrEP) with once daily Truvada is efficacious in preventing HIV infection, protection is highly dependent on adherence. There is a clear dose response relationship between PrEP adherence and prevention of HIV transmission.[2] Post-hoc analyses of the iPrEX data (corroborated by the PROUD and iPERGAY studies) found that individuals whose drug levels were consistent with taking 4 or more doses of TDF/FTC (e.g., Truvada) a week had a greater than 90% level of protection from HIV; but only 50% of MSM in iPrEX achieved consistent adherence.[2,4-6] Substance use, especially stimulant use, among MSM occurs syndemically in the context of other mental health vulnerabilities (most notably depression, sexual trauma, and intimate partner violence[7] that increase their risk for condomless anal sex and HIV infection. Similarly, among HIV-infected MSM, the impact of substance use on ART adherence and HIV treatment outcomes is also well established[8,9] and recent studies have already identified substance use as a significant barrier to optimal PrEP adherence among MSM.[10,11]

In this study, we plan to develop and deploy a novel smartphone based intervention, PrEPsteps. PrEPsteps, a smartphone-based intervention that addresses real-time PrEP nonadherence among MSM with non-alcohol substance use (MSM+S). PrEPsteps is a brief Cognitive Behavioral Therapy intervention to improve PrEP adherence among MSM+S. It is comprises an established, empirically supported adherence intervention (LifeSteps[12-14]) augmented for this population by the inclusion of A) app-delivered booster sessions; B) contingent reinforcement/corrective feedback[15-17]; and C) evidence based Screening, Brief Intervention and Referral to Treatment (SBIRT) addressing non-alcohol substance use.[18,19] Innovatively, PrEPsteps responds to objective, real-time PrEP adherence data obtained from a digital pill that directly measures TDF/FTC ingestion. I will conduct focus groups among HIV negative MSM+S to inform the specification, presentation and design of PrEPsteps, and test the usability and sustainability of PrEPsteps and the digital pill in a pilot randomized controlled trial (N=60) of MSM+S using PrEP. Finally, we will conduct qualitative interviews to assess the response to PrEPsteps and digital pill in order to further optimize PrEPsteps.

II. Specific Aims

Aim 1: *To inform the specification of the PrEPsteps adherence intervention with participant-generated content solicited through five focus groups. We will solicit feedback from the focus group participants on all the components of the PrEPsteps intervention delivery content and platform.*

Aim 2: *To test, through a pilot randomized controlled trial (N=30x2), the feasibility, acceptability and potential for an effect of PrEPsteps on PrEP adherence, compared to treatment as usual (TAU) in HIV seronegative MSM with non-alcohol substance use who are initiating or continuing PrEP.*

Aim 3: *To assess the acceptability of the PrEPsteps intervention components (and the digital pill) through qualitative exit interviews with those randomized to the PrEPsteps condition.*

III. Recruitment

Eligible participants are HIV-negative cis-gender MSM who have non-alcohol substance use (identified in medical record) and are currently taking PrEP. We will use recruitment techniques previously employed in Fenway studies, including venue outreach (bar, club, cruising areas), community outreach, word of mouth from past or present participants in FCH studies, and advertising (print, clinic flyers and electronic media). Potential participants will also be screened during clinical appointments at Fenway Health by study staff. New patients at Fenway Health are given a Notice of Privacy Practices which informs them that their protected health information may be utilized for research when the research proposal is IRB-approved and conducted in accordance with HIPAA privacy and confidentiality rules. Further, under HIPAA, as employees of the covered entity (Fenway Health), the study staff may utilize medical records to identify potential participants. Potentially eligible patients will be identified using electronic reports from the data team. A study staff member will then work with medical assistants and/or providers before approaching patients to assess interest. After entering the room and prior to screening, the study staff member will explain the study before asking permission to complete the screening questionnaire. Those who appear to be eligible will be invited to participate in the study after their appointment, or set up an appointment in the future.

During periods of remote work (i.e., when in-person recruitment on Fenway Health medical floors is not feasible due to COVID-19-related restrictions), we will additionally run a Tableau report (after securing a HIPAA waiver from Fenway Health IRB), to identify patients who meet basic eligibility criteria. For patients that meet initial eligibility criteria, we will reach out via phone and/or patient portal to those who gave permission to be contacted directly by TFI for research opportunities. For individuals who have not yet opted-in, we will reach out to their provider for permission to contact them. If a provider does not respond to emails, we will attempt to call them or connect with their support staff via email or phone. We will document patients' permission or providers' permission to contact their patients in a password-protected file, which will be saved on Dropbox. Upon receiving permission from providers to contact their patients directly, we will reach out to patients via the patient portal. The initial message will not contain any sensitive information (e.g. mention of PrEP status, HIV status, etc.), and will use the subject line, "Paid Research Study Opportunity." We will respond to general questions about the study (e.g., related to eligibility criteria) directly in the patient portal for the patient's convenience; however, we will not respond to non-study-related questions and will ask participants to contact us directly should they require more information. The portal message will allow patients the option of opting out of future communications from the PrEPsteps study team. If a patient opts out, we will not contact

them again, unless they decide to opt back in. If a patient does not opt out within 7 days, we will reach out either via phone or via email with a provider letter. We will abide by patients' stated contact preferences. The provider letter sent via email will not include any sensitive information, and will use the subject line, "Paid Research Study Opportunity." After 7 days or more of no response, we will send an additional communication. We will additionally use Tableau reports to identify HIV-negative individuals who are currently receiving Truvada for PrEP from the Fenway Pharmacy. We will include study flyers in the mailed Truvada prescriptions for these patients, which will contain details about the study, as well as contact information for those interested.

The PrEPsteps study team will also utilize the recruitment database established from the TechPrEP study to recruit potential participants. The recruitment database was created from TechPrEP participants who gave permission to be contacted for future studies, and elected to provide their email address, cell phone number, and/or zip code. The recruitment database is saved as a password-protected Excel file on Dropbox, which the study staff will access to recruit potential participants for PrEPsteps. The staff will contact potential participants who provided a zip code located in or near Boston, MA either via phone or via email. We will abide by potential participants' stated contact preferences.

Our recruitment efforts, in line with our previous recruitment initiatives, will include targeted recruitment of men of color, by adapting our recruitment materials, and conducting recruitment drives in minority communities. Initially, a potential participant will contact study staff, express interest in the study, and provide the staff person with their name and telephone number for future contact. Also, staff will use a study screener on Fenway medical floors that cover inclusion criteria for PrEPsteps (as well as a screener for an investigation recruiting a similar study population, the IMPACT study). The staff will briefly describe the study requirements and procedures for IMPACT and PrEPsteps, and if the prospective participant is interested, an eligibility screening will be conducted for both studies. This recruitment method has been utilized by the recruitment team at Fenway Health for biomedical studies with similar inclusion criteria. Contact information for individuals who were ineligible for or have completed IMPACT, and are interested in enrolling in PrEPsteps, will be stored in a password-protected spreadsheet on a shared folder in the Fenway server accessible only to members of the PrEPsteps study team.

We will advertise aim 2 of the study on social media (e.g., Grindr, Growlr, Facebook, Twitter, Reddit, Instagram, Craigslist) in coordination with the recruitment team at the Fenway Institute. We will also receive referrals for potentially eligible participants through the use of a centralized pre-screener facilitated by the recruitment team and BSRP. Finally, BIDMC will be used as a site for passive recruitment, in which a PowerPoint slide advertising the study will be shared/presented at regular HIV conference meetings attended by BIDMC faculty.

IV. Subject Selection

Inclusion Criteria	Exclusion Criteria
Aim 1: 1) Cis-gender MSM with problematic stimulant use (identified in medical record as stimulant dependence or recurrent stimulant use that interferes with daily life: ICD 304, 305 and 292) or self-report (e.g. reported stimulant use in the past 6 months) 2) HIV-negative 3) On PrEP or qualifies for PrEP 4) Age 18 or older	**Aim 1:** Does not speak English
Aim 2: 1) Cis-gender MSM with moderate to severe non-alcohol substance use disorder (via MINI assessment) 2) HIV-negative 3) On PrEP or initiating PrEP 4) Has qualifying laboratory testing: Cr clearance, HBV, liver function tests 5) Owns a smartphone with Android or iOS 6) Age 18 or older	**Aim 2:** 1) Does not speak English 2) HIV positive 3) History of Crohn's disease or ulcerative colitis 4) History of gastric bypass, bowel stricture 5) History of GI malignancy or radiation to abdomen 6) Unable/unwilling to ingest digital pill 7) Allergy to gelatin, silver or zinc (components of the digital pill) 8) Does not qualify for PrEP (abnormal liver function, or Cr Clearance <60)
Aim 3: Participants in Aim 2 will be enrolled in Aim 3	**Aim 3:** Did not participate in Aim 2

Justification for Inclusion Criteria
MSM represent the largest risk group for new HIV infection nationally (Centers for Disease Control and Prevention, 2015). We did not include women or heterosexual men in the current study because the intervention approach may vary in different communities. Moreover, Fenway's extensive experience working with MSM makes this site most appropriate for the development of an intervention that focuses on MSM. This study proposes to recruit biological MSM. The decision not to recruit transgender men or women is based upon the following considerations. The priority for this treatment development study is to develop a treatment that will identify important relationships between non-alcohol substance use and PrEP nonadherence so that we can modify these experiences to improve adherence in this population. If we are successful in developing PrEPsteps in the MSM population, we will expand our study to explore if the intervention can be translated towards transgender individuals who may have different barriers to PrEP adherence.

Justification for Substance Use Disorder
Among MSM enrolled in the iPrEX study, individuals who experience suboptimal and eventual nonadherence had concomitant substance use disorders. While the majority of MSM with PrEP nonadherence in iPrEX were stimulant users, substance use in general has been a predictor of PrEP nonadherence, especially after the end of

a structured clinical trial (Hoenigl JAIDS 2019). Additionally, all substance use has been associated with increased incidence of sexually transmitted infections, suggesting that risky sexual activity occurs in the context of substance use (Hoenigl Emerg Infect Dis 2018). MSM who use substances also experience other concurrent risk factors for nonadherence including missed appointments and disengagement with care (Zucker JAIDS 2019). These concurrent risk factors for nonadherence are increasingly exaggerated in individuals with moderate to severe substance use disorder who have increasingly disorganized lives. The aim of this investigation is to develop the PrEPSteps intervention to address personalized barriers to adherence in these individuals for whom substance use disorder impacts their PrEP adherence.

Justification for Exclusion Criteria
We are excluding individuals with bowel strictures, Crohn's disease, ulcerative colitis, bowel neoplasm or radiation to the abdomen in order to minimize the risk of retention of digital pill components. Despite safety data that has demonstrated no risk of retained components of the digital pill in individuals, potential participants that are at risk of developing bowel stricture or obstruction would be at the highest risk of experiencing adverse events related to the digital pill.

V. Subject Enrollment

For all aims, we will publicize the study at Fenway Health primary care provider (PCP) meetings. We will additionally distribute flyers and palm cards at Fenway Health and at local sites including local bars and clubs in coordination with our recruitment team. For recruitment from the medical floors at Fenway, we will utilize CPS/Centricity to access the patient scheduler in conjunction with electronic reports (HIPAA waiver) in order to know if potential participants are scheduled for appointments at Fenway locations, their providers (so that we can approach them or nursing staff on the appropriate floor and time), and whether or not potential participants have confirmed their appointment or cancelled them. If Fenway PCPs have eligible participants we will ask the PCP if they are willing to refer them to us. We will also screen participants at scheduled Fenway Health appointments using electronic reports generated from the data team under our HIPAA waiver.

Participants who consent and are recruited for aim 1 and also meet eligibility criteria for aims 2/3 will be additionally approached regarding aims 2/3 if they are interested. Potential participants will contact the study team through the study email, call the BSRP team phone line, or meet with study staff in person to confirm eligibility. If participants meet eligibility criteria, we will then schedule them for the first study visit.

Finally, we will also advertise on social media, and flyering through clubs and other venues in the Greater Boston area. We will also advertise through local electronic billboards in the greater Boston area.

VI. Study Procedures

Aim 1: In this aim, we will conduct a series of 8 focus groups that will inform the specification of PrEPSteps, a smartphone-based adherence intervention that responds to feedback from a digital pill. We will schedule focus groups based on availability of participants. Participants in all focus groups will be verbally consented. On the day of the scheduled focus group, we will have participants complete a quantitative assessment (PrEPsteps_quantatitveassessment_v1). In the first two exploratory focus groups, we will discuss the digital pill and PrEPsteps as a whole. We will explore themes of the interconnection between digital pills, adherence data, and interventions based on nonadherence. We will also explore the hardware relationships between digital pills,

the Readers and smartphone app. Additionally, we will solicit methods to prepare potential participants for using digital pills in PrEP adherence monitoring.

Next, we will conduct five focus groups that will explore the structure of PrEPsteps. The focus groups will start with a general description of PrEPsteps. Next we will discuss each component of PrEPsteps: the LifeSteps framework, contingent reinforcement/corrective feedback (CR/CF) and SBIRT interventions. Iterative refinements to the structure of PrEPsteps, the wording of messages in CR/CF and content within SBIRT interventions. We will additionally inform the design features that improve the acceptability of each component of PrEPsteps: the timing of delivered interventions, how many messages are delivered daily, and the design and appropriate display of messages on the smartphone interface.

We will compile important themes in digital pill presentation, preparing participants for digital pill investigations, the structure and delivery of PrEPsteps and content of PrEPsteps into a final product package of digital pill hardware, smartphone app interface and interventions that comprise PrEPsteps. We will present this package to one final focus group (N=10) to ensure that all components are acceptable and understandable by potential study participants. Once this final focus group is complete, we will program PrEPsteps with our industry partner, etectRx, into the smartphone app and conduct a series of pilot tests in response to mock episodes of adherence and nonadherence to ensure the technology functions and correct components of PrEPsteps are displayed in response to detected ingestion patterns.

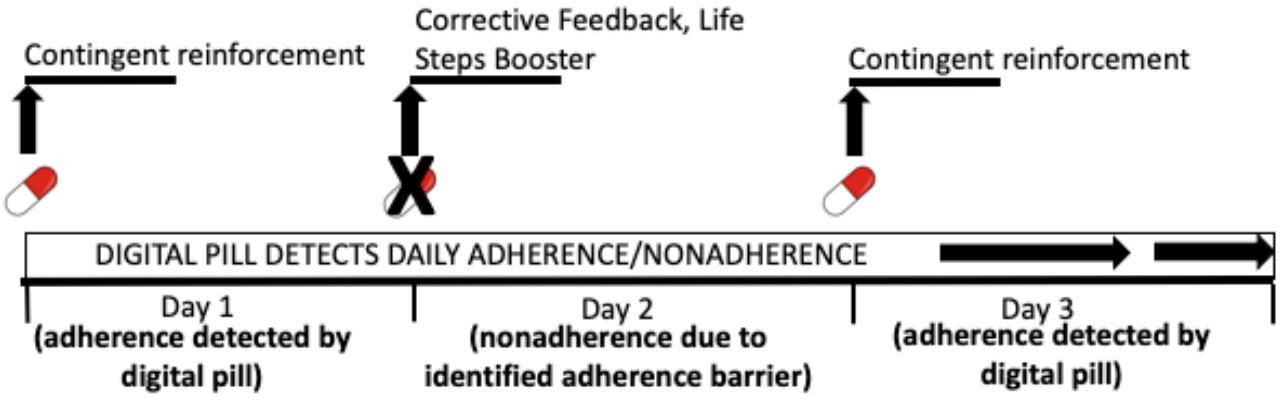
Aim 2 and 3: In Aims 2 and 3, we will deploy PrEPsteps in a pilot randomized controlled trial in MSM with non-alcohol substance use who are on PrEP. This portion of the study will involve 7 study visits (most of them remote) over the course of 6 months where participant ingest digital pill PrEP daily. Details of the PrEPSteps intervention, delivery of intervention and all study visits are described below:

Intervention Condition (PrEPsteps): The PrEPSteps intervention integrates feedback from focus groups completed in aim 1 to specify the content of this intervention. At the core of PrEPSteps are text messages that are housed in the etectRx app that respond to adherence and nonadherence events detected by the digital pill. Daily messaging is triggered based on detection of adherence. There are three major parts to PrEPSteps:

1) Contingent reinforcement: These are neutral positive feedback messages (e.g. “ingestion detected”) that are delivered to the participant confirming that their digital pill ingestion was recorded. These messages are delivered each time the participant ingests a digital pill and successfully uses the technology.
2) Corrective feedback: In the setting of detected nonadherence, participants will receive a message of corrective feedback, reminding participants that they did not take their PrEP. This message will be linked to the third component of PrEPSteps, a LifeSteps booster.
3) Life Steps booster sessions: As part of study visit 3, we will conduct an initial session of LifeSteps with the study participant. We will use this session to identify major perceived barriers to adherence and solutions to these barriers. We will focus specifically on substance use (Non-alcohol) as a potential barrier to adherence given our study population. These barriers and solutions are displayed in concert with corrective feedback messages after every nonadherence event detected by the digital pill. Participants are prompted to select the barrier that they may have encountered. They will also have the option to select “other,” which will generate a free text field to describe the barrier they faced. If they select one of the barriers they previously identified during LifeSteps in study visit 3, they will also receive their previously identified solution to that barrier.

Timing of Message Delivery: Contingent reinforcement messages are delivered immediately upon collection of digital pill ingestion events. Corrective feedback tied to Life Steps booster messages are delivered 1-2 hours after digital pill nonadherence is detected outside of the participant's self-defined dosing window (e.g., participant-identified regular PrEP ingestion time). For example, if a participant defines their dosing window as 9-11am, they will receive corrective feedback in the context of not taking their digital pill between 12pm-1pm.

See below for a figure of PrEPSteps algorithm:



Components of PrEPSteps Intervention
(see attached, *PrEPsteps_Study Messages_Participants Only)*:

Intervention Component	Message Content	Timing of Delivery
Contingent Reinforcement	Standardized "Ingestion detected" message and weekly summary of adherence metrics	Immediately after every digital pill ingestion; once weekly
Corrective Feedback	Standardized "It looks like you missed your medication today. What happened?"	2 hours after dosing window has closed without ingestion event
LifeSteps Booster	Participant-generated interventions during study visit 3, linked to corrective feedback content	Linked with corrective feedback message

Control Condition: The control condition will receive the digital pill as a medication adherence monitoring device. Participants will be trained on the digital pill device, operation of the reader and the accompanying app. For individuals in the control arm, they will receive confirmation messages surrounding digital pill ingestion. If participants want to see if they ingested a digital pill, they will be able to query this in the app. Participants will receive weekly adherence metrics (please see attached list of PrEPSteps messaging for both conditions).

Study Visits:

Screening Visit: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. If this visit is conducted entirely onsite, individuals will be roomed in the 8th floor consult rooms. We will conduct the informed consent process and answer questions about the study. If they consent, we will ask participants to sign the Fenway Institute Medical Release Form, Fenway Locator Form, and the Informed Consent Form. Once we verify consent is signed, we will ask participants to either show us their most recent screening lab work, or send results via secure email. If participants do not have qualifying lab work, or are initiating PrEP, we will draw labs specimens (Chem 7, Hepatitis B status, liver function tests). All lab tests will be processed by Quest Diagnostics. Next, after the consent process, a trained member of the study team will walk the participant through the substance use screener (*MINI 7.0 Substance Use Disorder Subscale)* via Zoom. Once the substance use screener is complete, participants will complete the acute HIV screener (*PrEPsteps_Screening Visit_Acute HIV Screener*). If their responses indicate potential for acute HIV, they will receive HIV viral load testing or be referred to their PCP. We will also ask for permission to contact the participant's PCP via Mimecast secure email to inform them that the participant has enrolled in the study. All participants will then receive a 3rd generation rapid HIV test. If participants test positive, we will refer to them to Fenway Health for confirmatory testing. If participants do not wish to continue care at Fenway, we will refer them to the infectious disease clinic at Brigham and Women's Hospital. If participants are eligible, and have all qualifying laboratory work, we will contact them to schedule Study Visit 1.

In the event that the Screening Visit is conducted in a partially remote format, we will email participants the Fenway Institute Medical Release Form, Fenway Locator Form, and the Informed Consent Form prior to the virtual (Zoom) portion of the visit. We will conduct the informed consent process via Zoom and answer questions about the study. If they consent, we will ask participants to electronically sign all three of these forms while study staff remain on the Zoom line. Also during the virtual portion of this visit, we will review recent lab work, walk the participant through the substance use screener, and ask participants to complete the acute HIV screener. During the onsite portion of this visit, we will conduct the rapid HIV test, and any required lab work.

Study Visit 1: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. If this visit is conducted entirely onsite, participants will complete the baseline quantitative assessment (*PrEPsteps_Quantative Assessment_Visit 1*) via REDCap. We will show participants optional training videos on how to operate the digital pill system (see *PrEPsteps_etectRx Training Videos Link*). We will then conduct a short training of operation of the components of the digital pill and Reader. We will instruct participants on basic troubleshooting of the technology. We will also identify a 2-4 hour dosing window (e.g., period of time during which the participant usually takes their PrEP) and program this window into the online interface. This dosing window will be used to time the corrective feedback and LifeSteps booster components of PrEPSteps at Study Visit 3 if the participants are randomized to the intervention arm. Participants will then ingest their first digital pill PrEP under the observation of a study team member, to demonstrate their understanding of how to operate digital pills and to ensure that the technology is functioning properly. Finally, participants will electronically sign an acknowledgement of receipt of privacy practices from ARx Pharmacy (*ARx_Receipt of Notice of Privacy Practices*) via a link provided by ARx Pharmacy. A copy of this receipt will be emailed to the study team and filed in the participant's study file. Participants will be scheduled for a 2-week follow-up (Study Visit 2), and provided with 21 days of Truvada digital pills (14 pills to cover the 2-week period, plus 7 additional pills to serve as a buffer if scheduling issues arise). We will contact study participants via text message on days 2, 5, and 7 to ensure the technology is functioning.

In the event that Study Visit 1 is conducted in a partially remote format, we will send participants the baseline quantitative assessment (*PrEPsteps_Quantative Assessment_Visit1*) via email or REDCap survey link, and ask them to complete it prior to the onsite portion of this visit. We will also send participants optional training videos on how to operate the digital pill system (see *PrEPsteps_etectRx Training Videos Link*). During the onsite portion of this visit, we will conduct all training on the use of the digital pill and Reader, and observe the participant ingest their first digital pill PrEP. Participants will also sign the receipt of privacy practices from ARx Pharmacy during the onsite portion.

As part of the PrEPsteps supplement (3K23DA044874-05S1, funded in September 2022), additional questions were added to the baseline quantitative assessment at Study Visit 1 (*PrEPsteps_Quantative Assessment_Visit 1*). Participants who enrolled after the start of the supplement project completed the updated baseline quantitative assessment with the additional questions integrated. The study team will seek to contact participants via phone who enrolled prior to the start of the supplement, and therefore did not complete the additional questions. If interested in completing the additional quantitative questions, participants may complete the PrEPsteps supplement baseline questions via REDCap, or over the phone with a study team member. If participants complete these questions verbally via phone, their answers will be recorded in REDCap by a study team member. Participants who elect to complete the additional questions will be remunerated.

Study Visit 2: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. This visit will take place 2 weeks after Study Visit 1. We will contact participants on day 7 to remind participants of their appointment. Participants will be randomized into the control arm (treatment as usual with digital pills to measure adherence) or the intervention arm (PrEPsteps). Randomization will occur via a predetermined schema using REDCap. We will review the previous 2 weeks of adherence data and reconcile discordant or nonadherent events with participants. At this study visit and subsequent study visits, participants will have the option of viewing the original digital pill training videos used in Study Visit 1 as a refresher course for technology training if they desire. Participants will return any unused digital pills from the prior 14-day period (to be counted by study staff), and will additionally undergo a blood draw for dried blood spot (DBS) testing for tenofovir diphosphate (to measure adherence and compare DBS against the digital pill). For all participants, a 30-day supply of Truvada digital pills will be dispensed at this study visit. We will contact participants via text message on days 16, 19, 21 to ensure technology is functioning. *This contact schema (i.e., reminder messages for study visit) will remain the same for each subsequent visit.*

In the event that Study Visit 2 is conducted in a partially remote format, we will randomize the participant, review the previous 2 weeks of adherence data, and provide the link to the digital pill training videos during the virtual (Zoom) portion of this visit. All remaining study visit procedures will be conducted during the onsite portion of this visit. If necessary, the 30-day supply of digital pills may be mailed to participants if they are unable to attend the in-person portion of the visit due to COVID-19.

Arm	**Study Visit 2 Procedures**

PrEPsteps	• Life Steps counseling (remote) • Responses to Life Steps programmed into PrEPsteps (remote or onsite) • Substance use counseling (remote) • Dispense digital pills, technology training, digital pill ingestion (onsite) • Return unused digital pills from prior 14-day period (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite)
Treatment as usual	• Life Steps counseling (remote) • Substance use counseling (remote) • Dispense digital pills, technology training, digital pill ingestion (onsite) • Return unused digital pills from prior 14-day period (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite)

Study Visit 3: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. This visit will take place 30 days post-randomization. We will contact participants prior to their appointment via text or phone call to remind them of their visit. We will review the previous 30 days of adherence data over and reconcile discordant or nonadherent events with participants in both study arms. Participants will return any unused digital pills from the prior 30-day period (to be counted by study staff). Participants will additionally undergo a blood draw for dried blood spot (DBS) testing for tenofovir diphosphate (to measure adherence and compare DBS against the digital pill), and a urine drugs of abuse immunoassay assessing non-alcohol substance use. Upon participant request, we will inform them of the results of the urine drugs of abuse screen via phone or in-person. A 60-day supply of Truvada digital pills will be dispensed to participants in both study arms at this visit.

In the event that Study Visit 3 is conducted in a partially remote format, we will review the previous 30 days of adherence data during the virtual (Zoom) portion of this visit. During the onsite portion of this visit, participants will return any unused digital pills, and a 60-day supply of Truvada digital pills will be dispensed. If necessary, the 60-day supply of digital pills may be mailed to participants if they are unable to attend the in-person portion of the visit due to COVID-19. The blood draw for DBS, and a urine drugs of abuse immunoassay will also be completed during the onsite portion.

Arm	**Study Visit 3 Procedures**
PrEPsteps	• Return unused digital pills from prior 30-day period (onsite) • DBS testing to confirm PrEP adherence (onsite) • Urine drugs of abuse screen (onsite) • Digital pill refill, technology refresher, digital pill ingestion (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite)
Treatment as usual	• Return unused digital pills from prior 30-day period (onsite) • DBS testing to confirm PrEP adherence (onsite) • Urine drugs of abuse screen (onsite) • Digital pill refill, technology refresher, digital pill ingestion (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite)

Study Visit 4: Procedures for this visit will be conducted entirely remotely. We will check in with the participant via Zoom 60 days post-randomization. We will review the previous 30 days of adherence data over Zoom and reconcile discordant or nonadherent events with participants in both study arms. We will also ask participants via Zoom to conduct a pill count of any unused digital pills from the prior 30-day period. Participants will be asked to hold onto any unused digital pills and return them the following month, during the in-person portion of Study Visit 5.

Arm	**Study Visit 4 Procedures**
PrEPsteps	• Pill counts of remaining digital pills (remote) • Review of adherence data, discussion surrounding nonadherent events (remote) • Technology refresher, digital pill ingestion (remote)
Treatment as usual	• Pill counts of remaining digital pills (remote) • Review of adherence data, discussion surrounding nonadherent events (remote) • Technology refresher, digital pill ingestion (remote)

Study Visit 5: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. We will contact participants on day 83 to remind participants of this study visit. We will remind participants to bring all PrEPsteps equipment with them to be returned to the study team. Participants will have DBS testing for adherence onsite at Fenway Health, a urine drugs of abuse screen, and will also return all remaining unused digital pills from the prior 60-day period (to be counted by the study team). Upon participant request, we will inform them of the results of the urine drugs of abuse screen via phone or in-person. For participants who are in the PrEPSteps arm, we will conduct a 20 minute semi-structured qualitative interview (*Aim 3 Exit Interview*) to assess the user experience working with PrEPsteps. Participants in both study arms will also complete a brief quantitative assessment via REDCap (see attached *PrEPsteps_Quantitative Assessment_Visits 5+6)*.

In the event that Study Visit 5 is conducted in a partially remote format, the participants in both study arms will complete the brief quantitative assessment virtually, which will be sent via email or REDCap survey link during the virtual (Zoom) portion of this visit. Participants in the PrEPsteps arm will so complete the 20 minute semi-structured interview via Zoom. All remaining study visit procedures will be conducted during the onsite portion of this visit.

Arm	**Study Visit 5 Procedures**
PrEPsteps	• Return unused digital pills from prior 60-day period (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite) • DBS testing to confirm PrEP adherence (onsite) • Urine drugs of abuse screen (onsite) • Audio-recorded review of adherence data from digital pill with focus on nonadherence episodes or PrEPsteps-triggered corrective feedback to describe episodes of nonadherence (remote or onsite)

Treatment as usual	• Return unused digital pills from prior 60-day period (onsite) • Review of adherence data, discussion surrounding nonadherent events (remote or onsite) • DBS testing to confirm PrEP adherence (onsite) • Urine drugs of abuse screen (onsite)

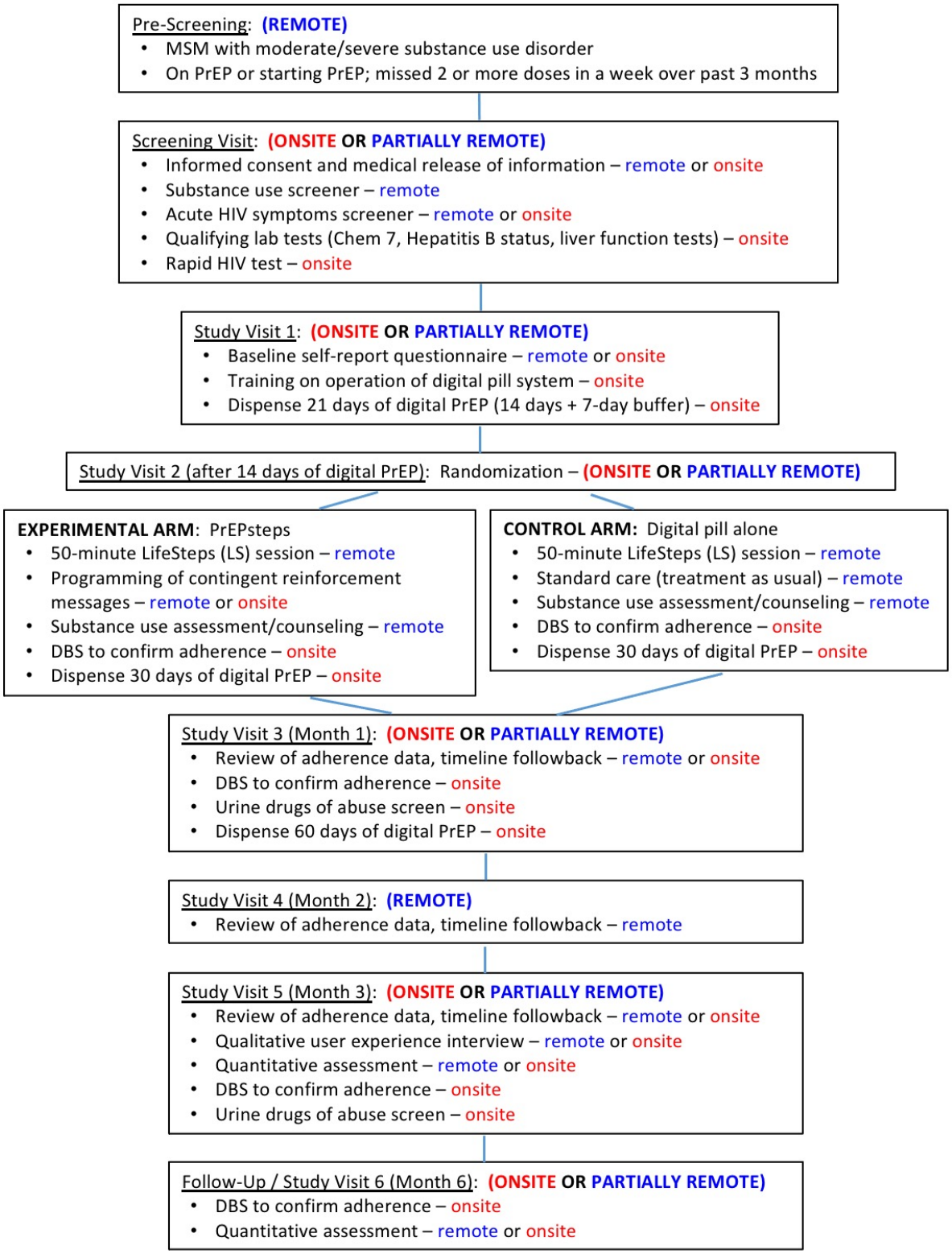
Study Visit 6: Procedures for this visit will be conducted onsite at Fenway Health, or partially remote, if necessary, in response to COVID-19. This visit will take place 3 months after study visit 5 (6 months post randomization). We will conduct a DBS to assess PrEP adherence. We will ask participants to complete a brief quantitative assessment (see attached *PrEPsteps_Quantitative Assessment_Visits 5+6)*, via REDCap.

In the event that Study Visit 6 is conducted in a partially remote format, we will connect with participants via Zoom and ask them to complete a brief quantitative assessment (see attached *PrEPsteps_Quantitative Assessment_Visits 5+6)*, which will be sent via email or REDCap survey link. For the onsite portion of this visit, we will conduct a DBS to assess PrEP adherence.

See study schematic below for a breakdown of Aims 2 and 3 study procedures:

PrEPsteps Aim 2 Study Flow

Onsite & Remote Procedures



At the conclusion of this study, we will provide the following avenues in which study participants can continue to access PrEP outside of the study: First, participants can return to their primary care provider and ask them to prescribe PrEP, second, we can refer participants to a provider at Fenway Health to prescribe PrEP and finally, participants can access PrEP through the Brigham and Women's Infectious Disease Clinic.

Remuneration: Participants will be remunerated via ClinCards using the following schedule. Participants will only receive compensation for completed study visits. Participants who enrolled prior to the start of the PrEPsteps supplement in September 2022, and who elect to complete the additional questions added to the baseline quantitative assessment, will be compensated an additional $20.

Study Visit	Compensation
Screening Visit	$20
Study Visit 1	$20
Study Visit 2	$30
Study Visit 3	$30
Study Visit 4	$30
Study Visit 5	$40
Study Visit 6	$50
Additional Supplement Questions (if applicable)	$20
Total	**$240**

Participant Contact: We will contact participants via text message at described times after study visits (see *PrEPSteps Study Messages_Participant Only*). Additionally, if participants do not respond to text messages (e.g., technology check-ins at days 2, 5, 7, 16, 19, 21), we will contact them via phone, and/or email. We will also contact participants to remind them of upcoming study visits via phone, Nomi text message, patient portal, and/or email. Upon participant request, we will inform them of the results of the urine drugs of abuse screen at study visits 3 and 5 via phone or in-person. As part of the PrEPsteps supplement, questions were added to the baseline quantitative assessment (*PrEPsteps_Quantitative Assessment_Visit 1*). The study team will contact participants via phone who completed the Study Visit 1 baseline quantitative assessment prior to the addition of the PrEPsteps supplement questions (in September 2022) to inquire about their interest in completing the additional supplement questions.

Standard Operating Procedures for Nonadherence: The digital pill technology has the potential to report real time PrEP adherence data during the course of this study. Recognizing standard medical care does not include daily reminders around PrEP adherence, we have developed a standard operating procedure to surround nonadherence/non-detection of digital pill ingestion during the study. Communication surrounding nonadherence is detailed in a separate document (SOP_nonadherence).

Drug Procurement: Digital pills are procured from ARx Pharmacy (our collaborating pharmacy). Once participants sign informed consent during the Screening Visit, and we have confirmed qualifying laboratory work and eligibility, we will fax a Patient Prescription and Enrollment Form to ARx. This order form will contain the following information, as required by ARx per drug dispensing requirements: (1) participant's name; (2) participant's date of birth; (3) participant's study ID number; (4) participant's phone number; (5) participant's mailing address; (6) participant's drug allergies and current medications (if applicable); (7)

participant's anticipated start date; (8) target drug delivery date; and (9) delivery information for pharmacist at Fenway Pharmacy. Following receipt of the Patient Prescription and Enrollment Form, ARx will mail 21 digital Truvada pills to cover the 14-day run in period (including 7 digital pills for any operational delays). Upon determination that the participant is eligible to continue in the study, the study team will fax a second Patient Prescription and Enrollment Form to ARx (same order form as for initial run-in period). ARx will then mail 90 digital pills (three 30-day supplies) to the Fenway Pharmacy. Confirmation of all shipment receipt will be documented in the PrEPSteps Pharmacy SOP binder. At Study Visits 1, 2, and 3, we will complete a Prescription Card that study staff will bring to the Fenway Pharmacy, who will sign out drug to us. If participants no-show during their study visit, we will return and sign back in drug to the Fenway Pharmacy. Leftover drug (during study visits, or in the case of lost to follow up) will be kept at Fenway. Pharmacy labels will be scratched off and destroyed to protect participant privacy prior to return to our industry collaborators at a time to be determined.

Study Visit Scheduling: We will schedule study visits as close to 30 days apart as possible. Recognizing that participants may have scheduling conflicts, we will seek to schedule participants for study visits within 7 days prior to the 30-day mark in order to prevent participants from running out of digital PrEP pills. For participants who have completed the screening visits (Study Visits 1 and 2), we will continue to contact them if they are eligible for the study in order to progress to Study Visit 3. We will review participants who are lost to follow up at this stage to determine if continued attempts to contact them are warranted. All remote portions of study visits (via Zoom) will be scheduled as close in proximity as possible to the in-person portions of those visits.

Risk Assessments: A licensed clinician will be onsite during all study visits where the quantitative assessment component is completed in-person. If a participant answers "nearly every day" to question #9 on the PHQ9, indicating suicidality, this will trigger a safety evaluation by a licensed clinician (e.g., Dr. Peter Chai) before the participant is released. The clinician will review the results of the assessment with the participant, evaluate their safety and risk of harm, and make clinical referrals to Brigham and Women's Hospital if needed. In the unlikely event that the PI cannot be reached, another licensed clinician will conduct the safety evaluation. The participant's primary treating physician will be notified of the any clinical referrals made as a result of this evaluation.

VII. Biostatistical Analysis

Aim 1: We will conduct qualitative analysis on individual interviews in aim 1 to elucidate themes of technology acceptance, design, and optimal timing and delivery of messaging.

Aim 2: We will calculate descriptive statistics regarding the degree of adherence collected from the digital pill. We will also calculate the accuracy of the digital pill in comparison to pill counts and validate ingestion data compared to DBS. We additionally will report overall percent adherence and measure the association between percent adherence and PrEPSteps. Additionally we will report weeks of adherence (>4 doses a week) and measure the association between weeks of adherence and the use of PrEPSteps. Because this is a pilot, proof-of-concept study, we will not be powered to determine the degree of adherence the use of a digital pill alone confers upon study participants.

Aim 3: We will conduct an applied thematic analysis on all recorded interviews using NVivo 12.

VIII. Risks and Discomforts

We anticipate the major risks due to PrEPsteps are the potential for exposure to metal components in the digital pill, retention of the radiofrequency emitter portion of the digital pill, and allergic reaction to the silver and zinc components of the radiofrequency transmitter and to the gelatin pill capsule. Participants may also experience psychological discomfort in working with study staff to program PrEPsteps, and a risk of discoverability of their involvement in the study from PrEPsteps. Major psychological discomforts could occur during study interviews when participants are asked about their adherence patterns. We have addressed each of these risks below:

Exposure to Metal Components in Digital Pill: The Digital Pill is manufactured from the same basic components as other ingestible medical devices. The radiofrequency tags contain minimal amounts of silver, zinc and magnesium that are significantly less than the recommended daily intake of these metals. In order to prevent absorption of these metals, the radiofrequency tag is coated with an epoxy and ethylcellulose coating in a technique that is used for other ingestible medical devices.[20,21] Extensive experience in the use of ingestible small bowel endoscopy cameras has not reported adverse events related to the exposure of electronic components.[22,23]

Digital Pill Radiofrequency Emitter Retention: Study participants may experience retention of the radiofrequency emitting portion of the digital pill. A study assessing the efficacy of the capsule portion of PrEPsteps among healthy volunteers documented 560 successful ingestion events without any adverse effects. Dr. Chai has completed a pilot study that recorded 96 ingestions with the digital pill containing oxycodone without any adverse events.[2] Additional pilot data from Novartis of over 100 participants who ingested radiofrequency tagged gelatin capsules revealed no reports of sensor retention (Personal communication from Joris VanDam, Novartis). An additional investigation to determine the safety of digital pills demonstrated no retention of any of the components of the digital pill by abdominal imaging.[21] The best comparison to the digital pill are capsule endoscopy pills which are over twice the size of digital pills. Over a decade of experience of capsule endoscopy has revealed a capsule retention rate of less than 2%.[22,24] In the case of a retained endoscopy pill, patients were mostly asymptomatic, and treatment consisted only of oral fluid administration. Patients who elected to have the capsule removed successfully underwent elective partial small bowel resection with pathologic findings including mild bowel stricture or intimal ulceration from capsule retention.[25] Complication rates among patients with Crohn's disease, bowel neoplasm, radiation enteritis, or stricture were higher.[26,27] In high-risk patients, standard therapy for retained endoscopy pills included aggressive oral hydration with successful removal of the retained pill.[28] We believe that the risk of retention of a PrEPsteps capsule will be less than that of a capsule endoscopy pill given the smaller dimensions of the digital pill. Unlike a capsule endoscopy pill, PrEPsteps is dissolvable with only the radiofrequency emitting portion of the capsule passing through the gastrointestinal tract. In order to minimize the risk of PrEPsteps capsule retention, we plan to exclude patients with underlying bowel disease or surgical intervention to the bowel.

Allergic Reaction: There is a risk of allergic reaction to the silver and zinc components of the radiofrequency transmitter, and to the gelatin pill capsule used to encase the radiofrequency transmitter and PrEP inside the capsule. In order to minimize the risk of a potential allergic reaction, we plan to exclude patients with a known allergy to silver, zinc or gelatin.

Risk of Discoverability from PrEPsteps: There is a risk of discoverability of PrEP use or participation in the study in the case when a study participant's messages from the PrEPsteps app is discovered by a bystander, or if PrEPsteps messages are discovered by individuals outside of the study. We will take 4 major steps to ensure that we maximally protect participants from the risk of discoverability.

- *Password protection on participants' cellphones:* We will ensure that participants' cellphones are enabled with password protection (or Touch ID, for iPhones). Participants will be the only individuals who have access to their personal cellphones.
- *Messaging that does not directly reveal PrEP ingestion:* During focus groups in aim 1, we will craft messages from PrEPsteps that avoid inadvertent disclosure that participants are on PrEP to protect against individuals who are uninvolved in the study reading messages from PrEPsteps. Although messages are password protected, we will take the additional step of ensuring the text of messaging protects participants against PrEP discoverability.
- *Masking the icon of the PrEPsteps app to prevent discoverability:* We will mask the icon of the PrEPsteps app as a generic "ID Cap" app to avoid discoverability of PrEP ingestion or participation in PrEPsteps.
- *Opaque digital pill capsules:* The digital pill gelatin capsule is opaque, prevent discoverability of PrEP ingestion by recognition of the color of TDF/FTC.

Psychological Discomfort of Disclosing Adherence Patterns: Participants may experience psychological discomfort in disclosing and learning of their adherence data during study visits.

IX. Potential Benefits

Participants may indirectly benefit from participation in the study by improving their adherence to PrEP. Interacting and using PrEPsteps may confer some increased adherence among study participants.

X. Data Transmission from Digital Pills

It is important to note that no protected health information flows through ingestion events recorded by the digital pill. There is no medication data that identifies study drug as Truvada, nor personal identifiers within the digital pill system. Ingestion of the digital pill activates a generic radiofrequency signal that is collected by the Reader. The Reader then transmits ingestion data via low energy Bluetooth to the participant's cellular phone. This data is collected by an app housed on the participant's smartphone. Within the app, data is converted to Java Script notation that describes the presence of an ingested medication. This data is transferred to servers at our collaborating industry partner, etectRx. This data is then stored on a secure server. Access is limited to etectRx maintenance technicians and the study team. For PrEPSteps interventions and text messages, receipt of digital pill ingestion data is sent to the NOMI dashboard- this dashboard automates the PrEPSteps intervention and pushes messages via SMS text messaging to the participant's phone in response to their ingestion patterns. Study participants are identified on the etectRx and NOMI dashboard only as study numbers. Their PHI is kept within secure Fenway computers. A secure excel spreadsheet that links study numbers to participant names is kept on desktop computers at Fenway accessible to the PI and study team.

XI. Data Monitoring and Quality Assurance

We will review and monitor data from PrEPsteps for each study participant. At each study visit, participants will undergo pill counts to correlate adherence data from PrEPsteps, and calculate the accuracy of the digital pill to measure PrEP adherence. Any discrepancies between the digital pill and pill counts will be addressed in real time at each study visit with the participant. For each participant, we will also review signaling from the digital pill to the Reader with our industry collaborator (etectRx) to ensure there are no errors in data transmission contribution to missed adherence events. If errors occur as a result of data transmission, we will correct the participant's adherence data, and convey these changes to participants' PCP via Mimecast secure email. We will additionally obtain dried blood spot testing at study visits 3 and 4 to confirm adherence (see section V. study procedures)

Recorded interviews: Audio-recorded interviews (Aim 1 and 3) will be transcribed using a HIPAA compliant transcription service (Landmark transcription), and scrubbed of identifiers

Aim 2 QA review: Study investigators will conduct QA review of baseline adherence data after the first 10 participants are enrolled. Additionally, we will review adherence data and interactions with PrEPsteps after the first 10 participants randomize to PrEPsteps. We will similarly conduct QA review after the first 10 participants randomize to treatment as usual. We will continue to conduct subsequent QA reviews in increments of 10 participants enrolled in each arm to ensure fidelity of the study data.

Data Safety Monitoring Board (DSMB): Three investigators who are external to the study and external to Dr. Chai's mentoring team as defined by his NIH K23 award with expertise in PrEP, non-alcohol substance use disorder, technology security and behavioral interventions, will comprise a DSMB for Aim 2 (pilot randomized controlled trial) of the research plan. The DSMB will convene annually during Aim 2. Additionally, the DSMB will meet when N=30 study participants are enrolled in Aim 2. They will review the data, and any potential study related adverse events prior to approving the continuation of recruitment. The responsibilities of the DSMB will include:

- Reviewing the research protocol, consent form, and plans for DSMB.
- Evaluating the progress of the pilot randomized controlled trial: recruitment, retention, data quality, site performance, adverse events.
- Protection of participant safety
- Making recommendations to Dr. Chai and the Fenway Institute IRB regarding continuation, termination or modification of the study depending on benefits or adverse events.
- Ensuring the confidentiality of study data.
- Reviewing adverse events.
- Providing annual written reports to Dr. Chai, and NIH regarding safety concerns, continuation or modification of the research plan.

We will additionally comply with all Fenway regulations regarding reporting of adverse events and ensuring data quality.

Data Tracking: Ingestion data will be automatically logged into the web interface hosted by etectRx with a date/time stamp to ensure accurate record keeping of all data and linking to the results. All data will be securely accessed at Fenway Health.

Data Entry Process: Protected health information, including study participant demographics, non-alcohol substance use disorder history, and HIV risk factors will be collected by Dr. Chai and the research assistant and entered into REDCap, a secure web application being used for data storage and management. A separate spreadsheet of study participant contact information and a technology log including participant mobile phone number, electronic mail (email) address, identifiers of the Receiver, study smartphone and a log of dispensed digital pills will also be maintained by Dr. Chai and the RA. All logs will be stored behind TFI firewall and password protected. Each variable with missing data (such as an interruption between smartphone and sensor) will be identified and a placeholder ("<<-99>>") entered to connote a missing value. Data from the digital pill is recorded on the etectRx interface and automatically transferred via a HIPAA-compliant secure link to the adherence interface (NOMI). Ingestion data may potentially require editing if there are transmission failures, errors from the reader device, or manually recorded data from study participants. All of these potential edits will be identified by etectRx in collaboration with the study team. Edits to data will be agreed upon by both parties and approved by the PI. An audit trail of all potential edits will be maintained. We will additionally comply with Fenway regulations regarding reporting of adverse events and ensuring data quality. Landmark Associates Inc, an external company, will be contracted to transcribe audio-taped exit interviews.

Data Storage: Raw ingestion data, transcripts from this study and self-report questionnaires will not be made publicly available. De-identified data may be shared with NIH who is funding the study, as well as industry collaborators etectRx and NOMI. For future investigations that use de-identified participant data, we will submit IRB protocols detailing the use of this data. Mass General Brigham Dropbox is being used for file storage in the study.

XII. References

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