DigiPrEP Detailed Protocol

Official title: Feasibility and Acceptability of Digital Pills to Monitor PrEP Adherence in MSM With Substance Use

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Detailed Protocol for Feasibility and Acceptability of Digital Pills to Monitor PrEP Adherence in MSM with Substance Use Disorder (DigiPrEP)
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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 substance use disorder. 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 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 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[18, 20] and recent studies have already identified substance use as a significant barrier to optimal PrEP adherence among MSM.[19, 21]

II. Specific Aims

Aim 1: Technology Optimization. To optimize the acceptability of DigiPrEP among MSM or transgender individuals with self-reported substance use through individual interviews (N=30);
Aim 2: Technology Deployment. To deploy DigiPrEP in MSM with self-reported substance use who are on PrEP (N=15) in a 90-day open label, proof-of-concept trial; and
Aim 3: Technology Evaluation. To evaluate the user response and primary care physician response to using DigiPrEP in the real-world through qualitative interviews.

III. Subject Selection

Aim 1 Inclusion Criteria:	Aim 1 Exclusion Criteria:
1. MSM (cisgender male) 2. Self-reported use of non-alcohol substances of abuse in past 6 months 3. On PrEP or qualifies for PrEP 4. Age 18 or older	1. Does not speak English 2. HIV positive

Aim 2 Inclusion Criteria:	Aim 2 Exclusion Criteria:
1. MSM (cisgender male) 2. Self-reported use of non-alcohol substances of abuse in past 6 months 3. Currently taking PrEP 4. Has qualifying laboratory tests (Cr, hepatitis B immunization, STI testing and syphilis) 5. Age 18 or older	1. Does not speak English 2. HIV positive 3. Identifies as transgender 4. Estimated creatinine clearance <60ml/min 5. Active hepatitis B treatment 6. Does not own a smartphone 7. Taking proton pump inhibitors 8. History of Crohn's disease or ulcerative colitis 9. History of bowel surgery, gastric bypass, bowel stricture 10. History of GI malignancy or radiation to abdomen 11. Unable/unwilling to ingest digital pill
Aim 3 Inclusion Criteria: 1. Participants in Aim 2 will be enrolled in Aim 3.	Aim 3 Exclusion Criteria: 1. Did not participate in Aim 2.

Due to the exploratory nature of this proposal, we will enroll only MSM individuals (cisgender male) in this study with the intent of generating preliminary data on feasibility of the digital pill in order to conduct future studies with transgender men and women.

IV. Subject Enrollment

For all aims of this study, we will publicize the study at Fenway Health primary care provider (PCP) meetings.

Recruitment of Fenway Patients

Aim 1: We will advertise the study through monthly research meetings at The Fenway Institute, and we will ask Fenway Health primary care physicians and other Fenway Health clinicians to refer patients to us. 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 crystal reports. 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. We will also post flyers and cards advertising the study at Fenway Health and throughout the greater Boston area, as well as via social media platforms (Grindr, Scruff, Growler, and Facebook). Participants who are interested in the study will call the RA and undergo a phone screen to ensure they meet enrollment criteria prior to being scheduled for a study visit.

Aim 2/3: We will utilize chart review, as well as screening during clinical appointments at Fenway Health (as described above) to identify HIV negative MSM with a history of substance use disorder who have qualifying laboratory evidence and are prescribed PrEP at Fenway Health. We will also identify potential participants through posted flyers in the greater Boston area, email blasts from the Fenway Health recruitment team, and social media advertisements. Email blasts from the Fenway Health recruitment team are received by patients and general public who sign up to receive general emails from Fenway Health regarding its daily operations, events and research studies. If applicable, we will inform their treating clinicians that their patient might be eligible for the study. The clinician will tell the patient about the study and acquire permission from the patient for study staff to speak with them at their next regularly scheduled clinic appointment or provide them with contact information for the study team. We otherwise will utilize crystal reports using our HIPAA Waiver to

screen potential Fenway Health participants, and approach them on the medical floors after consultation with the medical team. If potential participants are interested in the study after a discussion with their primary care physician, we will arrange a time to contact the participant and discuss the study in further detail. We will schedule an appointment with the study staff to discuss DigiPrEP. If participants enroll in the study, we will have them sign a medical release of information form to notify their treating clinician at Fenway Health about their participation. Additionally, we will ask participants in Aim 1 if they would be willing to participate in Aims 2/3. Participants who are interested in the study can respond to posted flyers, recruitment emails, or social media advertisements will call the RA and undergo a phone screen to ensure they meet enrollment criteria prior to being scheduled for a study visit.

Passive Recruitment
We will also post flyers and cards advertising the study at Fenway Health and throughout the greater Boston area, and engage in recruitment via social media platforms (Grindr, Scruff, Growler, and Facebook) in order to extend our reach to as many potentially eligible individuals as possible. Participants who are interested in the study will call or email the RA and undergo a preliminary phone screen to ensure they meet basic enrollment criteria prior to being scheduled for a study visit.

Shared Cross-study Recruitment
As potential participants are screened for DigiPrEP, they may additionally be eligible for a parallel study that is testing the use of the digital pill for PrEP adherence linked to a smartphone behavioral intervention in MSM with moderate to severe stimulant use disorder (PrEPSteps- IRB 1162312). While screening participants, if their schedules do not allow them to participate in DigiPrEP, but they indicate willingness to participate in other Fenway Studies, we will discuss the PrEPSteps study with them as described in our cross study screener. Participants who would benefit from learning about their PrEP adherence would likely also benefit from interventions that boost adherence as studied in PrEPSteps. We therefore will share screener data between the two studies in the case that participants also qualify for PrEPSteps and would like to participate. Both studies are conducted by the same PI and study coordinators.

V. Study Procedures

Aim 1: In this aim, we will conduct individual interviews (see uploaded document *Aim 1 Interview*) of MSM with self-reported substance use currently on or qualifying for PrEP. Study participants will sign informed consent prior to the qualitative interview. An audio-recorded individual interview will be conducted by the RA or study investigator. We will explore the digital pill, acceptance of the technology, willingness to use technology for PrEP adherence and willingness to interact with the technology to reinforce adherence and address influencers of adherence. Interviews will be audio recorded, transcribed, and analyzed by the study team (see section VI), after that audio recordings will be destroyed. Participants will also complete a brief self-report questionnaire (see uploaded document (DigiPrEP_selfreport_questionnaire). At the end of the visit, the participant will be remunerated via a $40 gift card.

Aim 2/3: In Aims 2 and 3, we will deploy DigiPrEP in MSM who are already prescribed PrEP. This portion of the study will involve 5 study visits over the course of 3-4 months where participant ingest DigiPrEP daily. Participants will be prescreened via phone to assess initial eligibility for participation; if eligible, they will be scheduled for an in-person Screening Visit, where they will sign informed consent and full eligibility will be determined via rapid HIV test and review/conduct of necessary blood work. If determined to be eligible at the Screening Visit, participants will be scheduled for Study Visit 1; in the interim, a 90-day supply of digital pills will be ordered for shipment to the Fenway Pharmacy. At Study Visit 1, participants will be trained in the use of the digital pill and complete a self-report questionnaire (same questionnaire as in Aim 1). At Study Visit 2, we will dispense an additional 30-day supply of the digital pill, review adherence data with the participant, conduct a pill count of remaining pills, and conduct a blood draw for adherence. At Study Visit 3, we will dispense a final 30-day supply of the digital pill, review participant adherence data, and conduct a pill count of remaining pills. Following both Study Visits 2 and 3, we will also forward adherence data from the study visits to the participant's Fenway Health PCP, if applicable. At Study Visit 4, the final visit, we will review adherence data,

conduct a pill count of remaining pills, and conduct a blood draw for adherence. Additionally, as part of Aim 3, we will conduct a 20-minute semi-structured exit interview to assess participants' experiences in the study.

Aim 2 – Prescreening: Study participants prescreened on the phone who do not have a PCP at Fenway Health will be asked to bring their most recent copies of laboratory data to the in-person Screening Visit (chemistry or creatinine, evidence of hepatitis immunization status (within the past 6 months), sexually transmitted infection screening (STI) and syphilis screening (within the past 3 months)). If participants do not have qualifying laboratory tests, we will notify the participant that we will conduct any needed laboratory testing at the Screening Visit. We will send participants an email with a list of labs they should bring as part of the reminder for the Screening Visit.

Aim 2 – Screening Visit: This is the first study visit. During this visit, the participant will meet the RAs and study team. We will explain the course of the study, obtain written informed consent, and obtain a signed medical release of information form and completed locator form from participants. During the informed consent process, we will ask if participants want us to relay adherence data from the digital pill to their PCP; if they opt in, we will send monthly adherence information to their PCP. After obtaining consent, we will conduct a rapid HIV test to ensure that participants are HIV negative. We will also review laboratory data with participants; if they did not bring lab results with them (or grant us access to lab results via an online patient portal, following signing of medical release form), we will call their PCP and confirm their eligibility for PrEP (see *DigiPrEP_PCP_communication_script*). If participants are missing any required labs, they will receive those tests at this visit. If individuals screen positive for active hepatitis infection, or have creatinine clearance <60ml/min, they will be ineligible for the study and referred back to their PCP for continued medical care. Individuals who test positive for STIs will be referred to their PCP for treatment. If they do not have a PCP, they will be referred to HIV care or STI care at Fenway Health or Brigham and Women's Hospital. Once we have reviewed all required laboratory work, and confirmed HIV status as negative, we will schedule participants for Study Visit 1. Additionally, following this visit, and prior to Study Visit 1, we will order a 90-day supply of digital PrEP for eligible participants (process detailed below following description of study visit procedures).

Aim 2 – Study Visit 1: During Study Visit 1, participants will complete a baseline self-report questionnaire, and the study team will conduct a short training around operation of the digital pill system (i.e., digital pills, Reader device, and mobile application) and instruct participants on basic troubleshooting of the technology. We will also help participants to download the mobile application where their adherence data will be recorded and accessible, train them on how to use the app, and register them on the collaborator interfaces (iAssist and Nomi). Participants will be provided with a 30-day supply of digital PrEP (Truvada); participants will then ingest their first digital PrEP dose during the visit to demonstrate their understanding of how to operate the digital pill system and to ensure the technology is functioning properly. Participants will receive a brief reference guide (see *refguide*) with key contact information and basic information regarding the digital pill and Reader. Participants will be scheduled for Study Visit 2, which will occur a maximum of 30 days (i.e., 23-30 days) after Study Visit 1, in order to ensure that participants do not run out of digital pills prior to receiving a refill. We will contact study participants via text message on days 1, 2, 5, and 7 to ensure technology is functioning. Additionally, beginning one week after Study Visit 1, participants will receive brief weekly surveys through the Nomi interface asking them to self-report substance use and sexual activity (see *DigiPrEP Study Messages_Participant Only)*. At the end of Study Visit 1, participants will be remunerated via a $25 check.

Aim 2 – Study Visit 2: We will contact participants on days 23, 25, and 29 to remind participants of their Study Visit 2 appointment. During this study visit, participants will have blood drawn via phlebotomy and placed on a blood spot card in order to assess PrEP adherence. De-identified specimens will be banked for future use in drug abuse screening. We will review digital pill adherence data with participants in Nomi and conduct a pill count to validate adherence data from the digital pill and Reader. We will review discordant counts, periods of Reader activity that suggest no use of the Reader device, and digital pill use with the participant. We will additionally review any potential nonadherent events detected by the digital pill with participants using timeline followback to gauge potential reasons for nonadherence. We will view the adherence interface with study participants and discuss events surrounding potential nonadherence events. We will record user responses to

each of these timeline followback events. We will also dispense an additional 30-day supply of digital pills to participants. We will schedule participants for Study Visit 3 prior to discharge, which will occur a maximum of 30 days (i.e., 23-30 days) after Study Visit 2. Participants will be reminded that we will pass their adherence data along to their PCP; participants will have the option of opting out of this mechanism at each study visit. At the end of Study Visit 2, the participant will be remunerated via a $25 check.

Aim 2 – Study Visit 3: We will contact participants on days 53, 55, and 59 to remind them of their Study Visit 3 appointment. During this visit, we will review adherence data from the digital pill in Nomi, conduct pill counts with participants, address discordant counts and review reader activity with the participants and address any nonadherence events potentially linked to sexual activity or substance use. The participant will receive a final 30 day refill of digital pills and will be remunerated via a $50 check.

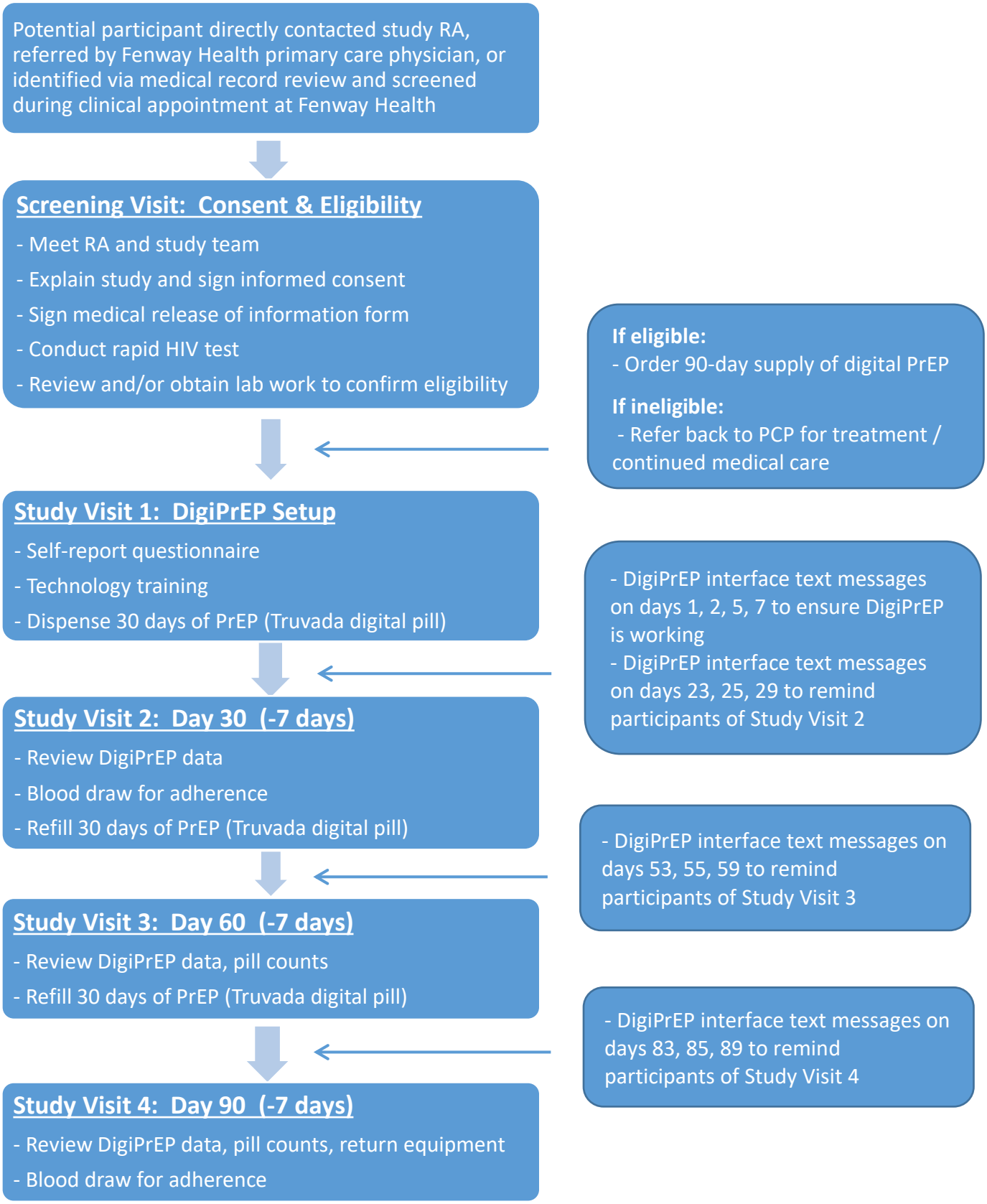
Aims 2/3 – Study Visit 4: This is the final study visit. We will contact participants on days 83, 85 and 89 to remind participants of Study Visit 4, including a reminder to bring all DigiPrEP equipment to this visit to return to the study team. Participants will have blood drawn for adherence, and we will review adherence data from the digital pill in Nomi and conduct pill counts. Additionally, we will conduct a 20-minute semi-structured interview (see *Aim 3 Exit Interview*) to assess participants' experience working with DigiPrEP and participating in the study. Participants will be encouraged to return to their PCP for continued PrEP prescribing. If they do not have a provider who can continue to prescribe PrEP following the end of the study, we will refer them to a provider at Fenway Health or the Brigham and Women's Hospital infectious disease clinic. Participants will be remunerated a total of $150 at the end of this visit (i.e., the planned $75, as well as an additional $75 for assistance finding and troubleshooting bugs in the mobile app, and for completion of all study procedures).

Participant contact: We will contact participants via text message at described times after study visits (see *DigiPrEP Study Messages_Participant Only*). Additionally, if participants do not respond to text messages (e.g., technology check-ins at days 1, 2, 5, 7), or to study appointment reminders, we will contact them via phone, text, and/or email. If we do not detect digital pill ingestions for 48 hours (2 doses) or if there are more than 2 missed doses in a week, we will contact participants via phone, text, and/or email to understand if there are issues with operating the digital pill or if missed doses represent true medication nonadherence. If we are unable to reach participants, we will leave phone or text messages, and call participants back the next business day. We will also communicate information about the study, including required lab work documentation for the Screening Visit, to participants via email.

Drug procurement: Digital pills are procured from Curant Pharmacy (our collaborating pharmacy). Once participants sign informed consent during the Screening Visit, and we have confirmed qualifying laboratory work and eligibility, we will securely email a Drug Order Form to Curant. This order form will contain the following information, as required by Curant: (1) participant's name; (2) participant's date of birth; (3) participant study ID number; (4) participant's anticipated start date; (5) target drug delivery date; and (6) delivery information for pharmacist at Fenway Pharmacy. Following receipt of the Drug Order Form, Curant will FedEx 90 digital pills (three 30-day supplies) to the Fenway Pharmacy. Confirmation of shipment receipt will be documented in the DigiPrEP 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. In the event that a participant drops out of the study and we have remaining drug assigned to them in the Fenway Pharmacy, we will securely email a Cancel Order Form to Curant, along with a new Drug Order Form, requesting the required number of replacement bottles of drug, and/or new participant labels (as applicable). Curant will mail new participant labels to place on existing bottles of drug, as well as any additional bottles of drug, as needed.

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 2, 3 and 4 within 7 days prior to the 30-day mark in order to prevent participants from running out of digital PrEP pills.

Participant messaging: Participants will receive standard SMS text messages, as well as notifications from the mobile application which receives their adherence data from the digital pill. Upon enrollment in Nomi and iAssist interfaces at Study Visit 1, participants will receive a welcome message, including a contact number for the DigiPrEP study team. Participants will receive three technology check-in messages during the first week using the digital pill (on days 2, 5, and 7); these messages will prompt participants to respond with "0" for "I need help with something," or "1" for "Everything's OK!" If participants text back "0," the study team will contact the participant to assist them further. Beginning one week after Study Visit 1, participant will also receive an anonymous REDCap link to a brief weekly survey, asking them to self-report substance use and sexual activity for the past week. Participants will also receive text messages reminding them of upcoming study visits. Depending on messaging settings in the Nomi interface, participants may also receive app notifications for ingestion confirmations, as well as messages related to Reader battery life and confirmations of manually recorded ingestions (see *DigiPrEP Study Messages_Participant Only* for detailed content and timing of all participant messaging).


Potential participant directly contacted study RA, referred by Fenway Health primary care physician, or identified via medical record review and screened during clinical appointment at Fenway Health
Screening Visit: Consent & Eligibility
- Meet RA and study team
- Explain study and sign informed consent
- Sign medical release of information form
- Conduct rapid HIV test
- Review and/or obtain lab work to confirm eligibility
If eligible:
- Order 90-day supply of digital PrEP
If ineligible:
- Refer back to PCP for treatment / continued medical care
Study Visit 1: DigiPrEP Setup
- Self-report questionnaire
- Technology training
- Dispense 30 days of PrEP (Truvada digital pill)
- DigiPrEP interface text messages on days 1, 2, 5, 7 to ensure DigiPrEP is working
- DigiPrEP interface text messages on days 23, 25, 29 to remind participants of Study Visit 2
Study Visit 2: Day 30 (-7 days)
- Review DigiPrEP data
- Blood draw for adherence
- Refill 30 days of PrEP (Truvada digital pill)
- DigiPrEP interface text messages on days 53, 55, 59 to remind participants of Study Visit 3
Study Visit 3: Day 60 (-7 days)
- Review DigiPrEP data, pill counts
- Refill 30 days of PrEP (Truvada digital pill)
- DigiPrEP interface text messages on days 83, 85, 89 to remind participants of Study Visit 4
Study Visit 4: Day 90 (-7 days)
- Review DigiPrEP data, pill counts, return equipment
- Blood draw for adherence

VI. 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 dried blood spot data. 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.

VII. Risks and Discomforts

We anticipate the major risks due to DigiPrEP are the potential for exposure to metal components in the digital pill, and retention of the radiofrequency emitter portion of the digital pill. Major psychological discomforts could occur during study interviews when participants are asked about their adherence patterns.

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 ethyl cellulose coating in a technique that is used for other ingestible medical devices.[8,9] Extensive experience in the use of ingestible small bowel endoscopy cameras has not reported adverse events related to the exposure of electronic components.[10,11]

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 DigiPrEP 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.[9] 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%.[10,12] 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.[13] Complication rates among patients with Crohn's disease, bowel neoplasm, radiation enteritis, or stricture were higher.[14,15] In high-risk patients, standard therapy for retained endoscopy pills included aggressive oral hydration with successful removal of the retained pill.[16] We believe that the risk of retention of a DigiPrEP capsule will be less than that of a capsule endoscopy pill given the smaller dimensions of the digital pill. Unlike a capsule endoscopy pill, DigiPrEP is dissolvable with only the radiofrequency emitting portion of the capsule passing through the gastrointestinal tract. In order to minimize the risk of DigiPrEP capsule retention, we plan to exclude patients with underlying bowel disease or surgical intervention to the bowel.

Psychological discomfort of disclosing adherence patterns: Participants may experience psychological discomfort in disclosing and learning of their adherence data during study visits. As their Fenway Health PCP may be given participant's adherence data, participants may also experience the psychological discomfort knowing that their PCP knows about their adherence to PrEP during the study period.

VIII. Potential Benefits

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

IX. Data Monitoring and Quality Assurance

We will review and monitor data from DigiPrEP for each study participant. At each study visit, participants will undergo pill counts to correlate adherence data from DigiPrEP, 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 annotate this on the ingestion data.

The study investigators will conduct QA to review data after half of the patients (N=7) of Aim 2/3 are enrolled to ensure that data is accurate and no errors have been made.

The principal investigator (Dr. Chai) will be responsible for monitoring adverse events during the study, but Drs. Mayer and O'Cleirigh will assume this responsibility in the event that Dr. Chai is unavailable. The role of the responsible person is 1) to identify the concern, 2) develop and appropriate response that involves consultation whenever possible to alleviate or minimize any adverse event, and 3) to ensure that the adverse event is reported in a timely manner to the responsible authority.

Participants will be monitored for occurrence of events defined as any undesirable experience or unanticipated benefit. Events may occur during recruitment, technology deployment, and qualitative interviewing. For example, a participant may become distressed when asked questions about substance abuse and its impact on PrEP adherence. Based upon previous research couched in technology among hidden populations, we anticipate that these effects will be minimal. The principal investigator will assess whether an undesirable experience occurred (adverse event) and will record details of all adverse events (death, life threatening illness, new serious or permanent disability) that occur. Should such an event occur, the principal investigator will report the event within 24 hours to the Fenway Institute IRB.

The adverse event case report form will include a description of all undesirable experiences, required interventions, and an assessment of the subject after the event if possible. An estimate of the extent of injury, and prevention strategies will be reported. The principal investigator will classify the relationship of the study protocol to the event as follows:

- Not related: The event is clearly related to factors such as the subject's clinical state, not with the study protocol.
- Remote: The event was most likely related to factors such as the subject's clinical state, not with the study protocol.
- Possible: The event follows a reasonable temporal sequence associated with participating in the study and/or is consistent with events related to responding to queries about stress/drug craving but is possibly related to factors such as the subject's clinical state.
- Probable: The event follows a reasonable temporal sequence associated with participating in the study and/or is consistent with events related to responding to DigiPrEP or digital pills and cannot be reasonably explained by factors such as the subject's clinical state.

  The severity of an adverse event in both groups is defined as a qualitative assessment of the degree or intensity of an adverse event as determined by the principal investigator as follows:

- Mild: No impact (in anyway) on the subjects.
- Moderate: Impacts on the subject but is not life-threatening or incapacitating.
- Severe: Fatal, life threatening, permanently disabling; severely incapacitating; requires/prolongs inpatient hospitalization.

All adverse events will simultaneously be reported to the NIH project officer. The report will summarize the facts of the case, including the date and a description of the subject; whether the event is related to the study's protocols; the steps that have been taken to address the issue; whether the event provides emerging knowledge about the risks of the study that should be conveyed to respondents; and whether the consent form should be revised.

Data Safety Monitoring Board
Dr. Chai, will select three external investigators with expertise in PrEP, substance use disorder, technology security and behavioral interventions to participate on a data safety monitoring board (DSMB) for aim 2 (pilot randomized controlled trial) of the research plan. The DSMB will convene annually during aim 2 of the research plan. Additionally, the DSMB will meet when N=10 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 Gilead Sciences (study sponsor) required regarding safety concerns, continuation or modification of the research plan.

Data Safety. The protection of data for this study includes the following: 1) Data are collected through a HIPAA compliant web server hosted by eTectRx, then securely relayed to a cloud-based program (NOMI) that drives smart interventions in DigiPrEP. The cloud-based database is hosted behind the secure firewall through eTectRx, and accessed through Fenway Health computers. 2) Study participants are identified by a unique numeric identification; their protected health information (PHI) is never linked to ingestion data captured by eTectRx, or the cloud-based program. 3) Study participant PHI is collected and stored on a secure Microsoft Excel worksheet which will be created on a secure, password protected desktop computer located at TFI where only Dr. Chai, his study mentors and a trained research assistant (RA) will have access. 4) All data (ingestion data on the cloud-based database and PHI) is stripped of all identifying information by Dr. Chai prior to transmission to collaborators at BWH, MGH, BIDMC and Children's hospital. We will also share deidentified data with our sponsor, Gilead Sciences. 5) Deidentified ingestion data as well as demographic data will be securely stored on the TFI server; we will access this data for later investigations under a separate IRB protocol. 6) At study completion, the link between the identifying information and their data is destroyed, as is contact information. Two sets of the cleaned data set will be maintained—one working copy at Brigham and Women's Hospital, and one at the Fenway Institute. This approach ensures that the data survives a failure of one storage location. 6) Finally, all study staff have completed the CITI Course in the Protection of Human Subjects online training in research ethics and good clinical practice to ensure that all staff are compliant with confidentiality training.

Data Tracking: 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, 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. Dr. Chai will also maintain a second copy of the logs as a backup in his secure office behind the BWH firewall Data loaded onto the interface cannot be edited. Each variable with missing data (such as an interruption between smartphone and sensor) will be identified and a placeholder ("<<-99>>") is 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, one copy at eTectRx and one copy at TFI. 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 transcribed audio-taped interviews.

Data storage: Raw ingestion data, transcripts from this study and self-report questionnaires will not be made publicly available. Deidentified data may be shared with Gilead Sciences who is funding the study, as well as industry collaborators eTectRx and NOMI. For future investigations that use deidentified participant data, we will submit IRB protocols detailing the use of this data. Partners Health Dropbox is being used for file storage in the study.

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