Evaluation of Life-Steps to Enhance Adherence and Engagement in PrEP Care

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1) Protocol Title

Evaluation of Life-Steps to Enhance Adherence and Engagement in PrEP Care

2) Objectives*

1) Specific Aim 1: To determine, in a two-arm randomized trial, the efficacy of Life-Steps for PrEP (Pre-exposure prophylaxis), a stepped-care (text messaging, then counseling) intervention to increase medication adherence, in men who have sex with men (MSM) prescribed PrEP who evidence a risk factor for non-adherence.

Those assigned to the Life-Steps for PrEP stepped-care intervention arm will start with text messaging to promote adherence. Participants in this arm that evidence non-adherence "step up" to also receive the Life-Steps in-person adherence counseling intervention. Those assigned to the comparison condition receive standard of care (SOC).

Our primary outcome is enhanced maintenance of PrEP adherence (Measured by the concentration of PrEP medication in dried blood spots (DBS), displaying levels consistent with adherence (4+ pills per week), and PrEP adherence self-report. and retention in PrEP care. A secondary outcome is total condomless anal sex acts occurring in the context of insufficient PrEP protection. Major assessments are conducted at baseline, 3, 6, 9, 12, 15 & 18 months.

2) Specific Aim 2: To examine the degree to which enhanced maintenance of PrEP adherence occurs in the context of the conceptual mediators and potential moderators of the intervention.

Conceptual mediators include increased use of PrEP adherence skills and strategies to take PrEP (e.g., use of text message reminders, use of study staff as a resource, communicating with providers, managing mood/coping, daily schedule, etc.) and increased self-efficacy. Potential moderators include sociodemographic and behavioral variables.

3) Specific Aim 3: To estimate the total and incremental costs of the Life-Steps for PrEP, stepped-care PrEP adherence intervention relative to SOC, from healthcare sector and societal perspectives.

Data on health services utilization will also be collected to estimate changes in healthcare costs during the trial.

3) Background*

MSM are the largest group of individuals acquiring HIV in the U.S., with Black and Latino/Hispanic MSM at greatest risk. In the United States, MSM represent two thirds of all HIV-infected individuals (4,5). Additionally, MSM in the U.S. account for the largest number of new HIV infections (70%), and the rate of new diagnoses is over 44 times greater than heterosexual men (4,5,25).

Despite advances in treatment and prevention, MSM in Miami and Boston remain at great risk for HIV. Miami-Dade County has the highest rate of new HIV infections in the U.S. (15) with MSM from communities of color constituting the largest number of new infections. To date, uptake of PrEP has not increased in proportion, even while the rate of PrEP prescribing has escalated rapidly in other areas of the U.S (26-28).

PrEP is highly efficacious for HIV prevention in MSM. The iPrEx study found that HIV incidence among MSM randomized to take daily tenofovir and emtricitabine (TDF/FTC) was 43.8% less than among the men assigned to placebo (8). The subsequent open-label PROUD study conducted in UK STD clinics found that MSM assigned to receive PrEP had an 86% decrease in HIV incidence compared to those who were on a PrEP waiting list (9). The French iPERGAY study of peri-coital TDF/FTC PrEP found an 86% decrease in HIV incidence among MSM assigned to TDF/FTC compared to those receiving placebo and standard prevention services in the intent-to-treat analysis. Incidence reduction went up to 97% when all participants had access to open-label TDF/FTC PrEP, suggesting that MSM may become more adherent as they learn about PrEP efficacy (10).

Myriad reasons for PrEP non-adherence exist among MSM, including psychosocial syndemic problems, racial/ethnic minority status, and economic marginalization. In the initial PrEP studies, side effects were generally mild, self-limited, and did not result in product discontinuation (8,38). Some participants report forgetting to take their PrEP because their sexual risk behavior occurred when using substances (13). Other participants were non-adherent because they chose to take the medication only when they knew they were going to have high-risk sex, and may not have felt the need to take medication daily. Notably, non-adherent PrEP users had behavioral health conditions common in at risk populations (39,40), including depression, substance use, and post-traumatic stress, and violence/victimization which impeded health-related behaviors. This would place them at higher need for more intensive intervention (and proactive referral for treatment for behavioral health problems).

Real world, scalable PrEP adherence promotion programs are needed to optimize PrEP's effectiveness. Prior studies that have evaluated the effectiveness of PrEP included some efforts to optimize adherence, but did so in the context of clinical trials i.e. were focused on measuring

adherence, rather than developing tools that clinicians can use to efficiently support the greatest level of adherence. Engagement of health care providers in PrEP delivery will be essential, because for the foreseeable future, PrEP will only be available via prescription from a medical provider, who may be too busy to give individualized counseling (47).

Theoretical framework guiding the "Life-Steps for PrEP" intervention. The intervention is grounded in the social-cognitive and contextual realities (e.g., participants' living circumstances, support systems, work situation/financial challenges, substance use, and mental health) of high risk MSM. The conceptual model underlying the specific aims is based on general principles of cognitive-behavioral therapy (e.g., problem solving, psychoeducation, and motivational interviewing) (61-63), syndemics theory (16, 64), and our formative qualitative research (22) that led to the development of a theoretically-driven intervention ("Life-Steps for PrEP") for MSM with multiple psychosocial problems.

Life-Steps is an effective evidence-based antiretroviral adherence intervention for HIV treatment. The intervention, developed by Safren et al, (48, 49), showed improved HIV medication adherence in people living with HIV (PLHIV). It has been adapted for other populations, including Chinese PLHIV (50) and African heterosexuals in HIV-discordant relationships in a PrEP trial (51). Life-Steps for PLHIV has been optimized for adolescents living with HIV, which was found to be successful in improving ART adherence compared to a standard of care (SOC) comparison group in a pilot RCT among HIV-positive youth (52, 53), and is currently being evaluated in a two-city efficacy trial (R01 NR017098-01).

4) Inclusion and Exclusion Criteria*

Inclusion criteria. Eligible participants will meet the following criteria:

1. Age: 18 years or older
2. Male sex at birth or trans man (current gender identity is male) assigned female sex at birth
3. Self-reports as a person who has sex with men
4. PrEP naïve or is currently prescribed PrEP and reports uncertainty about future adherence
5. Medical providers at each site will determine that the participant is indicated for PrEP per CDC guidelines
6. Screens in for currently having one or more of the following psychosocial syndemic problems: depression; heavy alcohol use; problematic substance use or polydrug use; history of trauma or abuse; and/or current interpersonal violence

7. Owns a cell phone that has texting and internet / data capacity

Exclusion criteria. Participants will be excluded for any of the following:

1. Unable to provide informed consent due to severe mental or physical illness, cognitive impairment, or substance intoxication at the time of interview
2. Discovery of active suicidal ideation or major mental illness (e.g. untreated psychosis or mania) at the time of enrollment (these patients will be referred immediately for treatment, but may join the study when this is resolved)
3. Laboratory or clinical findings that would preclude PrEP initiation (e.g. decreased creatinine clearance)

Study staff will track all screened participants, and complete an inclusion/exclusion checklist for screenings.

This study excludes vulnerable groups: adults unable to consent, individuals who are not yet adults (infants, children, teenagers), pregnant women (only men are included), and prisoners.

5) Number of Subjects*

We propose to enroll 300 study participants across two sites (Miami, FL and Boston, MA). We anticipate this will be roughly 150 at each site. At present we have obtained IRB approval for both the Miami and Boston sites.

6) Study-Wide Recruitment Methods*

Active recruitment will be carried out by trained study staff in both the Miami sites and at Fenway Health in Boson.

Recruitment at Miami Sites:

In Miami, study recruitment staff will be at the FLDOH and UM PrEP clinics, both located in the Jackson medical center area. Additionally, study recruitment staff will join mobile PrEP clinic staff providing PrEP services in the community. Our primary method of recruitment will be to engage potential participants at the clinic (or mobile clinic) immediately after they have been prescribed PrEP.

Recruitment at Fenway (Boston) Site:

Potential participants will be identified via a secure report provided by the Fenway Institute data team abstracted from the Fenway Health Electronic Medical Records (EMR). This report will only include contact information for individuals who meet basic study inclusion criteria and who have signed consent to contact for future research. Study staff will then engage the Primary care physicians of the potential participants and ask if they approve of having their patient receive a message about the study through

the secure and HIPAA compliant MyFenway patient portal. Alternatively, providers may contact study staff directly to recommend patients who have signed consent to contact and may be interested and eligible for study participation. The secure message sent to potential participants will not include patient protected health information and will not describe the specific nature of the study. The message will include a secure link for pre-screening, and contact information for study staff. All recruitment text and materials will be submitted for IRB approval prior to use. Primary care physicians at Fenway Health will be responsible for assessing initial interest of eligible patients for study participation. Patients will not receive a message in MyFenway if their provider did not give approval for a message to be sent to them.

Recruitment at both Boston and Miami sites:

The study staff will provide in-service education to clinicians about the study so that clinicians at the places where PrEP is prescribed can refer participants. At the conclusion of a PrEP prescription visit, providers will ask potentially eligible patients if they are interested in learning more about a research study involving people who are just starting PrEP. Providers will refer individuals who meet basic inclusion criteria for study participation (men who have sex with men, over age 18, currently prescribed or will be prescribed PrEP). If the individual is interested, they will be directed to on-site study staff who will brief them on the study, obtain consent specific to the screener, and administer the screening instrument via tablet (or, if / when technical problems arise, a paper version), and invite eligible participants to join the study. Eligible participants will be scheduled for a baseline visit which includes full written consent and the baseline assessment battery.

Passive approaches will also include: posting study information via flyers, posters, and palm cards describing the study within the clinics' waiting areas and exam rooms, and, at the Miami PrEP clinic, STI (sexually transmitted infection) testing sites, and at local HIV prevention organizations.

Facebook and other media outlets: We will also actively recruit participants from popular social and sexual networking sites and location-based apps (e.g., Grindr, Scruff, Bareback.net) for MSM if they are currently taking PrEP or have started PrEP within a month of being able to schedule their randomization/baseline visit. Interested potential participants can call to speak to study staff who will describe the study, obtain verbal consent specific to the screening, and administer the phone screener instrument. Alternately, interested individuals may answer basic eligibility questions online via HIPAA compliant REDCap survey. If potentially eligible, they will be given the option to leave their contact information if they would like study staff to call them back provide more information and possibly administer phone screening (also via HIPAA compliant REDCap survey). Potential participants who prefer to self-

report or are not otherwise able to attend an in-office visit can be sent a unique secure link to the full screener in REDCap. Participants who consent to screening, meet eligibility criteria, and are interested in participating in the study will be contacted by study staff.

Expanded recruitment and enrollment strategies: Given our capacity to conduct all study procedures remotely (due to the COVID-19 pandemic), we will also recruit participants from other U.S. states outside of Florida and Massachusetts. In addition to broad and targeted social media outreach campaigns, we will collaborate with remote PrEP providers (e.g Nurx Inc.) who will distribute IRB approved recruitment materials to new and existing PrEP clients. Nurx currently serves clients in 34 of the 48 contiguous U.S. states. Procedures for screening potential participants will be the same as described above, with pre eligibility screening conducted via HIPAA compliant REDCap survey or by phone, per participant preference. All study related procedures, including assessment, biological measures collection, intervention, payment, and safety procedures, are the same for all participants regardless of geographical location.

7) Study Timelines*

The first 6 months after funding will be dedicated to study startup. This will involve programming the tablet-based assessment (via REDCap, which we have used in prior studies), finalizing all study related documents, purchasing study supplies, hiring staff, and training the nurse interventionists in the counseling approach. Additionally, we will solidify all study operations procedures (SOPs) and QC policies. Any changes to this protocol will be handled by a modification.

After participants are enrolled, they are followed for 18 months. Accordingly, we hope to enroll participants over a 2.5 year period. They are then followed for 1.5 years, which brings us to year 4.5. This would allow for the final 6 months of the award funding period to conduct data analyses and manuscript preparation. Within this timeline, we will be continually cleaning the data in the REDCap system, to minimize the amount of data cleaning required once the final participant completes. When the baseline data are complete, we will do a full cleaning of that dataset and "lock" with the goal of having this complete after two months. We will then incrementally be cleaning and locking the data as the final participant completes consecutive major study visits, again, to minimize the amount of data cleaning needed at year 4.5 (month 54) when the analyses will be conducted.

Months	Study Timeline and Activities
1-6	Study start up; IRB; Hire, select, and train nurse interventionists and other research staff at Fenway and U-

	Miami; SOPs. Obtain IRB approval at the Miami site, and then, as possible, submit modifications to add the Boston site.
7-36	Participant recruitment, screening, and accrual (based on R34 grant) for 2.5 years
7-54	Complete intervention and comparison condition visits
7-54	Complete all assessments visits, including all 18-month follow up assessments
54-60	Analyze data; preparation of manuscripts and plan for an effectiveness trial

8) Procedures Involved*

- We propose to test the efficacy of a stepped-care "adaptive" Life-Steps for PrEP intervention for high-risk MSM prescribed PrEP, at risk for adherence difficulties by having at least one syndemic indicator of risk. Participants who are ongoing PrEP users (not-PrEP naïve) must also report uncertainty about their future PrEP adherence. Stepped care is a healthcare delivery model in which the least resource intensive part of an intervention is delivered first, and only those who do worse will then receive the high intensity, more resource intensive part of an intervention. This randomized controlled trial uses a parallel study design in which participants are assigned to one of two treatment conditions for the duration of their participation in the study.

  In this RCT, we expand on the success of our prior studies to examine a stronger control condition (Aim 1), the role of conceptual mediators and proposed moderators (Aim 2), and to estimate cost-effectiveness (Aim 3).

  Aim 1: Participants will be equally randomized to the Life-Steps for PrEP or the SOC control. Those randomized to Life-Steps for PrEP will begin with daily text messaging reminders aimed at enhancing optimal adherence. Participants with continued adherence challenges over the study period (e.g., taking <4 pills over a 7-day period) will progress to the more intensive 4 nurse/allied health professional-delivered counseling sessions. The "progression window" for participants to progress to the more intensive intervention can occur anytime during follow-up (beginning at least two weeks after baseline); this will be determined from PrEP adherence monitoring via weekly survey reminders delivered via text, biological assessment (DBS) indicating suboptimal PrEP level, or self-report of PrEP non-adherence. The "step-up" trigger via the weekly survey is a participant self-report of taking fewer than 4 PrEP pills in one

week. The “step-up” trigger for the follow-up assessment DBS is a measured level of tenofovir diphosphate (TFV-DP) in the blood indicating < 4 pills per week. Note, the value of this threshold is determined a priori by the testing lab and varies by medication (Truvada vs. Descovy) and testing procedures. Adherence thresholds may also change as laboratory methods improve or new data emerge. For example, the Anderson lab determined that < 800 fMol per 3mm punch was consistent with taking fewer than 4 pills per week for Truvada for blood obtained via venipuncture, however, later analysis showed that DBS blood obtained via finger prick had a higher adherence threshold of <900 fMol per 3mm punch. We will interpret DBS adherence based on the most current and accurate guidelines put for by the testing lab. The final step-up triggers via the follow up assessment are a response of < 4 to the question “How many days per week do you usually take your PrEP?”, and/or self-report of missing 12 or more pills (40%) in the past 30 days per the Wilson adherence measure.

Those randomized to SOC will receive the multidisciplinary health services offered at each site (e.g., mental health, STI testing) and a brief animated tutorial on PrEP adherence. After randomization, participants in both study arms will come in for follow-up assessment visits every 3 months for 18 months, to coincide with clinical monitoring for PrEP, for biological (blood spot) and behavioral evaluation of adherence, sexual behavior, and related variables.

Aim 2: Follow up assessments at 3, 6, 9, 12, 15, & 18 months will allow us to test whether conceptual mediators, including increased use of PrEP adherence skills and strategies to take PrEP (e.g., use of text message reminders, utilizing study staff as a resource for problem solving, communicating with providers, managing mood/coping, daily schedule, etc.) and increased self-efficacy, statistically mediate the efficacy of “Lifesteps for PrEP” to enhance maintenance of PrEP adherence. Proposed moderators, including sociodemographic variables, will be statistically tested as well.

Aim 3: To estimate the total and incremental costs of the Life-Steps for PrEP, stepped-care PrEP adherence intervention relative to SOC, from healthcare sector and societal perspectives. Data on health services utilization will also be collected to estimate changes in healthcare costs during the trial. Data will be obtained via participant self-report at baseline, 3, 6, 9, 12, 15 and 18 months.

Major assessments. There are seven major assessment points: baseline, 3, 6, 9, 12, 15 and 18 months. At each major assessment time point the participant will complete the self-report battery, with tablet or computer based data collection for sensitive data because people are more likely to

disclose sensitive information via computer than in person (paper version may be used in the event of technology problems, and for non-sensitive data). CASI=computer assessment interview. For participants who need assistance, the research assistant or other study staff may read the questions to them and key answers into the tablet) (81). The assessment battery is similar in length to the one used in our pilot RCT, and has been acceptable to our study participants. It will be available in English or Spanish.

The following relates to remote study procedures to address social distancing requirements due to the COVID-19 health crisis. We anticipate that after mandatory shelter in place orders are lifted, there will be an ongoing need to limit exposure risk for both study participants and study staff. Therefore, remote study procedures may be employed over the full course of this study. Additionally, in the event that a participant moves out of the study catchment area, is not able to come into the office for baseline or assessment visits, or for another reason an in-office visit cannot be completed, we may conduct informed consent, enrollment, and/or assessment, via phone or video-conferencing. Note that consent forms, other forms, and all assessments are administered via secure REDCap survey regardless of whether participant is completing them in the office or remotely. If a visit will be completed remotely, the participant will be sent a secure unique REDCap survey link. Study staff will work with participants in real time to conduct consent procedures and monitor form status should participants have difficulty. Participants completing consent remotely will be informed beforehand that a witness will be joining the consent meeting. Note that per existing study inclusion criteria, participants must own an internet capable smart device, meaning that all study participants will have the ability to provide an electronic signature.

When scheduling any Lifesteps intervention session, baseline, or remote follow-up assessment, prior to the appointment a study staff member will request participant address. Note that procedures for remote Lifesteps intervention sessions are described under Treatment Conditions. Although we do not assess for suicidality, if there is a concern for safety, just as with any participant seen in the office, the study staff will adhere to the established suicidality protocol. If the participant is at high risk, study staff will contact the nearest emergency services to the participants' address. When participants complete a remote session or assessment, they will be provided with their incentive either by mail (check or gift card), using money transfer, or at their next in-person visit.

For remote follow-up visits, if HIV test results and dried blood spot (DBS) are not available from participants' PrEP provider, participants will be asked to complete their HIV test and DBS card at a testing facility of their choosing. If a participant is unable or does not wish to complete testing at a facility, they may be offered to be mailed the Oraquick HIV screening

test and home DBS collection kit. The at-home DBS testing kit includes instructions, supplies, and a special prepaid mailer to safely return the sample card. The Oraquick is a screening test, with preliminary positive results needing to be confirmed with a blood test, which is consistent with the in-office protocol. The procedures for administering the HIV screening test if mailed to participants will be the same as the in-office visits. Participants will be asked to share their results with the study staff (e.g., showing the test results via the videoconference for the remote assessment). Participants who test preliminary positive for HIV during the remote assessments will receive referrals per existing protocol for in-office visits or may utilize the 24-hour support center associated with the at-home test kit for immediate support.

Alternatively, PrEP level and HIV screening may be conducted using a single DBS card, without the additional administration of the Oraquick HIV screener. Using a single test rather than two tests reduces participant burden and avoids potential logistical problems with multiple mailers and participant self-administration of the Oraquick. Upon ordering the DBS test kit to be mailed to the participant, study staff will indicate whether the returned sample is to be tested for PrEP level alone or for both PrEP level and HIV screening. Note that these will be preliminary HIV antibody/antigen screeners which do not require reporting of results, as opposed to confirmatory testing which does require reporting. At the time of participant DBS administration, study staff will schedule a follow up meeting in approximately 5-7 days to give HIV screening results to the participant. Should a participant test preliminary positive on the HIV screener, they will be immediately connected to a local resource for confirmatory testing and HIV treatment, if needed. Study sites are also prepared to connect participants with support and mental health services as indicated.

Participant event timetable

<u>All study participants:</u>

Screening

- Consent for screening
- Abridged demographics and syndemic indicators (CASI self-report)

Baseline

- Informed consent
- Baseline assessment battery (CASI self-report)
- Random assignment

Follow-up (3, 6, 9, 12, 15, 18 -month)

- Assessment battery (CASI self-report)
- Dried blood spot sample (see below)

- Obtain HIV results from provider (see below for exceptions)

Participants assigned to Life-Steps condition:
(Can occur any time after 2-weeks post baseline if participant demonstrates medication non-adherence)

- 4 weekly sessions of nurse-delivered Life Steps for PrEP
- Up to 2 optional monthly booster sessions

Primary outcomes:
DBS TFV-DP concentrations and PrEP adherence self-report (3, 6, 9, 12, 15, and 18 months).

Title: Effectiveness of Life-Steps on medication adherence according to biological samples

Description: Measured by the concentration of PrEP medication in dried blood spots (DBS), displaying levels consistent with adherence (4+ pills per week).

Time Frame: 3, 6, 8, 12, 15, & 18 months

Title: Effectiveness of Life-Steps on medication adherence as self-reported (Wilson Medication Adherence Self-Report)

Description: Measured by the use of the Wilson 3-item Medication Adherence Self-Report. The self-report assesses the number of days of medication is missed (scores range from 0 to 30), frequency of medication taking (scores range from 1 [“never”] to 6 [“always”]), and rating of medication (scores range from 1 [“very poor”] to 6 [“excellent”]) taking for the last 30-days (at each major visit). This yields a single summary score with a range of 0-1.

Time Frame: 3, 6, 9, 12, 15 & 18 months

We hope to time study visits to regular medical follow-up visits for PrEP monitoring that would happen outside of the study. These follow-up visits are routine for individuals taking PrEP, and they should occur independent of participation in this study. These non-study visits for regular PrEP care occurring as they would normally regardless of study participation require HIV testing (where they are consented, again, not related to the study, and follow all relevant procedures that are not part of the study) and typically include testing for STIs and kidney/liver function. Accordingly, we will obtain a release of medical information for HIV and STI testing results that happen at their clinic as part of

their routine PrEP care. STI testing results will only be obtained by medical release of information and participant self-report (described below).

When possible, these outside PrEP providers (e.g. FLDOH clinic, UM PrEP clinic) will draw an additional tube of blood (approximately 4 ml, or < 1 teaspoon) which they will provide to study staff for dried blood spot (DBS) testing for PrEP level. Again, this is not for HIV testing or for STI testing, this is only for analysis of PrEP levels in the blood, where, as a reminder, PrEP is taken in this case to prevent HIV not treat HIV).

When study staff are unable to obtain a recent blood sample provided by participants' PrEP care provider (within 1 week prior to follow-up assessment visit), they will draw a blood sample for DBS at the assessment visit. Staff will then prepare the DBS to be sent (de-identified) to an outside lab to test for tenofovir-diphosphate (TFV-DP), which will serve as biological measure of PrEP adherence. As our primary measure of adherence (83-86), DBS samples will be tested for protective levels of PrEP metabolites corresponding to amounts consistent with taking 4+ pills per week) (82).

As per our prior trials assessing PrEP adherence and ARV treatment adherence, we will ask about 30- and 7-day PrEP adherence using the Wilson 3-item measure validated against electronic monitoring for ART treatment (119). These measures include participants' self-reported medication frequency ratings and percentage estimates, which we have found helps minimize discrepancy between DBS monitoring and self-report.

HIV and STI Testing.

All confirmatory HIV testing will be conducted outside of the study. For those who continue in care for PrEP, it will be done by participants' PrEP provider (e.g. FLDOH clinic, UM PrEP clinic, Fenway Health PrEP clinic), and results will be obtained by study staff through medical release of information. For those not in regular PrEP care, see procedures below.

In the event we are unable to obtain results from medical release of information, (or lack of a test within 6 months of a study visit, or, at the 18-month assessment, within one month of that assessment), trained study staff will collect the necessary samples and we will perform HIV screening. The results of HIV screening are not reportable to state or other agencies, as this is a screening test only. Therefore, the UM (or other) HIV specific consent form would not be relevant. All HIV screening performed by study staff will be conducted using Oraquick Advance Rapid HIV 1/2 antibody test (oral swab) or similar screening test. Again, the UM (or other) HIV specific consent forms are not relevant because these tests do not involve venipuncture and results are not reportable.

Again, results of such HIV antibody screening tests are not reportable to the state given that this is a preliminary test. Accordingly, if a participant screens positive, participants would be referred for confirmatory testing outside of the study should they receive a positive or inconclusive antibody test result. If they then test positive, outside of the study with confirmatory testing, their testing sites will provide referral for treatment. Additionally, study staff will stay in touch with the participant, and, as needed, provide referral for treatment. This may be to the participant's primary care provider. If they are a Miami participant, this may to the Special Immunology Clinic at Jackson Memorial Hospital at the University of Miami Medical School, or to one of the FDOH HIV/STI support services locations (1350 NW 14th St, Miami, FL 33125). In these cases, referral to Jackson Health System will be made in real time with study staff assistance. For the Fenway site, appropriate and similar referrals will also happen in a similar fashion.

As stated above, the exception to this is participants who complete a remote assessment. See procedures described above for HIV screening if completing a remote assessment.

Self-assessment measures.

Title: Weekly Adherence and Sex Risk (Experimental Condition Only)

Description: Measured by self-report survey consisting of 2 questions: (1) "Not counting today, how many times did you have condomless sex (anal or vaginal) in the past 7 days?" and (2) "2. Not counting today, on how many days did you take PrEP in the past 7 days?"

Time Frame: Weekly

Title: Status of PrEP Use/Participant Reason for Drug Discontinuation

Description: This adaptive measure asks which PrEP medication participants are using (at baseline and follow-ups), and whether they have discontinued medication or altered their dosing schedule (only post-baseline). If participants have discontinued or changed medication, they are asked when and why. This measure also asks about past-week frequency and type of sexual behavior.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: Demographics

Description: Demographic variables will include basic demographics such as age, ethnicity, race, education level, sexual identification,

insurance status, relationship status, and living situation. Relevant items that don't change are collected at baseline only.

Time Frame: Baseline

Risk activity/sex partners.

Title: Self-reported condomless anal sex (Sexual Behavior Questionnaire)

Description: Measured by the Sexual Behavior Questionnaire. The self-report assesses the number of male sexual partners, known HIV-status, type of sexual activity, and condom use in the past 3 months.

Time Frame: Baseline, 3, 6, 9, 12, 15 & 18 months

We will ask about sexual behavior in the past month as an indicator of HIV acquisition risk behavior [e.g., (35,36)]. The questionnaire first asks about the number of male sexual partners, of these the number whose HIV status were known, and of these the number whose HIV status were HIV-positive. This therefore yields the number of positive, negative, and unknown status partners. It then asks about how many of these sexual encounters with men were without a condom, of these how many times were with partners whose HIV status the participant did not know, and then asks about the number of times were with partners who were HIV-positive.

We will also examine, for each participant, a cumulative number of prevalent (at baseline) and incident STIs diagnosed through their outside provider. Because different providers may test for different STIs at different anatomical sites, and maybe different intervals, these data will be exploratory, and we anticipate, randomization will account for some of this variance.

Psychosocial Syndemic Problems:

Title: Heavy alcohol use

Description: Measured by the use of the Alcohol Use Disorders Identification Test (AUDIT). The 10-item screening tool developed by the WHO assesses alcohol consumption, drinking behaviors, and alcohol-related problems (87). The scores range from 0 to 40, with a score of 8 or more indicating hazardous or harmful alcohol use.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: Polydrug use

Description: Measured by the use of the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST). The screening tool developed by the WHO assesses hazardous or harmful drug use (i.e.,

tobacco, alcohol, cannabis, cocaine, amphetamine type stimulants, inhalants, sedatives/sleeping pills, hallucinogens, opioids and ‘other drugs) (88). The scores range from 0 to 39, with a score of 27 or more indicating hazardous or harmful drug use for a specified substance.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: Depression

Description: Measured by the use of the Center for Epidemiologic Studies Depression Scale (CESD). The 20-item screening tool assesses both diagnostic criteria and depression severity (118). The scores range from 0 to 60, with higher scores indicating the presence of more depressive symptomatology.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: Childhood sexual abuse (CSA)

Description: Measured by the use of the Childhood Sexual Abuse Scale (CSA) via three standard questions using the Finkelhor definition (91). The clinician administered screening tool assesses experiences of unwanted or forced sexual touching or intercourse with a person when they were 13 years old or younger. The scores range from 0 to 3, with a score greater than 0 indicating the presence of CSA.

Time Frame: Baseline

Title: Intimate partner violence (IPV)

Description: Measured by the use a 4-item measure adapted from the HPTN061 study (93), and our recent syndemics study in MSM. The measure assesses for lifetime experiences of emotional or physical abuse by an intimate partner. The scores range from 4 to 20, with a score greater than 4 indicating the presence of IPV.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Hypothesized Mediators (Informed by Principles of CBT):

The Life-Steps intervention seeks to help participants, via cognitive-behavioral skills-building and motivational interviewing, (68), to reduce barriers and increase facilitators to PrEP adherence. We will therefore assess the following constructs:

Title: Life-Steps Problem Solving Skills

Description: Measured by the use a 15-item measure adapted from our pilot study and prior studies of the Life-Steps intervention. The measure assesses 90-day behavior frequency of specific skills addressed in Life-Steps. Item scores range from 0 to 4 (“never” to “always”).

Time Frame: 3, 6, 9, 12, 15, and 18 months

Title: PrEP Adherence Self-Efficacy

Description: Measured by the use of 15 items similar to the Life-Steps Problem Solving Skills questions, however, asking how “hard” or “easy” it would be to do these behaviors. Item scores range from 0 to 4, with higher scores indicating greater anticipated difficulty.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

PrEP stigma will be assessed across three domains using adapted measures of pre-PrEP initiation (120)

Title: PrEP Stigma (Self)

Description: This is a 5-item measure an individual’s perceived stigma about their own PrEP use. Scores range from 5-25 on a 5-point Likert scale (“strongly disagree” to “strongly agree”), with higher scores indicating greater perceived stigma.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: PrEP Descriptive Norms

Description: This is a 5-item measure an individual’s beliefs about how friends and sexual partners would view their PrEP use. Scores range from 5-25 on a 5-point Likert scale (“strongly disagree” to “strongly agree”), with higher scores indicating greater perceived acceptance of the respondent’s PrEP use.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: PrEP Descriptive Norms

Description: This is a 5-item measure an individual’s beliefs about how positively or negatively friends and people in their community would feel about using PrEP. Scores range from 5-25 on a 5-point Likert scale (“strongly disagree” to “strongly agree”), with higher scores indicating more positive views of PrEP at the community level.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: Structural Barriers to Taking PrEP

Description: This is a 9-item measure assessing how much one's PrEP adherence was hindered by specific structural barriers, including transportation and lack of health insurance. Scores range from 0-36 on a 5-point Likert scale ("not at all" to "a great deal"), with higher scores indicating greater structural interference with medication adherence.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: Motivation to Take PrEP

Description: This8-item measure assesses behavioral intentions to take PrEP and PrEP attitudes (Walsh120). Scores range from 0-32 on a 5-point Likert scale ("strongly disagree" to "strongly agree"), with higher scores indicating greater motivation to take PrEP.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Potential Moderators. In addition to examining sociodemographic characteristics as potential moderators of the intervention effect, we will assess sexual compulsivity and social anxiety as potential moderators.

Title: Kalichman Sexual Compulsivity Scale (SCS) (98)

Description: The SCS is a 10-item measure of one's ability to control sexual thoughts and behaviors. Item responses are on a 4-point Likert scale, with total scores ranging from 10 to 40. Higher scores indicate less perception of control over sexual thoughts and behaviors.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: Social Phobia Inventory (SPIN) (99)

Description: The SPIN is a 17-item diagnostic screening measure of the presence and severity of social anxiety. It is also sensitive to change over time. Item responses are on a 5-point Likert scale, with a total score of 20 or greater suggesting the presence of social anxiety.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Additional measures:

Title: Service Utilization Measure

Description: This instrument asks about services received in the past 30 days, including medical and psychiatric inpatient and outpatient treatment. In addition, it asks about insurance and employment status, and justice system involvement. Administration of this measure will involve branching logic so that respondents are presented with the fewest possible relevant follow-up questions.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: COVID-19 Add On Questions

Description: This instrument was created by the study team to evaluate the impact of the COVID-19 pandemic and mandatory lockdown period on sexual health, mental health, and access to services. Administration of this measure will involve branching logic so that respondents are presented with the fewest possible relevant follow-up questions. This measure is permanent addition to the assessment battery intended to be administered to all study participants.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: Attention Check Questions

Description: The attention check consists of five questions distributed throughout the survey battery, intended to indicate whether or not respondents are reading and understanding the questions. A sample question is “Please select the answer choice “Often” (from a list of five choices). Before beginning each assessment, participants will be informed of the attention check questions. Participants who miss three or more attention check questions will be invited to repeat the assessment. Assessment batteries that include 3 or more failed assessment check questions will be flagged as invalid.

Time Frame: Baseline, 3, 6, 9, 12, 15, and 18 months

Title: Client Satisfaction Questionnaire (CSQ-8)

Description: This is an 8-item measure of participant’s general satisfaction with the LifeSteps for PrEP intervention. A sample question is “How satisfied are you with the amount of help you received?” Responses are on a 4-point Likert scale that varies by question type. This measure will only be administered to participants who are randomized to the LifeSteps condition and receive the intervention after demonstrating medication non-adherence. The measure will be included in the follow-up assessment battery one time after the participant completes the LifeSteps

intervention sessions (which can be administered any time over the course of the study). Therefore administration timing is variable by participant.

Time Frame: Variable. Post-baseline and post receipt of intervention

9) **Arms and Interventions**

As described above, this is a two-armed stepped-care RCT, meaning that half of the participants will be randomly assigned to standard of care (SOC), and half will be assigned to the experimental Life-Steps condition. All participants assigned to the experimental condition will receive daily text message reminders, and only participants in this condition who demonstrate medication non-adherence will "step up" to the more intensive Life Steps intervention. Each treatment condition is described below.

Randomization and Blinding

Randomization will occur in blocks, with alternating block numbers ranging from 4 to 8 so study staff cannot guess the condition to which a participant will be assigned. Block randomization will ensure balanced representation in the two study conditions at each site as recruitment progresses, with half of the sample randomized to Life Steps for PrEP and half to SOC. Random assignments will be computer generated.

Study staff will not be blinded to participant treatment condition. All study assessments are either objective (e.g. dried blood spot testing) or participant self-reported via CASI.

Treatment Conditions

Condition 1: Life-Steps for PrEP Intervention. This stepped-care intervention is given to participants in the experimental condition only, and comprises two steps.

Step 1: Daily Text Message Reminders. Daily text messages will be delivered, as done in our pilot RCT. The system or company used for text messaging will be HIPAA and HITECH compliant. All data will be securely stored on secure servers. Daily text message reminders will be sent to all patients randomized to the Life-Steps for PrEP intervention, according to their preferred schedule, for their duration in the study.

WeeklyText Message Survey Link Assessment of PrEP Adherence. We will monitor weekly medication adherence among the intervention arm only. Participants can also contact us to troubleshoot any problems. Participants will receive a weekly text message that contains a link that they will follow to complete a secure survey in REDCap. Questions are: 1) "Over the past 7 days (not counting today), how many days did you take PrEP?". 2)" Over the past 7 days, how many times did you have sex

(anal or vaginal) without a condom?" For confidentiality purposes, we will tell participants in advance that they will be receiving a link to a secure survey, and we will show them how to put a PIN on their phone in the event that they do not already have one. If participants do not respond, they will get the same survey link text later that day, and then the next day. We will enable a monitoring system for use throughout the study in which the study team is notified if the participant has not responded successfully (i.e., no response on-numeric responses) to the weekly text for three consecutive days.

As noted above, all text and survey procedures will be conducted via HIPAA and HITECH compliant systems with multiple security features, including encrypted servers, data destruction policies, intrusion detection systems, managed firewalls, and additional security features. In other PrEP studies, the study PIs have used procedures and systems developed in coordination with Dimagi (www.dimagi.com). Alternately, REDCap with integrated Twilio functionality offers similar HIPAA compliant services.

Step 2: Life-Steps: 4 Nurse/Allied health professional-Delivered Counseling Sessions. In this study, the reason for nurses as interventionists is to utilize professionals that will be involved with PrEP care delivery who are not physicians and who are not professional mental health counselors (e.g psychologist, social worker, licensed mental health counselor). Accordingly, throughout the study protocol, a nurse is defined as any licensed or unlicensed nurses (any training level) or other student/trainee in a similar allied health profession (e.g. physician assistant), who has the requisite knowledge and experience with HIV treatment and prevention, and specific training related to PrEP, which can be acquired through study training. The experimental intervention (78) was derived from Life-Steps for HIV treatment adherence and consists of four weekly sessions and two optional booster sessions. One of the booster sessions occurs during the month following completion of the 4 nurse-delivered counseling sessions; the second booster session occurs during the month following booster session one. The intervention component of each visit lasts approximately 40-50 minutes. After the first visit, we will encourage participants to do these counseling visits in person. However, if there are scheduling difficulties or other situation barriers, remote visits (through secure video conferencing) or, if that does not work, telephone counseling will be conducted. When participants complete a remote session they will be provided with their incentive either by mail (check or equivalent), or at their next in-person visit.

Standard of Care Comparison Condition (SOC). We define the control condition for this study to include the multidisciplinary health services offered at each site (e.g., mental health services, STI testing, etc.) and a brief PrEP adherence educational session. Because the standard-of-care for PrEP-related care differs in practice, as well as within clinical trials,

we have standardized implementation of PrEP adherence education for this trial. The standardized adherence education will consist of a ~10-minute tutorial which explains the importance of adherence in relation to PrEP effectiveness. It is specifically designed for viewers who have no science background and is appropriate for all age groups. The video is titled, "How to Take PrEP and the Importance of Adherence," which was created by COURSERA, a digital media company, in collaboration with the Johns Hopkins University Information Technology Center (102). This adherence tutorial, narrated by Jill Crank, MSN, MPH, an HIV Certified Registered Nurse Practitioner, has been used with MSM in our prior studies. The educational session will be implemented following the baseline assessment with all enrolled participants.

10) Data and Specimen Banking*

Blood for dried blood spot analysis will be stored at the local site in approved freezer space and sent for analysis in batch. Specimens will be identified with participant ID number, not with participant name.

We will obtain HIV and STI test results from their PrEP provider.

Specimen analysis (for adherence dried blood spot monitoring) procedures are described above in primary outcomes.

Data management will be described below.

11) Data Management*

University of Miami will be the data coordinating site. The UM Data team will develop a data management protocol in collaboration with the MPIs, site staff, and the cost effectiveness investigator.

The data team may additionally collaborate with Dr. Mimiaga, the study consultant. The data team will also be responsible for generating data sets and quality control reports for the sites during the data collection phase. The data team will work with the coordinators to make sure data-related information is communicated clearly to the sites.

12) Provisions to Monitor the Data to Ensure the Safety of Subjects*

Given that there are two sites for the proposed project, we have carefully developed an organizational system for the study that is well-coordinated from a data management perspective. The overarching context for the data monitoring and management procedures will be to maintain active, clear communication at each site and between sites. Specifically, Drs. Mayer, Krakower, Safren and Doblecki-Lewis will hold weekly video (e.g. Zoom) meetings with site-specific study staff to direct study activities. This meeting schedule will be maintained throughout all years of the project.

These meetings will address consistency of procedures, problems/challenges, and general training issues. For example, we will address issues of data collection, budget, recruitment, data management and analysis, and perform training and ongoing review of the protocol and assessment procedures. We will discuss any human subject issues related to the ongoing work. In addition, Drs. Safren and Psaros will be involved in supervision and training of study nurses at their local sites, with Dr. Psaros and/or other trained provider doing monthly or more frequent (as needed) group supervision for the nurse interventionists. These meetings will focus on supervision of intervention and assessment procedures. Additional team meetings are specified in the Multiple PI plan. The University of Miami research assistant and data manager will generate data related QC reports to feed back to the sites to make any corrections in as close to real time as possible. The PIs and co- PIs, Drs. Mayer, Safren, Dobecki-Lewis and Krakower will meet weekly to discuss study operations This is required when research involves more than Minimal Risk to subjects.

Data Management Organizational Structure.

Data forms will undergo a systematic and rigorous editing process prior to being keyed into the REDCap database. The graduate student data manager will routinely evaluate the data and discuss any problems and questions with the study staff and the investigator team at the regular weekly team meetings. Data management formal reports on record status across the three following domains will be employed: entered, verified, and edited. These reports of data records will be evaluated once a month during the final team meeting of the month. To help ensure data protection, backup copies, automatically generated by our computer systems, will be available. Data collected from study assessments and questionnaires, will be entered, via secure uplink, to the UM REDCap server.

Confidentiality is assured as participants will be identified on all study materials only by participant number, visit number, and date of visit. By recording the study data in this manner, the information can be considered 'de-identified,' and therefore, compliant with the Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule") of the Health Insurance Portability Act of 1996 ("HIPAA").

DATA SAFETY AND MONITORING BOARD AND ADDITIONAL MONITORING ACTIVITIES

The following procedures will be followed, in compliance with NIH requirements, to ensure the safety of study participants and the validity and integrity of data. The study will have a data safety and monitoring board (DSMB).

Functional Organization of the DSM Committee. The DSMB will meet annually in real time, and will be updated semi-annually with a report. The

yearly meeting will be in the form of a conference call to review randomization data as well as adverse events. These adverse events are tracked for IRB submission as well. Per our IRB submission, study related adverse events will be reported in real time, and study unrelated adverse events will be reported at continuing review.

Monitoring of Safety Data by the DSMB.

Unblinded Reporting. Safety information for this study will be reported to the Committee in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the Committee.

Unblinded data will not be released to site investigators unless necessary for safety reasons. If requested by the DSMB, other unblinded data will be reported to them.

Range of Safety Reporting to the DSM Committee. It is considered necessary for the purpose of monitoring the safety of the study that the committee review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between groups. This includes treatment retention rates and reasons for dropout.

Centralized Data Repository (UM Site). The study PIs have coordinated research initiatives over 2 decades together. The MPIs will oversee the data manager and study staff working on this aspect of the study. Specifically, the UM team will develop a study specific data management protocol and standard operating procedures for the creation and testing of all study CRFs, data collection, quality control, and data extraction. We will provide ongoing oversight of data management throughout the study, and will be responsible for generating reports and datasets for quality control and data analysis. All data management activities will utilize REDCap, a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. REDCap provides secure, HIPAA compliant, web-based applications with an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. Data management reports will be made to the DSM Committee. Cleaned data files (without identifiable data) will be provided to Dr. Safren for analysis, and to Dr. Mimiaga, the statistical consultant for the study.

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Serious Adverse Events. Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs; i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient

hospitalization, or any congenital anomaly). This also includes any event that a study investigator or the Committee judges to impose a significant hazard, contraindication, side effect, or precaution. For purposes of this study, all SAEs will be required to be reported to the Committee, regardless of any judgment of their relatedness to the study. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, study condition, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Information will be reviewed and a determination made of whether there was any possible relevance to the study interventions. Reporting to site-specific IRBs will be done within the current guidelines of the UM IRB; reporting to NIH will be made according to their respective regulations governing SAE reporting. SAE reporting to the DSMB will occur at the regular meetings, unless deemed significant and related to the study. We do not anticipate any serious, study related adverse events.

Non-Serious Adverse Events. At yearly intervals during the course of the study and then again at its completion, the IRB and the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase.

Data on individual non-serious adverse events is not expected to be needed for this review.

Other Safety-Related Reports. At yearly intervals throughout the course of the study, the DSM Committee and the IRB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.

Study Stopping Rules. If at any time during the course of the study, the Committee judges that risk to subjects outweighs the potential benefits, the Committee shall have the discretion and responsibility to recommend that the study be terminated. We do not, however, have a pre-specified stopping rule. The IRB may request unblinded data to make this determination at any time.

Monitoring of Data Quality by the DSMB

Semi-annually, during the course of the study (starting after study start up), the DSMB will receive a report on data quality and completeness and participant flow. At a minimum, this will include an overview of the progress of participant intake and retention; summary reports describing participant compliance with visits, evaluations, a summary of key baseline data elements to examine balances in randomization. These reports will be used by the DSM Committee to evaluate the capacity of the data capture and processing to support scientifically valid analyses. For ease of understanding, reports are done graphically, similarly to the CONSORT figures.

13) Withdrawal of Subjects*

Generally, we are not anticipating withdrawing subjects from the study. If, as part of their treatment, participants exhibit the need for additional intervention beyond what the study can provide, they will be referred for additional care as part of the prevention case management approach.

If any study subject is threatening to study staff, or is not able to adhere to a plan to prevent harm, it is likely that they would be removed from the study, and, following all applicable laws and regulations, be referred for higher level care.

14) Risks to Subjects*

It is unlikely that participants will be at substantial risk for physical harm as a result of participation in this research study. Participants may experience emotional discomfort at result of completing quantitative assessments or the intervention. Another risk is that participants may experience discomfort or accidental injury as a result of blood draw. Breach of participants' confidentiality presents another possible risk.

Procedures will be in place to protect participants who may experience higher than usual levels of behavioral challenges, regardless of treatment assignment. Nurse interventionists and other staff who interact with participants will be trained by Drs. Steven Safren and Christina Psaros to be sensitive to signs of distress in study participants. They will be free to deviate from the counseling protocol to ensure participant safety. In addition, the study Clinical Supervisor will either be on-site or on-call and contactable by cell phone, and there will be adequate medical or psychological personnel available to the study nurses at all times for backup. Dr. Psaros (with the help of Dr. Safren) will provide supervision and additional counseling if required. In addition, other staff psychologist support is available at Fenway Health and the University of Miami.

Each team has a protocol in place for addressing potential self-harm or harm to others should that arise as an issue in the counseling sessions. This involves a more comprehensive clinical assessment under the supervision of a doctoral level psychologist or licensed mental health professional. Each team will follow local laws for potential involuntary hospitalization should that be needed, which will be specified in the consent form. The assessment of self-harm involves asking questions such as “Has it ever gotten so bad that you thought life isn’t worth living”, “Are you feeling suicidal right now”, “Have you ever thought about how you would do it”, “On a scale of 0-10, 0 being I do not want to commit suicide and 10 being I have a definite plan to commit suicide, where do you fall”? Procedures depend on the outcome of this assessment. Generally, if 5 or less, then a contract for safety is made. Higher scores require more intensive referral. If a participant is currently suicidal and/or scores higher than a 5 on this item, they are evaluated further by a trained professional, and appropriate action is taken which, depending on the severity, may include involuntary

further evaluation at an emergency room or crisis services. Additionally, with the assistance of the on-site clinical supervisor, a written report is completed, as well as, when appropriate, a notice to the IRB.

Other Protection Against Risks

Study procedures do not preclude participant referral for additional care and treatment and in each case where additional levels of care are required, decisions regarding the participant's continuation in the study will be based solely on a consideration of the participant's' welfare.

The exclusion criterion prohibiting participants with serious untreated mental illness from participating in the study ensures that those who would be most likely to experience this high level of distress in response to the study procedures are not enrolled.

With respect to blood draws, each of these procedures will be carried out by trained phlebotomists, nurses, or physicians to minimize the accidental injury or discomfort to the participants. Participants who experience harm as a result of these procedures will receive first aid from study staff and referral to a medical professional if needed.

In terms of confidentiality, all data will be kept confidential, electronically locked via password-protection available only to authorized staff. The passwords will change periodically, accessible only to specified study staff. Participants' study data will be identified by an ID number only in the REDCap database, and a link between names and ID numbers will be kept separately under password protection. As part of the informed consent process and throughout the study therapy and assessment procedures, all participants will be advised that they may decline to answer any study questions. These procedures will be implemented to provide study participants with the assurance of confidentiality around very sensitive and personal information relating to their mental health, sexual and substance use history, and HIV/STI status. All study personnel working on the project will be educated about the importance of strictly respecting participants' rights to confidentiality and will have completed study specific trainings.

Recording of intervention sessions is part of the procedures. The purpose of the recording will be explained, confidentiality will be respected, and both informed consent and authorization for recording will be obtained. All digital audio recordings of therapy sessions will be uploaded to the study computer immediately following the session and the audio file deleted from the digital recorder. Computer audio files will be secured by password and will be accessed only by authorized study personnel (i.e., PI, site-PI, the study staff member conducting the fidelity check). Digital recordings will be stored and moved between sites (to the study clinical supervisor, Dr. Psaros) using a secure, password-protected and HIPAA-compliant website. Recordings will be maintained until at least five years after the publication of study results.

15) Potential Benefits to Subjects*

Subjects who participate in this study may benefit from the close monitoring of their PrEP use, sexual and behavioral health, and medication adherence. Those assigned to the experimental intervention may benefit from the intervention to support improvements in their PrEP medication adherence. These potential benefits are provided without charge. Information provided as part of PrEP follow-up in both arms may also help participants better understand their patterns of sexual behavior and medication adherence, and remain HIV uninfected over the long-term.

16) Vulnerable Populations*

Not Applicable. This research does not involve individuals who are vulnerable to coercion or undue influence. The additional safeguards or other considerations to be enrolled in the study will not be required. The study will exclude Children, Decisionally Impaired, or Cognitively Impaired Adults.

17) Multi-Site Research*

This is a two-site study – University of Miami and Fenway Health. The reviewing IRB will be at the University of Miami site. One coinvestigator is at Massachusetts General Hospital and we will solicit an authorization from them as well. Some of the study visits for University of Miami will be at the Department of Health PrEP Clinic which is run by co-investigator Susanne Doblecki-Lewis. We will also obtain an authorization agreement from DoH for this. Other UM visits will happen at the UM PrEP clinic, also run by Dr. Doblecki-Lewis and/or the PrEP mobile van, and at the Health Promotion and Care lab offices in the UM Clinical Research Building. At Fenway Health in Boston, study visits take place in their research and clinical facilities.

18) Community-Based Participatory Research*

One central component of our work involves community engagement. Accordingly, we have budgeted for recruitment and community engagement activities on a yearly basis to allow for bidirectional community involvement. This includes input as to acceptability of our recruitment and retention efforts, any changes to the protocols during the startup period, and then active community dissemination as findings from both this trial and related developments in PrEP emerge. In this fashion, the team will stay connected to the community throughout the duration of the study. We will participate in community advisory board (CAB) meetings at both sites through the UM Developmental AIDS Research Center CAB. In Boston, we will utilize the Fenway CAB as the primary CAB. We will solicit input from the CABs as to how to best stay engaged with the community in terms of dissemination of findings.

19) Sharing of Results with Subjects*

We anticipate holding a community forum at both sites at the end of the study in order to disseminate the findings locally, inviting and advertising to the community at large, and making outreach efforts to trial participants specifically.

Study staff will monitor participants' screening patterns for HIV and sexually transmitted infections in the course of the study, and will communicate with primary care providers and facilitate triage if timely STI monitoring is not undertaken, or if participants acquire HIV or a new STI.

20) Setting

Some of the study visits for University of Miami will be at the Department of Health PrEP Clinic which is run by co-investigator Susanne Doblecki-Lewis. We will also obtain an authorization agreement from DoH for this. Other UM visits will happen at the UM PrEP clinic, also run by Dr. Doblecki-Lewis and/or the PrEP mobile van, and at the Health Promotion and Care lab offices in the UM Clinical Research Building, or other UM offices as needed/available. At Fenway Health in Boston, study visits take place in their research and clinical facilities.

21) Prior Approvals

This was submitted for initial conceptual approval for NIH "just in time" requirements. It was later submitted for full approval as required by NIH.

22) Recruitment Methods

Section 6 describes study wide recruitment methods. This is the same for both sites and detailed there.

23) Local Number of Subjects

We propose to enroll 150 subjects at the Miami, FL site, and 150subjects enrolled at the Boston, MA site. (total of 300 participants enrolled).

24) Confidentiality

Check all that apply:

☒ Data obtained or created for this research will be stored on an encrypted electronic device or system owned by the University of Miami or on a cloud storage system that has been approved by the University of Miami for storage or research data.

☐ The Investigator (or research staff) will record (e.g. write down, abstract) data collected in a manner that does not include

any indirect or direct identifiers and the recorded data will not be linked to the individual's' identity.

☒ The investigator (or research staff) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers of the subject. The investigator will assign a code to each subject and link the code to the subject's identity. The research team will maintain the link to the subject's identity on a document separate from the research data. Both documents will be stored in separate files on a University of Miami encrypted device or on a University of Miami approved cloud storage system. The research team will destroy the identifiers at the earliest opportunity.

☒ The research team will maintain the research data for at least three years.

☒ Bio-Specimens obtained for this research will be stored without any direct or indirect identifiers.

☒ Bio-Specimens obtained for this research will be stored in a de-identified coded manner.

☒ When required to transport data or bio-specimens for this research, the research team will transport the data and bio-specimens in a de-identified (or anonymous) manner with a link to the individual subject's identity maintain separately from the data and/or bio-specimen.

25) Provisions to Protect the Privacy Interests of Subjects

All study staff will be trained in ethics, confidentiality, and privacy interest. All study staff will have extensive experience and knowledge in working with people with HIV.

Subject identifiers will be kept in a separate database that is password protected. Only trained study staff will have access to name files and to the link between the name and the number files.

26) Compensation for Research-Related Injury

The study does not involve more than minimal risk. There is not a plan to compensate participants for research related injuries.

27) Economic Burden to Subjects

To reduce attrition, participants will be paid for completing the final study assessments at escalating amounts. The participant payment is not

contingent upon improvement or any other study data at the time of assessment or follow-up. Participants will receive modest reimbursements for the baseline and quarterly follow up assessments which escalate over the course of the follow-up (currently budgeted at $50 for the initial visits, $30 for months 3 and 6, $$50 for months 9, 12, and 15, , and $$125 for month 18. Additionally, participants who attend the Lifesteps intervention session will receive $10 per session (typically up to $60 for 4 regular and 2 booster sessions) to cover travel expenses. In the event that a participant, after completing 4 LifeSteps and 2 boosters, is found to decline again in their adherence to less than 4 pills per week, they will be offered 2 additional booster sessions. Participants will receive $10 for each session completed, up to a maximum of $80 for 4 regular and 4 booster sessions.

In some cases, participants will not be able to collect a satisfactory dried sample (DBS). Reasons include, but are not limited to, insufficient amount of blood collected; normal viability window has been exceeded; logistical errors; etc. In order to provide an incentive for participants to repeat the dried blood sample, we will provide an additional $15 incentive for every time participants do not satisfactorily complete a DBS sample at follow up.

Some potential participants will be approached by research staff immediately after completion of the appointment in which they receive their first PrEP prescription. To encourage participants to complete the screener measure after their long medical appointment, these participants will be offered $5 in compensation (cash, gift card, or equivalent). Participants who complete the screener online or in a scenario other than immediately following their PrEP medication initiation visit will not be offered compensation for screening.

28) Consent Process

Prior to the in-office assessment battery, a trained study staff member will assess participants' consent. The staff member will ensure that the participant understands the risks associated with the disclosure of information that could indicate imminent threat to self or others. Verification of comprehension of informed consent will be accomplished by asking participants to recall central points in the consent process; points of confusion will be clarified. Once participants have fully understood the consent, they will be asked to sign the consent form. Study staff will be instructed to contact the PI or project coordinator if he or she is unsure about any participant's capacity to consent. In the event an in-office visit cannot be completed, consent procedures will be completed via video-conference or phone call. Note that for all study participants, consent is confirmed electronically via REDCap. Participants will be given a copy of the signed consent form.

The site research assistant, recruiter, and study nurses will coordinate subject recruitment. Interested potential participants recruited through

participating clinics' referrals will speak with one of these study staff members in person or on the telephone to do an initial screen. Initial screening responses will be recorded electronically through the HIPAA compliant REDCap system, which allows for branching logic to end the survey if it is determined that the participant is ineligible. If preliminary criteria are met, participants will then be scheduled for a future visit to complete the informed consent process and the psychosocial assessment battery. The consent process will include consent to study procedures, consent to release of information from their medical record regarding clinical parameters related to PrEP and potential HIV seroconversion, and consent to share results of study assessments with their treatment team. The staff member will ensure that the participant understands the risks associated with the disclosure of information that could indicate imminent threat to self or others. Verification of comprehension of informed consent will be accomplished by asking participants to recall central points in the consent process; points of confusion will be clarified. Once participants have fully understood the consent, they will be asked to sign the consent form. Study staff will be instructed to contact the PI or project coordinator if he or she is unsure about any participant's capacity to consent. We anticipate that the consent will occur electronically, through the HIPAA-compliant REDCap e-consent module which separates names and identifying information from study data. Participants will receive a hard-copy of this form, and the e-copy is kept in the confidential HIPAA-compliant database. We will follow SOP HRP-091 for written documentation of consent, including procedures described in section 5.1.3 (for electronic signatures).

Non-English Speaking Subjects

In addition to English speaking study participants, we seek to enroll Spanish monolingual participants at the Miami study site. The feasibility of doing so will be dependent on finding qualified, bilingual nurse interventionists/allied health professional.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

N/A

Cognitively Impaired Adults

N/A

Adults Unable to Consent

N/A

29) Process to Document Consent in Writing

We anticipate that the consent will occur electronically, through the HIPAA-compliant REDCap e-consent module which separates names and identifying information from study data. Participants will receive a hard-copy of this form, and the e-copy is kept in the confidential HIPAA-compliant database. We will follow SOP HRP-091 for written documentation of consent, including procedures described in section 5.1.3 (for electronic signatures).

30) Authorization for Use and Disclosure of Protected Health Information (HIPAA)

Participants will be asked to sign a HIPAA authorization to use and disclose health information (release of medical information) authorizing study personnel access to their medical records for the duration of the study to access their clinical response to PrEP (e.g. renal function), as well as bacterial STI screening results.

Potential participants at the Fenway (Boston) site may be obtained via a secure, abridged report generated on site via Electronic Medical Records (EMR) (described above in section 6). We are therefore requesting a HIPAA waiver of authorization for access to medical record for subject identification/recruitment. To reiterate, only subjects who have previously signed consent to contact for future research may be included on the EMR list of potential research participants.

Type of Request:

☒ Waiver of Authorization for access to medical record for subject identification/recruitment. (For relying site Fenway Health in Boston, MA)

☐ Waiver of Authorization for access to medical record to obtain data for the research.

Confirm that you will destroy or de-identify the information you collect at the earliest opportunity.

☒ **I confirm**

Confirm that the information you collect will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

☒ **I confirm**