Developing a Patient Navigation Intervention for PrEP Continuum of Care Among Young Latino MSM (PrEParate)

Study Protocol and Statistical Analysis Plan

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Using a randomized controlled trial design, a pilot test of the PN intervention will be conducted in collaboration with the Family Health Centers of San Diego (FHCSD), a federally qualified health center.[17] Bilingual research assistants will recruit 60 young adult Latino MSM at-risk for HIV in San Diego County, California; this sample size is well within the bounds of recommendations for pilot trials.[18] After a research assistant obtains informed consent, participants will complete baseline surveys, and then the research assistant will individually randomize each participant to 1 of 2 conditions: usual care plus written information (UC) or PN. At 3- and 6-month follow-up, participants will be asked to complete surveys. Individuals randomized to PN will also be asked to participate in a key informant interview at 6-months. Participants' electronic health records (EHR) will be reviewed at 6-month follow-up to assess their engagement in the PrEP continuum. The study methods and PN intervention will be reviewed for feasibility and acceptability, as well as preliminary impact of the PN intervention in preparation for a future full-scale efficacy trial. In addition, the pilot test will evaluate preliminary impact on seven PrEP continuum-related primary outcomes (i.e., scheduled and attended PrEP consultation; PrEP prescription received; PrEP prescription filled; PrEP initiated; self-reported PrEP adherence; and PrEP follow-up medical appointment attended). Analyses will be performed under the intent-to-treat (ITT) principle. Participants will be compensated with a $50 gift card to an online retailer at each of the three assessment time points (baseline, 3-month follow-up, 6-month follow-up). (See Appendices 1-3 for informed consents and WHO Trial Registration Data Set)

Patient and Public Involvement

As suggested by Intervention Mapping, a Participatory Planning Group (PPG) of program stakeholders guided the design of the PN intervention. The PPG includes a consultant and HIV expert, potential program implementers, young Latino MSM, and community members who interact with or deliver services to people who may benefit from the intervention. The PPG was instrumental in helping us develop the intervention materials and recruitment approaches. This group will continue to meet on an as needed basis (with compensation for their time) and will assist with dissemination of research findings both in the community and in peer-reviewed publications and presentations.

Setting

The pilot RCT will take place in San Diego County, California. In 2017, San Diego had an estimated population of 3,337,685 people,[19] 33.9% of whom identified as Hispanic and 50.3% identified as male. Between 2012 and 2014, it was estimated that 3.9% of San Diego County's population identified as a sexual minority.[20] Our study is being conducted in partnership with FHCSD, which is San Diego's largest federally qualified health center, providing care to more than 140,834 patients in 2018. FHCSD delivers comprehensive healthcare in 42 sites throughout San Diego County. Each site provides a wide range of health care services to sexual and gender minority patients. Although we are partnering with FHCSD on this study, participants are recruited throughout San Diego County and obtain health care in various health systems, centers, and practices in the community.

Inclusion/Exclusion Criteria

The following criteria are required for study inclusion: 1) age 18 to 29 years; 2) identifies as male; 3) identifies as gay/bisexual or reports having sex with men in past 12 months; 4) identifies as Latino/Hispanic; 5) self-reports being HIV-uninfected; 6) resides in San Diego County, California; 7) speaks English or Spanish; 8) is willing and able to provide informed consent; and 9) reports at least one HIV risk factor as informed by Centers for Disease Control and Prevention (CDC) guidelines.[21] MSM are at elevated risk for HIV if they report one of the following: 1) an HIV-positive sexual partner; 2) diagnosis of a bacterial sexually transmitted infection (STI) within the past 12 months; 3) engaging in

condomless anal sex with a non-monogamous partner in the past 12 months; 4) engaging in commercial sex work in the past 12 months; 5) injection of illicit drugs and sharing of injection equipment in the past 12 months; or 6) engaging in drug treatment for injection drug use in the past 12 months. Individuals will be excluded if they self-report being HIV-positive. The intervention is designed to meet the needs of MSM who self-report their gender identity as male, but other gender identities are allowed in the study. If a potential participant indicates that their gender identity is not "male" (e.g., trans-gender, non-binary, gender fluid), then the participant will be informed that the study was designed for cis-male MSM; and will then be invited to determine whether they feel that they will benefit from the study based on their gender identity. Participants who previously were prescribed or are currently taking PrEP will be included in the study. Participants are not required to seek care at FHCSD to be included in the study.

Recruitment

Non-probability (convenience) sampling will be used to recruit participants within the greater San Diego area via a variety of methods, including through FHCSD outreach and HIV/STI testing programs, a Spanish language Latino MSM support group, gay-friendly events, such as Pride, and flyering local LGBT community centers, gay-identified/friendly coffee shops, gyms, and bars. We will also utilize online recruitment methods, including targeted ads through Facebook and Instagram, and use of geolocation social networking mobile applications tailored to sexual minority men (e.g., Grindr, Scruff, Jack'd). Potential participants recruited using flyering or targeted ads will be requested to contact study personnel via email or telephone. A bilingual member of the study team will contact each potential participant via telephone to explain the study and screen for inclusion. The bilingual research assistants will be native Spanish speakers who are bilingual in English and Spanish; they will have some university education and research experience. If a potential participant screens positively for the study, an in-person baseline visit will be scheduled, in which the inclusion/exclusion criteria will be assessed in further detail. Reasons for non-participation of potential participants will be documented.

Randomization

The research coordinator will use the Randomizer for Clinical Trial computer application to randomize each participant to either UC or PN via an iPad[22] immediately following the baseline survey data collection. Randomizer for Clinical Trial will implement a blocked randomization sequence (in blocks of 4 participants) to balance randomization across the arms of the study. The randomization sequence will be concealed from all members of the study team prior to randomization.

Usual Care Intervention

Immediately following randomization, the research team member will provide participants randomized to UC the CDC's 2-page *PrEP Information Sheet* in the participant's preferred language (either English or Spanish). This 2-page booklet includes the following information: 1) overview of PrEP; 2) eligibility for PrEP; 3) efficacy of PrEP; 4) safety of PrEP; and 5) obtaining, initiating, and adhering to PrEP. Participants will also be provided with both verbal and written information regarding available sexual health and HIV prevention services, including PrEP, at FHCSD. Comprehensive HIV-prevention healthcare, including PrEP, is available to study participants at FHCSD at no or minimal cost.

PN Intervention

Based on extensive formative research and using Intervention Mapping,[23] the study team developed, pre-tested, and produced the PN intervention materials. The produced PN intervention includes an introductory module, five educational modules (HIV prevention, PrEP introduction, PrEP efficacy, PrEP side effects, and PrEP adherence), and a module focused on decision support. Patient education is facilitated using infographics, palm cards, and a decision support tool. The educational

modules are designed to be delivered as needed in addition to personalized strategies to improve access and decrease barriers to PrEP initiation and adherence. The intervention also consists of barrier reduction strategies to assist individuals with implementing HIV prevention, including the use of PrEP. Two part-time Spanish-English bilingual peer lay navigators hired by FHCSD will provide the PN intervention during the study. Navigators were hired based on their familiarity, as well as cultural and linguistic competence, with the intended audience, young Latino MSM. The study team will train the patient navigators using training manuals developed in formative research and via the Patient Navigation Research Program training approach.[24]

Following patient randomization, the research coordinator will notify the patient navigators regarding the patient's assignment to PN. A patient navigator will contact the participant to schedule the first in-person meeting at a time and location of the participant's convenience. The navigators will provide services to patients using PN intervention manuals and materials the team has developed (see Figure 1 for examples of PN services provided at each level of PrEP continuum). Services will generally focus on: 1) overcoming community, health system, interpersonal, and individual barriers to accessing PrEP-related healthcare; 2) increasing each patient's knowledge, attitudes, and self-efficacy for initiating and adhering to PrEP; 3) improving communication between the patient and healthcare team through appointment scheduling and reminders; and 4) sexual risk reduction counseling. PNs do not meet participants at their homes but at any safe location to conduct the intervention (e.g., private rooms in a library, clinic, or community outreach center). Meeting locations are coordinated between the participants and the PNs. PNs communicate with participants via text, phone call, and videoconferencing, based on the participant's preference.

The FHCSD HIV Services Program Manager will provide day-to-day supervision of the patient navigators and will meet with each navigator weekly and document successes and challenges to PN intervention implementation through a weekly written report. The study staff also provide weekly supervision and will rate patient navigators' delivery of the intervention, via audio recordings, using an intervention fidelity monitoring form.

Data Collection

Survey and Interview Data Collection. Following informed consent, the research coordinator will administer self-report baseline surveys using Qualtrics in-person in the participant's preferred language of Spanish or English, assess time required to complete surveys, and note any participant difficulty in answering survey items. Participants will be asked to complete 3- and 6-month follow-up surveys using a mixed mode approach, consisting of an initial Qualtrics (online) survey followed by an emailed survey if the Qualtrics survey is not completed. At baseline, 3-month follow-up, and 6-month follow-up, participants will be asked to complete measures of PrEP knowledge, PrEP awareness, PrEP attitudes, PrEP barriers, PrEP efficacy beliefs, PrEP adherence, PrEP initiation, sexual behaviors, beliefs about medications, medication self-efficacy, mental health, substance use, and social support (see Table 1 for information regarding study surveys, including evidence of their validity and reliability). Self-report demographic information will be obtained at baseline. Self-report surveys assessing client satisfaction with PrEP-related healthcare services[25] will be administered at 3-month and 6-month follow-up. Those randomized to PN will complete a self-report survey assessing satisfaction with the interpersonal relationship with the patient navigator[26] at 3-months and 6-months. In addition, all participants randomized to PN will be contacted by telephone at 6-months to complete a key informant telephone interview to assess acceptability of the intervention; these key informant interviews will be conducted by members of the assessment team and not by PNs.

Measures were chosen following a literature review of existing validated instruments, and psychometrically validated instruments were chosen when possible. However, as PrEP was only recently

recommended for the prevention of HIV, there are few validated surveys measuring constructs related to PrEP. For these constructs, the team created new measures, adapting from existing scales when possible. Surveys not available in Spanish were translated using a dual panel approach.[27-29]

Table 1: Description and Timing of Surveys and Health Record Data Collection

Construct	Description of Measure	Source	BL	3 m	6 m	6m EHR
PrEP Knowledge	16-item self-report measure of knowledge related to PrEP, including use and effectiveness. Data are collected using a Likert scale.	Team developed	X	X	X	
PreP Awareness	One survey question assessing awareness of PrEP Categorical data are collected.	Team developed	X	X	X	
PrEP Adherence	2-item self-report survey assessing ability to take PrEP over the past 7 days, and frequency (%) with which PrEP was taken over the past 7 days. Data are collected using a Likert scale.	Team developed	X	X	X	
PrEP Attitudes	10-item PrEP Stigma and Positive Attitudes Measure assessing personal opinions about PrEP and people who use PrEP; 16 additional items assessing general attitudes and beliefs about PrEP use, provider comfort and medical mistrust related to PrEP use, side-effect concerns about PrEP use, disclosure concerns and social norms related to PrEP use, and sexual risk concerns about PrEP use. Data are collected using a Likert scale.	Mustanski et al., 2018; Pulsipher et al., 2016	X	X	X	
PrEP Barriers	5 survey items related to concerns about PrEP use, efficacy, and stigma; 5 additional items assessing potential access barriers to obtaining PrEP, including lack of health insurance coverage, difficulty finding a provider, and cost of PrEP. Data are collected using a Likert scale.	Golub et al., 2012; Pulsipher et al., 2016	X	X	X	
PrEP Efficacy Beliefs	2-item measure of beliefs regarding the efficacy of PrEP, Data are collected using a Likert scale.	Pulsipher et al., 2016	X	X	X	
Medication Self-Efficacy	4 items assessing self-efficacy to adhere to PrEP; adapted for PreP use from the Self-Efficacy for Appropriate Medication Use Scale (SEAMS). Data are collected using a Likert scale.	Adapted from Risser, Jacobson, & Kripalani, 2007	X	X	X	
Beliefs about Medicines	Items from the Beliefs about Medicines Questionnaire (BMQ), including the BMQ-Specific subscale, a 10-item scale assessing representations of medications, and the BMC-General subscale, an 8-item subscale assessing beliefs about medicines. Data are collected using a Likert scale.	Horne, Weinman, & Hankins, 1999	X	X	X	
Sexual Behaviors	3 items measuring over the past 3 months the total number of male anal sex partners, number of partners in which condoms were not used exclusively, and the HIV status of partners. Data are collected using numeric text entries.		X	X	X	
Mental health	21 item Depression, Anxiety, Stress Scale (DASS-21) measuring depression, anxiety, and stress over the past week. Data are collected using a Likert scale.	Lovibond & Lovibond, 1995	X	X	X	
Substance use	15 items measuring drug, alcohol, and tobacco use over the past month. Data are collected using a Likert scale.	Team developed	X	X	X	
Social support	8-item PROMIS Informational and 7-item Emotional Support Scales, respectively, measuring perceived sources of support over the past month. Data are collected using a Likert scale.	Hahn et al., 2014	X	X	X	
Patient Satisfaction with PrEP-related services	8-item Client Satisfaction Questionnaire (CSQ-8) measuring of satisfaction with PrEP-related health care services received Data are collected using a Likert scale.	Attkisson & Greenfield, 2004		X	X	
Satisfaction with Interpersonal	For participants randomized to PN intervention only; 9-item measure of satisfaction with care provided by a patient navigator. Data are collected using a Likert scale.	Jean-Pierre et al., 2012		X	X	

Relationship with Navigator						
PN Intervention Acceptability	For participants randomized to PN, brief telephone key informant interview assessing acceptability of the PN intervention. Data are qualitative.	Team developed			**X**	
PrEP Initiation	Up to 10 survey items assessing whether patient had received a prescription for PrEP, decided to fill a PrEP prescription, and taken at least one dose of PrEP since the start of the study. Categorical data are collected.	Team developed	**X**	**X**	**X**	
Demographic Characteristics	Demographic items (e.g., age, race, gender, sexual orientation, relationship status, country of origin, U.S. citizen status, primary language, education level, employment status, income, health insurance status) have categorical response options. Age data are collected with numeric text entry.		**X**			
Medical Characteristics	Comorbid medical conditions, medications prescribed, history of STI testing					**X**
PrEP-Related Health Care Received	Date(s) appointment scheduled for PrEP consultation; Date attended appointment for PrEP consultation; Date(s) health care provider wrote PrEP prescription(s); Date the first follow-up PrEP appointment(s) scheduled; Date(s) of follow-up medical appointment attended; Data recorded in EHR regarding adherence and discontinuation; other data regarding PrEP-related health care	Team developed				**X**

Abbreviations: BL = baseline; 3m = 3 month follow/up appointment; 6m = 6 month follow-up appointment; EHR = electronic health record; STI= sexually transmitted infection; PN = patient navigation

MEMS Device Data Collection. At baseline and 3-month follow-up, all participants will be asked if they have obtained a prescription for PrEP. Those who indicate that they have been prescribed PrEP and have taken at least one pill will be asked to track their PrEP adherence via a Medication Event Monitoring System (MEMS) device.[30] A MEMS device is a standard prescription bottle that includes a larger lid containing a MEMS monitoring cap. During the baseline or at a 3-month follow-up visit, the research coordinator will give participants a MEMS device with instructions for its use. Participants will be instructed to place all PrEP pills into a MEMS container so when a pill is removed, the device will record date and time of removal of the medication dose using a small microcircuit. A medication "event" is removal of bottle closure, followed by replacement of closure. A study staff member will collect MEMS devices from participants in-person at the 3- and/or 6- month follow-up and connect them to a MEMS® Reader, which transfers data to a secured server via a secured web platform. Timing adherence will be calculated as percentage of time each participant took PrEP as prescribed by determining number of doses of PrEP taken at 24-hour intervals for a once daily PrEP regimen and dividing it by number of days adherence was monitored with MEMS.

Medical Record Data Collection. We will collect the following data from electronic health records (EHRs) 6 months following study enrollment after obtaining a written release of information: 1) date(s) initial appointment to speak to a health care provider regarding PrEP was scheduled; 2) date participant attended an initial appointment to discuss PrEP; 3) dates and number of prescriptions written for PrEP by a health care provider; 4) date the first follow-up visit related to PrEP was scheduled; and 5) dates the participant attended follow-up appointments related to PrEP. We will document EHR data regarding PrEP initiation and adherence, barriers to PrEP adherence, exams and laboratory tests required to obtain an initial or follow-up PrEP

prescription, side effects attributed to PrEP, diagnosis and treatment of illness during the study, prescription medications, comorbid health conditions, and history of STI testing. We will also note whether the EHR indicates that participants decided to cease taking PrEP and the date of discontinuation.

PN Intervention Encounter Data. Using an approach developed by the Patient Navigation Research Program (PNRP),[31] patient navigators will record process data related to the PN services provided, including: 1) number of encounters; 2) length of time of each encounter; 3) barriers experienced by patients; and 4) actions taken to reduce barriers**.** The patient navigators will also be asked to keep detailed qualitative notes regarding telephone, text, and in-person encounters with participants, including participants' progress in the PrEP continuum, successes in implementing the PN intervention, and challenges in implementing the PN intervention.

Feasibility Evaluation. A feasibility evaluation will examine areas critical to success of a larger research study. First, we will evaluate recruitment strategies by assessing the number of individuals eligible for the study, number with whom we could establish contact, number who agreed to participate or did not, reasons for non-participation and ineligibility, and difficulty with implementing the randomization process. Second, we will assess methods of data collection including participant time burden for completing baseline surveys, participant difficulty in answering survey questions, difficulty of using MEMS, reliability of surveys, number and types of missing survey data, timing of follow-up data collection, and rates of completion of follow-up surveys. Third, we will examine feasibility and processes of delivering the PN intervention by assessing the actions taken by the patient navigators and frequency and type of encounters. Data will be examined descriptively to identify areas for improvement of the study or PN intervention methods before a larger research study is initiated.

Acceptability Evaluation. An extensive acceptability evaluation will examine how both individuals randomized to the PN intervention and those involved in implementing the program reacted to the intervention.[32] Data will be collected for the acceptability evaluation using multiple quantitative and qualitative methods, including patient navigator encounter logs, patient navigator client notes, patient navigator supervisor notes, participant surveys, and participant key informant interviews. Quantitative acceptability data will be collected from pilot test participants at the 6-month follow-up using validated surveys assessing satisfaction with PrEP-related healthcare[25] and Interpersonal Relationship with the Navigator,[26] as well as from the patient navigators through the PN intervention encounter logs. Qualitative data will be collected from pilot test participants at the 6-month follow-up via 3 open-ended survey questions assessing the aspect of the PN intervention participants liked the best, the aspect of the PN intervention participants liked the least, and one thing that could be changed about the PN intervention[25] as well as via a brief telephone key informant interview conducted by a trained bilingual research coordinator. The semi-structured key informant interviews will be conducted in the participant's preferred language and will use a 28-item standardized interview guide designed using Sekhon et al.'s theoretical framework of acceptability.[33] Interviews will last approximately 45 minutes and will be recorded, transcribed verbatim, and translated (if necessary) into English. In addition, both the patient navigators and the supervisor of the patient navigators will record observations regarding the implementation of the PN intervention, including success and challenges.

Monitoring

Consistent with NIMH requirements, a data monitoring committee is not required given this is not a phase III clinical trial and because of the low-risk nature of this exploratory study.

Statistical Analysis Plan

Qualitative data. Qualitative data (key informant interviews, navigator qualitative notes, supervisor notes) will be saved in a text file to import into NVivo[34] for analysis. The study PIs will review the qualitative data using a content analysis technique, which identifies emergent themes occurring during discussion. Code mapping[35] will be used to develop a preliminary set of codes (themes) corresponding to each potential strength of the PN intervention as well as every potential aspect for improvement. Then, the co-PIs will independently code the remaining data and meet to discuss and achieve consensus in coding. Once coded, the data will be summarized by theme. These data will be used to modify the PN intervention, if necessary, or will provide further indication that the PN intervention should be tested in a larger scale study.

Quantitative data. All quantitative data will be summarized descriptively to determine aspects of the PN intervention that worked well and potential areas of improvement of the PN intervention. Our biostatistician will be blinded to intervention assignment for participants and will conduct statistical analyses using SAS 9.4.[36] Univariate statistics will be conducted for outcomes measured at baseline and 6-month follow-up to describe sample characteristics between the two groups (UC versus PN). Attrition in the two groups will be compared. Characteristics of individuals with missing values and individuals with no missing values will be studied. Multiple imputation technique will be implemented and sensitivity analysis will be conducted to assess if missing data is at random. Assumptions of statistical tests will be evaluated. For assessing preliminary impact, the primary outcomes are seven behaviors associated with the PrEP care continuum (i.e., appointment scheduled for PrEP consultation; appointment attended for PrEP consultation; PrEP prescription received; PrEP prescription filled; PrEP initiated; self-reported PrEP adherence over the past seven days; and PrEP follow-up medical appointment attended).

To test the preliminary impact of the intervention, a series of logistic regression models will be conducted, with each of the 6 binary PrEP continuum primary outcome variables set as a criterion: 1) appointment scheduled for PrEP consultation; 2) appointment attended for PrEP consultation; 3) PrEP prescription received; 4) PrEP prescription filled; 5) PrEP initiated; and 6) PrEP follow-up medical appointment attended. In addition, we hypothesize that receipt of the PN intervention will be associated with increased self-reported PrEP adherence over the past seven days (also a primary outcome variable). To test the preliminary impact on the two measures of self-reported PrEP adherence, we will conduct two linear regression analyses with intervention group assignment entered as the independent variable and each measure of PrEP adherence entered as the dependent variable. Potential demographic variables (e.g., age) will be assessed for inclusion in the models as well. Finally, linear mixed models will be conducted to examine changes in 1) barriers to PrEP-related care; 2) PrEP knowledge, 3) PrEP efficacy beliefs; 4) medication beliefs, 5) PrEP attitudes; and 6) medication self-efficacy. Linear mixed models allow us to account for the dependence of the repeated measures. Different covariance structures will be implemented and the information criterion such as AIC or BIC will be used for model selection. We hypothesize that participants randomized to PN will have greater engagement in PrEP continuum behaviors compared to participants randomized to UC. Since data analyses are exploratory, and there is not adequate statistical power to evaluate efficacy of the PN intervention, these tests can only provide information regarding data trends and effect sizes. If the study and PN intervention methods are found to be feasible and acceptable, a larger study with adequate statistical power will be conducted to appropriately evaluate the efficacy of the PN intervention.

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