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Rationale and design of an integrated bio-behavioral approach to improve adherence to pre-exposure prophylaxis and HIV risk reduction among opioid-dependent people who use drugs: The CHRP-BB study

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ABSTRACT

Background: Few primary HIV prevention strategies have successfully integrated both behavioral and biomedical components, with modest HIV risk reduction outcomes among opioid-dependent people who use drugs (PWUD). In response to this unmet need, we developed a brief, bio-behavioral intervention to simultaneously promote PrEP adherence and reduce HIV risk among opioid-dependent PWUD.

Methods: Using a Hybrid Type I implementation science design, we will examine the efficacy of the integrated bio-behavioral, Community-friendly Health Recovery Program (CHRP-BB) compared to a time-and-attention matched control condition among HIV-negative, opioid-dependent PWUD who are prescribed PrEP and enrolled in a methadone maintenance program (MMP) using a randomized controlled trial (RCT). Participants are assessed at baseline, immediately post-intervention (8 weeks) and follow-ups at weeks 20, 32, and 44 post-intervention. The primary outcome is biomedical (PrEP adherence), with secondary outcomes including behavioral (self-reported drug- and sex-related HIV risk behaviors), ongoing drug use (confirmed with urine drug testing), and related domains of the theoretical information-motivation-behavioral skills (IMB) model of behavior change related to PrEP adherence and HIV-transmission-risk reduction. Additionally, we will conduct a process evaluation of delivery/implementation of the intervention to collect valuable information to be used in future implementation.

Conclusions: This study will be among the first prospective trial to test an integrated bio-behavioral intervention to improve adherence to PrEP and HIV risk reduction among opioid-dependent PWUD.

1. Introduction

Although HIV incidence nationally among people who use drugs (PWUD) has decreased, new outbreaks of HIV and hepatitis C virus (HCV) emerging from the volatile opioid epidemic make them a priority population for HIV prevention [1–4]. In the Northeast, where almost half of all new HIV infections occur among PWUD, opioid-related harms, including opioid overdose, are creating a tremendous public health challenge [5]. While various harm reduction programs, including opioid substitution therapy (OST) and syringe services programs (SSP), help reduce the risk of HIV acquisition among PWUD, access to and utilization of these services are sub-optimal (< 10%), due to multiple, predominantly legal and political, restrictions that have blunted prevention, treatment, and care responses for people with opioid use disorder (OUD) [6–9]. The national behavioral surveillance reveals persistent risk behavior engagement in PWUD, with 72% reporting past year receptive syringe sharing or condomless sex [10]. As evident by recent HIV outbreaks linked to PWUD [11,12], the introduction of HIV into networks of PWUD with frequent syringe sharing and sexual risk-taking behaviors is, therefore, a significant concern. This evolving and expanding opioid epidemic, thus, necessitates innovative strategies to improve access to combined harm reduction and HIV prevention services.

Pre-exposure prophylaxis (PrEP), when taken as prescribed, may simultaneously reduce harm from both sexual- and injection-related risk [13–15], but there are little data supporting its use among PWUD in

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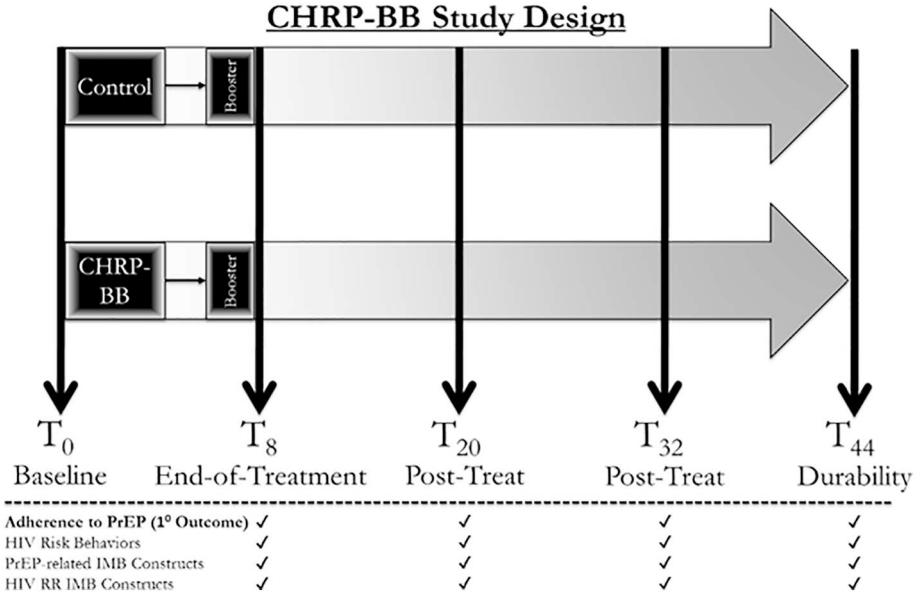

Fig. 1. Overview of the study design.

the US [16]. PrEP scale-up in PWUD has been hampered due to concerns about poor adherence in this at-risk group. Increasingly, research indicates that optimal PrEP adherence may be compromised by high levels of neurocognitive impairment (NCI), a common characteristic of many PWUD. Due to chronic drug use, related lifestyle experiences, and other health challenges [17–27], many PWUD experience NCI to the extent that it impedes medication adherence, HIV risk reduction, and treatment retention [28–32]. For example, our recent findings revealed interaction (moderation) effects between NCI and HIV risk reduction information such that individuals characterized by higher levels of NCI were less likely to benefit from the HIV risk reduction intervention and, hence, were less likely to engage in HIV preventive behaviors [33]. The potentially disruptive impact of NCI must, therefore, be addressed when designing contemporary intervention strategies targeting PWUD.

Issues related to adherence, uptake, and decision-making processes associated with biomedical interventions can be readily accommodated by behavioral strategies that enhance medication adherence and HIV prevention knowledge and skills. To date, however, primary HIV prevention efforts have primarily relied on singular strategies (e.g., either behavioral or biomedical alone) with relatively modest HIV prevention outcomes (e.g., medication adherence, HIV risk reduction) for PWUD [34–37]. Integrating behavioral and medical prevention creates new synergies to optimize outcomes [38]. This combination strategy is especially important when intervening among PWUD with NCI due to the potential decreased effectiveness from PrEP when adherence is suboptimal, thereby necessitating behavioral interventions that emphasize reducing HIV risk and increasing PrEP adherence. Contemporary intervention approaches must also be cost-effective and usable in real-world treatment settings, such as MMP where high-risk PWUD are concentrated and can be readily reached.

In response to this unmet need, we developed a brief, bio-behavioral intervention – now known as the Bio-behavioral Community-friendly Health Recovery Program (CHRP-BB) – tailored for use with PWUD in the context of an MMP. Specifically, we integrated the biomedical component (PrEP) into the Community-friendly Health Recovery Program (CHRP) [39,40]. Briefly, the CHRP is an evidence-based behavioral intervention designed to reduce sex- and drug-related HIV risk behavior among PWUD in treatment. It has been designed for implementation within community-based drug treatment organizations, such as MMP, where large numbers of high-risk drug users routinely participate in treatment [41]. The CHRP-BB intervention also includes specific strategies, such as multimodal presentation of materials, mHealth strategy (e.g., text messaging) and cognitive remediation strategies to enhance PrEP adherence and HIV risk reduction while effectively accommodating those with NCI (*described below*). Results from our pilot work showed excellent feasibility in terms of incorporating the bio-behavioral intervention into the MMP and promising adherence to PrEP and HIV risk reduction outcomes [39,40]. We are now prospectively testing the efficacy of this integrated approach. Thus, the purpose of this paper is to describe our ongoing trial protocol, including aims, design, framework, and evaluation plan.

2. Methods

2.1. Study design

In this trial, we are using a Hybrid Type I implementation design [42] where we are testing the CHRP-BB intervention while gathering additional information on its delivery during the conduct of the efficacy trial and potential for future implementation in similar real-world settings. We are using a randomized controlled trial (RCT) to test the efficacy of the CHRP-BB intervention vs. a time- and attention-matched control condition provided in drug treatment among opioid-dependent patients without HIV. Given the Hybrid Type I implementation design [42], we are also collecting process measures (at multiple time points throughout the trial period) to more precisely understand implementation factors that might influence future scale-up if the CHRP-BB is found to be efficacious. Specifically, we are examining the potential barriers and facilitators to “real-world” implementation of the intervention, what problems are encountered during intervention delivery, and how they might translate to real-world implementation. We describe these findings in order to guide potential modifications to the CHRP-BB intervention to optimize future implementation efforts.

For the efficacy component, we hypothesize that the experimental intervention (CHRP-BB) will be significantly more efficacious than the active control condition in terms of the primary outcome of high levels of PrEP adherence and secondary outcome of HIV risk reduction behavior. In order to test this hypothesis, we are using a two-condition trial design (Fig. 1) in which the standard of care within a methadone treatment program (i.e., being prescribed methadone) *and* being on PrEP remain constant, and the experimental CHRP-BB intervention is being compared to a time-and-attention-matched control condition. Including a comparison condition that provides equal contact with intervention staff and non-overlapping intervention content protect

Table 1
Study activity and measures.

Timeline	Study time point from day of screening (Weeks)													
	-1	0	1	2	3	4	5	6	7	8	9	20	32	44
Study activity														
Screening for eligibility	X													
PrEP eligibility assessment/prescription	X													
Determination of capacity to Consent		X												
Informed consent		X												
BINI		X									X	X	X	X
Randomization		X												
Release of information		X									X	X	X	X
Behavioral skills assessment		X									X	X	X	X
MINI Interview		X												
Text message (PrEP reminder)		X	X	X	X	X	X	X	X	X				
Structured interview														
Sociodemographic characteristics		X									X	X	X	X
PrEP adherence (VAS)		X									X	X	X	X
HIV risk reduction		X									X	X	X	X
Potential covariates		X									X	X	X	X
PrEP adherence assessment														
TDF levels (dried blood spot)		X									X	X	X	X
Pharmacy refill data		X									X	X	X	X
Weekly assessment														
Intervention session			X	X	X	X								
Booster session										X				
Weekly structured interview			X	X	X	X	X	X	X	X				
Urine toxicology		X	X	X	X	X	X	X	X	X	X	X	X	X
Payments	$45	$25	$25	$25	$25	$25	$25	$25	$25	$45	$45	$45	$45	

against differential attrition and demand characteristics and, thus, improve the internal validity of the experimental design.

Participants are being assessed at baseline, immediately post-intervention (8 weeks) and follow-ups at weeks 20, 32, and 44 post-intervention measurement points. This approach will allow us to examine whether outcomes among participants in the CHRP-BB condition are superior to those in the control condition both at the end of the intervention and whether there is a post-intervention benefit. Importantly, this approach will allow us to examine short-term outcomes as well as the decay and emergence of intervention effects. Additionally, we will carry out cost-effectiveness analysis (CEA) of the intervention to understand the potential population-wide health gains and costs of the intervention [43]. This will enable us to precisely examine the relative cost and cost-effectiveness of each condition regarding both individual-(efficacy: e.g., PrEP adherence, HIV risk reduction behavior) and population-level health outcomes (effectiveness: e.g., new HIV infections prevented, life years gained, quality of life) (Table 1).

2.2. Study setting

This study is being conducted at the APT Foundation, Inc., which is the largest addiction treatment program in CT. It provides addiction treatment to 7923 patients per year, including a census of 4723 patients chronically maintained on methadone at five sites within the greater New Haven area, including in jail.

2.3. Ethical oversight

This protocol was approved by the institutional review board at the University of Connecticut and received board approval from the APT Foundation, Inc. This study is registered at ClinicalTrials.gov (NCT03282890).

2.4. Study procedures

2.4.1. Recruitment and screening

Recruitment for the trial started in 2017 and will continue until 2021 at the APT Foundation, Inc. Participants are recruited using clinic-based advertisements and flyers, word-of-mouth, and direct referral from counselors in the methadone clinic. All participants must meet DSM-V criteria for opioid-dependence, be enrolled in methadone treatment, and be HIV uninfected. Additional inclusion criteria include: a) being 18 years or older; b) reporting unsafe injection drug use practices or unprotected sex within (past 3 months); c) having a cell phone; d) being able to understand, speak, and read English; and e) not being actively suicidal, homicidal, or psychotic. Anyone meeting initial eligibility is asked about their interest in PrEP and are then referred to a local PrEP provider of their choice for clinical eligibility screening and PrEP prescription. Those who meet the above criteria and initiate PrEP in the past week are then offered enrollment in the trial.

2.4.2. Informed consent, enrollment, and randomization

After confirming eligibility criteria and providing informed consent, all enrolled participants undergo a baseline assessment and sign a medical release of information (ROI) form, allowing study staff to contact their PrEP provider and pharmacy for information regarding PrEP prescription and refill information, respectively.

After completing the baseline assessment, enrolled participants are randomized (1:1) to receive either: a) 4 weekly group sessions and an 8-week booster session that comprise the experimental CHRP-BB intervention or b) 4 weekly group sessions and the 8-week booster session that comprise the time-and-attention matched control condition. Randomization is stratified by the presence of moderate/severe NCI levels based on the validated brief inventory of neurocognitive impairment (BINI) [44], to ensure that there is an equal proportion of participants with NCI in each condition. Based on our preliminary studies [45,46] and our ongoing NCI screening data, we expect 30–40%

of study participants to meet criteria for moderate-severe NCI. Randomization is performed using a computerized "urn" randomization to ensure fair allocation of women and minorities to each condition. The urn design imposes a balance restriction on the probability of treatment allocation throughout the length of a trial and incorporates probabilities of assignment that adapts according to the degree of treatment balance [47]. The system's computational algorithm automatically adjusts the randomization probability based on the characteristics of all the previously randomized participants, thus minimizing the total covariate imbalance between arms after each new patient is randomized. Efron's biased-coin method [48] is applied to protect allocation concealment with the use of non-extreme randomization probabilities.

Study participants are reimbursed for the time required to complete structured assessments, but not for participating in the intervention (or active control group sessions).

2.5. Intervention procedures

Participants in both conditions receive routine services as part of their enrollment in the MMP, which includes daily methadone and case management consisting of a minimum of one hour of monthly contact with a counselor/case manager.

2.5.1. Experimental condition (CHRP-BB intervention)

The CHRP-BB intervention is based on the information-motivation-behavioral skills (IMB) model [49], which asserts that information, motivation, and behavioral skills are important determinants of health behavior change. Information and motivation work mainly through behavioral skills to influence change in behavior. The model also specifies that information and motivation may have direct effects on behavior change.

Participants assigned to the CHRP-BB: a) receive the standard of drug treatment care (as described above); and b) attend four weekly 50-min HIV risk reduction and PrEP adherence group sessions and one 50-min booster session (at 8-weeks). The group sessions include: *a) Making the most of PrEP as an active health manager; b) Reducing drug risk and taking PrEP; c) PrEP adherence and sex risk reduction strategies; and d) Negotiating partner support for HIV prevention*; and a booster session which is designed to review and maintain PrEP adherence and HIV risk reduction skills as covered in the prior four group sessions (Table 2). The groups use a coping skills training approach to primary prevention and are delivered in a small group modality by two trained intervention facilitators using a motivational enhancement therapeutic style. The delivery approach is designed to accommodate participants with moderate to severe NCI using several strategies: 1) Material for each group is delivered using three modalities: verbal (e.g., didactic presentation of material by counselor and group discussion); visual (e.g., slides, videos, handouts, group responses written on flipcharts); and experiential (e.g., behavioral games, demonstrations, practice exercises); 2) assessment with immediate feedback (e.g., post-group quiz); 3) emphasis on prospective memory (e.g., maintaining routines, developing cues, spaced retrieval); 4) simple language and frequent review of material; 5) structure and consistency (e.g., group agenda, timing of each item on the agenda); 6) stress management (e.g., relaxation exercise); 7) motivation enhancement style (e.g., helping individuals resolve ambivalence about behavior change using principles and skills of motivational interviewing [50]). Additionally, the intervention includes a mHealth strategy (i.e., short messaging service; SMS) delivered through text messaging to help remind participants to take PrEP properly. As such, participants receive daily SMS reminders to take PrEP that are timed to coincide with individual-stated dosing preferences.

2.5.2. Control condition (time-and-attention matched)

Participants randomized to the active control condition: a) receive the standard of care for addiction treatment care (as described above); and b) participate in a time-and-contact-matched, non-contaminating support group modeled after similar psycho-educational groups offered at the methadone clinic. Much like information-based support groups described in the literature, which emphasize sharing treatment and service-related resources and opportunities to gain insight from others' experiences [51], the control condition provides a valuable service to participants. The content for the time-matched standard of care control group has been used as a comparison condition in prior NIDA-funded trials [41]. There is no overlap between the content of the control condition and experimental intervention condition, although the basic structure is the same. Thus, each participant attends four 50-min weekly group sessions and a booster session at eight weeks, led by two trained facilitators. The control condition does not systematically introduce any components contained in the experimental intervention content and does not use the delivery strategies that characterize the CHRP-BB intervention (e.g., motivational enhancement therapeutic style, use of NCI-accommodating strategies). If PrEP/HIV risk reduction topics arise in the control condition, it is due to a natural conversation, and the trained co-facilitators redirect the group discussion. Control group meetings focus on sharing information among participants (e.g., local treatment-related services/resources). These issues are addressed using psycho-educational techniques described in several other supportive interventions [52,53], including the use of handouts and didactic presentations. The four-session topics are: a) *Improving Your Social Support Network* (Session 1); b) *Social Support and Personal Advocacy* (Session 2); c) *Making Community Resources Work for You* (Session 3); and d) *Thinking about Treatment Options* (Session 4). At week 8, a booster session provides a review of the four primary sessions.

Table 2
Outline of the CHRP-BB intervention sessions.

Group topics	Information, Motivation, and Skills Taught	Relationship to IMB Model
1. Making the most of PrEP as an active health manager	• Actively participating in health care; • Improving skills for partnering with health care provider; • Understanding PrEP; Pros/Cons of taking PrEP; • Building PrEP adherence skills	• *Information*: Modules provide relevant information on PrEP and HIV risk reduction • *Motivation*: Increases personal and social motivation to improve adherence to PrEP and HIV risk reduction • *Behavioral Skills*: Self-efficacy and demonstrated skills to improve PrEP adherence and HIV risk reduction
2. Reducing drug risk and taking PrEP	• Identifying drug-related HIV-risks; • Learning about proper needle cleaning; • Managing drug cravings; • Reducing the use of drugs while on PrEP	
3. PrEP adherence and sex risk reduction strategies	• Identifying sex-related HIV risks, • Learning about latex products and their correct use; • Use of latex protection while on PrEP	
4. Negotiating partner support for HIV prevention	• Negotiating the use of latex; • Communicating about PrEP and sex and drug-related HIV risk	

2.6. Intervention fidelity and preventing cross-contamination

We use several procedures to guard against potential threats to internal validity. First, as part of our NIDA-funded work [41,54,55], we have in place a detailed intervention manual that includes session outlines and all other supporting materials needed to conduct the intervention sessions. Second, facilitators complete pre-session checklists and post-session quality assurance forms. Third, we audiotape all intervention sessions to monitor the content and time allocation of intervention sessions. Using procedures from prior and ongoing intervention trials, all sessions are coded for protocol adherence [41,54,55]. Fourth, intervention facilitators meet with the project director and the PI for weekly clinical supervision. Meetings focus on protocol adherence, resolving issues that arise in sessions, and managing potential facilitator "drift." Additionally, when we become aware of relationship partners concurrently enrolling in the study, we force-randomize them to the same condition to avoid cross-contamination and violation of group independence. If we find that relationship partners constitute > 5% of participants, we will include partner status as a factor in our outcome analyses.

2.7. Strategies to maximize recruitment and retention

Based on experience from our prior research and pilot study, several steps have been taken to maximize recruitment and reduce the potential for attrition [41,54,55]. We provide participants wide-ranging options of PrEP-prescribers, including those housed within the MMP, at a local mobile health care center/ SSP, and via their health care provider of choice. We also provide each potential participant with a list of local PrEP-trained providers, as well as step-by-step instructions to help them navigate PrEP care linkage. Additionally, we maintain contact with potential participants while they are being assessed for PrEP and facilitate follow-up appointments. Furthermore, the research team routinely meets with physicians, nurses, and counselors at the MMP as well as local clinics to ensure proper screening of participants as well as smooth operations of all aspects of the study. Finally, in conjunction with the University IRB and the APT Foundation's board, careful consideration was given to the market rate for study participant reimbursement from similar studies in this area in order to ensure that we are respectful of the time required for patients to fully participate and in order to minimize barriers to participation.

Additional strategies include rapid assignment (usually the same day) to study conditions after the provision of informed consent, thorough explanation of study conditions, close monitoring of participants' clinical status, integration of the research with the clinical program, and accessibility to patients of study staff for questions and problems. Participant locator forms, including name, address, phone number, family/friend contact are collected and updated at each visit. We use phone calls between appointments to update information. Research staff, with participant's prior permission, call participants the week before the date of their assessment appointments. We issue appointment cards at each visit for subsequent visits. Furthermore, we reimburse study participants for the time and effort required for them to complete the assessments and have found that to be essential to retention [56]. Based on previous research using similar procedures, we expect to retain approximately 90% of participants over the entire study period (44 weeks).

2.8. Outcome measures

All of the self-report measures are administered using audio computer assisted self-interview (ACASI), an approach documented to reduce self-report biases [57,58] and minimize participant response reactivity [59].

2.8.1. Primary outcome

Adherence to PrEP: This outcome is assessed using a biomedical and behavioral approach: a) Biomedical - A dried blood spot (DBS) test is used to measure tenofovir levels, which is an accurate and precise marker of the extent to which an individual has taken PrEP during the preceding week [60]; b) self-reported adherence (in the last 30 days) using the visual analogue scale (VAS) [61]; and c) pharmacy refill data. This allows us to triangulate PrEP adherence so that we can assess the correlation (r) between biomedical and self-report measures as well as compare with pharmacy refill data.

2.8.2. Secondary outcomes

HIV risk reduction behavior: The HIV risk assessment, adapted from NIDA's Risk Behavior Assessment [62] is used to measure several aspects of HIV risk behaviors in the past 30 days, including a measurement of "any" high-risk behavior (sexual or drug-related) as well as measurements of event-level (i.e., partner-by-partner) behaviors. "Any" risk behavior is dichotomously parsed as those who have engaged in HIV transmission risk behaviors with those of unknown or HIV positive status [49,63]. Event-level data are continuous, analyzed using Poisson regression, and will allow us to examine the magnitude of risk behaviors for a small number of individuals who engage in large numbers of events with unknown and HIV-positive individuals. These measures have been consistently used in our prior clinical trials [54,63,64], confirming high test-retest reliability (0.88 to 0.98) [65].

IMB construct measures: Data collection at all assessment points include measures of IMB model constructs [66] including (a) Information – PrEP- and HIV risk-related knowledge (e.g., PrEP - "*PrEP provides protection against other sexually transmitted infections*"; HIV risk - "*If an HIV+ person only has sex with another HIV+ person, they don't need to use condom*"); (b) Motivation - readiness to change and intentions to change PrEP adherence and HIV risk behavior (e.g., PrEP - "*I think I would be less worried about HIV infection if I were on PrEP*"; HIV risk – "*I plan not to have sex during the next 3 months*"); (c) Behavioral Skills - PrEP adherence skills and risk reduction skills (e.g., PrEP - "*How confident are you that you could make PrEP part of your daily routine?*"; HIV risk - "*How hard would it be for you to always use condoms or latex protection if you have oral, vaginal, or anal sex?*"); and (d) Behavioral Outcomes – PrEP adherence and HIV risk reduction behaviors. Behavioral skills are also assessed as in prior controlled trials [41,67] by having patients demonstrate (a) the specific steps necessary to properly clean a needle/ syringe and (b) demonstrate the specific steps to properly select and apply a male and female condom using replicas.

Urine drug testing (UDT): A four-panel (heroin, cocaine, oxycodone, and benzodiazepine) UDT immunoassay (with confirmation of positive results) are conducted at baseline, weekly during the 8-week intervention phase, and again at post-intervention, and follow-ups to detect the most common illicit substances of abuse in this patient population. UDT results are used to validate the self-report use of substance use.

Potential covariates: A number of covariates are measured to examine the differential impact of some characteristics that might influence outcomes. For example, substance use disorders (M.I.N·I) [68], mental illness (M.I.N.I.) [68], depressive symptoms (CES-D) [69], alcohol use disorder (AUDIT) [70], social support (Medical Outcomes Study Social Support Survey) [71], patient-physician relationships (Trust in Physician Scale) [72], active drug use (urine toxicology screening using the NIDA-4 panel measuring heroin, cocaine, oxycodone, benzodiazepines and marijuana), and NCI [44].

2.9. Statistical analyses

This study is designed to test the primary hypothesis that the experimental intervention (E: CHRP-BB) is significantly more efficacious vs. the control condition (S: time-and-attention-matched intervention), for the primary outcome of high levels of PrEP adherence (e.g., ≥700 fmol/punch or ≥ 4 pills/week) [73,74] and the secondary outcomes

pertaining to HIV risk reduction behavior. The null hypothesis is that CHRP-BB is not superior to control condition, expressed as H_0: $p_E = p_S$, where p_E is the proportion of participants in CHRP-BB who demonstrate high levels of adherence (e.g., ≥700 fmol/punch or ≥ 4 pills/week) [73,74] and are free from HIV risk behavior T_{32} post-intervention. Our alternative hypothesis is that the experimental intervention is superior to the control condition, and is expressed as H_1: $p_E > p_S$. Before analyzing treatment effects, the degree of pre-test equivalence between experimental and control groups on key variables (e.g., baseline demographics and clinical characteristics) will be evaluated. Baseline data will be evaluated via *t*-tests and ANOVAs on continuous items when normal or Kruskal-Wallis when we have a non-normal distribution of those items and chi-square tests of categorical items to evaluate pretest equivalence between and within the experimental and control groups. The presence of moderate/severe NCI will be included as a covariate to control for each of the dependent variables. We will use the Bonferroni approach [75] to correct for alpha inflation with a 0.05 family-wise alpha. Variables in which inequality at baseline is identified will be used as covariates in further analyses to address potential non-equivalence across conditions [76]. Differential attrition analyses will also be conducted on the data set to assess differential attrition by condition between baseline and subsequent measurements. A series of ANOVAs parametric or non-parametric of Condition (intervention, control) by retention on PrEP (retained, not retained) will be conducted on continuous pretest measures [77]. Any variable influencing differential attrition will be included as a covariate in subsequent analyses.

Separate logistic regression models will be used to assess the log odds of having high levels of PrEP adherence and being free from injection or sexual transmission risk behaviors at week 44 post-intervention using intervention assignment as a binary coded predictor while controlling for any potential confounders. As an alternative analytical plan for assessing the impact of the two intervention arms on adherence to PrEP, we will use mean adherence levels over time. For all analyses, intervention assignment will be included in the model as a binary predictor. Because multiple measures of adherence will be taken from each participant over time, adherence will also be analyzed using a mixed effects general or generalized linear model, depending on variables meeting the parametric assumption or not, respectively [78]. There are several strategies by which PrEP adherence will be measured. We will utilize Spearman correlation coefficients and scatterplots to assess relationships between biomedical measure (TFV-DP and FTC-TP concentrations in red blood cells measured via DBS) [73,74,79,80], self-report measure (VAS: visual analog scale) [61], and pharmacy refill data of PrEP adherence.

Growth curve mediation modeling: Based on the IMB model of health behavior change [49], we will assess participants' knowledge, motivation, and behavioral skills related to primary intervention outcomes (e.g., PrEP adherence and HIV risk reduction). Using Mplus [81] and the mediation package from R [82,83], we will test the association between the intervention outcome variables mediated by changes over time in the theoretical IMB model variables, assuming the time points cluster within individuals. The possible mediators will be included in the final model if they show a significant intervention effect when tested as an outcome.

2.10. Sample size and power calculations

Power was computed for effect size (d) of 0.37, a small-medium effect size to be conservative, based on similar intervention studies in similar facilities comparing groups in terms of high levels of medication adherence and changes in HIV risk behavior [41]. The computations assume an intra-class correlation (ICC) of 0.500, as we assume conservatively large dependence within participant over time. Over 44 months, 300 participants taking PrEP and enrolled in MMP will be recruited and randomly assigned to the two study cells (150 per cell). The criterion for significance (alpha) has been set at 0.05. The test is 2-tailed, which means that an effect in either direction will be interpreted. Given these assumptions (for the effect size, ICC), criteria (for alpha and tails), and plans (for the number of clusters and sample size within the cluster), the study will have the power of 98.5% to yield a statistically significant result. These same assumptions (for the ICC), and plans (for the number of subjects and time points within subject) will allow us to report the effect size (d) with a standard error of approximately 0.089. In order to maintain that power level, we must 288 retain patients at post-intervention, 276 at 3-month follow-up, 258 patients at 6-month follow-up, and 224 patients at 9-month follow-up. Even in the event that only 71% of participants complete the final 9-month follow-up assessment, which would be a conservative estimate based on the previous randomized controlled trials in the same facility among the same patient population, the proposed sample size will still provide sufficient power (94.5%) to detect the expected range of effect sizes.

While our previous studies of patients enrolled in MMP have demonstrated high levels of retention in the study, we have a plan to address missing values, either by missing the entire study visit or for certain variables. First, we will use Little's MCAR test to determine if the values are missing completely at random (MCAR). If the variables are MCAR, then we will apply multiple imputation (MI), which is considered robust under such a structure [84]. If not MCAR, then time-dependent outcomes will be measured using generalized estimating equations (GEE), which will overcome some challenges with missing data.

2.11. Potential limitations

First, recruitment for this study is restricted to a single community-based MMP, potentially limiting the generalizability of the findings to PWUD, not in MMP or receiving methadone in other settings. Second, we are relying on self-reported measures of HIV risk behaviors and several correlates of primary outcomes, which may be subject to reporting bias, particularly underreporting risk behaviors. Third, the findings from this efficacy trial will not allow us to distinguish which component of the intervention (e.g., behavioral, biomedical, or mHealth) is making an impact on the outcomes.

3. Implementation science research

As recommended for Hybrid Type I implementation science design [42], we are observing and gathering information on delivery and implementation of the CHRP-BB intervention at multiple time points throughout the trial in order to inform future implementation efforts. In addition, at the end of the trial we will conduct open-ended interviews with relevant stakeholders, including participants, recruitment staff, and medical (e.g., treatment providers and counselors) and administrators/leaders at participating methadone clinics ($n = 10$). We will administer a process measure to assess overall satisfaction and perceived utility of each intervention with regard to organization-level factors (e.g., perceived relevance of intervention components and characteristics to target population needs, the usefulness of intervention to the organization, and barriers to intervention implementation as designed). These questions will be designed to elicit feedback about the potential barriers and facilitators to implementing the CHRP-BB intervention - as currently designed - in terms of issues ranging from specific intervention components to the more general organizational dynamics (e.g., time/resource constraints). The process evaluation will provide a nuanced understanding of the intervention effects, intervention fidelity, barriers, and facilitators to the intervention implementation, and refinement needed to maximize implementation success in the real-world setting. All data obtained from study participants, co-facilitators, and treatment providers will then be used to systematically develop intervention refinements for future implementation in various clinical settings.

4. Summary

The ongoing trial will be among the first to test the efficacy of an integrated bio-behavioral approach to improve PrEP adherence and primary HIV prevention among opioid-dependent PWUD. This research is especially crucial, given the disproportionate burden of the HIV epidemic among PWUD and the existing gap in primary HIV prevention efforts targeting this underserved group. If found to be efficacious, the CHRP-BB intervention can be rapidly disseminated as a primary HIV prevention model for implementation within common drug treatment programs – a true integration of HIV prevention science and drug treatment services.

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