Title: Buprenorphine Treatment at syringe exchanges to reduce opioid misuse and HIV risk
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Study Protocol

Title: Buprenorphine treatment at syringe exchanges to reduce opioid misuse and HIV risk

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I. Overview and Specific Aims:

The goal of this research is to change the paradigm of addiction treatment by starting opioid use disorder (OUD) treatment in community settings frequented by opioid users, instead of relying on referral to treatment facilities. In 2014, of the 2.5 million Americans in need of treatment for OUD, fewer than 490,000 were admitted to treatment facilities, leaving a large treatment gap.[1,2] Barriers to OUD treatment are often structural, including health system fragmentation, costs, and stigma toward people who use drugs in traditional medical settings.[3-8] Buprenorphine maintenance treatment (BMT) may be offered in diverse settings addressing some structural barriers; however, after buprenorphine became available in the US, up to 80% of those with OUD remained out-of-treatment.[9] BMT reduces illicit opioid use, HIV risk behaviors, and opioid overdose, which makes BMT engagement critical to address the consequences of opioid use, including overdose deaths and HIV transmission. This project will bring BMT directly to out-of-treatment opioid users reducing barriers to care.

The objective of this study is to test the effectiveness and safety of initiating buprenorphine treatment onsite at syringe exchange programs. In 2013, there were 204 syringe exchange programs (SEPs) in the United States and Puerto Rico, distributing 46 million syringes, and at least 80% of SEP participants report use heroin or other illicit opioids.[32] Our research group has years of experience studying attitudes of SEP participants and working with SEP staff.[10] We found that most opioid-using SEP participants express interest in BMT, but experience structural barriers to BMT -- most commonly, not knowing where to go for treatment.[5,11-13] Therefore, we trained SEP staff to facilitate linkage to BMT for participants who were interested in treatment, but this did not increase BMT engagement.[14] However, most SEP participants reported that they would prefer to receive BMT onsite at SEPs instead of referral to addiction treatment facilities or medical clinics.[15] Thus, based on formative data and experience, we propose to initiate BMT onsite at SEPs before transferring care to a community health center (CHC) for maintenance treatment.

In a 24 week RCT based in a large urban area with high rates of OUD and HIV, we will recruit 250 out-of-treatment opioid users who utilize syringe exchanges and randomize 1:1 to O-BMT or enhanced referral. Over 2 weeks, participants in the O-BMT arm will see a buprenorphine provider twice, receive weekly medication, and then their care will be transferred to a CHC for maintenance BMT. In the control arm, participants will receive enhanced referral to the CHC for maintenance BMT. Data collection will include urine drug tests, questionnaires, and medical and pharmacy record review. We will study rates of *BMT engagement* (defined as receiving BMT at 30 days following randomization), treatment outcomes (opioid use, HIV risk behaviors), and programmatic service utilization and costs to establish effectiveness and economic viability. We will assess buprenorphine diversion by using electronic monitors that measure medication adherence, testing urine samples for buprenorphine, and through sequential surveys regarding buying or selling illicit buprenorphine. We will also explore changes in self-efficacy and quality of life in both study arms. Our specific aims are:

1. To test the **effectiveness** of initiating onsite buprenorphine treatment at syringe exchange programs.
Hypothesis 1: More participants randomized to O-BMT (vs. referral) will be engaged in BMT at 30 days.
Hypothesis 2: Reductions in opioid use (on self-report and weekly urine drug testing) will be greater among participants randomized to O-BMT (vs. referral) over 24 weeks of follow-up.
Hypothesis 3: Reductions in HIV risk behaviors will be greater among participants randomized to O-BMT (vs. referral) over 24 weeks of follow-up.

2. To test the **safety** of O-BMT by determining the frequency of buprenorphine diversion.
Hypothesis 4: Diversion of buprenorphine during the 24 weeks of follow-up will not be significantly greater among participants randomized to O-BMT (vs. referral).

3. To determine the **cost effectiveness** of O-BMT by comparing costs and health service utilization between study arms.
Hypothesis 5: O-BMT will be cost-effective according to commonly accepted thresholds.

II. Background

Most Americans with OUD remain out-of-treatment. Rates of opioid use, disorder, and overdose have skyrocketed over the past decade. In 2014, of the 2.5 million Americans in need of treatment for opioid use disorder (OUD), fewer than 490,000 were admitted to addiction treatment facilities, leaving a large treatment gap.[1,2] Buprenorphine maintenance treatment (BMT) was approved in the United States in 2002 with the goal of improving access to treatment. BMT may be offered in diverse medical settings, addressing the stigma of attending addiction treatment programs and increasing the number of locations where opioid use disorder treatment is available;[16-20] however, despite BMT availability, 80% of those with OUD remained out of treatment in the United States through 2013.[9] Therefore, there is a large and increasing population of out-of-treatment opioid users (approximately 1.9 million), but with thirty-eight states having more than ¾ of their opioid treatment programs operating above 80% capacity, new treatment venues will be necessary.[21,22]

Efforts needed to engage out-of-treatment individuals. After buprenorphine became available, between 2003 and 2013, OUD treatment utilization remained low (<20%) with minimal change.[9] Instead of recruiting out-of-treatment opioid users, early BMT models may have encouraged methadone patients to change to BMT. Between 2007-9 in a large Medicaid population, rates of OUD treatment increased, and buprenorphine prescriptions doubled, but overall utilization of agonist medications (i.e, buprenorphine and methadone) did not change.[23] White race, insurance type, and living in areas with more waivered physicians have been associated with receiving BMT, but more marginalized groups may remain out of care.[24-26] Barriers to OUD treatment are often structural, including health system fragmentation, costs, and stigma in medical settings toward people who use drugs.[3-7,27] Thus, structural interventions are needed to improve engagement.

Syringe exchange programs (SEPs) reach a high-risk, out-of-treatment population. Emergency departments, hospitals, and correctional facilities have been targeted as novel sites for BMT initiation because they frequently encounter out-of-treatment opioid users who need linkage to treatment.[28-31] Likewise, SEPs, which provide sterile syringes and other health-related services to PWID, are important locations to target. In 2013, there were 204 known SEPs in 33 states, Washington DC, and Puerto Rico, distributing 46 million syringes, and at least 80% of SEP participants report using heroin or other illicit opioids.[32-34] Recently, states that have opposed syringe exchange have changed laws to allow SEPs, and programs in high-risk areas

like rural appalacia are developing best practices.[35] SEP participants have greater drug use and HIV risk behaviors than other PWID; however, many are unwilling or unable to access traditional medical services.[5,33,36] Because SEPs reach a high-risk population, others have studied linkage to addiction treatment, but with referral alone as few as 9-16% enroll in opioid agonist treatment.[37,38] *Importantly, structural interventions, focusing on on case management or financial assistance, appear to be more promising than behavioral interventions, such as motivational enhancement therapy, to improve linkage to treatment*.[37-40] However, none of these interventions have become standard practice at SEPs. BMT regulations allow for prescribing from diverse settings, including SEPs, which means that initiating BMT from SEPs is possible and could increase engagement in OUD treatment.[41] Small pilot programs have implemented BMT at SEPs or provided outreach to SEPs with a mobile clinic, which supports feasibility of this approach (see below).[42-45] Thus, in order to address structual barriers to care and facilitate initiation of BMT, we propose to bring BMT directly to SEP participants and rigorously investigate an onsite model of BMT at SEPs.

Pilot programs have demonstrated that onsite treatment is feasible. Descriptions of three BMT pilot programs at SEPs have been published. In New York City, a single physician assessed SEP participants for interest in BMT, substance use and co-morbidities, gave instructions for home induction, and prescribed one week of medication with a follow-up appointment after one week. At the follow-up appointment, the physician made dose adjustments, referred for psychosocial support, and continued to see the patient every 1-2 weeks. Treatment retention was 68% at 3 months and 42% at 12 months, but self-reported drug use, urine drug testing, and diversion of medication was not reported.[42] In Los Angeles, heroin-using SEP participants were offered a 15-day onsite buprenorphine treatment protocol where medication was dispensed twice weekly. Participants were also provided with psychosocial counseling and support. Of 9 participants in the pilot, 7 completed the protocol, and 3 (33%) were transferred to a maintenance treatment program.[43] In New Haven, a mobile medical clinic provided BMT to SEP participants, including both induction and maintenance treatment. By 2006, more than 166 PWID were engaged using this model, but long-term outcomes were not reported.[45]

Theoretical framework of health service utilization. The Behavioral Model for Vulnerable Populations is commonly used to explain health seeking behaviors and predict health outcomes of vulnerable populations, including PWID.[46] According to this model, predisposing, enabling, and need components will predict BMT utilization, which in turn will predict health outcomes. The model is useful in health services research, because factors that contribute to vulnerability may impede service utilization and should be considered as predisposing or enabling factors. Figure 1 outlines the components of the model that are relevant to this proposal. As illustrated, our target population is likely to have many predisposing factors that affect health behaviors and outcomes, including minority race/ethnicity, criminal behavior, substance use,and mental illness. Enabling factors are resources that facilitate OUD treatment, including insurance, transportation, ability to negotiate complex systems, and access to BMT providers. Need factors are determined by individuals' perceived and evaluated health care needs. In an environment with adequate insurance (i.e., Medicaid), transportation (i.e., public transportation), and access to BMT providers (see section D.3), our structural intervention of onsite treatment, is predicted to increase BMT initiation and engagment. The enabling factor of onsite treatment will allow participants to initiate BMT when they are ready, instead of finding a provider, scheduling and waiting for an appointment, completing paperwork, and then waiting for assessment – potentially while in withdrawal. Of previously described barriers to BMT, health system fragmentation, waiting times, and fear of discrimination in medical settings can addressed

through onsite treatment.[45] This enabling factor will help participants meet their perceived health needs (i.e., need for OUD treatment), which will have a positive effect on health outcomes.

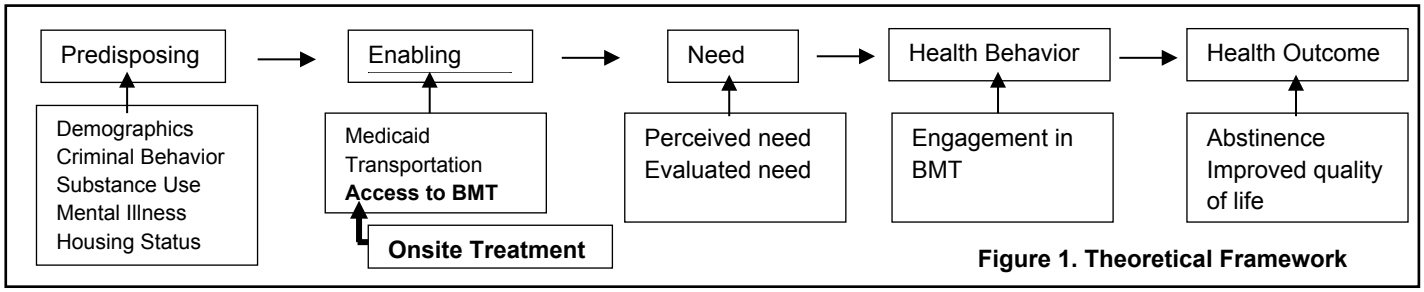


Figure 1. Theoretical Framework

Concerns about buprenorphine diversion are common, but data are lacking. Diversion, meaning that patients who are prescribed buprenorphine (including buprenorphine-naloxone) give or sell the medication to others who are not engaged in treatment is a major concern for prescribers and policy makers.[47-50] Those taking diverted medication may be "self-treating" withdrawal symptoms, which is common among PWID, or seeking euphoric effects.[48,51-56] Buprenorphine-naloxone is more commonly prescribed than buprenorphine alone, because the naloxone may reduce abuse potential.[57] Buprenorphine is a partial opioid agonist that is unlikely to cause euphoria among individuals with high levels of opioid tolerance when taken sublingually. However, it can be adulterated and injected for euphoric effects. The naloxone in the combination product is unabsorbed when take sublingually, but it is more bioavailable if injected and will provide antagonism at opioid receptors.[58] Therefore, PWID are unlikely to seek diverted buprenorphine-naloxone to inject for euphoric effect; however, they could divert medication to others posing a public health risk.[48,51,59] Making BMT available at SEPs, where there is active drug use, could increase risk of diversion; however, it could also address an unmet need for treatment. In 2013, we found that among 102 SEP participants, 57 had taken diverted buprenorphine, and this was most common among those with barriers to BMT.[13] In focus groups, SEP participants directly reported that they took diverted buprenorphine due to insufficient access to BMT.[5] Other studies have found inadequate BMT access as a risk factor for using diverted buprenorphine.[51,60] *Therefore, onsite BMT at SEPs could also paradoxically reduce diversion*. There are also other important areas that require inquiry. Though 35-100% of BMT patients initiating treatment have reported taking diverted buprenorphine, estimates of how many BMT patients divert their own medication to illicit markets are limited.[56,59,61,62] Among inmates enrolled in trials of BMT initiation prior to jail or prison release, 10-20% were removed from the trials for attempting to divert their medication;[28,29] however, data relevent to community BMT patients are needed to inform clinical practice and policies regarding buprenorphine prescribing (e.g., establishing monitoring guidelines).

Measuring diversion. There are no standard measures to assess buprenorphine diversion, but we will draw upon a robust adherence literature related to HIV and other chronic conditions. Electronic monitors measure adherence most accurately.[63] Wisepill electronic monitors can measure the time when participants remove their dose from the Wisepill monitor.[64] Prior studies have mostly relied on self-report of diversion, while one study attempted to quantify diversion by testing parolees' urine samples for buprenorphine.[50] Estimating diversion solely based on collected urine has major methodologic limitations, though. The investigators did not know whether subjects had been prescribed buprenorphine, and examining those taking diverted buprenorphine does not answer questions about the amount of prescribed buprenorphine that BMT patients divert to others. Electronic monitors will allow us to study whether medication is taken at prescribed intervals, supplementing self-report and urine drug testing data. Improving methods to detect buprenorphine diversion could also improve the safety of office-based BMT.

Summary. Rates of opioid use, disorder, and overdose have skyrocketed over the past decade. Injection drug use continues to be an important risk factor for HIV transmission. The majority of Americans with OUD remain out-of-treatment. Syringe exchange services are increasingly offered in areas with high rates of OUD. Pilot programs offering BMT at SEPs support feasibility, but effectiveness, safety, and cost-effectiveness of onsite treatment is unknown. Addressing the opioid epidemic will require increased access to and uptake of OUD treatments. Onsite BMT at SEPs holds promise in reaching a high-risk out-of-treatment population.

III. Research Design and Methods

Overview of study approach. In a 24 week RCT based in a large urban area with high rates of OUD and HIV, we will recruit 250 out-of-treatment opioid users from SEPs and randomize 1:1 to onsite BMT initiation (**O-BMT**) or enhanced referral. Over two weeks, participants in the O-BMT arm will see a buprenorphine provider twice, receive prescriptions of medication, and then their care will be transferred to a community health center (CHC) for maintenance BMT. In the control arm, participants will receive enhanced referral to a CHC for initiation and maintenance BMT. We will assess participants with urine drug tests, questionnaires, and medical record review studying treatment engagement, treatment outcomes (opioid use, HIV risk behaviors) and programmatic service utilization in order to establish effectiveness and costs. We will also assess buprenorphine diversion using electronic monitors, urine drug testing, and sequential surveys.

Setting. A. New York Harm Reduction Educators (NYRHE) is the largest harm reduction agency in New York City with over 35 staff members and serving over 5000 clients annually. At two community-based offices and 11 street-side locations, NYHRE provides participants with syringe exchange; referral for medical, dental and addiction treatment; and other supportive services. The majority of NYHRE's clients are Hispanic or black, male, 40-49 years old, and PWID. Diverse staff members (case managers, outreach workers, and syringe exchange staff) have received training on BMT. O-BMT will be offered at community-based offices only.

B. Washington Heights CORNER Project (WHCP) is another harm reduction agency situated in an area highly affected by OUD and HIV. At its community-based office, WHCP provides clients with syringe exchange; referrals for medical, dental, or addiction treatment; and other supportive services. WHCP serves over 1500 clients annually with similar characteristics as NYHRE. WHCP staff members have received training on BMT.

C. BOOM!Health Is a harm reduction agency located in the South Bronx that now delivers a full range of prevention, syringe access, health coordination, behavioral health, housing, legal, advocacy and wellness services to over 8,000 of the hardest to reach communities in the Bronx, New York. BOOM!Health strengthens efforts to remove barriers to accessing medical care, with particular emphasis on HIV and viral hepatitis prevention and care services. BOOM!Health has private space for medical assessment and staff have experience with referrals to buprenorphine treatment.

Montefiore's Community Health Center (CHC) will serve as a referral source for the study. The CHC offers primary and specialty care to over 15,000 adult patients annually and has worked closely with SEPs to facilitate referral of clients with HIV, HCV, or OUD.[10] The CHC has provided BMT to more than 1000 patients since 2006 and has been used extensively for BMT research.[65-70] There are 11 general internists who are waivered to provide buprenorphine and a clinical pharmacist coordinator who receives referrals. The CHC has assisted in recruitment and retention of study subjects, and electronic medical records can easily be extracted to ascertain study outcomes. The CHC is representative of those serving low-income

urban neighborhoods; over 65% of patients have public insurance and most live in the surrounding neighborhoods, which are 57% Hispanic and 39% non-Hispanic Black, and remain devastated by drug use and HIV.[71]

Participants. *Eligibility criteria*: 1) age ≥ 18 years; 2) opioid use disorder by DSM-V criteria; 3) interest in BMT; 4) motivation for OUD treatment; and 5) willingness to accept CHC referral. *Exclusions*: 1) receiving opioid agonist treatment in the past 30 days (confirmed by NY Prescription Drug Monitoring Program); 2.) inability to provide informed consent; 3) unstable mental illness (e.g., suicidality, psychosis, etc.); 4) severe alcohol use disorder or benzodiazipine use disorder by DSM-V criteria; 5) hypersensitivity to buprenorphine or naloxone; or 6) pregnancy (confirmed via urine testing). In our BMT program,[65] transaminase elevation (5X upper limit of normal) limited buprenorphine treatment in <1% of patients, therefore we will not draw blood to assess liver function prior to study enrollment.

Recruitment. Staff members at the SEPs will receive training on BMT (buprenorphine education and referral to the CHC).[14] Active recruitment will occur by staff members discussing BMT with participants and contacting a research assistant (RA). Passive recruitment will occur by posting study flyers at study sites and asking study partcipants to recommend other acquantainces for the study.

Screening procedures: The RAs will screen all participants for exclusion and inclusion criteria. A diagnosis of opioid use disorder and exclusions (unstable mental illness, alcohol use disorder, benzodiazepine use disorder) will be established by applying the Mini International Neuropsychiatric Interview (MINI), a widely used psychiatric structured diagnostic interview instrument for unstable mental illness and Post Traumatic Stress Disorder and the DSM-V checklist for opioid, alcohol and benzodiazepine use disorder. For this assessment (for both alcohol and benzodiazepines), there are 11 questions asked, if the participant answers with a Yes to 2-3 of these questions, their use severity will be assessed as Mild, if they score a 4 or 5, their severity use will be assessed as moderate if they score 6 or greater, their severity will be considered Severe. Interest in BMT and motivation for treatment will be established with previously published measures.[12,73] In addition, the PCL-5, PTSD Checklist for DSM-5 and the Life Events Checklist for *DSM-5* will be conducted. Women of childbearing age will be screened with a urine pregnancy test.

Randomization: An RA will meet with eligible participants at the SEPs to describe the study. At enrollment, written informed consent including a consent quiz to monitor comprehension will be obtained, including a release for medical records. Randomization will be stratified by site (A, B or C, occur in blocks of 4-8, with 1:1 allocation of O-BMT vs. referral.

Participant tracking: To facilitate tracking participants over the 24 week follow-up period, we will use procedures that we developed to retain people who use drugs in our previous research studies, in which we have had an 84% retention rate over 6-month follow-up.[74] Locator Forms will list information about: 1) participants' address and phone number; 2) contact information of participants' family members, friends, case managers, physician, pharmacy, and drug treatment program; and 3) locations where participants hang out.

Protocol for O-BMT. This study will build off of this infrastructure at the SEPs for clinical care by adding a trained, buprenorphine-waivered physician or physician's assistant to initiate BMT during two

Table 1. Description of study arms

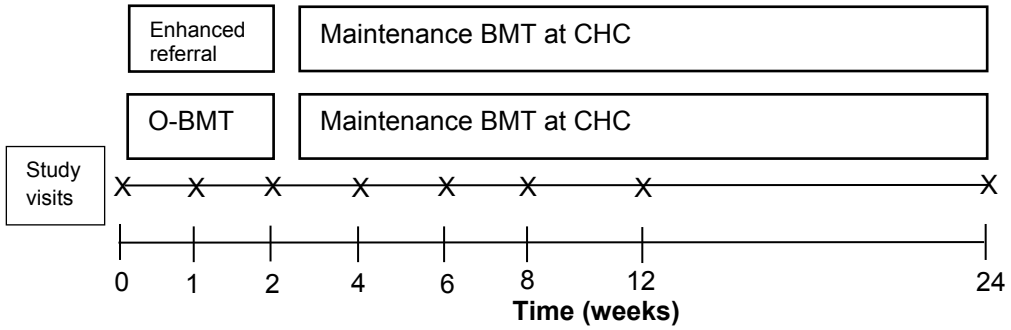
	O-BMT	**Waitlist**
Site of initiation	SEP	CHC

Site of maintenance	CHC	CHC
Type of referral	Staff-facilitated	Staff-facilitated
Primary Outcome	Engagement	Engagement
Assessment for diversion	Wisepill Technologies medication adherence + Urine Tests + Questionnaires	Wisepill Technologies medication adherence + Urine Tests + Questionnaires
Onsite program service utilization	Provider + Transfer	Enhanced Referral
SEP = syringe exchange program; CHC = community health center		

half-day sessions weekly. Participants will be registered as CHC patients to ensure continuity of care. For example, the provider will document encounters in the CHC's electronic health record via a web-based portal and patients will be able to access medical advice during off-hours through the CHC (see Human Subjects). Participants will be prescribed BMT from the SEP and then staff members will facilitate transfer a CHC for maintenance treatment. Details are presented below and in Table 1.

Initiation. Over two weeks, participants will see the study provider twice onsite at the SEP. The first visit will include: assessment of opioid use disorder, contraindicactions to BMT, and co-morbidities; instructions for initiating treatment; prescription for one week of medication (buprenorphine-naloxone provided by prescription and transferred by patient to a Wisepill Technologies Medication Adherence Tracker); and planning for one week follow-up. Participants will start taking medication at home, which is safe, effective, and a standard practice.[75-78] Participants will be prescribed 4-16 mg of buprenorphine daily based on their withdrawal symptoms following a standard algorithm. After one week, the study provider will make dose adjustments, provide another prescription for one week of medication (second prescription), and arrange for linkage to the CHC for maintenance BMT. The SEP staff will provide psychosocial support between visits and facilitate transfer of care to a CHC as specified in pre-intervention training.. Participants who do not pick up their second prescription within 14 days will not be eligible to repeat O-BMT procedures, but they still may be referred to the CHC for maintenance BMT.

Figure 2: Study arms



Maintenance. After two onsite visits with the study provider, BMT will be transferred to a CHC via enhanced referral. The CHC will guarantee access to a BMT provider within one week (see Letters of Support) and research staff will assist with scheduling appointments. Physicians at the CHC are experienced treating OUD and will provide standard BMT (weekly visits at initiation, change to monthly visits with clinical stability, urine drug testing, psychosocial counseling) according to a written protocol (see appendix 1.). Participants will receive reminder calls the day before their appointment.

Risk mitigation strategy for participants who take sedatives: Clinical decisions regarding BMT dosing, treatment continuation, and referral for additional psychosocial treatments will be based on the clinical judgement of BMT providers (i.e., buprenorphine-waivered physicians). Consistent with FDA-guidance,

physicians will provide the following aspects of care to participants who are taking benzodiazepines or other sedatives (including alcohol):
• Education about the serious risks of combined use, including overdose and death, that can occur with CNS depressants even when used as prescribed, as well as when used illicitly.
• Developing strategies to manage the use of prescribed or illicit benzodiazepines or other CNS depressants when starting BMT.
• Tapering the benzodiazepine or CNS depressant to discontinuation if possible.
• Verifying the diagnosis if a patient is receiving prescribed benzodiazepines or other CNS depressants for anxiety or insomnia, and considering other treatment options for these conditions.
• Recognizing that patients may require BMT indefinitely and their use should continue for as long as patients are benefiting and their use contributes to the intended treatment goals.
• Coordinating care to ensure other prescribers are aware of the patient's buprenorphine treatment.
• Monitoring for illicit drug use, including urine screening

If the risks of BMT outweigh the clinical benefits, participants will be referred to an opioid treatment program for care and treatment.[108]

Rationale for 2 week intervention. The goal of this intervention is to encourage BMT engagement, which we expect to increase from initiating pharmacotherapy. Drop out from BMT is most pronounced in the first week of treatment, but SEP staff will be available for psychosocial support throughout this time.[75,79] Starting treatment at home does not increase dropout from treatment.[67,77] After BMT initiation, linkage from community-based settings to primary care is feasible.[80] We considered continuing BMT onsite for longer than two weeks to accommodate participants who are comfortable with SEP staff but uncomfortable in traditional medical settings;[3,4] however, there are potential benefits to transfering care. Maintance BMT at SEPs could expose participants to cues of drug use, which may trigger opioid craving;[81] transfer to a CHC may improve access to medical services (mental health counseling, HIV treatment, etc.);[82] and segregating care of PWID outside of the traditional health care system risks entrenching "separate and unequal" care.[33]

Assessment of buprenorphine diversion. We will assess buprenorphine diversion in three ways. For the first two weeks of treatment in both study arms, electronic monitors will be used enabling us to monitor medication adherence in real time. Participants will be incentivized to return electronic monitors, thereby strengthening the assertion that they did not sell or give away an entire pack. We will ask participants directly about selling their buprenorphine through sequential surveys. Audio computer-assisted self-interview technology through REDcap (see below) may reduce social desirability bias in reporting stigmatized behaviors, and prior studies of medical marijuana diversion have detected high rates of diversion through self-report.[83-85] Additionally,all participants will have urine samples tested to confirm presence of prescribed buprenorphine.

Control: Enhanced referral to BMT. The control condition will be enhanced referral to a CHC for initiation of BMT and maintenance treatment. Similar to O-BMT, the research staff will facilitate linkage to care. Participants will receive an expedited appointment within 1 week of the referral and a reminder phone call the day before their appointment. If participants do not attend their first appointment at the CHC, enhanced referral procedures will be repeated as long as the request occurs within two weeks of study enrollment (in parallel with the timing of O-BMT). We will assess fidelity to these referral procedures (see below). Buprenorphine providers at the CHC will follow the same procedures for BMT initiation as provided in O-BMT: assessment for OUD and co-morbidities, instruction on starting treatment at home, weekly electronic medical adherence monitors for two weeks with 4-16 mg of buprenorphine, dose adjustment after one week, and then monthly visits. Providers at the CHC will receive instruction on study procedures before commencing the trial, and procedures will be reviewed at monthly buprenorphine provider meetings at the CHC (see Letters of Support).

Training the SEP staff. Referral to addiction treatment and psychosocial support are standard services provided by the SEPs. Prior to enrolling participants, we will enhance services by providing 3 hours of training

on BMT eligibility and procedures for making appointments and reminder phone calls. We have provided these trainings to SEP staff and peer mentors with good acceptability and fidelity to procedures.[14]

Methods common to all aims. We will assess for BMT engagement (at 30 days), treatment outcomes (illicit opioid use and treatment retention), HIV risk behaviors, buprenorphine diversion, programmatic costs and service utilization, and participant attitudes over the study period.

Research Visits: An RA will meet with all participants at enrollment and after 1, 2, 4, 6, 8, 12, and 24 weeks have elapsed. Research visits will occur in private at the SEP office or CHC and participants will receive a $10 Clincard payment (weeks 1, 6) or a $25 Clincard payment (weeks 0, 2, 4, 8, 12, 24) compensation. Interviews and urine samples will be collected at each study visit. Medical records will be extracted at the completion of the study.

Data sources and measures: A complete list of measures is presented in Table 2.

Medical Records: We will extract medical record data from the CHC, including prescription and visit information to assess *treatment engagement* and *retention in care*. Prescription data will include information both from the electronic medical record (prescriptions) and the NY Prescription Drug Monitoring Program (medications dispensed). As mandated by law, the later source includes all controlled substances dispensed by all pharmacies in New York State. Prescription data will include medication name, strength, directions, number of pills, number of refills, date of prescription, prescriber, and date medication was filled. Visit data will include date of visit, and provider. If participants request referral to a different site for BMT or are transferred to an alternative form of OUD treatment (e.g., methadone maintenance), we will request medical records using the signed, HIPAA-compliant release for medical records.

Urine Drug Testing: All research visits will include urine collection, which will be tested for buprenorphine, opiates, oxycodone, methadone, cocaine, methamphetamine and benzodiazepines.

Table 2. Timing and delivery of intervention and study measures

Measure	**Study Instrument**	**Assessment Period (week)**							
		0	**1**	**2**	**4**	**6**	**8**	**12**	**24**
Urine Drug Tests									
Opioid use	Urine Drug Testing	x	x	x	x	x	x	x	x
Questionnaires									
Sociodemographic information	BHIVES Study[66]	x							
HIV Risk Behaviors	RBS[86]	x		x				x	x
Self-reported drug use	Addiction Severity Index[87]	x			x		x	x	x
Depressive Symptoms	CES-D[88]	x		x				x	x
Self-efficacy	DTCQ-8[89]	x		x				x	x
Quality of Life	EQ-5D[90]	x		x	x		x	x	x
Patient satisfaction	PCBSS[91]			x				x	

Motivation for treatment	SOCRATES[73]	x		x				x	
Stigma and Discrimination	Ahern et al.[92]	x						x	x
Buprenorphine Diversion	MGH Medication Questionnaire			x	x		x	x	x
Non-study resource utilization	Non-Study Resources Form	x			x		x	x	
Criminal justice resource utilization	Criminal and Legal Activities Form	x			x		x	x	
PTSD symptoms	PCL-5				X		X	X	X
Traumatic reexposure	LEC-5				X		X	X	X
Medical Record Review									
Treatment engagement	-	30 days							
Retention in care	-	3 month, 6 month							
RBS = HIV Risk Behavior Survey; CES-D = Center for Epidemiologic Studies Depression Scale; DTCQ-8 = Drug-Taking Confidence Questionnaire, 8 item version; EQ-5D = EuroQol 5D-5L; PCBSS = Primary Care Buprenorphine Satisfaction Scale; SOCRATES = The Stages of Change Readiness and Treatment Eagerness Scale									

Questionnaires: Using the survey feature on REDcap which plays an audio recording of questions as it displays the question on a computer screen, will be used by the RA to administer questionnaires. Interviews will assess for sociodemographic information, motivation for treatment, HIV risk behaviors, buprenorphine diversion, and other variables (see below). Interviews will last 45-60 minutes.

Electronic medication adherence monitors: Wisepill electronic monitors will be used allowing us to monitor if and when medication is taken. Participants will receive a prescription for buprenorphine. After receiving the prescription, research staff will supervise the patient as they place their medication into the Wisepill Medication adherence monitors. Each time the device is opened it sends a signal to a password protected database.

Fidelity of referral: The SEP staff will follow identical procedures for referral or transfer of care to a CHC. We will not be able to blind participants or staff to study allocation. Therefore, we will record the number of appointments and reminder phone calls performed in each arm to ensure that SEP staff members are not providing differential effort in facilitating referral to a CHC.

Main outcome variables: *Aim 1: Primary outcome (efficacy)*: we will use a dichotomous measure (yes/no) of **BMT engagement** defined as having an active buprenorphine prescription at 30 days after randomization.[30] Secondary outcome measures assessed at 24 weeks will include: proportion who filled a prescription for BMT, total weeks prescribed BMT, and time to BMT initiation (all continuous measures).

Aim 1: Secondary outcomes (efficacy): a.) **Illicit opioid use**: We will check urine drug testing at each research visit and use the Addiction Severity Index (ASI) to assess self-reported substance use.[87] We have adapted the ASI to also assess use of illicit buprenorphine.[13] We will report the following continuous measures in each study arm: the percentage of urine drug tests that are positive for illicit opioids (opiates, oxycodone, methadone, illicit buprenorphine), self-reported days of illicit opioid use, and percent of participants achieving *opioid abstinence*, defined as no illicit opioid use based on self-report and urine drug testing.

b.) **Retention in treatment**: For participants initiating BMT, we will determine whether they are retained in treatment at three and six months following initiation (dichotomous measure). We will define retention as having a medical visit and active buprenorphine prescription each month after BMT initiation. We will also determine the proportion of days following BMT initiation that participants had an active prescription in order to detect lapses in treatment (continuous measure).

c.) **HIV risk behaviors**: We will determine changes in drug-related HIV risks using the HIV Risk Behavior Survey – a validated, well-studied instrument that documents injection and sexual behaviors over the previous 30 days. This instrument has been studied among out-of-treatment PWID and BMT patients.[86,93] As previously reported, we will create a dichotomous measure (yes/no) of injecting risk based on self-report of at least one risk behavior (sharing syringes, not using bleach to clean syringes, sharing cookers, or front/back loading of syringes).[93] Individual risk behaviors will be explored individually.

Aim 2: Primary outcome (safety): We will use a dichotomous measure (yes/no) of **buprenorphine diversion** for all participants to determine how many sell or give away prescribed medication. We will define diversion as having at least one problem behavior over the 24 weeks: non-adherence to prescribed medication on electronic monitoring, self-reported diversion, or a urine sample consistent with diversion. Adherence will be determined weekly with Wisepill adherence for one week equaling X/7Y, where X = number of openings in one week and Y = number of doses prescribed per day. For the composite measure, non-adherence will be considered < 90% adherence. We will adapt the MGH Medication Questionnaire, which assesses misuse of prescribed medications, including selling medication, letting others take prescribed medication, or taking medication to get “high”. For the composite measure, self-reported diversion will be defined as an affirmative response to the question, “In the past 2 weeks , have you sold your buprenorphine to others?” We will also test each urine sample for buprenorphine, and if absent among participants prescribed BMT, the urine sample will be considered consistent with diversion. Each behavior will also be explored individually.

Aim 2: Secondary outcomes (safety): We will also report illicit buprenorphine use (i.e., buprenorphine detected in urine samples of participants who are not prescribed BMT), and determine changes in illicit buprenorphine use from baseline to study completion among participants in each study arm.

Aim 3: Primary outcome (incremental cost-effectiveness ratio, ICER): The ICER will be calculated by dividing the incremental mean cost of the O-BMT arm relative to the control arm by the incremental mean effectiveness of the O-BMT arm relative to the control arm (instruments used to measure costs and effectiveness are described in detail below). The primary economic effectiveness outcome will be the quality-adjusted life-year (QALY), a measure that incorporates both duration and health-related quality-of-life and is recommended as the primary economic effectiveness measure.[94] The QALY captures a wider range of consequences than other clinical effectiveness measures, and permits comparisons across disorders and interventions, allowing for broader economic interpretation. Also, generally accepted value thresholds have been established for QALYs, but not for clinical measures.[95]

Aim 3: Secondary outcomes (ICER, clinical) We will also calculate ICERs using the clinically meaningful effectiveness measure of duration of opioid abstinence, which will be operationalized as the proportion of the year the participant was abstinent from opioids (the *abstinent year*). The calculation of cost-per abstinent-year enables comparisons with existing economic evaluations that have utilized similar effectiveness measures.[96]

Health-related quality of life: will be measured using the EuroQol 5D-5L (EQ-5D).[90,97] Preference weights obtained from the EQ-5D will be used to calculate QALYs. The EQ-5D is the most widely used generic, preference-based health-related quality of life instrument in prospective cost-effectiveness analyses.[98]

Criminal and legal activities: will be self-reported using Timeline Followback, and measured using the Criminal and Legal Activities Form. The following measures will be obtained: days involved in criminal activity; average number of crimes/day on days when illegal activity occurred; days incarcerated in any facility; specific crimes committed, and charges and convictions for those crimes; visits to parole/probation officer; and parole/probation violations.

Non-study resources: Non-study medical resources (e.g., medications, and use of inpatient, outpatient and emergency services) will be self-reported using Timeline Followback and collected using the Non-Study Resources Form. Use of non-medical resources (e.g., travel time to medical care) will also be self-reported and collected by the Non-Study Resources Form.

Intervention Resource Utilization and Costs: The resource utilization and resulting cost of implementing and administering the O-BMT intervention will be estimated using a tailored version of the Drug Abuse

Treatment Cost Analysis Program (DATCAP) instrument.[99,100] The DATCAP is a standardized, customizable tool used to estimate costs of addiction treatment programs in diverse settings.

Other covariates: We will measure factors that may be associated with BMT outcomes, including sociodemographic characteristics, insurance status, depressive symptoms, motivation for treatment, and prior buprenorphine exposure. We will also measure other outcomes that are important for clinical care, including self-efficacy, perceived discrimination in medical care, and treatment satisfaction.

Data management. Urine drug tests will be conducted at the syringe exchange program or CHC and will be entered onto a paper Case Report Form and then entered into a password protected database. The entry will be verified by another staff member. Interviews using REDcap surveys allow for direct data entry by study participants. To ensure confidentiality, participant identifiers will not be recorded on interviews or other data forms. Instead, participants will be assigned a unique study ID that will be used on all data documents and in databases. Participant's names and consent forms will be stored separately from research data in locked file cabinets. Electronic data will be stored in a password-protected server, which will be back up daily and can only be accessed by the research team. Because we will be collecting data on buprenorphine diversion, we also received a Certificate of Confidentiality from NIDA to provide additional protection of confidentiality (see Human Subjects for details).

Analysis: All primary analyses will be intention to treat, including participants who are lost to follow-up. In secondary analyses, we will conduct per-protocol analyses to ascertain outcomes among participants who actually initiate BMT at the SEP or CHC. We will conduct additional exploratory analyses on a per-protocol basis to further assess outcomes (e.g., satisfaction with buprenorphine treatment)

Preliminary analyses. We will first review and summarize data using descriptive summaries and graphical analyses to ensure that reported values are within appropriate ranges, to check for the presence of outliers and abnormal values, and to verify that the distributions of measures meet the assumptions of the statistical tests that are planned as described below.

Missing data. For missing categorical data, we will use multivariate multiple imputation using the fully conditional specification method.[101] We will repeat imputations 20 times, and then we will compare statistical results using datasets that include imputed values and the dataset that drops missing values. This will guide our interpretation of our assessment of the impact of missing data on our study findings, as well as our interpretation of overall results.

Aim 1: To test the effectiveness of O-BMT. *H1: more participants randomized to O-BMT (vs. control) will be engaged in BMT at 30 days.* Our primary analysis will determine the effect of the intervention (O-BMT). We will use a chi square test comparing the proportion of participants in each study arm who have an active buprenorphine prescription 30 days after enrollment. We will also conduct a multivariable logistic regression adjusting for mental illness, polysubstance use, and addiction severity.

H2: Reductions in opioid use will be greater among participants randomized to O-BMT (vs. control) over 24 weeks. We will use generalized estimating equations to compare changes in opioid use between study arms over the 24 week study period. One model will use results from urine drug tests at 1, 2, 4, 6, 8, 12, and 24 weeks. A second model will compare the mean number of days (of the prior 30 days) with self-reported opioid use at 4, 8, 12, and 24 weeks.

H3: Reductions in HIV risk behaviors will be greater among participants randomized to O-BMT (vs. referral) over 24 weeks of follow-up. We will use generalized estimating equations to compare changes in injecting risk at 2, 12, and 24 weeks.

Aim 2: To test the safety of onsite buprenorphine treatment at syringe exchange programs.

H4: Diversion of buprenorphine will not be significantly greater among participants randomized to O-BMT (vs. control). By definition, participants who are not prescribed buprenorphine will not have an opportunity to divert their medication, but we will use an intention to treat approach to maintain randomization. The risk difference

threshold margin for non-inferiority will be 5%. We will construct Wald 95% confidence intervals (CIs) for a difference in diversion rates between the two arms and examine if the lower bound of the 95% CI is greater than the threshold margin. If potential confounding factors are unbalanced and require adjustment, we will apply logistic regression and estimate the Odds Ratio (OR) and its CI, examining if the lower bound of the OR is greater than the OR converted from the risk difference.

Aim 3: To determine the cost effectiveness of O-BMT by comparing costs and health service utilization between study arms. *H5: We hypothesize that O-BMT will be cost-effective according to commonly accepted thresholds.* Our comprehensive economic evaluation will follow well-established guidelines and, in accordance with recently revised guidelines, be conducted from both the perspective of the healthcare system and the broader societal perspective.[94,102,103] Both of these perspectives represent the viewpoint of the public, because city or state governments are the primary funder of SEPs and we expect that SEP participants will be publically insured or uninsured.[13] The healthcare system perspective will include costs associated with OUD treatment and other healthcare services received by this population. The societal perspective includes additional non-healthcare system costs (e.g., criminal justice resources) attributed to participants regardless of who shares the burden of these costs (e.g., healthcare system costs, time costs to the patient, criminal justice costs, and productivity costs). Effective OUD treatment can lead to savings in non-healthcare system costs, so ignoring these costs would underestimate the intervention's true benefit to society.

First, we will estimate the service utilization and resulting costs associated with implementing and sustaining the O-BMT intervention in the SEPs. Second, we will estimate the relative economic value of the intervention, including extrapolating the downstream savings resulting from reduced opioid misuse and injecting risk behaviors relative to the control condition (e.g., reduced utilization of high-cost healthcare services and criminal-justice resources). The outcome of the cost-effectiveness analysis will be the ICER. We will also calculate "net monetary benefit," a measure of cost-benefit, by applying a generally accepted willingness-to-pay threshold range of $100,000/QALY - $200,000/QALY.[94,95]

Next, we will estimate participant-level costs using the resource costing method, in which we determine a price weight for each resource unit consumed and multiplying price weights by units of service utilized.[94,102,103] Unit costs will be derived from various sources reflecting "real-world" costs faced by the stakeholders considered here (i.e., the healthcare system and society). All values will be adjusted for inflation. Since no follow-up measurements will be obtained beyond 24 weeks following baseline, discounting for time preference will not be required.[103,104] We will model the person period monthly during the first 12-weeks of intervention. Given the differences in mechanisms to generate data, separate multivariable generalized-linear models (GLMs) will be estimated to predict the mean cost associated with each resource category at each time point. GLMs permit us to choose the most appropriate mean and variance functions according to the fit of the data.[103] A multivariable GLM will also be used to predict health-related quality of life preference weights and days abstinent for each participant at each time point. QALYs gained and days abstinent for the intervention will then be estimated by using the area under the curve methodology.[103-5] The method of recycled predictions will be used to obtain the final predicted mean values for each resource category and outcome, by study arm, which will then be summed and tested according to the relevant perspective.[103] To account for sampling uncertainty in point estimates, both the p-values and standard errors, as well as the confidence intervals for the ICER, will be estimated using nonparametric bootstrapping techniques within the multivariable framework. Parametric methods based on parameters obtained from bootstrapping will be used to estimate acceptability curves, which illustrate the probability that the intervention is a good value for different willingness-to-pay thresholds. Sensitivity analyses will be performed to account for uncertain precision in assumptions and parameter estimates applied in the analysis.[104]

D.10 Power analysis. To estimate the effect size for the O-BMT intervention, we drew from prior pilots of onsite treatment. Stancliff et al.[42] offered BMT to SEP participants (N = 100) and 68% were engaged in BMT at 3 months (30 day engagement was not reported). Tringale et al.[43] offered BMT to SEP participants (N=9) over 15 days and then transferred care to treatment program. Following onsite initiation, 33% ultimately engaged in BMT. Daniels et al.[80] offered BMT at a community-based recovery center (N = 78) and 49% were transitioned to primary care site to continue treatment. For enhanced referral, we estimated rates of engagement in BMT

Table 3. Sample size calculation for hypothesized BMT engagement rates

Enhanced referral arm	O-BMT arm 33%	O-BMT arm 49%	O-BMT arm 68%
0%	40	26	18
9%	80	36	18
16%	200	62	26

Note: Sample sizes determined based on Fisher exact test when engagement rate in referral arm is 0.1%. For other tests, the sample sizes were determined based on Chi-square tests.

from our own pilot data and several studies that referred SEP participants to MMT. Engagement after passive referral may be as low as 0%,[14] while referral to MMT has resulted in 9-16% of SEP participants engaging in treatment.[37-39] Therefore, we will recruit a sample of 250, which allowing for up to 20% attrition (n=200), giving us at least 80% power for the primary outcome (**BMT engagement**) in all proposed scenario.

For Aim 2, we chose the intention to treat analysis as the primary outcome. With a sample size of 250 and an expect rate of diversion of 10-25%, we will only have 80% power to declare that diversion rate in the O-BMT arm is non-inferior to the referral arm if the inferiority margin of the risk difference is 10-14%. Though this is larger than tolerable margins for non-inferiority, we will have good estimates of the frequency of diversion in the O-BMT arm, which will provide important safety data for onsite treatment.

For Aim 3, assumptions are based on differences in cost and effect, standard deviations of cost and effect, the correlation of the difference in cost and effect, desired confidence and power levels, and the maximum willingness-to-pay value.[106,107] We estimated the power for the primary outcomes of our economic analysis (cost-per QALY and cost-per abstinent year) using the target sample size of 250 (125 per group), and a range of values for the aforementioned assumptions, based on prior economic evaluations of substance use disorder interventions. We estimate at least 90% power to be 95% confident that an intervention is acceptable at the commonly cited willingness-to-pay threshold of $100,000 per QALY.[95]

PROTECTION OF HUMAN SUBJECTS

Human subjects involvement and characteristics: We will enroll 250 participants from syringe exchange programs (SEPs) with opioid use disorder (OUD) who are interested in buprenorphine maintenance treatment (BMT) and are motivated for treatment.

Eligibility criteria include:
1) age ≥ 18 years
2) opioid use disorder by DSM-V criteria
3) interest in BMT
4) motivation for OUD treatment, based on SOCRATES
5) willingness to accept CHC referral

Exclusion criteria include:
1) receiving opioid agonist treatment in the past 30 days (confirmed by NY Prescription Drug Monitoring Program);
2) inability to provide informed consent
3) unstable mental illness (e.g., suicidality, psychosis, etc.)
4) severe alcohol use disorder or benzodiazepine use disorder by DSM-V criteria
5) hypersensitivity to buprenorphine or naloxone.
6) pregnancy (confirmed via urine testing)

Rationale for inclusion/exclusion criteria: Study participants will include out-of-treatment SEP participants with OUD. We will only include participants who are interested in BMT, motivated for OUD treatment, and willing to accept referral to a CHC for treatment, because our goal is to increase engagement in comprehensive BMT. Providing BMT onsite at SEPs could attract participants who are unready to stop illicit opioid use and only want buprenorphine temporarily to reduce withdrawal symptoms or because they do not have access to their illicit opioid of choice. There may be benefits to this type of symptom treatment, but our study is not designed to evaluate these benefits. We will exclude those with clinical contraindications to BMT,

such as severe alcohol or benzodiazepine use disorders, in order to ensure participant safety. In our treatment program, transaminase elevation (5X upper limit of normal) limited buprenorphine treatment in <1% of patients, therefore, we will not assess liver function prior to study enrollment, but all participants who continue BMT at the community health center will have liver function tests monitored as clinically warranted. We will exclude adolescents < 18 years old, because the CHC where we will be referring participants only offers BMT to adults. We will exclude pregnant women because initiation of BMT would require them to experience opioid withdrawal, and our practice is to refer pregnant women to initiate methadone maintenance treatment, which does not require a period of withdrawal.

Recruitment: Staff members at the SEPs will receive training on BMT (buprenorphine education and referral to a CHC). Active recruitment will occur by staff members discussing BMT with participants and contacting a research assistant (RA). Passive recruitment will occur by posting study flyers at study sites and asking study participants to recommend other acquaintances for the study.

Participant tracking: We will use tracking procedures that we developed to retain drug users in previous research studies where there has been 84% retention rate. On locator forms, we will record information about: 1) participants' address and phone number; 2) contact information of participants' family members, friends, case manager, physician, and pharmacy; and 3) locations where participants hang out.

Characteristics of participants: The SEPs are located in neighborhoods made up of mostly racial/ethnic minority groups; therefore, we expect to have no trouble recruiting minority groups. In prior studies at the two SEPs proposed as study sites, participants with OUD had the following characteristics: 70% were male, 60% were Hispanic, 21% were non-Hispanic black, and 16% were non-Hispanic white. We will attempt to limit the ratio of male to female participants to 2:1. Specifically, we anticipate the following characteristics of the 250 participants we will enroll: 83 women and 167 men; 150 Hispanics, 53 non-Hispanic blacks, 40 non-Hispanic whites, and 7 participants with another race/ethnicity.

Participant compensation: Brief visits (weeks 1, 6) where only urine is collected will include a $10 Clincard payment. Longer visits (weeks 0, 2, 4, 8, 12, 24) where urine and interviews will be collected will include a $25 Clincard payment. We will compensate a $20 Clincard payment to incentivize return of Wisepill medication adherence devices.

Sources of materials. We will collect interview data, urine samples for drug testing, and we will extract electronic medical records.

Urine Drug Testing: All research visits will include urine collection, which will be tested for buprenorphine, opiates, oxycodone, methadone, cocaine, methamphetamine and benzodiazepines. Results will be recorded on paper forms and entered into a web-based data base. Forms will contain only participant study ID (no identifying information).

Computerized interviews: At enrollment, the RA will administer interviews using REDcap survey (which is a self interview) technology where the participant is given headphones and the survey question is read aloud by the computer, the participant will then select the answer to collect descriptive data and baseline measures. Interview data will be directly entered on a lap top computer or tablet, which will be password protected, and will contain only participant study ID (no identifying information).

Medical record data: will be electronically extracting from Montefiore's centralized clinical database, and will include data on buprenorphine prescriptions and clinical visits. The electronic file will be created by

Montefiore health technology staff, emailed to the PI in a password protected file, and saved on a password protected computer. We will also collect prescription data from the NY Prescription Drug Monitoring Program (medications dispensed). As mandated by law, the later source includes all controlled substances dispensed by all pharmacies in New York State. Prescription data will include medication name, strength, directions, number of pills, number of refills, date of prescription, prescriber, and date medication was filled. For those participants who receive community treatment not at a Montefiore site, a medical records release form will be signed by the participant and data on their visit dates and medication dispensed will be given to research staff following the institutions policies.

Electronic adherence data: Wisepill electronic adherence monitors will be used allowing us to monitor if and when medication is taken. Electronic signal is sent to a password protected database when the device is opened and this data will be used to calculate adherence (or non-adherence) to prescribed medication. Adherence data will be downloaded and saved on a password protected computer.

Vulnerable population. SEP participants with OUD could be vulnerable to undue influence, because of physical dependence to opioids and challenges engaging in BMT. We will also be collecting sensitive information on diversion of buprenorphine, which is a controlled substance. In the following sections, we discuss the risks of enrolling SEP participants and procedures to minimize these risks.

Potential risks. The primary risks of this study are: (1) breach of confidentiality leading to embarrassment, dismissal from SEP, or legal consequences; (2) inconvenience and discomfort associated with interviews; (3) fear that refusal to participate will affect care at the SEP; (4) diversion of prescribed BMT; (5) induced withdrawal after initiating BMT; (6) polysubstance use

Confidentiality issues: We will collect personal information from participants to facilitate tracking, and we will be asking personal questions including substance use and HIV risk behaviors. We have outlined our procedures to maintain confidentiality below.

Inconvenience and discomfort associated with interviews: Participants will be asked about substance use and opioid use disorder treatment. It is possible that such questions could produce anxiety in participants. Participants will be instructed that they may withdraw from the study if this occurs. Dr. Fox (a board-certified general internist) will be involved with all study activities and will assess for severe discomfort or other severe community health center or emergency department.

Fear that refusal to participate will affect care or services: Participants may use services at the SEP, such as housing assistance or mental health counseling. In the informed consent process, they will be clearly instructed that refusal to participate will in no way affect their care at the affiliated SEP.

Diversion of prescribed BMT: For the first two weeks after initiating treatment, prescribed buprenorphine will be provided in electronic adherence monitors to monitor adherence. This should dissuade diversion of buprenorphine. However, if participants do sell or give away their medication, there could be legal consequences or disciplinary action at the SEP. After initiating BMT, participants will be asked about whether they divert their medication, and we will also check urine drug tests with the expectation that participants who are prescribed buprenorphine will have detectable buprenorphine in their urine.

Induced withdrawal after initiating BMT: Participants will start taking their medication at home, so they are subject to induced withdrawal if they take the buprenorphine before fully experiencing opioid withdrawal. This could include diarrhea, nausea, vomiting, musculoskeletal pain, sweating, and anxiety. Standard protocols for home inductions will be followed with similar procedures in the O-BMT and enhanced referral arms. The risk of induced withdrawal will not be increased from routine clinical practice.

Polysubstance use: Though buprenorphine has pharmacologic properties that make it safer than other opioid agonists (e.g., ceiling effect, partial agonist, co-formulation with naloxone), it does lead to some sedation, and overdoses are possible if taken with other sedating substances. If SEP participants are using multiple illicit substances, initiating BMT could add to their risk of overdose.

Adequacy of protection against risks

Recruitment and informed consent: We will obtain informed consent for all participants of the RCT prior to collecting any information with personal identifiers (e.g. locator form or medical record release forms), administering the baseline REDcap interview, and randomization to an intervention arm. Informed consent will be obtained by the RA.

Protection against risk: We will institute the following processes to ensure confidentiality is maintained:

1. We will create a system that prevents linking sensitive material to participants' personal identifiers. We will have a "name-based" system and "ID-based" system that will remain separate. In the name-based system, all documents that have patient identifiers will be filed together. Some of these documents will have participants' signatures (e.g. consent forms) and others will have personal information (e.g. locator forms). In the ID-based system, all documents that do not include identifying information or signatures will use participants' IDs (rather than names), and will be filed together. All forms will contain either participants' names or their study IDs, but not both. We will maintain one electronic document that links participants' names and study IDs, which will be stored on a password-protected file located on Montefiore Box.
2. We obtained a Certificate of Confidentiality to protect participants' sensitive information.
3. Letters and/or phone messages that are left for participants (to schedule research visits or referrals to the CHC) will not include any personal identifying information, and will not mention buprenorphine treatment.
4. Study records will be kept in locked files and/or within limited access, password-protected computer files, available only to the investigators and study personnel.
5. Publication or presentation of study results will not identify subjects by name.

Inconvenience, discomfort, and distress: Dr. Fox will be contacted by cell phone if any study participants become overly distressed. Participants may be referred for individual medical or psychiatric attention at Montefiore's community health center or the emergency department (depending on severity).

Diversion of prescribed BMT: Risks to the public and risks to study participants from diversion are different. Risks to the public from diversion will be managed by taking steps to minimize risk of diversion. During the trial, we will have monthly meetings with SEP staff to discuss whether they are noticing buprenorphine diversion onsite. If the SEP staff reports concerns about increased buprenorphine diversion onsite after implementation of O-BMT, we will take measures to increase monitoring of prescribed medication (e.g., more frequent visits). Use of electronic adherence monitoring may reduce the risk of buprenorphine diversion. We will also perform interim analyses to detect diversion in aggregate, and if we detect higher levels of diversion than have previously been reported (> 30%), we will stop the trial and implement measures to reduce diversion with assistance from the SEP staff. Importantly, if there is diversion, there are also risks to study participants in self-reporting illegal activity or if diversion is detected from electronic monitoring or urine tests. We will keep this data confidential during the study. Urine results will not be reported in the electronic medical record, so it will not be available to treatment providers. Interim analyses to detect diversion will only be performed in aggregate. We obtained a Certificate of Confidentiality from NIDA to reduce the chances of this data being obtained without participant consent.

Induced withdrawal after initiating BMT: We have produced patient-centered home induction materials that instruct the reader on estimating severity of withdrawal by counting the number of withdrawal symptoms (e.g., piloerection, yawning, rhinorrhea, etc.). Our research group and others have published clinical data demonstrating that home inductions are safe and induced withdrawal is rare. Also, study clinicians will be available by phone if participants have complications after initiating BMT or have questions about side effects. Even though O-BMT participants will see the study clinicians at the SEP, they will be registered as patients of the CHC, so additional medical advice is available 24 hours a day from an on-call physician. In an emergency, participants would be able to reach an on-call physician through the CHC, and the physician would be able to see their medical intake and assessment in the electronic medical record.

Polysubstance use: All BMT providers will follow national guidelines for patient selection and clinical monitoring. Participants will be screened for alcohol or benzodiazepine use disorder prior to study enrollment or being prescribed buprenorphine. A buprenorphine-waivered clinician will assess all study participants for other clinical contraindications before they are prescribed buprenorphine. Participants will only be prescribed a small supply of medication when they initiate BMT. The study clinicians will use clinical judgment about discontinuing BMT at the second onsite clinical visit, if they have concerns about polysubstance use. According to a safety announcement released by the FDA on September 20, 2017, "Based on our additional review, the U.S. Food and Drug Administration (FDA) is advising that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks." [108]

Potential benefits. If effective, O-BMT could increase engagement in BMT, which could reduce opioid use, HIV risk behaviors, and opioid overdose. Additionally, O-BMT could have public health benefit by reducing HIV transmission or opioid overdose.

Risk/benefit ratio. The O-BMT intervention has the potential to improve engagement in BMT among out-of-treatment opioid users, but it will require testing for safety and effectiveness. Given the steps that we will take to ensure that participants meet clinical criteria for BMT, minimize the chances of breach of confidentiality, and monitor for BMT diversion, study participation presents risks that are commensurate to risks of standard office-based buprenorphine treatment and the risk/benefit ratio is favorable.

Importance of study findings. Our intervention will encourage OUD treatment in a high-risk out-of-treatment group of opioid users. The United States is in the midst of an opioid overdose epidemic, yet 80% of opioid users remain out-of-treatment. Effective interventions are needed to encourage treatment engagement.

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Appendix 1.

CHCC BUPRENORPHINE MAINTENANCE TREATMENT (BMT) PROTOCOL

1. **Intake**
    a. On the first visit, gather the H&P w attention to the substance use history, set expectations, check LFTs and utox
    b. Use smart phrase to gather complete substance use history
    c. Use smart phrase to generate BMT Patient Agreement
2. **Induction**
    a. Second visit, the patient will receive Bupe induction instructions and COW scale.
        i. Tips: Start with 8 mg tabs/films and ask patient to break in 1/2 or even 1/4. Also prescribe clonidine, loperamide, and ibuprofen for withdrawal symptoms.
        ii. Induction can be done at home or in the office
            1. Home induction has been tolerated and successful at CHCC
3. **Induction and Stabilization**
    a. See the patient for follow-up in 1 week, then again 1-2 weeks later until the patient is on a stable dose
    b. Doses can be adjusted based on symptoms of withdrawal and cravings. Sometimes this can be challenging as anxiety can mimic withdrawal symptoms.
    c. Total daily dose: The usual dose is 16 mg total daily (the vast majority range between 8-24mg daily) and doses can be increased by 4 mg/day.
    d. Frequency: Can be dosed daily or bid, adjust according to symptoms, often pts like to split their doses, which is fine
4. **Maintenance**
    a. Once dose is stable, can space out visits to monthly
    b. Check urine drug testing at every follow-up visit
    c. Assess for use of other substances (cocaine, alcohol, benzodiazepines, etc.) at each follow-up visit
    d. Adopt an uniform approach about cocaine, alcohol, or benzodiazepine use

        i. Refer to social worker for psychosocial counseling
        ii. Counsel all patients to minimize use of alcohol, benzodiazepines, and other sedatives
        iii. Refer to an opioid treatment program if polysubstance use makes risks of continuing buprenorphine treatment greater than benefits
5. **Discharge from Treatment**
    a. If patients are hostile to staff or adulterate urine they will be given an administrative warning. These expectations should be made clear from day 1.
    b. Repeat offenders should be discharged from the practice and referred to an opioid treatment program
6. **Lost to Follow Up:**
    a. Track patients who have ever been evaluated for Bupe at your clinic, and periodically review with program coordinator and community outreach worker about outreach/retention efforts for loss to follow up patients.