Study Title: Randomized Trial of Buprenorphine Microdose Inductions During Hospitalization (Micro-bupe)

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SECTION E: PROJECT 3: RANDOMIZED TRIAL OF BUPRENORPHINE MICRODOSE INDUCTIONS DURING HOSPITALIZATION

A. SPECIFIC AIMS

Our goal is to increase buprenorphine (BUP) treatment initiation among patients with chronic pain (CP) and opioid misuse or opioid use disorder (OUD). Of 2 million Americans with OUD, between 1/3 – 2/3 have ≥1 CP condition.[1] Eleven million Americans misuse opioid analgesics with 62% reporting pain as the primary reason for their misuse.[2] There are >700,000 opioid-related hospitalizations annually.[3] During hospitalization, OUD and other medical conditions are rarely managed together leading to suboptimal treatment outcomes.[4,5] Initiating BUP treatment could prevent re-hospitalizations while improving pain and opioid-related outcomes.

BUP reduces opioid misuse and overdose in people with OUD and is an approved CP treatment making it ideal for people with OUD and CP.[6,7] As a partial mu opioid receptor agonist, BUP avoids the opioid-induced hyperalgesia that limits long-term use of full opioid agonists for CP; however, transitioning from full agonists to BUP can be difficult due to BUP's pharmacology.[8] Standard approaches to initiating BUP (i.e. "induction") require stopping opioids for >24-72 hours, which leads to withdrawal and fear of escalating pain.[9-12] Avoiding withdrawal could increase BUP initiation, especially for patients taking long-term opioid therapy.

Our multidisciplinary team will test *a BUP microdosing protocol where patients start very low doses of BUP without stopping other full opioid agonists*. We hypothesize that microdosing will increase BUP uptake by (1) avoiding the 24-72 hour period of withdrawal required for standard inductions and (2) reducing the risk of precipitating withdrawal.[13] BUP binds mu opioid receptors with higher affinity than other opioids but provides only partial agonism. Therefore, if full agonists occupy mu opioid receptors when patients take normal BUP doses, they will experience the relative reduction in agonism as "precipitated" withdrawal. During standard inductions, patients avoid displacing full agonists by waiting to take BUP until they are in moderate opioid withdrawal. BUP "microdoses" do not displace enough full agonist to precipitate withdrawal; therefore, patients can start and gradually increase BUP doses without stopping other opioids. Case studies suggest that BUP microdosing is feasible and minimizes withdrawal,[14] but no clinical trials have established safety and efficacy.[15]

Targeting hospitalized patients will allow us to reach people at high-risk for opioid-related harms who are not already connected to outpatient care.[16] Hospitalization is a critical "touchpoint" that often preceeds opioid overdose.[17] Even when pain consultants are available, they rarely have experience managing both CP and opioid misuse or OUD. Evidence supports starting BUP during hospitalization to increase linkage to outpatient OUD treatment,[18,19] but microdosing could change clinical practice by improving BUP treatment uptake. Our premise is that microdosing will improve long-term pain outcomes and reduce unnecessary hospitalizations specifically by facilitating initiation of BUP treatment in a non-treatment-seeking population.

We propose to test BUP microdosing vs. treatment as usual (TAU), meaning standard BUP induction. We will conduct a hybrid type 1 effectiveness-implementation study, using a pragmatic, open-label, randomized controlled trial (RCT). We will randomize 270 hospitalized patients with (a) CP and (b) opioid misuse or OUD to a 4-day microdosing protocol (without stopping full agonists) or 2-day standard induction (with stopping full agonists), and link them to outpatient BUP treatment. Study assessment visits will occur at baseline, 1 week, and 1, 3, and 6 months. The primary outcome will be BUP treatment uptake (taking BUP 7 days after baseline). Secondary OUD outcomes will be illicit opioid use and retention in care at 1, 3, and 6 months. Secondary pain outcomes will be pain intensity, pain interference, and quality of life at 3 months. Changes in pain and quality of life will be mediated by BUP treatment uptake and retention. During induction and 3-months of follow-up, we will also collect data for Ecological Momentary Assessment (EMA) of opioid withdrawal, craving, pain, and anxiety ("opioid- and pain-related symptoms"). These EMA data will allow us to assess whether BUP microdosing's targets of engagement—opioid- and pain-related symptoms—mediate OUD outcomes. Exploratory analyses will also examine pain as a trigger for opioid relapse.

Aim 1: To test the effectiveness of microdosing (vs. TAU) on OUD outcomes.

H_1: *The microdosing arm (vs. TAU) will have better BUP treatment uptake and retention, and less illicit opioid use.* ***H_2:*** *Improvements in H_1 will be mediated by opioid- and pain-related symptoms.*

Aim 2: To test the effectiveness of microdosing (vs. TAU) on pain outcomes.

H_3: *The microdosing arm (vs. TAU) will have less pain intensity and interference, and improved quality of life.*
H_4: *Improvements in H_3 will be mediated by OUD outcomes.*

Aim 3: To inform future implementation and dissemination efforts, we will: 3a) Examine factors influencing reach, adoption, implementation, and maintenance of BUP microdosing. We will use qualitative and quantitative methods to describe multi-level factors influencing these domains; **3b) Calculate**

the cost and examine cost-effectiveness of BUP microdosing. ***H_5****: Compared with TAU, BUP microdosing will be cost-effective from a societal and a health sector perspective.*

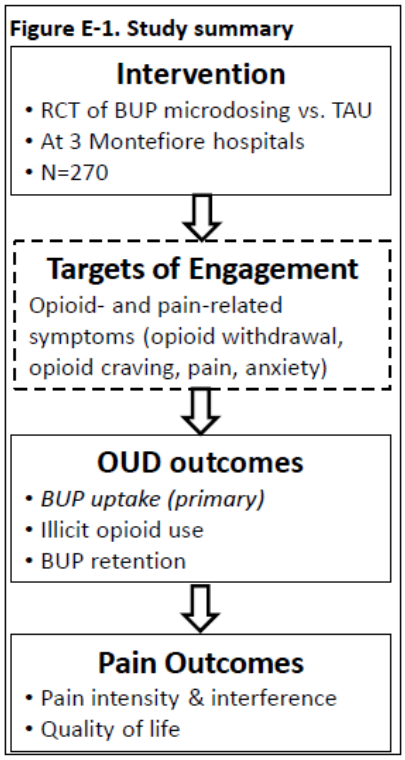
B. SIGNIFICANCE

B.1 Opioid use disorder (OUD) and chronic pain (CP). There is a complex bidirectional relationship between CP and OUD.[20] Chronic pain (i.e., pain lasting ≥3 months) is common among people with OUD; long-term opioid use may worsen CP.[21] Depending on the medical setting, between 1/3 and 2/3 of patients with OUD have CP conditions.[1,22,23] CP etiologies may precede development of OUD. The 2015 National Survey on Drug Use and Health estimates that 62% of the 11.5 million Americans who misuse prescription opioids do so to control pain.[2,12] A substantial percentage (1-8%) of patients who start prescription opioids for CP develop incident OUD.[21,24] Patients with CP and psychiatric co-morbidity are likely at increased risk for developing OUD when taking prescription opioids.[25] Chronic pain may also stem from OUD-related conditions, such as HIV or HCV, and following accidents or trauma related to OUD.[26] Alternatively, the pharmacologic effects of full opioid agonists can worsen CP through opioid-induced hyperalgesia, in which pain sensitization is enhanced despite opioid therapy.[27] Ultimately, preventing OUD-related harms will require better management of CP.

B.2 Buprenorphine (BUP) may be the ideal medication for OUD and CP. BUP treatment (i.e, buprenorphine or buprenorphine-naloxone) for OUD reduces illicit opioid use, HIV risk and opioid overdose mortality.[28-30] BUP is also US Food and Drug Administration approved for CP treatment.[7,31] Approved BUP formulations differ for OUD and CP, but the medication itself remains the same.[32] As a partial opioid agonist at mu opioid receptors with high affinity binding and slow dissociation, BUP can prevent opioid withdrawal, reduce opioid craving, and block the effects of other misused opioids without causing euphoria in people with physiologic dependence to opioids ("opioid-dependent").[33-35] Despite being a partial agonist, BUP's analgesic efficacy is comparable to that of morphine and other full agonists.[34,36,37] Though the mechanism is incompletely understood, long-term BUP use likely results in less opioid-induced hyperalgesia than full opioid agonists, which can lead to improvements in pain and functioning.[34,38-41] Because BUP has a ceiling effect, where doses above a threshold (probably 24-32 mg) do not cause additional respiratory depression, overdoses are less frequent with BUP than other prescription opioids.[42-44] Studies that examine pain outcomes in patients taking BUP for OUD demonstrate reductions in pain, even without other pain-focused treatments.[45-47] Nonetheless, work is needed to increase BUP treatment uptake - only 20% of 2 million Americans with OUD receive evidence-based treatment annually.[48,49] Improving pathways to enter BUP treatment could prevent OUD-related harms and improve pain. **Figure E-1** demonstrates how our microdosing strategy is proposed to improve OUD outcomes, which will in-turn improve pain outcomes.

B.3 Fear of withdrawal prevents people from initiating BUP. Needing to transition to BUP from opioid agonists (i.e. heroin or prescription opioids) prevents people with opioid misuse or OUD from starting BUP. There are two challenges: 1) patients must typically avoid opioids for 24-72 hours before starting BUP; and 2) *precipitated* or *persistent withdrawal* during BUP induction can lead to early treatment cessation. If BUP is taken too soon after full opioid agonists, opioid-dependent people will experience precipated withdrawal when BUP displaces other opioids at mu opioid receptors while providing only partial agonism. Relative reduction in opioid agonist activity is experienced as withdrawal,[44,50,51] which can reduce interest in BUP treatment.[52,53] People taking prescribed opioids express fear of stopping opioids due to worsening pain and withdrawal.[9,10,54-57] Two early studies that attempted to transition patients with CP and likely OUD from prescription opioids to BUP highlight induction challenges. In one trial, 21 patients consented to transition from prescription opioids to BUP, but only 12 took BUP and 4 successfully completed induction.[58] In a retrospective pain clinic study, only 104 of 271 patients receiving prescription opioids who were offered BUP successfully transitioned to BUP.[8] One study of 76 CP patients with opioid misuse used an inpatient protocol to transition to BUP; the protocol included conversion to intravenous opioids and giving small doses of intramuscular or sublingual BUP.[59] This worked, but elective hospitalization for BUP induction is too resource intensive to be generalizable. Even when BUP induction is successful, as many as 28% of patients drop-out during the first week of treatment, likely due to

Figure E-1. Study summary

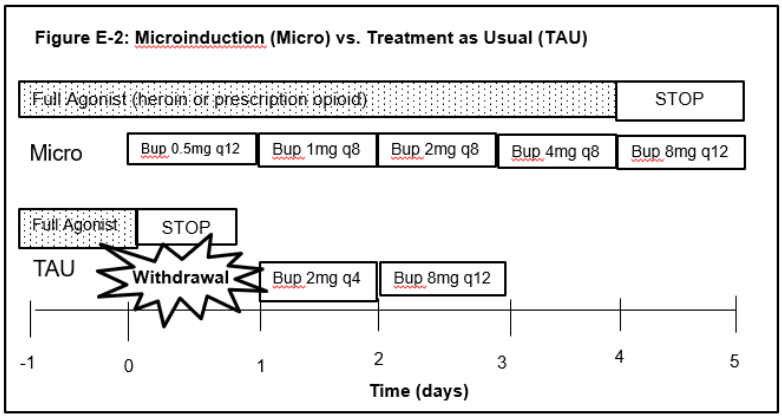


uncontrolled craving and withdrawal.[60-64] Improved BUP induction protocols are needed.

B.4 Hospitalization is an important "touch-point" to reach people who misuse opioids. People with opioid misuse or OUD are frequently hospitalized for reasons other than opioid overdose.[65] As the number of Americans experiencing overdoses has skyrocketed, hospitalization rates for other opioid-related conditions, such as cellulitis or psychosis, have increased in parallel.[65-67] People with OUD and CP are also frequently hospitalized for trauma and surgical procedures.[68] A common scenario is that a hospitalized patient with opioid misuse or OUD has opioids started or increased to control pain, but uncertainty about opioid tapering prolongs hospitalization. In our hospital system, patients with an opioid positive urine test have a 1.6 day longer length of stay (7.6 days vs. 6.0 days) than patients with urine drug tests that are positive for other substances or negative for illicit substances (unpublished data). Opioid analgesics may be stopped abruptly to facilitate discharge, which could lead to pain, withdrawal and re-admission. Patients with OUD who are not receiving OUD treatment when hospitalized very rarely newly initiate OUD medications.[69] Following hospitalization for OUD-related infections, patients are 50 times more likely to die from opioid overdose than the general population.[17] Though BUP microdosing protocols could be used in many treatment settings, hospitalization is a particularly important time to initiate BUP treatment.

B.5 Microdosing as a strategy to facilitate BUP treatment induction. When BUP displaces opioid agonists, opioid-dependent patients experience precipitated withdrawal from the relative change in agonism. Microdosing starts low BUP doses (0.5 mg) that do not precipitate withdrawal, and then gradually increases dosage while continuing a full opioid agonist, thereby avoiding withdrawal and pain that occurs during standard inductions (see **Figure E-2, Table E-2**).[13,15] Interest in microdosing has grown tremendously outpacing evidence of effectiveness. A recent meta-analysis of published data on BUP microdosing included 20 studies, but all are case series and include 57 total participants.[70] One series examined BUP microdosing for 8 CP patients taking high-dose prescription opioids and demonstrated success with 6 transitioning to BUP.[71] Our group has developed BUP microdosing protocols (see D.2.7), which warrant testing in a rigorous clinical trial.

Figure E-2: Microinduction (Micro) vs. Treatment as Usual (TAU)



B.6 Evaluating opioid- and pain-related symptoms during BUP induction. Understanding patients' experiences with BUP induction could contribute to other interventions that facilitate treatment initiation and improve clinical practice. Persistent and precipitated withdrawal are relatively common experiences during induction.[72-74] In BUP clinical trials, where participants are selected based on their willingness to undergo withdrawal before induction, standard inductions are highly successful (>94%), but elevated levels of opioid craving and withdrawal are reported for weeks following induction.[64,75] Additionally, patients with CP may be ambivalent about stopping opioid analgesics. *Collecting detailed qualitative and quantitative data regarding opioid- and pain-related symptoms will help identify how successful participants cope with these symptoms.*

B.7 Ecological momentary assessment (EMA) to evaluate pain as a trigger for illicit opioid relapse. During the trial, we will collect EMA data to examine the relationship between opioid- and pain-related symptoms with OUD outcomes. Analyses will clarify how these symptoms differ between arms and affect BUP uptake during the induction and other OUD outcomes during follow-up. Thus, *the BUP microdosing targets of engagement will be measured using EMA data (i.e., opioid- and pain-related symptoms).* In a clinical trial where BUP was maintained for 12 weeks and then tapered for 4 weeks among people with OUD and CP, high and fluctuating pain scores during maintenance BUP treatment were associated with relapse to illicit opioid use during the taper phase.[76] Other studies document CP as a predictor of illicit substance use.[41,77-80] Interestingly, a few studies that have examined pain and illicit opioid use outcomes among patients taking maintenance BUP or methadone did not report an association between pain and illicit opioid use.[46,81,82]

EMA is a method for collecting electronic, real-time data that captures subjective states (e.g., pain) and occurrences of specific behaviors (e.g., illicit opioid use) as individuals go about their day.[83] EMA overcomes limitations of in person assessments and other real-time sampling methods that use written reports (e.g., daily diaries), including retrospective bias and poor compliance.[84] All EMA technologies tag participant inputs with a time/date stamp and record failures to respond to prompts.[83] Thus, while people who misuse prescription

opioids report pain as the reason for their use, *we will collect detailed data regarding opioid- and pain-related symptoms, and examine if these symptoms mediate the relationship between study arm and OUD outcomes.*

B.8 Implementation and dissemination promise and challenges. A key implementation challenge is engaging low-income Black and Hispanic patients in BUP treatment.[85] Barriers include access to BUP and stigma of OUD treatment. We will collaborate with people with lived experience and the Stakeholder Board to minimize stigma, for example, with messaging that frames positive aspects of BUP treatment. Microdosing dissemination challenges include engaging hospital clinicians who have not had extensive training in addiction medicine. We will conduct qualitative interviews with clinical staff who support our research team in conducting the RCT to understand strategies for maintaining microdosing protocols once the study has been completed.

B.9 Expanding evidence of BUP cost-effectiveness. CP is associated with greater estimated costs than cancer, cardiovascular disease, and diabetes.[86] Total annual costs range from $560 billion to $635 billion annually in direct health expenditures and lost productivity. Hospitalization costs are also increasing. In a national sample, from 2011 to 2015, average costs per hospitalization for patients with OUD and CP increased from $37,029 to $47,480 even though length of stay remained stable between 5.74-5.82 days.[68] BUP treatment is known to be cost-effective, and has the potential to reduce hospital length of stay and re-hospitalization.[87] However, the 5-day microdosing protocol could also delay discharges. Examining how hospital-based microdosing affects re-hospitalization, acute care utilization and other health system or social costs would provide additional incentives for wide-spread implementation and dissemination of BUP microdosing.

B.10 Summary. CP and OUD can be effectively managed together with BUP. Helping out-of-treatment patients with CP and opioid misuse or OUD to start BUP during hospitalization would be beneficial in preventing opioid-related harms, improving pain, and potentially lowering health system costs. Microdosing is a promising approach to facilitate BUP induction – particularly for people with CP who fear stopping opioids – but rigorous clinical trials are necessary to demonstrate benefits in comparison to standard inductions. With high rates of opioid use and uncontrolled pain in the US, improving BUP treatment utilization will be highly impactful.

C. INNOVATION

C.1 First RCT of BUP microdosing. The first case study proposing BUP microdosing was published in 2016.[13] Since then there have been more than 20 microdosing case reports/series and much enthusiasm about the approach. However, no RCTs have demonstrated safety and efficacy in generalizable samples. Additionally, studies have not fully evaluated microdosing for people with opioid misuse or OUD and CP.

C.2 Rigorous assessment of BUP for opioid misuse or OUD and CP. Some data support use of BUP for controlling pain in people with OUD, but because different formulations are approved for OUD treatment and CP, few experimental studies examine both outcomes concomitantly. We will recruit hospitalized patients with opioid misuse or OUD, prescribe the buprenorphine/naloxone formulation used for OUD treatment, and rigorously study pain outcomes and the OUD treatment cascade of care over a 6-month follow-up period.

C.3 Ecological momentary assessment (EMA) will allow us to collect information in real-time, investigating relationships between BUP microdosing, opioid- and pain-related symptoms, and OUD outcomes. We will have detailed information about opioid withdrawal, opioid craving, pain, and anxiety during induction and follow-up, which can help elucidate reasons for suboptimal OUD outcomes. Follow-up data collection over 1-week periods will also allow us to investigate opioid- and pain-related symptoms during different aspects of participants' lives (e.g., during work vs. weekends) and contextual events that may lead to opioid use. We will provide participants with cell phones so that EMA data can be collected in a socioeconomically diverse sample.

D. APPROACH

D.1 <u>Preliminary studies:</u> For over 15 years, our research group has been at the forefront of BUP treatment and innovation in primary care and community settings.[88-96] We have developed a large primary care-based BUP treatment network (H97HA03793) and are conducting an RCT of BUP treatment initiation at syringe services programs (R01DA044878, PI: Fox). We have studied numerous BUP innovations, including home inductions, community-based referrals (R34DA031066), group medical visits (R34DA039041, PI: Fox), and "low-threshold" treatment.[11,72,97-103] Our team also includes early-stage investigators trained in qualitative research and longitudinal data analysis. With 3 hospitals, 20 community health centers, and 5 opioid treatment programs in the Bronx, Montefiore provides the optimal setting for answering clinical questions about BUP. We have treated >1300 patients with BUP, ~1000 patients are hospitalized annually with OUD and CP, and we have conducted numerous NIH-funded BUP clinical trials.

D.1.1 OUD and chronic pain: In an observational cohort, we studied 82 patients with OUD who initiated BUP treatment in primary care and found that 60% had significant pain at baseline before starting BUP (i.e., pain ≥ 5 out of 10 using the Brief Pain Inventory) and 38% had persistent pain over 6 months (i.e., pain scores

≥ 5 at 1, 3 and 6-month follow-up visits). The average pain score for patients with baseline pain was 7.3 and decreased to 6.0 at the 6-month follow-up visit.[46] These data suggest that out-of-treatment patients with OUD and CP will have clinically meaningful improvements in pain and will be retained in BUP treatment.

D.1.2 Failure to initiate BUP: Qualitative and quantitative data suggest that fear of withdrawal is a barrier to initiating BUP among people with opioid misuse or OUD and CP. In a qualitative study with people using illicit BUP, those who had experienced precipitated withdrawal when taking BUP were reluctant to consider formal BUP treatment.[53] We have also documented CP patients' fear of worsening pain with stoppage of prescription opioids.[57] Among 324 patients who inquired about our outpatient BUP treatment program, only 56% started treatment, demonstrating the need to improve the process of initiating BUP treatment.[93]

D.1.3 Inductions complicated by withdrawal symptoms are common: Our research has demonstrated that complicated BUP inductions (i.e. precipitated withdrawal after taking BUP) are regular occurrences happening in at least 17% of inductions.[72] In addition, patients who have complicated inductions are less likely to remain in BUP treatment at 30-days than those who do not.[11]

D.1.4 BUP microdosing: Based on the literature, our group has developed outpatient and inpatient BUP microdosing protocols. Since 2020, we have used these protocols with 18 patients. Among the 18 patients who attempted microdosing induction, 11 were successful in initiating and continuing BUP treatment (unpublished data). Only 1 of 5 patients who were taking methadone treatment at the time of microdosing were successful with the transition. Therefore, we will exclude participants who are enrolled in methadone treatment programs.

D.1.5 Previous EMA research: We have expertise in conducting research and collecting substance use data via EMA, including analysis of complex longitudinal studies with repeated measures. Using hand-held devices including smartphones, we have conducted NIH-funded research studies in which approximately 180 data points have been successfully collected from each study participant.[104-106]

D.1.6 Previous research for costs-effectiveness analysis. Our team also has expertise in assessing costs and cost effectiveness of substance use interventions using data from EHR, clinical tracking systems, and claims. Our health economists leads the cost analysis in an ongoing HEAL initiative project (UF1MH121944**)** to test collaborative care approaches to co-existing OUD and mental health conditions in primary care. We will also be supported by the CHERISH Center, a NIDA-funded Center of Excellence, with outstanding resources for economic evaluations alongside clinical trials (see letter of support).

D.1.7 Summary: Taken together these studies demonstrate our ability to conduct clinical trials with BUP, as well as, EMA and cost-effectiveness methods; the feasibility and acceptability of microdosing; likelihood of improved pain with BUP treatment; and the high volume of admissions to our hospital system for CP and OUD.

D.2 Research Design and Methods:

D.2.1 Overview of study approach: We will conduct a hybrid type 1 effectiveness-implementation study, using a pragmatic, open label RCT. We will recruit 270 hospitalized patients with (a) CP and (b) opioid misuse or OUD, randomize them 1:1 to BUP microdosing or TAU, and link them to outpatient BUP treatment. We will assess BUP treatment uptake (primary outcome) and other OUD and pain outcomes. The microdosing arm will use a 5-day BUP microdosing protocol (see **Figure E-2** and **Table E-2**) – BUP doses will be gradually increased while a full opioid agonist is continued. In the TAU arm, participants will stop other opioids and wait until they are in moderate opioid withdrawal before starting BUP. Both arms will receive follow-up care at Montefiore clinics to continue BUP treatment (with buprenorphine-naloxone) and manage CP. Assessment visits will occur at baseline, 1 week, and 1, 3, and 6-months. We will use EMA to assess opioid- and pain-related symptoms during induction and three 1-week periods over 3 months. We will also collect detailed information on microdosing implementation and cost-effectiveness.

D.2.2 Setting. We briefly describe study sites below and details are provided in the Facilities section. Montefiore Medical Center is the largest healthcare provider in The Bronx. The neighborhoods served by Montefiore are representative of low-income urban areas: over 65% of patients have public insurance, 57% Hispanic and 39% Non-Hispanic Black, and neighborhoods have been devastated by drug use. There are three Montefiore hospitals in the Bronx. Hospitalized medical patients are typically cared for by hospitalists with the availability of pain, addiction medicine, and psychiatry consultants. Montefiore also has 20 community health centers, the BUP Treatment Network (situated in 7 community clinics), and 5 opioid treatment programs. In outpatient settings, patients receive BUP treatment integrated with primary care services.

D.2.3 Participant Eligibility: We will enroll hospitalized patients with CP and opioid misuse or OUD who are taking opioids and eligible for BUP treatment. Opioid misuse will be defined as heroin use or prescription opioid misuse (defined as: 1) use without a prescription; 2) use in greater amounts, or more often than prescribed 3) running out of prescription pain medication early).[107] CP will be defined as pain that is chronic

(on most or all days for ≥ 3 months) and at least moderate intensity and interference (score ≥4 on Pain, Enjoyment of Life and General Activity scale [PEG]).[108,109] We will exclude patients who are currently receiving any OUD treatment (see **Table E-1**).

Table E-1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Age ≥ 18 years • Opioid misuse or OUD (see D.2.3) • Chronic pain (see D.2.3) • Currently taking opioids • Fluency in English or Spanish • Planned hospitalization for ≥ 48 hours	• Current OUD treatment (BUP, methadone, naltrexone) • Severe alcohol or benzodiazepine use disorder • Hypersensitivity to BUP or naloxone • Pain due to malignancy • Severe untreated mental illness (suicidality, psychosis) • presence of an acute or chronic medical condition that would make participation medically hazardous • Resting respiratory rate >20 or O2 saturation <92% • Pregnancy • Unable to consent due to pain or cognitive impairment

D.2.4 Recruitment: We will actively and passively recruit hospitalized patients. Clinicians in the hospital, including pain and addiction consultants, will be informed about the study. Study information will be posted electronically and in common areas (e.g., physicians' lounges). Dr. Torres-Lockhart, Director of Montefiore's Addiction Consult Service, and Dr. Shaparin, Director of the Pain Service, will oversee recruitment of patients on whom they are consulted. Hospital Medical Directors will also assist in recruitment. We will also have the Epidemiology Informatic Unit (EISMU) produce daily recruitment data lists with identifiable information about hospitalized patients who have opioid use disorder and at least one chronic pain condition. We will contact the attending physician for hospitalized patients before approaching the patient for study recruitment. If given permission by the attending physician, the research coordinator will approach the hospitalized patient for recruitment.

Feasibility of recruitment: In 2019, 987 patients with OUD and CP diagnoses of back pain, arthritis, or neuropathy were hospitalized at Montefiore. Co-morbidities that would be exclusions for this RCT were: BUP treatment (7%), methadone treatment (31%), severe alcohol use disorder (8%), and severe benzodiazepine use disorder (2%). Removing patients with ≥1 exclusion leaves 640 potential participants. In a prior RCT of BUP treatment for hospitalized patients, 21% of eligible patients were enrolled.[18] Using a more conservative estimate of enrolling 14% of eligible patients, enrolling 270 participants in 3 years will be feasible (640 eligible/year x 14% enrollment rate x 3 years = 270 participants).

D.2.5 Screening and Randomization: Initial screening and consent: Participants will be screened for eligibility and exclusion criteria by a trained research coordinator using a brief questionnaire. Participants will be informed of study procedures, risks and benefits of study participation, tested for their understanding, and they will provide written consent. During enrollment, female participants will have urine pregnancy tests.

Randomization will be unblinded, stratified, and blocked, with a 1:1 ratio across the two arms. To ensure balanced distribution between arms, we will stratify by OUD severity (misuse/mild vs. moderate/severe), heroin use (past 30 days, yes vs. no), and mood disorders (yes vs. no). We will randomize in blocks of 4-8 to ensure comparison groups of equal size. To ensure concealment of allocation, a centrally-located data manager will generate allocation sequences (with SAS Proc Plan) and store sequences in a password-protected file.

D.2.6 Participant tracking: We will use procedures that we have developed to retain people who use drugs in previous research, in which we have had an 84% retention rate over 6-month-follow-up.[110] Participants will complete locator forms at enrollment and update them at all research visits. Information will include: 1) participants' addresses, phone numbers, and social security numbers; 2) contact information of family or friends; 3) contact information of participants' community-based organizations and case managers; and 4) participants' "hang out" locations.

Table E-2. Microdosing Initiation Dosing Schedule

Day	Microdosing			Standard Induction		
	Full agonist	BUP	Daily Total	Full agonist	BUP	Daily Total
1	Full dose	0.5 mg q12	1 mg	**STOP**	--	--
2	Full dose	1 mg q8	3 mg	--	2 mg q4 h	8 mg
3	Full dose	2 mg q8	6 mg	--	8 mg BID	16 mg
4	Full dose	4 mg q8	12 mg	--	8 mg BID	16 mg

5	**STOP**	8 mg BID	16 mg	--	8 mg BID	16 mg

BUP = buprenorphine dosage; q4 = every 4 hours; BID = twice daily

Table E-3: Summary of Assessments and Schedule

Construct	Measure	Assessment period				
		0	**1w**	**1m**	**3m**	**6m**
Opioid Outcome Measures for Aim 1						
BUP uptake	BUP medication administration, prescriptions		X			
BUP retention	BUP prescriptions			X	X	X
Illicit opioid use	Addiction Severity Illness (ASI), urine drug test	X	X	X	X	X
Pain Outcome Measures for Aim 1						
Pain intensity	BPI pain severity subscale	X	X	X	X	X
Pain interference	BPI pain interference subscale	X	X	X	X	X
Quality of life	PROMIS-Preference (PROP-Pr) Scoring System	X		X	X	X
Physical functioning	PROMIS Physical Function short form	X	X	X	X	X
Additional Mediators/Moderators and Covariates						
Sociodemographics	Demographics questionnaire	X				
Opioid withdrawal	Clinic Opioid Withdrawal Scale (COWS)	X	X			
Opioid craving	Medication Craving Scale	X		X	X	X
Pain treatments	Prescriptions, pain-related visits/procedures	X		X	X	X
Mood symptoms	Patient Health Questionnaire (PHQ-9) Generalized Anxiety Disorder–7 (GAD-7)	X		X	X	X
Substance use	PROMIS alcohol use, ASI, urine drug test	X	X	X	X	X
Prior OUD treatment	NIDA JCOIN harmonized questionnaire	X				

**Additional measures will be included as required by the RFA, IMPOWR Coordination and Dissemination Center, and IMPOWR-ME Stakeholder Board.

D.2.7 Clinical Protocols: Microdosing (Experimental arm): Participants randomized to microdosing will start low-dose BUP while continuing a full opioid agonist according to a 4-day protocol (see **Figure E-2 &Table E-2**). Participants will be assessed for opioid withdrawal using the clinical opioid withdrawal scale (COWS) before the first BUP dose and 30 minutes after each administered dose while hospitalized.[111] A full opioid agonist will be continued until day 5 of the protocol.[112,113] If patients are planned for discharge before completing microdosing, they will receive at the time of discharge pre-packed medication clearly marked with the timing for each dose, instructions on how to take the medication and when to stop full agonist opioids. Opioid withdrawal will be assessed with the Subjective Opioid Withdrawal Scale (SOWS) via telephone.

Rationale for 5-day protocol: Published microdosing protocols range from 3 to 7 days or more. From 2012-2016, the mean length of stay for patients at Montefiore Medical Center with an opioid positive urine drug test was 7.62 days (95% CI: 7.44-7.80). Some evidence suggests that rapid titration to maintenance BUP treatment dosages prevents drop-out,[114] but rapid titration could increase precipitated withdrawal risk, therefore, we developed our protocol in the middle of the published range.

TAU (Control arm): Participants randomized to TAU will receive a standard BUP induction following clinical guidelines. Full opioid agonists will be stopped and a clinician will assess for withdrawal using the COWS scale. If participants have a COWS score of ≥8 they will be eligible to receive a 2 mg BUP dose. Participants will be reassessed for withdrawal 30 minutes after receiving their first BUP dose.

Withdrawal management: Participants with COWS score increases of ≥50% or an absolute increase of 4 or more will be considered to have precipitated withdrawal. If this occurs, induction will be postponed to the following day. Clinicians can administer non-opioid adjunctive medications (i.e., clonidine, loperamide) during induction based on hospital protocols. Medication use will be considered a covariate in analyses with withdrawal symptoms as an outcome.

Intervention fidelity: Study clinicians will be trained in the study protocol for microdosing and TAU and follow a check-list for induction procedures. All BUP doses administered will be recorded in medical records.

Follow-up BUP treatment: Participants will be discharged with 1 week of BUP and scheduled for clinical visits at Montefiore within 1 week. During clinical visits, participants will be assessed for BUP adherence, illicit opioid use, and opioid craving. All BUP prescriptions will be buprenorphine-naloxone film or tablet formulations.

Maintenance dosing: For both arms, the target BUP dose will be 16 mg daily at discharge, consistent with the mean BUP dose for patients treated at Montefiore and standard clinical dosing goals for OUD.[115] As per standard procedures, clinical visits will occur weekly during the first month. BUP dosage may be increased if needed (based on opioid use or uncontrolled pain).

Psychosocial counseling and support: At clinical visits, clinicians will provide 15 minutes of standardized counseling directed toward medical management.[116] Counseling will include discussion of current substance use, BUP adherence, and psychoeducation about avoiding relapse. *End of study*: At 6-months, all participants will have the option to continue clinical care at a Montefiore clinic, including those without insurance.

D.2.8 Assessment Visits: A research assistant (RA) will meet with all participants at baseline, 1 week, and 1, 3 and 6 months (see Table E-3). Research visits will occur in the hospital or at a Montefiore clinic, and participants will receive $50 compensation at visits for the week 1, month 1 and month 3 visits and they will

receive $100 for the baseline and month 6 visits. Questionnaires and urine drug tests will be completed at each study visit. Additionally, data will be collected using EMA in the hospital during induction and in between assessment visits (see below). To limit participant burden, EMA data will be collected only during induction over 2 weeks and then in three 1-week bursts during follow-up.

Table E-4. Ecological Momentary Assessment (EMA) Measures

Construct	Measure
EMA opioid- and pain-related symptoms	
Opioid withdrawal	Subjective Opioid Withdrawal Scale (SOWS)
Opioid craving	Visual analog scale
Pain intensity	Adapted BPI pain severity subscale
Anxiety	Generalized Anxiety Disorder–7 (GAD-7)
Exploratory EMA outcomes	
Illicit opioid use	Self-report
BUP dose	Self-report
Pain treatment	Self-report
*All measures will occur at bursts 1 & 2 weeks, and 1, 2, & 3 months	

D.2.9 Data Sources and Measures for Aims 1 and 2 are presented in **Tables E-3 and E-4**.

Questionnaires: Questionnaires will be administered in English or Spanish using REDCap, a well-established, HIPAA-compliant, web-based surveying platform and database that allows flexible instrument design, ease of contacting potential respondents, and reliable data collection and storage with error control. Additionally, items can be self- or interviewer-administered. Our team has transitioned to online evaluations due to the COVID-19 pandemic and all instruments can be filled out online. Therefore, questionnaires can be administered at a Montefiore clinical site or virtually.

Medical Records: We will abstract medical record data from the electronic health record (EHR), including administration of BUP during hospitalizations, BUP prescriptions and outpatient BUP visits. We will also abstract adjunctive medications administered in the hospital for managing opioid withdrawal and pain, and any pain medications prescribed in the outpatient setting during follow-up. We will abstract other pain-focused visits or interventions during the follow-up period (e.g., physical therapy).

Urine Drug Testing will occur at each study visit using enzyme-multiplied immunoassay (EIA) technique for opiates, oxycodone, fentanyl, methadone, BUP, amphetamines, benzodiazepines, cocaine, and cannabinoids, and urine creatinine concentration to ensure validity.

Study logs: We will use study logs to examine the number of potential participants screened, consented, and reasons for declining consent. Study clinicians will document the amount of time that they spend during BUP induction using the microdosing or TAU protocol following a check-list of steps.

Ecological momentary assessment (EMA): We will use EMA to examine opioid and pain-related symptoms (opioid withdrawal and craving, pain, anxiety), along with illicit opioid use, BUP dose taken, and pain treatments. Using smartphone mobile technology, participants will receive time-scheduled prompts to report symptoms, ecological conditions (e.g., current activities), and behaviors. We will record assessments in two periods: the first 2 weeks (induction) and 3-month follow-up. During induction, participants will report opioid- and pain-related symptoms at random times during 5 daily blocks. The relatively long period of data collection oriented to induction will allow EMA data collection in the hospital and after participants return home to resume normal activities. During follow-up, we will collect data during three additional 1-week “bursts” to complement data from in-person study visits. Bursts will be separated by at least 2 weeks and no more than 6 weeks over 3 months. Prompts will inquire about opioid- and pain-related symptoms, and context, such as physical activity, which may affect these symptoms and OUD or pain outcomes. As with our current studies, research staff will assist in downloading the secure customized EMA technology (www.Ilumivu.com) onto participant smart phones, and provide training to use the technology.[106] Participants without smart phones will be provided one. Each report will take 1-2 minutes to complete. Based on the lack of significant reactivity effects found in past research, 5 standard EMA random reports will be prompted daily.[117,118] EMA measures are summarized in **Table E-4**.

Adherence to EMA: Participants will receive $0.20 for each set of assessments completed. If they complete more than 90% of assessments weekly, they will receive a bonus of $10. Feedback regarding EMA adherence will be provided with reminders about compensation. Total compensation can be $17 per EMA week.

E.2.10 Key Outcomes for Aims 1 and 2:

The **primary outcome** will be *BUP uptake*, defined as receiving BUP 7 days after the baseline visit using EHR data on hospital medication administration or prescription (dichotomous, yes/no).

Secondary OUD outcomes include illicit opioid use and BUP retention. *Illicit opioid use* will be examined as the number of days of illicit opioid use (defined as self-reported use of heroin, fentanyl, or non-prescribed opioid analgesics) in the prior 30 days based on the Addiction Severity Index (continuous).[119] Because urine drug testing (UDT) only captures opioid use in the prior 24-72 hours, it is a less sensitive measure of substance use over time; however, UDT results will be a secondary outcome measure. *BUP retention* will be

defined as having a BUP prescription written the following number of days after baseline: 30-60 days (1-month retention); 90-120 days (3-month retention); and 180-210 days (6-month retention). To be retained at 3 and 6-months, participants will be required to have been retained at previous time points.[46] All OUD outcomes are consistent with elements of the Opioid Use Disorder Cascade of Care.[120]

Secondary pain outcomes include pain intensity, pain interference, and quality of life. *Pain intensity* will be measured using the Brief Pain Inventory (BPI).[121] We will use the mean of 4 items that assess pain intensity over the past 24 hours on a scale of 1-10 (1=minimal pain, 10=intense pain). We will use the mean of these 4 items. *Pain interference* will be measured using the pain interference scale from the BPI, which is a 7-item instrument measuring the impact of pain on daily activities and physical functioning. It is rated on a scale of 1-10 (1=minimal interference, 10=high interference). We will use the mean of these 7 items. *Quality of life* will be measured using the PROMIS-Preference Scoring System (PROP-Pr), which is described in detail as part of the cost-effectiveness analyses below (see D.4.1).[122-124] In our main analyses, we will examine changes from baseline to 3 months for all pain outcomes; in additional analyses, we will examine sustainability at 6 months.

Other covariates: We will include covariates that may be associated with study outcomes including: sociodemographic characteristics (age, race/ethnicity, sex, employment, housing, insurance), opioid withdrawal and craving,[111,125] adjunctive withdrawal medications (e.g., clonidine, loperamide), pain treatments including medications (e.g., NSAIDs, gabapentin) and other forms of treatment (e.g., physical therapy, steroid injections, surgery), mood symptoms (anxiety and depression),[126-128] and prior OUD treatment. We will also include holistic outcome measures developed by the IMPOWR Coordination and Dissemination Center with people with lived experience (RFA-DA-21-029) and collaborate with the IMPOWR-ME Stakeholder Board to ensure we include other measures important to them.

D.2.11 Analytic plan Aims 1 and 2: Main analyses will be completed using an intention-to-treat approach.

Preliminary analyses. We will first review and summarize data using descriptive summaries and graphical analyses to ensure that values are within appropriate ranges, to check for 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. We will also explore whether the microdosing and TAU groups are equivalent on potential confounding variables (age, sex, race/ethnicity, baseline substance use, and mood symptoms).

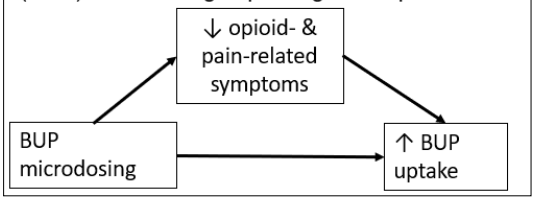
Missing data. For missing data, we will use multivariate multiple imputation using the fully conditional specification method.[129] We will repeat imputations five times, and then we will compare statistical results using datasets that include imputed values and the dataset that drops missing values. This will guide interpretation of our assessment of the impact of missing data, as well as, our interpretation of overall results.

Aim 1: To test the effectiveness of microdosing (vs. TAU) on OUD outcomes.

H_1: The microdosing arm (vs. TAU) will have better BUP treatment uptake and retention, and less illicit opioid use. Our primary analysis will be a logistic regression comparing the proportion of participants in each study arm who meet our definition of BUP uptake (see D.2.10). Secondary analyses will examine BUP retention and illicit opioid use as secondary outcomes. We will use a mixed effects logistic regression model to examine BUP retention at 1, 3, and 6 months and a mixed effects linear regression model to examine number of days of illicit opioid use (over 30 days) at 1, 3, and 6 months. Study arm will be considered a fixed effect, and participant and time (months) will be considered random effects. Additional analyses will include key variables mentioned above as covariates and potential confounders if they differ by study arm.

H_2: Improvements in H_1 will be mediated by opioid- and pain-related symptoms. Based on the model described in **Figure E-3**, we will use structural equation modeling to determine whether improvements in OUD outcomes are due to improvements in opioid- and pain-related symptoms. We will use EMA data (5 random reports per day) and data from in-person visits at baseline, 1 week, 1, 3, and 6 months. For example, when the dependent variable is BUP uptake, we will calculate the standardized total effect from the intervention (BUP microdosing) to BUP uptake, as well as the standardized mediational (i.e., indirect) effect of opioid- and pain-related symptoms (e.g., withdrawal). The mediational effect is calculated as the product of the effect from intervention to the mediator, and the effect from the mediator to the outcome. To account for the influence of the baseline measures (e.g., sociodemographic characteristics) on the outcome and the mediator, we will use a partial correlation matrix as the input matrix. This will be created by statistically parsing out the effects of the baseline measures cited above on the mediator and the outcome variable. Our proposed model will be estimated using Mplus.[130] Overall model fit will be assessed by: (1) the root mean

Figure E-3: Conceptual model for buprenorphine (BUP) microdosing improving BUP uptake



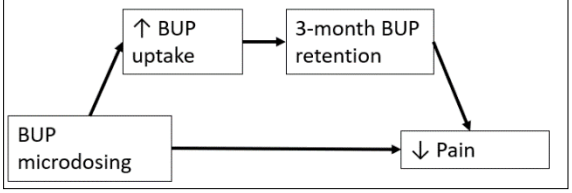
square error of approximation (RMSEA), (2) Bentler's comparative fit index (CFI),[131] and (3) the standardized root mean square residual (SRMR). To account for non-normal distribution of the model variables (e.g., BUP uptake), we will use Mplus's maximum likelihood with robust standard errors (MLR) as the estimator.

Aim 2: To test the effectiveness of microdosing (vs. TAU) on <u>pain outcomes</u>.

H_3: The microdosing arm (vs. TAU) will have less pain intensity and interference, and improved quality of life. We will use separate mixed effects linear regression models to compare each pain outcome from baseline to 3 months. Main analyses will use data from in-person visits at baseline, 1 week, 1 and 3 months. Study arm will be considered a fixed effect, and participant and time will be considered random effects. In additional analyses, we will include key variables mentioned above as covariates and potential confounders if they differ by study arm. We will also examine sustainability of outcomes at 6 months.

H_4: Improvements in H_3 will be mediated by OUD outcomes. Based on the model described in **Figure E-4** and similar to the analyses for H2 (see above), we will use structural equation modeling to determine whether improvements in pain outcomes are due to improvements in OUD outcomes. For example, when the dependent variable is pain intensity, we will calculate the standardized total effect from the intervention (BUP microdosing) to pain reduction at 3 months, as well as the standardized mediational (i.e., indirect) effect of BUP uptake, BUP retention, and illicit opioid use. For these analyses, our primary mediator is BUP retention. We will use both the EMA data (5 random reports per day) and data from in-person visits at baseline, 1 week, 1 and 3 months.

Figure E-4: Conceptual model for buprenorphine (BUP) microdosing improving pain outcomes



<u>Sex as a biological variable</u>. For Aims 1 and 2, we will examine sex as a biological variable by conducting stratified analyses by sex. In addition, we will conduct exploratory analyses to test whether there is a two-way interaction between OUD and pain outcomes and sex.

<u>Exploratory analysis</u>*: E_1: During induction, opioid withdrawal and pain will be lower in the microdosing (vs. TAU) arm.* We will use EMA data (5 random reports per day: within-individuals, repeated data) to examine if those in the microdosing arm report less opioid withdrawal and pain. Multilevel models will be used where random reports that record changes in opioid withdrawal and pain are assessed within individuals (level 1), and study arm is assessed between individuals (level 2). For example, study arm (level 2: microdosing vs. TAU) will be regressed onto opioid withdrawal (level 1). A significant coefficient for study arm indicates significant differences in overall levels of opioid withdrawal across study arms. We will also describe daily changes (linear or curvilinear) in opioid withdrawal and pain over time by including time (days since the beginning of induction) in the models above. Subsequently, a treatment x time interaction term will be included in models to examine if the trajectory (rates of changes over time) of opioid withdrawal and pain differ across study arms. Separate models will examine opioid withdrawal and pain, and separate models will examine induction (weeks 1, 2) and follow-up (1, 2, 3 months).

E_2: Increases in pain intensity will be associated with illicit opioid use in follow-up. We will use EMA data (5 random reports per day: the within-individuals, repeated data) to examine whether increases in pain are associated with illicit opioid use during the follow-up period (three 1-week bursts). We will use multilevel models to prospectively examine whether pain level at time 1 (T1) predicts illicit self-reported opioid use between T1 & T2, controlling for the previous pain level (T0), age, sex, and use of other pain treatments. In addition, we will include a pain x BUP initiation interaction term to test whether the relationships between pain and subsequent illicit opioid use differ across participants who do and do not initiate BUP treatment.

D.2.12 Power and Sample Size: We will power the study based on the primary outcome of BUP uptake. We plan to enroll 135 participants in each arm. While published case studies report high levels of success with microdosing (nearly 100%), we will use a more conservative estimate of treatment uptake from our experience with microdosing (61%). In a controlled trial of standard induction to transition patients with CP from full opioid agonists to BUP, only 24% were successful with BUP uptake.[58] To detect a difference of this size in BUP uptake, we would only need 27 participants in each arm to assure 80% power. However, we will recruit a larger sample to account for the possibility that uptake will be greater than 24% in the TAU arm (see **Table E-5**). Even with study attrition, we will be able to assess BUP uptake for all participants based on medical record extraction,

Table E-5: Power Analysis

		Projected Uptake Microdosing	
		61%	71%
Projected Uptake TAU	24%	27	17
	34%	53	28
	44%	135	52

For pain outcomes, we based our power calculations on expected changes in pain intensity from baseline to 3 months. Our pilot data (see D.1.1) suggests that mean (SD) pain intensity score will be 7.3 (±1.6) at baseline for all participants. With a sample of 270 participants (135 per arm), the minimum effect size (Cohen's d) that can be detected with power of 80% is 0.34. This effect size corresponds to a difference between arms (microdosing vs. TAU) of 8.4% for participants' reduction in pain scores (assuming that the SD of change is 1.8). Note that the SD for the pain score change is greater than that of the pain intensity score at each time point due to the intra-participant correlation in pain intensity over time. Because pain reduction is only considered for participants with BUP uptake, attrition is already incorporated into these estimates.

Table E-6: Aim 3a Implementation Measures

Construct	Quantitative Measures	Qualitative Assessment
Reach	# and % of pts with CP and OUD screened # and % of pts with CP and OUD enrolled # and % of pts with CP and OUD ineligible Rates of enrollment at each hospital	Log of verbatim reasons patients stated for declining enrollment
Adoption	# and % of participants assessed for induction # and % of participant completing induction # and % of participants referred for outpatient BUP treatment # and % of participants linked to outpatient BUP treatment	Interviews with participants about their experience, including barriers and facilitators to treatment initiation and linkage
Implementation	# and % of participants who receive ≥1 dose of BUP within assigned induction protocol Intervention fidelity check-list	Interviews with providers about barriers and facilitators to implementation
Maintenance	# of hospitals (of 3) conducting microdosing 3m after grant	Interviews with providers about current practices

D.3 Aim 3a) Examine factors influencing reach, adoption, implementation, and maintenance of the microdosing protocol.

D.3.1 Overview and hypotheses. In this hybrid type 1 effectiveness-implementation trial, we will use RE-AIM and CFIR frameworks to guide Aim 3a, in which we will use qualitative and quantitative methods to describe multi-level factors influencing reach, adoption, implementation, and maintenance of BUP microdosing.

D.3.2 RE-AIM and CFIR frameworks. The RE-AIM framework allows us to quantify implementation processes of Reach, Effectiveness, Adoption, Implementation, and Maintenance. We will determine how completely hospitals can deliver microdosing and whether protocols are continued at study sites 3 months after completing the RCT. Because RE-AIM may be less well-suited to explore how broader factors influence implementation, we will also apply the CFIR framework, which is comprehensive, widely used in substance use research, and explains how environmental context shapes implementation.[132,133] CFIR's 5 domains include: interventions, outer setting, inner setting, individuals involved, and process. RE-AIM will be used to construct quantifiable measures; complementary qualitative methods guided by CFIR will be applied to understand the factors that influence these measures. Both frameworks will allow us to better disseminate the BUP microdosing protocol, which will allow for greater transparency, reproducibility, and scientific contribution.

D.3.3 Quantitative methods. Using RE-AIM, we will first define reach, adoption, implementation, and maintenance measures (**Table E-6**) derived from program logs and EHR data. The primary implementation measure will be the % of participants in each arm who *complete induction* (defined as receiving ≥ 1 BUP dose on induction day). Quantitative implementation benchmarks: We anticipate that 14% of screened patients with CP and OUD will enroll in the RCT,[18] that > 95% of enrolled participants will be assessed for BUP induction, and that >70% of participants who initiate BUP will be linked to outpatient BUP treatment.[18] If we are unable to meet these benchmarks annually, then we will retrain study coordinators and clinical staff in recruitment, pharmacy, and referral procedures.

D.3.4 Qualitative data collection: Dr. Hayes (early-stage investigator) or an RA will conduct 45-60 minute semi-structured interviews with participants and hospital providers. We will sample 20-30 participants in the microdosing arm, including those who do and do not initiate BUP. Participant interviews will occur after BUP induction. We will also interview 10 hospital providers who care for study participants. After completing interviews, if new themes continue to emerge, we will randomly select additional participants until thematic saturation is achieved. Patient interviews: We will develop a semi-structured interview guide with input from people with lived experience that asks open-ended questions about patients' experiences with induction, particularly acceptability and reasons for BUP initiation or lack of initiation, and whether BUP helps with pain. Provider interviews will elicit information about factors associated with achieving RE-AIM outcomes (reach, effectiveness, adoption, implementation, and maintenance). The interview guide will be informed by CFIR domains regarding implementation of induction and referral procedures at the hospitals. Using the 5 CFIR domains, we will probe how various factors enable or hinder implementing the microdosing protocol. This includes ease of initiating BUP (e.g., feasibility), inner organization (e.g., fit and acceptability within hospitals), outer setting (e.g., social factors influencing clinical practice), perceptions of individuals involved (e.g., BUP

perceived benefits), and implementation processes (e.g., protocol adaptation). Questions will identify barriers, such as provider stigma about OUD, and facilitators, such as leadership endorsement of protocols.

D.3.5 Analytic Plan: Interviews will be audio-recorded, digitally stored on an encrypted password protected computer, and professionally transcribed without participant identifiers. We will use thematic analysis to identify key themes relating to BUP initiation and implementation. *Initial review of data*: In an iterative process, Dr. Hayes and team will read all interview transcripts and record concepts that emerge upon repeated readings. *Developing a coding scheme*: The coding scheme will be based on the interview data and the goals of this project. The codebook will be discussed and agreed upon by the entire research team. Any necessary changes will be made by consensus. *Coding*: Using the codebook, two research team members will code data independently. The research team will meet, discuss codes, and, if there are any inconsistencies, will come to a consensus agreement as to application of codes for each transcript. Using Dedoose software (SocioCultural Research Consultants, Los Angeles CA), codes will be applied to the dataset and data will be organized by code. *Sorting*: After data are sorted and main themes are identified, the research team will meet again to ensure that all concepts are properly represented and that thematic saturation has occurred. *Member-checking:* Identified themes will be presented to study participants to elicit interpretation and additional insight.

D.4 Aim 3b: To calculate costs and examine cost-effectiveness of the BUP microdosing protocol

H_5: Compared with TAU, microdosing will be cost-effective from a societal and a health sector perspective. Following recommendations of the Second Panel on Cost-effectiveness in Health and Medicine,[134] we will take two reference case perspectives: a health care sector perspective and a societal perspective, over a 6-month time horizon. We will use quality-adjusted life years (QALYs), a key indicator for patient wellbeing, as the effectiveness measure.[134] Health Related Quality of Life (HRQoL) at discrete time points will be measured using a utility score resulting from the PROMIS-Preference (PROPr) system.[123]

D.4.1 Measures: Health-related quality of life (HRQoL) will be measured with the Patient-Reported Outcomes Measurement Information System (PROMIS).[135,136] The PROMIS-Preference (PROPr) scoring system uses the respondent's scores for each of 7 PROMIS domains to calculate a health utility index value that represents the general US population's preference for the respondent's current health state: Cognitive Function–Abilities, Depression, Fatigue, Pain Interference, Physical Function, Sleep Disturbance, and Ability to Participate in Social Roles and Activities.[122,137] Construct validity for PROPr has been demonstrated using the EQ-5D-5L, the HUI, and two large datasets from the general US population.[124] The health-utility value is then used to calculate QALYs, as investigators from CHERISH, and many others have done in similar studies.[138-142]

Measures of employment status, work hours and hourly wage rates**:** At baseline, 1,3, and 6-months, we will collect data on employment status, and if employed, number of hours typically worked in a week and hourly wage rates, by adapting instruments developed and tested by CHERISH researchers in previous OUD studies.

Measures of criminal activities**:** At baseline, 1,3, and 6-months, we will collect data on criminal activities (in the past 3 months) in order to assess related societal costs, including criminal justice system-related costs (policing, prosecution, incarceration, etc.) and tangible and intangible costs to the victims. We will collect self-reported data on crimes committed for each major type of crime frequently reported by people with OUD.[143]

Measures of health care utilization outside the intervention: At baseline, 1,3, and 6-month health care utilization outside the intervention (including inpatient, outpatient, emergency services, and medications) during the past 3 months will be self-reported using a Non-Study Resources Form customized for this study. Use of non-medical resources (e.g., travel time to medical care) will also be self-reported and collected.

Table E-7 outlines the cost categories we will take into account when assessing incremental costs in each of the two reference case perspectives. We excluded cost categories not relevant to the timeframe of this study (e.g., impact on educational achievements). Because buprenorphine microdosing will occur during the index hospitalization only, we will not consider costs of patient time attending the intervention. The research team will have access to health insurance claims data for 40-50% of patients to be enrolled because their health plans make claims available to Montefiore for care management and research. For health care service costs, in addition to patient self-reports using validated questionnaires (see above) we will conduct a secondary analysis with these patients using the claims data, which are not subject to recall biases and not prone to missing data.

Table E-7. Cost components for the two reference case perspectives				
Cost Category	Health Care	Societal	Source(s) of Data	Unit Cost/Monetary Conversion Factor
Costs of intervention delivery	Yes	Yes	Medical records, micro-induction-protocol, and length of stay in hospital for the index hospitalization	Cost per night of hospital stay
Costs of other health care services	Yes	Yes	Non-Study Resources Form (see D.4.1)	Various sources[144] (e.g., Medicare/ Medicaid data, Kaiser Family Foundation)
Productivity – labor market earnings	No	Yes	Self-reports (see D.4.1)	Hourly wage rates reported at research interviews

Criminal Justice involvement	No	Yes	Criminal Activities Form (see D.4.1)	Unit societal cost estimates for various types of crime[145]

For each reference case perspective, to estimate the incremental HRQoL and costs associated with the intervention – BUP microdosing vs. TAU – we will use intent-to-treat design and estimate a mixed Generalized Linear Model of the HRQoL/costs at the patient-level and at each assessment point as a function of patient assignment to microdosing (vs TAU), site fixed effects, and patient characteristics bearing implications for the outcomes but possibly not balanced at baseline, with random effects at patient and site levels.[146] The method of recycled predictions will be used to obtain predicted mean values for HRQoL and each cost category, by study arm. QALYs gained will be estimated using the area under the curve methodology.[147-149] Predicted costs from different cost categories will be summed and tested according to relevant perspectives.[149] We will derive predicted *incremental* costs for intervention vs TAU for each individual patient based on the estimated models.

Cost-effectiveness analysis (CEA) will estimate an incremental cost-effectiveness ratio (ICER) associated with BUP microdosing vs. TAU. The ICER will be calculated by dividing (mean) incremental cost associated with microdosing vs TAU by (mean) incremental effectiveness. Sampling uncertainty in the estimated ICER will be taken into account by bootstrapping the study sample of the individual-level incremental cost and incremental effectiveness estimates and deriving non-parametric confidence intervals. We will further construct ICER acceptability curves for both reference case perspectives. Acceptability curves display the probability that an ICER would fall below a given willingness to pay for an incremental unit of the desired outcome and thus be considered a good value (that is, cost-effective).[150,151]

D.5 Design considerations and limitations:

Limitations: This study is designed as a pragmatic clinical trial to maximize generalizability. We will not be able to compare BUP vs. full opioid agonists regarding pain control; however, it would be unethical to prescribe opioid analgesics to participants with OUD. It is possible that some participants may receive prescription opioids from other prescribers,[152] and we will be able to determine medications prescribed using the EHR. If a participant transfers care to an out-of-state facility, or receives treatment with BUP or methadone at a program that directly dispenses medication, this information will not be available in our EHR. Nonetheless, participants will self-report whether they received medication from outside facilities.

Consideration of other approaches: *Why not integrate additional pain-focused interventions***?** We hypothesize that pain relief will stem from BUP. This study complements two others proposed in IMPOWR-ME. One proposed study will integrate Acceptance and Commitment Therapy and electronic care coordination into outpatient BUP treatment to improve pain outcomes. The other will study integration of yoga and physical therapy into outpatient opioid treatment programs. Together these studies will improve care for patients with CP and opioid misuse or OUD along a spectrum by evaluating strategies for initiating BUP treatment and then integrating OUD treatment and behavioral and physical interventions in two different outpatient settings.

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