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BUPRENORPHINE LOADING IN THE EMERGENCY DEPARTMENT (BUP LOAD-ED)

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
BUP	Buprenorphine
BUP/NX	Buprenorphine/Naloxone
CFR	Code of Federal Regulations
COWS	Clinical Opioid Withdrawal Scale
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DEA	Drug Enforcement Administration
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DSM-5	Diagnostic and Statistical Manual
ED	Emergency Department
EQ-5D-3L	EuroQol 5 dimensions, 3rd level
FFR	Federal Financial Report
FWA	Federalwide Assurance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
LFTs	Liver function tests (AST, ALT)
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
NYULH	New York University Langone Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	Buprenorphine Loading in the Emergency Department
Short Title	BUP LOAD-ED
Brief Summary	Buprenorphine (BUP) is FDA-approved for the treatment of opioid withdrawal and opioid use disorder. Prior studies have demonstrated feasibility, safety, and efficacy of Emergency Department (ED)-initiated BUP, but there are many barriers to widespread implementation of this intervention. Few ED providers have received the necessary DEA registration (aka X-waiver) required to prescribe BUP, and urgent appointments to continue ongoing BUP treatment may not be readily available, thus leading to medication discontinuity. A loading dose induction strategy with 32mg of BUP may help effectively link ED patients to outpatient treatment while minimizing known barriers to ED uptake. Administering a loading dose of BUP to saturate mu-opioid receptors would extend the duration of action, therefore providing additional time to secure ongoing treatment. Further, BUP's ceiling effect on respiratory depression makes it a remarkably safe drug even at high doses. In recent years, ED providers have begun to incorporate this approach into clinical protocols; however, it has not been formally studied in this clinical setting. Our study represents the necessary step of studying this novel approach in the ED setting to define the parameters for clinical protocols and large-scale studies.
Phase	Phase IV
Objectives	1. To evaluate the feasibility, acceptability, safety and utility of a BUP 32mg sublingual (SL) loading dose induction strategy in the ED. 2. To determine optimal processes for an ED protocol and clinical trial.
Methodology	This is an open-label, single arm study in which 35 ED patient-participants who have untreated moderate to severe opioid use disorder (OUD) and are experiencing opioid withdrawal will receive treatment with BUP 32mg SL along with referral for ongoing treatment. Assessments will occur in-person on days 0-3 and by phone on day 30, to assess the feasibility, acceptability, safety, and utility of this clinical intervention primarily by assessing its effect and the duration of effect on opioid withdrawal, craving, and sedation as well as evaluating engagement in ongoing treatment.
Endpoint	For the primary and secondary objectives, standardized and validated instruments will be used to measure the following: opioid and other illicit drug use using the timeline follow back method and urine or saliva drug screen (UDS); opioid withdrawal and craving using objective and subjective opioid withdrawal scales (e.g. COWS and SOWS) and visual analogue scales (VAS); level of awareness/sedation using the Richmond Agitation Sedation Scale (RASS), patient reported outcomes of quality of life and functional status using the PROMIS Global 10 and Treatment Effectiveness Assessment (TEA); healthcare utilization using the non-study treatment service use form, participant satisfaction and perceived utility of ED-initiated intervention. Engagement in treatment will be assessed by self-report and/or confirmed by treatment provider. An adverse event log will be maintained.
Study Duration	Duration: 7-10 months
Participant Duration	1 month

Population	Eligible participants will be recruited from the Bellevue Hospital ED and NYULH EDs, which have a large proportion of patients with opioid use disorder (OUD), among other substance use disorders (SUD). Individuals can be selected to participate if they are 18 years and older, speak English, meet DSM-5 criteria for moderate to severe OUD, have used opioids within 7 days, have not used methadone at a dose greater than 30mg within 72 hours or 10mg within 24hours, have objective signs of opioid withdrawal with a COWS score ≥8 or are expected to have a score of this level during their ED visit, are willing and able to participate, and have adequate locator information including access to a phone. Patients will be excluded if they are currently engaged in medication treatment for OUD (methadone, BUP, or naltrexone), are prescribed opioids for treatment of pain, cognitively impaired, in police custody, have an allergy to BUP, receive a dose of BUP greater than 8mg before study enrollment, or have acute medical or psychiatric conditions or co- occurring substance use disorders that are deemed to preclude safe participation, such as recent methadone use. Subjects will also be excluded if they do not have reliable access to a phone or if a 3-hour observation period in the ED is not feasible (may be limited by provider or patient availability).
Study Sites	The study will take place in the Emergency Departments at Bellevue Hospital and NYU Langone Health sites including NYULH-Tisch, NYULH-Brooklyn, NYULH-Winthrop, and NYULH-Cobble Hill.
Number of participants	35 participants
Description of Study Agent/Procedure	BUP 32 mg SL (in two doses of 8mg and 24mg)
Key Procedures	Urine or saliva test, administration of BUP 32 mg SL.
Statistical Analysis	Statistical analyses will consist of descriptive analyses and will provide summary tabulations and measures of central tendency, variance, and other distributional properties of the obtained results. Where applicable, we will also conduct cross-tabulations and comparative analyses of variance based on selected key characteristics of the study participants (e.g., sex, age categories, withdrawal scores at baseline).

1.1.1 Schedule of Research Events

	Research Visits				
	Index	**Day 1**	**Day 2**	**Day 3**	**Day 30**
Eligibility and Enrollment					
Potential participants identified by staff referral and/or research staff screening	x				
Approval of clinical provider (confirmation that medically and psychiatrically stable and appropriate for study participation)	x				
Written Informed Consent and Medical Release	x				
Eligibility Assessments and Checklist (DSM-5 OUD, Medical exam, COWS)*	x				
Assessments					
Demographics (PhenX)	x				
Drug Use Inventory and other Substance Use Measures (PhenX, TLFB)	x	x	x	x	x
Urine and/or Saliva Toxicology (Standard panel, BUP, FEN)	x				
Withdrawal and Craving Measures (COWS, SOWS, scales)*	x	x	x	x	x
Quality of life and treatment (PROMIS-GLOBAL-10, TEA)	x	x	x	x	x
Overdose and risk assessments	x	x	x	x	x
Qualitative Assessments/Participant Satisfaction	x	x	x	x	x
Non-Study Medical and Other Services (NMS)	x	x	x	x	x
Adverse Events	x	x	x	x	x
Administrative Actions and Review					
Appointment scheduling for research visits and follow up care	x	x	x	x	
Participant compensation (value)	80	40	40	40	40
Round Trip Metrocard	x	x	x	x	
Healthcare Utilization Review		x	x	x	

*Multiple assessments conducted before BUP dose 1, after BUP dose 1, and after BUP dose 2

Key Roles

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2 Introduction, Background Information and Scientific Rationale

Background Information and Relevant Literature[1]

Effective treatments to reduce morbidity and mortality associated with opioid use disorder (OUD) are known, yet few individuals are provided access to these treatments[2]. Narrowing the treatment gap by expanding access to treatment beyond specialized drug treatment settings is a widely accepted public health priority. For many reasons, the Emergency Department (ED) is a logical point of intervention: 1) There is a disproportionately high and growing prevalence of OUD among ED patients; ED visits associated with opioids doubled between 2004 and 2014, and visits for opioid overdose increased by approximately 30% from July 2016 through September 2017[3-6] ; 2) Both multiple ED visits and surviving an overdose are strong predictors for subsequent overdoses and even death[7,8] ; 3) For many individuals, the ED is the primary or only access point in the healthcare system, and, therefore, treatment,[4,5] 4) The ED visit may represent a critical, time-sensitive moment of motivation for treatment. This context provides a unique opportunity for interventions addressing OUD to gain entry into the ED; however, there is a need to translate treatment approaches to interventions that are feasible and effective in the ED setting.

The landmark trial conducted by D'Onofrio et al. demonstrated the feasibility, safety, and efficacy of ED-initiated buprenorphine (BUP) in the Yale-New Haven Hospital ED[9]. Despite this success, few EDs have adopted this intervention. ED providers often cite time and resource limitations[10]. Widespread implementation is difficult, as few ED providers have received the necessary DEA registration (aka X-waiver) required to prescribe BUP and appointments for linkage to ongoing care within 24 hours may not be readily available. Even in an optimized system, other factors such as problems with medication pre-authorization may delay access. Thus, a critical barrier to ED-initiated BUP is ensuring patients have access to ongoing treatment with BUP without medication discontinuity.

A novel induction strategy, in which a loading dose of Buprenorphine (BUP) 32mg is administered, has the potential to mitigate this barrier. ED providers can treat patients with BUP for opioid withdrawal since DEA registration (X-waiver) is not required unless they wish to issue a prescription. Current BUP induction protocols, developed for inpatient and ambulatory care settings as well as for unobserved self-administration via prescription, usually recommend a first day dose of 8mg given in divided doses of 2-4mg.[11] However, patients discharged with ≤ 8mg SL total dose may experience return of withdrawal symptoms and/or opioid craving within only 4 hours.[12,13] Treatment with a loading dose of 32mg in the ED may provide the necessary bridge treatment, relieving symptoms of withdrawal until a patient is able to attend a follow up appointment for further treatment.

Translating existing strategies by taking advantage of the unique and well-established pharmacological properties of BUP has the potential to alleviate the aforementioned barriers to ED-initiated BUP. Demonstrating that this efficacious pharmacotherapy can be initiated practically in the ED as a bridge to ongoing BUP treatment would support efforts to expand the delivery and impact of evidence-based opioid treatment. Further assessment is needed to define the clinical parameters for this induction strategy before incorporating it into clinical protocols and large-scale studies. Our proposal represents the necessary first step in studying this novel approach in the ED setting.

Name and Description of the Investigational Agent

Buprenorphine (BUP) is a lipophilic thebaine derivative with a high binding affinity at the mu-opioid receptor where it has partial agonist effects and at the kappa opioid receptor where it is a competitive antagonist. Like many opioids, BUP was initially commercially developed as an analgesic[14]. In October 2002, the FDA approved BUP for detoxification and maintenance treatment of opioid dependence. For these indications BUP is marketed as Subutex® (Reckitt Benckiser), and in a 4:1 ratio combination with naloxone (BUP-NX), as Suboxone® (Reckitt Benckiser). The BUP-NX combination was developed to limit abuse liability and diversion[13,15-18]. Generic formulations of BUP-NX are now available. Recently Reckitt Benckiser began marketing a sublingual BUP-NX film. In this document, we refer to BUP-NX as either BUP-NX or BUP. All study participants will be treated with BUP-NX formulations, though this document may refer to the study drug as simply "BUP".

BUP was first proposed as an alternative to methadone for treatment of opioid dependence in 1978 and has been studied extensively since. As reported by Jasinski, Mello, and Mendelson, buprenorphine has a low physical abuse potential and a high potential to substitute for heroin and reduce heroin self-administration.[19-22] These clinical studies suggested that BUP could be used safely and effectively used for pharmacotherapy in clinical settings, but formal approval for clinical use required systematic data on safety and efficacy of BUP when used in larger groups. A set of clinical trials were designed to evaluate the utility from a medication development perspective, and subsequent trials, compared buprenorphine to methadone; evaluated dose comparisons using dose response; and compared buprenorphine to placebo.[14,19,22-28]

Numerous clinical trials involving thousands of participants, have overwhelmingly established both the efficacy and effectiveness of BUP-NX in the community.[18,22,24,29-36] BUP and BUP-NX are safe and effective alternatives to methadone[20,37-41] and enable significant and substantial improvement over time in psychosocial functioning.[42]

Maximal drug effects typically occur at approximately 8 to 16 mg, although sublingual daily doses up to 32 mg have been safely administered for a period of up to a year.[20,43,44] Variability in individual dosing addresses the range and severity of opioid dependence across patients. Because of BUP's lipophilicity and high affinity to the mu-opioid receptor, less-frequent-than-daily dosing is possible for some patients.[45] BUP's slow dissociation from mu-opioid receptors contributes to its long duration of action and smooth day-to-day course, and minimizes symptoms and signs of withdrawal upon cessation.[46,47]

Prescribing and Safety: Details on BUP-NX (Suboxone®) prescribing, pharmacokinetics and pharmacodynamics, metabolism and elimination, safety and toxicity are described in the Suboxone package insert submitted with this protocol.

2.1.1 Preclinical Data

See package insert.

2.1.2 Clinical Data to Date

A small handful of studies to date have demonstrated the safety and effectiveness of high dose BUP induction, ranging from case reports to randomized controlled trials. Ang-Lee et al. observed a significant mean reduction in Clinical Opioid Withdrawal Scale (COWS) score in heroin-dependent patients using 24 mg SL BUP. Furthermore, participants in this small open-label study did not experience any significant adverse events, aside from one participant who had precipitated withdrawal which resolved within 4 hours, and withdrawal suppression lasted >72 hours.[48] A similar study by Kutz et al. treated 10 heroin-users in acute withdrawal with 32 mg BUP (8mg every 5 minutes for 20 minutes), and reported that nine of the participants completed detoxification with negligible withdrawal symptoms, with suppression also lasting > 3- 4 days. Again, no adverse events were reported.[39]

Within the past two years, four randomized controlled trials out of Iran[49-52] have provided evidence that high dose BUP for opioid withdrawal is both safe and reduces craving/withdrawal over an extended time frame following initial administration. One of these studies randomized 90 opioid-dependent men in withdrawal to three groups to receive single doses of 32 mg, 64 mg, and 96 mg respectively. They observed a significant reduction in craving symptoms using a Visual Analogue Scale (VAS) in all three cohorts that was more pronounced at 64 mg than 32 mg, but no greater effect was observed at 96 mg. The resolution of craving was maintained at 5 days post initial treatment. Only four participants developed side effects, which included hypotension, nausea and vomiting (expected side effects of BUP even at low doses), all of which resolved with hydration and anti-emetics[49]. This research group also published a recent case report of heroin detoxification using 120 mg SL BUP in a single patient experiencing severe withdrawal. Withdrawal suppression persisted for 4 days after initial administration, and the patient was discharged without need for additional buprenorphine. There were no side effects or adverse events reported in this case.

Of note, the other studies out of Iran specifically investigated the effectiveness of single, high dose buprenorphine in mitigating suicidal ideation/depressive symptoms in patient with concurrent opioid use disorder during withdrawal. Nonetheless, they provide support for its safety in single high doses at initiation[51,52].

2.1.3 Study Rationale

Study Rationale and Dose Rationale

Under most current BUP induction guidelines, only a partial induction is feasible during a brief ED visit, where 8mg is given in divided doses of 2-4mg.[11] Thereafter, a maintenance dose is reached ranging from 16 to 32mg, but this is not currently achieved during ED visits. The threshold for suppressing withdrawal and the rewarding effects of an opioid challenge occurs when greater than 70% of μ-opioid receptors are occupied, which typically occurs at plasma BUP concentrations of ≥ 2ng/mL[53]. Patients discharged after administration of ≤8mg SL BUP may have both incompletely treated acute withdrawal symptoms and return of opioid craving within only 4 hours.[9] Thus, a patient would need to successfully navigate a complex medical system to obtain BUP for continued unobserved induction – and would have return of withdrawal and craving if not done within a certain period of hours. In real-world settings, without the heavily supported conditions present in the published trials, high rates of failure to engage in treatment after ED discharge have been observed.[16,9,17]

Administration of a larger 32mg SL BUP dose during the ED visit may improve engagement in OUD treatment by producing both a greater reduction in opioid withdrawal intensity during the ED stay and prolonged suppression of opioid craving after discharge. A rapid ED induction eliminates the need for an unobserved induction after discharge, which relies on immediate access to prescribed buprenorphine and patient compliance with complex titration instructions.[12,13,53] Current data suggest both fewer acute withdrawal symptoms and increased duration of effect with BUP doses ≥8mg SL. Among heroin-dependent patients presenting with acute withdrawal treated with 8mg SL BUP, Oreskovich *et al.* observed a mean reduction in Clinical Opioid Withdrawal Scale (COWS) score from 15 to 8.[54] In a similar population, using 24mg SL BUP, Ang-Lee et al. observed a much larger mean reduction in COWS from 17 to 2 with withdrawal suppression lasting >72 hours.[6] Whitley et al. found that compared to higher doses, a low initial dose of BUP (2mg SL) was associated with increased rates of protracted withdrawal and treatment failure.[7]

In a 2014 meta-analysis, Mattick et al. showed that buprenorphine is superior to placebo in retaining people in treatment, but only at higher doses (16 mg or more), and not at low or medium doses (15 mg or less), based on objective urinalysis results.[55] The authors of studies included this meta-analysis suggested that a possible explanation for poorer retention in BUP maintenance treatment may have been too-slow induction onto buprenorphine. Given the relative safety of buprenorphine, it may be possible to

induct people to higher doses at a more rapid rate and thus overcome the problem of slightly poorer retention for buprenorphine compared with methadone.[56,57] Researchers have also suggested that, by nature of buprenorphine's different pharmacological properties, it may have advantages in some settings and under some policies where its relative safety and alternate-day administration are useful clinically compared to methadone.

For these and other aforementioned reasons, more practical alternative models have been proposed for ED settings. Specifically, the rapid induction method proposed in this study is already used widely across the state of California (as well as other regions) through the statewide SAMHSA-funded ED-BRIDGE program; the protocol is published on the ED-BRIDGE website and endorsed by ACEP and California Society of Addiction Medicine (CSAM). Thus, in this study, we wish to formally study an induction procedure that is already in clinical use. Also, it has been studied on a limited scale in controlled research settings conducted outside the ED. Existing data suggests this approach is feasible, acceptable, safe, and successful in effectively extending the duration of effect of BUP (Section 2.1.2 Clinical Data to Date).

In ED patients, return of withdrawal symptoms and opioid craving during the high-risk period after discharge but before formal linkage to care likely promotes early return to illicit opioid use and failure to engage in OUD treatment.[13] A SL dose of 4mg achieves a plasma BUP concentration sufficient to suppress craving and withdrawal for ≤2 hours; a SL dose of 8mg provides ≤ 4 hours of therapeutic effect.[13,53] A 32mg SL dose of BUP may provide effective treatment for over 24 hours or more. The dosage of BUP SL 32mg being used in this study has been approved by the FDA for the treatment of OUD for daily use in the maintenance phase.

ED-initiated BUP induction dosing potentially influences patient satisfaction and retention in opioid use disorder (OUD) treatment after discharge. Translating existing BUP induction and treatment strategies by taking advantage of the unique and well-established pharmacological properties of BUP has the potential to mitigate the aforementioned barriers to ED-initiated BUP. This study aims to evaluate the feasibility, acceptability, safety, and utility of the rapid loading induction strategy in the ED. Demonstrating that this efficacious pharmacotherapy can be initiated practically in the ED as a bridge to ongoing BUP treatment would support the efforts to expand the delivery and impact of evidence-based opioid treatment. We hypothesize that enrollment of 35 ED patients with OUD and opioid withdrawal in an open-label, single arm study of a BUP 32mg loading dose induction will provide necessary information on feasibility, utility, and identification of optimal processes for the development of a treatment initiation protocol suitable for the ED setting so that we can properly plan subsequent large-scale clinical trials.

Safety

Owing to its partial opioid agonist properties, BUP has limited respiratory depressant effects, low toxicity even at high doses, and limited risk of overdose. The closely monitored ED setting used in this study, in addition to BUP's ceiling effect on respiratory depression and sedation, makes it a remarkably safe drug, even at high doses.[39,58] At sufficient doses, BUP blocks the effects of exogenous opioids and can both reduce illicit use and afford some level of protection against overdose. Chart review of 94 ED patients at Highland Hospital who received 24-32mg SL BUP suggests this approach is feasible and safe—no cases of clinically significant sedation, precipitated withdrawal, or other adverse event were observed. Studies described in Section 2.1.2 (Ang-Lee, Kutz, and Ahmadi), have provided further evidence that this dosage is both safe and effective when administered in the ED setting.

BUP has abuse potential, though limited in contrast to full agonists like methadone.[37,40-42,44-47,59] Although there is a ceiling on BUP's respiratory depressant effects,[37] interactions with other CNS depressants, such as benzodiazepines and alcohol, are potentially dangerous,[60,61] and patients should be cautioned to avoid acute binge use of CNS depressants.[62] Because BUP is metabolized by cytochrome P-450 3A4,[63] drugs that inhibit or induce this system can affect BUP levels. Known inhibitors include erythromycin, ketoconazole, grapefruit juice and certain HIV protease inhibitors[63] which may increase BUP levels. Inducers include phenobarbital, carbamazepine, and phenytoin which could reduce BUP levels and lead to withdrawal symptoms, [62] though this has not been observed clinically.

The primary objective of this study is to provide further evidence for the safety, utility, and feasibility of a 32 mg initiating does of buprenorphine. While this dose has been approved for maintenance treatment, the FDA label recommends a lower dose for the first day of initial induction, specifically "an induction dosage of up to 8 mg/2 mg SUBOXONE sublingual film is recommended. Clinicians should start with an initial dose of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone and may titrate upwards in 2 or 4 mg increments of buprenorphine, at approximately 2-hour intervals, under supervision, to 8 mg/2 mg buprenorphine/naloxone based on the control of acute withdrawal symptoms."[64] We expect that this study will further support existing evidence that 32 mg dose of BUP is not only safe to administer, but will extend withdrawal suppression and facilitate linkage to care for patients with OUD.

Potential Risks & Benefits

2.1.4 Known Potential Risks

Medication Risks: Participants in this study will be treated with the BUP-Naloxone (BUP-NX) formulation currently in stock at Bellevue pharmacy, which is the BUP-X sublingual (SL) tablet. The package insert for Suboxone (BUP-NX sublingual) serves as the primary source of risk information. BUP SL is FDA-approved in tablet and film formulations as BUP-NX and as the BUP monoproduct (no naloxone) for the treatment of OUD. Naloxone is for abuse deterrence and is inactive when taken as prescribed (due to negligible absorption and metabolism through the hepatic first pass effect). The formulations have comparable indications, dosing, bioactivity, and risks. If the medication on formulary at Bellevue is different than BUP-NX tablet, the risks will be approximately identical.

The FDA label prescribing information states "an induction dosage of up to 8 mg/2 mg SUBOXONE sublingual film is recommended. Clinicians should start with an initial dose of 2 mg/0.5 mg or 4 mg/1 mg BUP-NX and may titrate upwards in 2 or 4 mg increments of buprenorphine, at approximately 2-hour intervals, under supervision, to 8 mg/2 mg buprenorphine/naloxone based on the control of acute withdrawal symptoms."[64] The dosage of BUP SL 32mg being used in this study exceeds this recommendation for the initial dose; it is, however, within the dose range approved for the daily maintenance phase (i.e., for continuation after the first day(s) of induction). No toxicity or long-term risks beyond those described in the prescribing instructions are expected. A medical screen will be performed in accordance with prescribing guidelines. As described in Section 2.1, the case review of 94 ED patients at Highland Hospital who received 24-32mg BUP SL and other published studies conducted in other clinical and research settings – as well as the unique pharmacological properties of BUP's ceiling effect on sedation– suggests this approach is feasible and safe.

The purpose of this study is NOT to amend the product labeling.

Two known risks of BUP are that it may cause **over-sedation** (particularly among individuals with certain medical problems or concomitant sedative use) and **precipitated withdrawal** (when BUP is taken too soon after full opioid agonist use, particularly methadone, before the individual is in sufficient opioid withdrawal). The higher dosing may have increased potential to cause over-sedation; it is less likely to increase the risk of precipitated withdrawal. In fact, worsening withdrawal is often treated by administering higher doses of BUP, including in the clinical protocol for the Bellevue Hospital ED (which recommends up to the dose being tested in this study). Given the pharmacology of BUP, the onset of these events would be expected within 30 to 90 minutes of receipt of the medication. During this time, all participants will remain monitored in the ED clinical research setting where there is capacity to address these issues should they arise. Management of over-sedation and withdrawal are within the scope of general ED practice; the principal investigator is a practicing ED clinician and has a wealth of expertise and experience in addressing these problems. We will have safety plans in our operating procedures and activate these plans should events occur.

The risks of over-sedation and precipitated withdrawal will be mitigated by rigorous patient selection criteria and research procedures and assessments. Prior to receiving any BUP, potential participants will be screened for co-occurring substance use and medical problems that would predispose them to over-sedation, and they will be screened for recent use of methadone or other long-acting opioid agonists and will have a formal assessment of opioid withdrawal severity to minimize the risk of precipitated withdrawal. For this reason, patients who have used methadone at a dose that is greater than 30mg within 72 hours

or greater than 10mg within 24 hours or at an unknown dose (e.g., obtained illicitly) will be ineligible for study participation.

Active use of opioids (within 7 days) will be confirmed by a positive toxicology test and/or by the clinical assessment by the study clinician or ED provider (e.g., self-report plus documented history of opioid use and objective findings consistent with opioid withdrawal). We will not rely on toxicology testing alone as synthetic and semi-synthetic opioids are not reliably detected for up to 7 days using currently available CLIA-waived, rapid toxicology tests. The use of urine and/or saliva toxicology tests that are not CLIA-waived will be for non-clinical, research purposes.

Participants will receive the BUP SL 32mg in divided doses, rather than all at once. If after an initial dose of BUP ≤8mg SL, a participant experiences over-sedation or another adverse event that would preclude further dosing, such as an allergic reaction, the subsequent dose will not be administered and the patient will be withdrawn from the study. The participant will be reassessed for other possible etiologies for these symptoms (for example, infection can cause sedation or mimic withdrawal). Precipitated withdrawal, however, would not necessarily preclude subsequent BUP dosing. In most cases, the treatment for precipitated withdrawal is to administer additional BUP in higher doses. In other words, the latter BUP 24mg dose would be the treatment for precipitated withdrawal in most cases. The determination of whether a participant who is experiencing apparent precipitated withdrawal should receive additional BUP will be determined on a case-by-case basis at the discretion of the study clinician.

2.1.5 Other Risks of Study Participation

Confidentiality: Risks to participants include possible loss of confidentiality/privacy pertaining to their protected health information. Participants will be asked to provide sensitive information, including drug use.

The PI and study staff have completed requisite IRB Human Subjects and HIPAA trainings. Any future staff will have completed requisite IRB Human Subjects and HIPAA trainings. The PI will provide any future staff with training in their responsibilities for maintaining participant confidentiality.

The PI will apply for a Federal Certificate of Confidentiality to encompass protocol activity and participant data and ensure against the release of confidential information. Research records apart from clinical assessments will be distinct from the medical record to help ensure the protections of the Certificate of Confidentiality.

EMR documentation will be similar for patients being treated for OUD whether or not they participate in the study. ED-initiated BUP is currently offered as first line treatment for OUD in the Bellevue ED to patients who are clinically appropriate to receive it. As per standard clinical care and usual practice, when BUP is initiated in the ED to a patient, the related elements of clinical care are documented in the EMR (e.g., diagnosis, assessments, medication administered, response to treatment, and referral information). Specific assessments and actions conducted by the study staff that are directly related to clinical care may be made available to the clinical staff and/or entered into the EMR to ensure accurate clinical documentation and closed-loop communication and safety. Specifically, elements that may be communicated may include vital signs, state of opioid withdrawal, craving, or sedation, details of last opioid use (frequency, timing, type, route), acute adverse events, follow-up appointment information, and drug administration and prescribing record. There will be no mention of the research-only assessments (e.g., legal and social problems, healthcare utilization, quality of life, satisfaction, etc.) or inclusion of the data resulting from them in the EMR; these data will only be entered into the research record (using a unique identifier).

All research data will be entered into NYU-internal REDCap surveys administered on tablets and/or PCs using Bellevue's and NYULH's secure networks for any data containing participant protected health information. The tablet devices have security protections that are HIPAA compliant. Hard copy Case Report Forms will be used if necessary and all data from paper forms will be copied into REDCap as soon as possible. Data will be stored on secure servers and/or in locked filing cabinets in my locked research office with only authorized study personnel as identified by the principal investigator and project manager for this study having access. Unique identifiers will be used to identify participants in the password-protected database. Study

findings will utilize only aggregate data and no publication or presentation will involve any use of individual information.

All safeguards for storage of information on password-protected servers with HIPAA compliant firewall will be in place to ensure data are secure. There is a risk that if the tablets and/or PC is lost, it will compromise study information. To prevent this, the tablets and/or PC devices used in this research will have security features that are designed to protect the device and data while enforcing strict network and platform security including strong passwords, remote and local wipe, network security, and certificate based authentication. The extensive precautions available to tablets and/or PC will minimize the risk involved with maintaining research databases on portable devices.

Emotional Discomfort: There is a small chance that participants may become upset during assessments that include their history of substance use problems, psychosocial, and other potentially sensitive topics. These risks are not beyond usual clinical procedures in OUD treatment. We will discontinue administration of research instruments if a participant shows great discomfort or asks to terminate an interview.

2.1.6 Protection Against Overall Risks

Protections against aforementioned risks are discussed above with the description of the specific risks.

This trial will be conducted in compliance with the current version of the protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. We will obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from the NYUMC IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to the IRB, according to its usual procedures.

This study offers patients FDA-approved BUP SL treatment for opioid dependence. As such, the potential risks of study participation are chiefly consistent with the usual care and use of these medications in everyday care practice – with the aforementioned small potential increased risks of over-sedation and precipitated withdrawal and those of data collection (time and effort, confidentiality). As described above, BUP exhibits a known ceiling effect on respiratory depression, which makes it remarkably safe compared to other opioids, even at high doses. The pharmacologic properties of BUP, the demonstration of safety of the higher initial dose strategy in a case series of 94 ED patients and in other clinical trials (as described in Sections 2.1.1-2.1.3 our plan to administer BUP in divided doses (as opposed to a single large dose) and the extended duration of clinical monitoring in a clinical setting fully equipped to address all potential adverse events, as well as the rigorous participant selection criteria are protective factors. More specifically, in order to minimize physical risks, patients who consent to participation and receive 32mg will be monitored closely every 30 minutes for at least 90 minutes (instead of 30-60 minutes as per clinical practice for ED-initiated BUP) using objective and subjective assessments by trained personnel. Naloxone (opioid reversal agent) will be available if patients begin to exhibit any signs or symptoms of respiratory depression or over-sedation. Patients will be screened prior to enrollment for history of adverse/allergic reactions to buprenorphine or any other opioids. They will be excluded from participation if they have history of adverse reaction. If patients begin to experience any signs or symptoms of allergic reaction, the appropriate medications and equipment will be available. Patients will be discharged with close follow-up and assessment (as part of the study), which will minimize any physical risks of BUP treatment.

To minimize any discomfort associated with reporting on sensitive behaviors, participants will be informed that they may refuse to answer questions that they are not comfortable answering. Questions related to eligibility determination and monitoring of safety and treatment response are not optional. If individuals

decline to answer these questions, the PI will advise them that they will not be able to participate and will make a referral to other treatment if interested. All studies involving substance use, including this one, will apply for the added protection of a Federal Certificate of Confidentiality that encompasses protocol activity and participant data and ensure against the release of confidential information. The PI and any future staff will have completed requisite IRB Human Subjects and HIPAA trainings. The PI will provide any future staff with training in their responsibilities for maintaining participant confidentiality; we will use unique identifiers to identify participants in the database; all data will be kept in locked filing cabinets in my locked research office or on our secure server to which only the study team will have access. Study findings will utilize only aggregate data and no publication or presentation will involve any use of individual information.

The study clinician will evaluate all pertinent screening and baseline assessments prior to participant randomization to ensure that the participant is eligible and safe to enter the study. Adverse events (AEs) will be assessed and documented at each visit and during phone check-ins. Individuals who experience an AE that compromises safe participation will be discontinued from further medication administration (as described in medication risks) and provided referrals for other treatment or to specialized care.

2.1.7 Known Potential Benefits

This study has the potential to benefit enrolled ED patients and society at large. This study will inform the further development of clinical protocols for the benefit of future patients with OUD; participants in this study will benefit from extra clinical support and expedited care coordination provided by study staff and may benefit from improved symptomatic treatment of OUD previously seen by higher dosing strategies. OUD has a large and growing public health impact, and ED patients are at particularly high risk for opioid associated morbidity and mortality. Treatment with BUP for OUD is associated with a variety of benefits including decreased fatal and nonfatal opioid overdoses, decreased opioid use, and decreased transmission of HIV and Hepatitis C. Yet, the vast majority of persons who would benefit from OUD treatment do not access this life-saving medication for reasons ranging from stigma to the need for a DEA X-waiver to write for a prescription of BUP and the other barriers more specific to providing BUP through the ED that are described in Section 2.1.3. Many ED clinicians are still early in gaining clinical experience with the clinical process, do not have an x-waiver to prescribe BUP, and are unaware of how to schedule urgent follow-up appointments. Study participants will directly benefit from having study staff available to provide guidance, prescribe BUP, and establish continuity of care.

Further, achieving therapeutic levels earlier and maintaining them longer through the proposed rapid loading strategy is expected to have better treatment outcomes. Specifically, higher doses of BUP have been shown to provide a greater reduction in withdrawal symptoms using COWS.[48] Larger initial doses of BUP have been associated with lower rates of treatment failure than lower initial doses.[65] In a large meta-analysis comparing buprenorphine to methadone, medium to high doses of BUP were superior to low doses of BUP in effectiveness (retention in treatment and suppression of illicit opioid use).[66]

On a societal level, defining the clinical parameters of this induction strategy may expand access to care for patients with OUD by addressing the aforementioned barriers that hinder programmatic implementation on a larger scale. Specifically, by reducing the severity of opioid withdrawal symptoms and craving for longer periods of time, this induction strategy would allow for more time to connect patients to follow-up treatment. Thereby, it would provide a practical strategy for ED providers without X-waivers or access to next-day follow up appointments with a BUP prescriber to initiate treatment. For those with OUD, widespread, simplified access to treatment is likely to reduce treatment failure, opioid withdrawal symptoms and craving, and morbidity and mortality associated with this condition. This study will inform the planning of a larger clinical trial that may influence practice on a larger scale.

3 Objectives and Purpose

Our primary overarching aims/objective are

1. To evaluate the feasibility, acceptability, safety and utility of a BUP 32mg SL loading dose induction strategy in the ED, administered as a BUP+Naloxone formulation;
2. To determine optimal processes for an ED protocol and clinical trial.

We hypothesize that enrollment of 35 ED patients with untreated OUD experiencing opioid withdrawal in an open-label, single arm feasibility study of a rapid BUP induction strategy using a loading dose of BUP SL 32mg will provide the necessary information on the feasibility, acceptability, safety and utility of this treatment approach to identify optimal processes for the development of a treatment initiation protocol suitable for the ED setting so that we can properly plan subsequent large scale clinical trials.

The primary endpoint is a binary global measure of successful rapid induction without clinically significant adverse events. This will be determined during the index visit alone, and will not be influenced by loss to follow up in subsequent research visits. Secondarily, we will use a wide-range of validated subjective, objective, and physiologic measures and patient reported outcomes at the index visit (day 0), during the first week (days 1, 2, and 3), and at day 30 to evaluate changes in opioid withdrawal, craving, level of awareness (level of activation/sedation), and other medication effects and to collect preliminary treatment effect and satisfaction data.

3.1 Primary Objective

1. To estimate the proportion and confidence intervals of participants who have *"successful rapid induction"* (as further defined below) amongst enrolled participants who receive a loading dose of BUP SL 32mg during the ED index visit. Successful rapid induction is defined only be the outcome of the participant's visit, and not by any following research visits.

Hypothesis: All participants who receive a loading dose of BUP SL 32mg will have successful rapid induction. Successful rapid induction is defined as receiving a total of 32 mg of buprenorphine SL at the index research visit without experiencing a clinically significant serious and/or severe adverse event related to the intervention. Loss to follow up in subsequent research visits will not impact this outcome measure.

3.2 Secondary Objectives

2. To evaluate changes in signs and symptoms of opioid withdrawal, opioid craving, level of awareness (activation/sedation) after administration of 32 mg BUP SL, and other medication effects during the index ED visit using validated subjective and objective instruments and physiologic measures.

3. To evaluate the safety of rapid induction via adverse events checklist prior to conclusion of the ED index visit.

4. To assess the duration of effect of BUP 32mg SL on treating opioid withdrawal and craving (days 1-3).

5. To assess patient experience domains related to treatment satisfaction and acceptability using self-reported measures and collecting data on reasons for non-participation in study amongst potentially eligible patients (at each assessment, Days 0-3 and 30).

6. To collect preliminary data and explore the treatment effect on linkage to treatment, quality of life and additional patient-level outcomes (drug use, overdose events, healthcare use) at 30 days.

Exploratory Analyses:
To evaluate participants' pre-study opioid use characteristics (opioid type [fentanyl or not], averaged daily quantity, route of administration) and other patient-level characteristics to explore their potential effect outcomes.

4 Study Design and Endpoints

4.1 Description of Study Design

This is an open-label, single arm, single site feasibility and acceptability study in which 35 ED patient-participants who have untreated moderate to severe OUD and are experiencing opioid withdrawal (COWS score ≥ 8). will receive treatment in the ED with a loading dose of BUP 32mg SL (administered in divided doses) at their index visit. We will assess the feasibility, acceptability, safety, and utility of this intervention and provide preliminary data on the effect on opioid withdrawal, craving, and sedation as well as additional patient-level outcomes (engagement in treatment, drug use, quality of life, healthcare utilization).

The first assessment will occur in-person in the ED at the index visit (day 0), and 4 additional appointments will be scheduled: 3 research visits and one follow-up care appointment with an OUD provider. Research assessments will be conducted in-person at clinical research space on Bellevue/NYULH campus on days 1-3, and by phone on day 30. Patients will be provided with appointment reminder cards with the time and location of their next appointment, and the contact information for the research study team. At the conclusion of their day 3 visit, participants will be given a prescription for BUP SL 16mg per day with a quantity sufficient to last until their scheduled clinical follow up appointment for ongoing treatment. The prescription will be provided earlier, at the day 1 or day 2 research visit, if the participant reports opioid withdrawal and/or craving and has objective signs of withdrawal at that time.

4.2 Data Collection and Study Measures:

Procedures for data collection, data management, monitoring of data quality and data analysis have been developed and refined in our previous studies. These procedures include utilization of a computerized data base system (REDCap) to monitor clinical and research activities, including enrollment, adherence to treatment interventions, and completion of scheduled assessments.

The study team will assess a range of pretreatment participant characteristics, process measures, and outcome using validated, reliable instruments that are widely-used, primarily derived from previous and ongoing studies. We will collect data and reason for non-inclusion for participants who are approached but not enrolled. The research team will obtain data by participant self-report, EHR abstraction, and contact with treatment providers. Multiple secondary endpoints using a wide-range of subjective and objective measures will be collected in-person at the index visit (day 0) and visits on days 1-3, and by phone at day 30. Details on each study visit are described in Section 7.4 (Study Schedule).

4.2.1 Study Measures

Study Measures will be selected from the Study Measures List (attached).

5 Study Endpoints

5.1.1 Primary Study Endpoints

1. To estimate the proportion having *"successful rapid induction"*

Successful Rapid Induction, the primary study endpoint, is defined as completing rapid induction with a loading dose of BUP SL 32mg without experiencing a clinically significant serious and/or severe adverse event (AE) related to the intervention – specifically, the receipt of a dose of BUP SL greater than 8mg during the Index ED visit. We will determine the proportion of participants who have successful rapid induction during the ED index visit amongst all study participants.

- *Clinically significant adverse events* (AEs) include the following: over-sedation (defined as requiring invasive or non-invasive ventilator support, having a Richmond Agitation-Sedation Scale (RASS) of ≤ - 3, and/or clinician determination), hemodynamic instability (e.g., persistent hypotension not attributed to other causes), development of severe precipitated withdrawal

(clinician determination), or experiencing other unexpected, SAEs, related to receipt of the second dose of BUP SL (for a total of BUP SL 32mg) as defined in *Section 8.1.* This measure will be assessed at the end of the ED index visit.

- Precipitated withdrawal: Clinicians will assess whether an event is considered precipitated withdrawal. This clinical determination will be based on the severity of the withdrawal signs and symptoms, the rapidity of the onset of withdrawal symptoms, and clinical factors (e.g. timing since last use of an opioid agonist(s), type(s) of opioid agonist, duration of action of opioid agonist(s) used, and route of administration). Scores will be based on objective components, eliminating nausea which can be a side effect of BUP administration. Patients who experience precipitated withdrawal will be treated with ancillary medications.

5.1.2 Secondary Study Endpoints

1. To evaluate opioid withdrawal, opioid craving, sedation during of index ED visit:

We will estimate the change in signs and symptoms of opioid withdrawal, opioid craving, level of awareness (activation/sedation) and other medication effects at repeated points of assessment during the index ED visit (spanning from enrollment in the study to a minimum of 90 minutes after the second dosage of BUP) using validated subjective and objective instruments and physiologic measures. For each domain (withdrawal, craving, sedation), we will determine the proportion of participants who experience changes in the specified measures and assess the magnitude of change and the time to change comparing repeated measures assessed during the index visit before treatment, after the first dose of BUP, and after the second dose of BUP.

The primary measures for opioid withdrawal and craving will be the Clinical Opiate Withdrawal Scale (COWS) and Opiate Craving Scale (OCS), respectively. Complete or near complete relief of withdrawal and craving will be assessed primarily by the point at which patient reports this endpoint ("Tell me when your withdrawal/craving has gone away completely"); we will secondarily note when patient has COWS score, Likert, or VAS score indicating absence of withdrawal or craving. Near complete relief will be assessed secondarily as "gone away almost completely" and using a COWS score of <3. Oversedation will be defined clinically as the need for non-invasive or invasive ventilation to maintain adequate oxygenation and ventilation; the Richmond Agitation Sedation Scale (RASS) will be used secondarily to assess level of awareness (the spectrum of sedation to agitation). Relief of (or recovery from) sedation is when invasive or non-invasive ventilator support is no longer required, with a RASS > - 2, and when patient is alert enough for discharge as determined by the treating clinician. Specific measures and times of assessment are further described in and Section 4.2.1 (Study Measures) and Section 7 (Study Procedures).

2. To evaluate the safety of rapid induction:

Adverse events will be assessed using an adverse events checklist to be completed at the conclusion of the index visit and at each study visit. Physiologic measure (vital signs) and objective measures of level of awareness (agitation-sedation) will be repeatedly assessed during the index visit (as discussed in Secondary Endpoint 1).

3. To assess the duration of effect of BUP 32mg SL on treating opioid withdrawal and craving (days 1-3).

We will generate appropriate descriptive statistics using the aforementioned validated objective, subjective, and physiologic measures of opioid withdrawal, craving, and drug effects on days 1-3. We will generate proportions for the number of participants who report withdrawal, report craving, have objective signs of withdrawal, return to use of other opioids, and/or require prescription for BUP on days 1-3 and estimate the time to occurrence and confidence intervals for these events.

4. To assess patient acceptability

Process data, including reasons for non-participation in some or all aspects of the study/clinical procedures, as well as self-reported measures of treatment satisfaction, good/bad treatment effects, and other patient experience domains (collected at each study visit/encounter) will inform acceptability.

5. To explore treatment effect

To provide preliminary treatment effect data, we will assess outcomes using measures employed in our other studies, such as linkage to treatment, quality of life, and additional patient-level outcomes (drug use, overdose events, healthcare use) at 30 days.

Preliminary data of treatment effect using outcomes measures employed in our other studies will be collected and assessed. We will explore the effect on initial linkage to and engagement in addiction treatment, quality of life and functional outcomes, and additional patient-level outcomes (drug use, overdose events, healthcare use), including but not limited to the following:

a. the proportion and confidence intervals of participants of patients engaged in treatment at 30 days, with time to initial linkage to treatment assessed secondarily;
b. changes in self-reported non-medical opioid use over first 30 days using the timeline follow back method;
c. changes in patient reported outcomes (using scales such as PROMIS GLOBAL-10 and Treatment Effectiveness Assessment (TEA)), self-reported healthcare utilization (non-study health services form) and overdose events.

These measures will be participant self-report of engagement in treatment, confirmed by the treatment provider, or by direct contact with the facility and/or treating clinician and/or through EMR abstraction. Linkage to addiction treatment will be defined as receipt of an encounter for formal addiction treatment after the index ED visit. Engagement in addiction treatment will be defined as enrollment and receiving formal addiction treatment on the 30th day after the index ED visit. Formal addiction treatment will be those treatments consistent with the American Society of Addiction Medicine's (ASAM) level of care (1-4) and will include a range of clinical settings, including office-based providers of BUP or naltrexone, OTPs, intensive outpatient, inpatient, or residential treatments.

5.1.3 Additional Exploratory Endpoints

We will explore the potential effect of patient-level characteristics on outcomes, including age, sex, fentanyl use, quantity of opioid use (high/low), injection/non-injection. We will explore associations between initial responses (change in withdrawal during the index visit) to duration of BUP treatment effect (as measured on Days 1-3).

6 Study Enrollment and Withdrawal

Eligible participants will be recruited from the Emergency Department at Bellevue Hospital and NYU Langone Health sites, including NYULH-Tisch, NYULH-Brooklyn, NYULH-Cobble Hill. The Bellevue Hospital ED has an annual patient volume of approximately 120,000 visits, which includes a large volume of patients with moderate or severe OUD who will be eligible for study participation. All patients who come to the Bellevue Hospital ED in opioid withdrawal may be screened by eligibility criteria for potential study enrollment (see Inclusion and Exclusion criteria, defined below). Patients may be referred to the study team by ED clinicians at NYULH sites listed above. Eligibility requirements will be determined by trained research staff in the ED and will be confirmed by the PI or co-investigator if there is any question of potential eligibility.

6.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Is 18 years or older
2. Is able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study. The study instruments have not been validated in Spanish (or other languages). Given the small size of this pilot, it would not be feasible to translate and validate them.
3. Meets DSM-5 criteria for moderate to severe OUD
4. Has used opioids within 7 days, confirmed by a positive toxicology test and/or by the clinical assessment by the study clinician or ED provider (e.g., self-report plus documented history of opioid use and objective findings consistent with opioid withdrawal).
5. Denies use of methadone at a dose that is greater than 30mg within 72 hours or greater than 10mg within 24 hours or at an unknown dose
6. Must be experiencing opioid withdrawal with a COWS score ≥8.
    a. Enrollment and assessments (but not study medication administration) may begin at COWS <8 if patient is anticipated to have a COWS score ≥ 8 during their ED visit.
7. Is willing and able to participate in the study and follow study procedures, including completing a 90-minute minimum observation period in the ED after their second dose of BUP, in-person assessments on days 1-3, and a phone assessment on day 30.
8. Is able to provide adequate and reliable locator information for follow-up
9. Has reliable access to a phone

6.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Is currently engaged in medication treatment for OUD with methadone, BUP, or naltrexone
2. Currently requires prescribed opioids for treatment of an ongoing pain condition
3. Has a known allergy to BUP
4. Is pregnant as determined by hCG testing at the index ED visit
5. Is breastfeeding as determined by self-report
6. Has medical, psychiatric, or concurrent substance use conditions or severe cognitive impairment that might preclude safe participation in the study as determined by the study clinician or the clinical provider, or such that they are unable understand the study procedures and provide written informed consent to participate in the study
7. Is a prisoner or in police custody at the time of the index ED visit
8. Has previously enrolled in the current study

6.3 Vulnerable Participants and Individuals

Eligibility requirements will be determined by trained research staff in the ED, and will be confirmed by the PI or co-investigator if there is any question of potential eligibility. This study will not include children, pregnant women, prisoners, or individuals with impaired decision-making capacity. By nature of the population served by the Bellevue Hospital ED and NYULH EDs, participants may include economically or educationally disadvantaged persons, but every effort will be made to consent these patients appropriately. Patients may also fear that they will not receive adequate treatment for OUD, overdose or withdrawal if they do not consent to participate in this study. It will be made explicit that their choice to participate or not will not affect their treatment. If there is any question that the nature of a subject's vulnerability has influence over participation in the study, the subject in question will be excluded.

6.4 Strategies for Recruitment and Retention

As described previously, potential participants will be identified and screened after presenting to the Bellevue Hospital ED in opioid withdrawal. Using methods employed successfully in our previous and ongoing studies, potential participants will be identified by clinician referral or clinical screening. Patients may be referred to the study team by ED clinicians at NYULH-Tisch, NYULH-Brooklyn, NYULH-Winthrop, and NYULH-Cobble Hill.

The research team will be notified of potential participants and determine whether they meet eligibility criteria. Subjects will be approached by trained research staff who will request the patient's verbal consent to inform them about the study and determine whether they are interested using an IRB-approved verbal consent script. Written informed consent will be obtained before any study activities are performed. After they are consented, we will perform additional assessments to confirm eligibility followed by pre-treatment

assessments as detailed in Section 6.9.4: *Dosing and Administration*. Individuals who meet any exclusion criteria will not be enrolled or will be withdrawn from the study if already enrolled as post-enrollment screen fails.

Efforts will be made to maintain contact with patient-participants throughout the duration of the study and to minimize missing data. Broadly, retention methods may include outreach to the participant and their identified contacts through email reminders, phone calls, text messaging, and social media.

A total of 35 participants will be enrolled in the study with the goal of having 30 participants complete the study in its entirety.

6.4.1 Use of DataCore/Epic Information for Recruitment Purposes

Patients will be recruited in-person by the research team during their ED visit without the use mail, email, or other messaging to patients or the use of patient-facing recruitment materials. Identification of potential participants will occur primarily through referral by clinical staff (health coaches, social workers, peer counselors, and volunteers) who operate an existing substance use screening and intervention program in the Bellevue ED. EPIC will be utilized in a limited capacity to identify participants. Specifically, the research team will review the census of current, active ED patients in EPIC to identify patients who have ED visits related to opioid use and/or who have been identified to have non-medical opioid use (e.g., nurse screening) and/or who have been identified and referred by clinical staff as potential study participants. The research team will inform the treating provider that their patient is potentially eligible for the study and will request permission to be introduced to the patient. The research team will use approved recruitment language to communicate the reason they are approaching the patient and ask if they are interested in participating in this specific study. Should the potential participants agree, the research team will provide the subjects with information regarding the next steps for participation.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

6.5 Duration of Study Participation

The study duration will be approximately 12 months. The duration of study participation for each individual participant will be 1 month, including screening/index visit, study intervention and follow-up. We will target 1 study enrollee per week, with a goal of 2 per week, and expect to enroll participants within an 11-month period. The study will end approximately one month after the final participant is enrolled, at the conclusion of that participant's one-month follow up. We know from our previous and ongoing studies that recruitment should not be limited by the number of eligible patients.

6.6 Total Number of Participants and Sites

Recruitment will end when approximately 35 participants are enrolled. Enrollment will take place out of the Emergency Departments in Bellevue Hospital, NYULH-Tisch, NYULH-Winthrop, NYULH-Brooklyn, and NYULH-Cobble Hill.

6.7 Participant Withdrawal or Termination

6.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- After the first 8 mg dose of BUP is administered, a study participant experiences any clinical AE (e.g., allergic reaction) that would preclude safe administration of the subsequent BUP 24mg dose during the index visit. The initial BUP 8mg is a standard dose used in the ED; it is only the subsequent BUP 24mg (for a total dose of BUP 32mg) that is being evaluated in this study.
- Thus, if a participant develops a reaction to the initial 8mg dose, the reaction would be attributed to the standard dose of BUP and not the larger dose of being tested.
- The participant meets an exclusion criterion (either newly developed or not previously

recognized) that precludes further study participation.
- The participant becomes a prisoner.

6.7.2 Handling of Participant Withdrawals or Termination

If participants are terminated from the study or withdraw themselves for any of the above reasons, the situation will be handled accordingly. If participants choose to withdraw themselves, but have no AEs, they will still be eligible to continue treatment for OUD, which may include BUP, and will be treated with the standard of care and connected to follow-up as clinic availability allows. If participants are terminated or removed due to any AE, they will be monitored and treated either in the ED or on an outpatient basis. If a participant meets exclusion criteria (either newly developed or not previously recognized), they will be formally withdrawn from the study, but may be still be eligible to continue BUP treatment outside of the study. If participants are withdrawn or discontinued early, enrollment will continue to meet a goal of 35 participants.

6.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agencies, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:
- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6.9 Acquisition

During the index visit, BUP (as a BUP-NX formulation) will be acquired from the Bellevue Hospital ED and NYULH Pharmacy medication dispensing system, where it is on formulary and approved for this indication. Upon completion of the third research visit or upon development of objective signs of opioid withdrawal (determined via COWS), participants will be provided with a prescription for sublingual BUP-NX, which they can acquire free of charge from the outpatient hospital pharmacy, located adjacent to the BHC ED.

6.9.1 Formulation, Appearance, Packaging, and Labeling

All BUP ordered as part of clinical care in the EMR and supplied through the Bellevue Hospital Clinical Pharmacy and NYULH Clinical Pharmacy. Currently on Bellevue Hospital formulary is the generic buprenorphine/naloxone (8mg/2mg) tablet and Subutex brand BUP monoproduct (the latter would be for use in patients/participants with a naloxone allergy only). The manufacturer will depend on what is currently on the hospital formulary and may change. Should this occur, participants will receive the equivalent medication dose. For example, if the formulary changes from BUP-NX (8mg/2mg) tablet to buprenorphine/naloxone (8mg/2mg) film, the participant will receive buprenorphine/naloxone (8mg/2mg) film sublingually (same bioavailability/dose).

Participants will also receive a prescription for BUP to pick up at their preferred outpatient pharmacy either after the third research visit, or when they demonstrate objective signs of withdrawal.

There will be no storage or administration of medication by the research pharmacy.

6.9.2 Product Storage and Stability

As above, medication will be ordered as part of clinical care and supplied through the Bellevue Hospital clinical pharmacy and NYULH clinical pharmacy. There will be no research medication stored/supplied by the study.

6.9.3 Preparation

The study agent does not require additional preparation.

6.9.4 Dosing and Administration

All participants will receive a total dose of BUP 32mg sublingually in divided doses during the index ED visit. After the participant has received a total of 8mg (as a single dose or in divided doses), BUP SL 24mg will be administered (i.e., 8mg + 24mg, or 4mg + 4mg +24mg). A dose of up to BUP 8mg SL may be administered by the clinical provider prior to enrollment of the patient-participant (i.e., given clinically, not as a research procedure).

After pre-medication assessments are complete and the participant is confirmed to have a COWS of ≥8, the participant will be given BUP SL to reach a dose of 8mg. Starting 30 minutes after BUP administration, the participant will be reassessed for withdrawal severity and any adverse events. As long as there are no unexpected significant adverse events, an additional BUP 24mg SL will be administered. Then, participants will be monitored and reassessed every 30 minutes for a period of at least 90 minutes after receiving the last dose of BUP.

Participants will return on days 1, 2, and 3 for research visits. At those visits, participants will be assessed for opioid withdrawal using the COWS scale. On the first day that the participant has objective signs of opioid withdrawal (via COWS), the Dr. McCormack, who is a licensed physician with an X-waiver for BUP prescription, or another study clinician (with the appropriate license and X-waiver) will electronically send a prescription the participant's preferred outpatient pharmacy for a daily dose of BUP 16mg (BUP or BUP/NX 8/2mg: two SL) to start immediately. Participants will be prescribed a quantity sufficient to ensure medication coverage until the date of their appointment for ongoing treatment with a (non-study) OUD treatment provider. Participants who do not exhibit opioid withdrawal at any of the visits on days 1-3, will be given a prescription upon completion of the day 3 visit with instructions to self-administer upon emergence of symptoms of opioid withdrawal or craving.

All participants will receive a referral to be seen by a provider experienced in treating OUD. Thereafter, continued treatment and specific daily dosage of BUP-NX will be a joint decision between the study participant and the healthcare provider.

6.9.5 Route of Administration

BUP will be administered sublingually.

6.9.6 Starting Dose and Dose Escalation Schedule

The starting dose and dose escalation schedule will be uniform among study participants during the index visit of the study. The regimen will vary only on timing of dosage administration, which will be determined based on each individual participant's withdrawal symptoms using various scales. After the Day 3 visit or if a participant has objective signs of withdrawal, a prescription for 16 mg BUP may be given to last until the participant's follow-up care appointment. Continued treatment and appropriate dosage of BUP-NX for each participant will be determined by the OUD-experienced provider they are referred to, and will be a joint decision between the study participant and provider.

6.9.7 Dose Adjustments/Modifications/Delays

All study participants will receive the 32 mg loading dose of BUP at the index visit. Thereafter, dose adjustments can be made on an individual basis, i.e. maintenance dosing of BUP can be escalated if withdrawal and craving are prevalent, or can be reduced if over sedation is a concern. Study assessments (see *Section 7.1*) will help the provider determine the course of action.

6.9.8 Duration of Therapy

This study aims to pilot a novel induction strategy for long term treatment of OUD with BUP. As part of the

study, participants will be monitored for one month after induction, but the goal is to facilitate continuation of treatment beyond this study; referral to continued treatment will be provided if desired.

6.9.9 Tracking of Dose

On days 1 – 3, following the index visit, participants will participate in in-person research visits and complete various assessments which will include objective and subjective measures of withdrawal and craving, and side effects. Participants will follow-up by phone at one month and again be asked to report adherence, as well as other substance use (Details of assessments can be found in *Sections 7.1 and 7.3*).

6.9.10 Study Agent Accountability Procedures

See *Section 6.9.6*. The initial 32mg loading dose of BUP will be dispensed from the Bellevue Hospital ED medication dispensing system and administered by a member of the research team in conjunction with the treating clinician. Participants will be given a prescription for BUP-NX (16mg daily in 8mg tablets/films) to last between their third research visit and their appointment for continuing treatment.

7 Study Procedures and Schedule

7.1 Study Specific Procedures

Baseline Measures
At baseline, socio-demographic information will be collected including age, sex, race/ethnicity, and housing status.. A broad range of tools selected from the Study Measures will be assessed at baseline and repeated at subsequent visits, include measures of substance use, opioid withdrawal and craving, risk behaviors, and quality of life. A urine pregnancy test will be used to confirm study eligibility among females of childbearing potential unless one has been performed already clinically. A urine and/or saliva toxicology test (standard drug panel plus BUP and fentanyl) will be collected for research-only purposes. No study-related activities will be performed prior to obtaining written informed consent.

Outcome measures
Engagement in treatment will be assessed by self-report and verified by contact with the participant's provider after the 30 day follow up visit. Tools selected from the Study Measures will also be used to assess substance use, functional outcome, opioid withdrawal and craving, general health, quality of life, and treatment preference.

7.2 Standard of Care Study Procedures

As part of standard clinical care, patients in opioid withdrawal will have a basic history and physical examination completed, including many of the assessments we will complete as study measures (e.g., drug use screening, DSM5, COWS). The provider may choose to obtain basic bloodwork and/or urine testing as indicated by clinical signs and symptoms or in anticipation of treatment. This includes, but is not limited to, a pregnancy test. Toxicology tests are not routinely obtained clinically in the ED primarily because the available tests are not capable of detecting fentanyl (or most other synthetic opioids) and because there are reliable, objective clinical signs and symptoms of opioid intoxication and withdrawal. It would be considered unethical to require toxicology testing to demonstrate the presence of opioid use in order for a patient to receive life-saving treatment (i.e., BUP) when the test itself cannot detect one of the most prevalent opioids being used. As such, toxicology testing in the ED is of little utility.

Whether they consent to study participation or not, all patients who present in clinical opioid withdrawal can receive symptomatic treatment for withdrawal. If an X-waivered provider is available in the ED, the patient will be able to receive BUP according to that provider's usual clinical practice. Patients with OUD can also receive referral for outpatient treatment and follow-up, as clinic availability allows

7.3 Laboratory Procedures/Evaluations

7.3.1 Clinical Laboratory Evaluations

See section 7.1 and 7.2 for laboratory evaluation that may be done as part of standard of clinical care or study procedures.

7.4 Study Schedule

7.4.1 Screening

7.4.2 Enrollment/Baseline

Index ED Visit (Day 0, 4 – 8 hours)

- Perform baseline assessments:
    - Obtain demographic information, medical/psychiatric history, medication history, substance use history.
    - Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
    - Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
    - Review history and verify inclusion/exclusion criteria.
    - Collect urine or saliva samples for toxicology testing, collect urine for a pregnancy test (in females of childbearing potential, if not performed clinically).
    - Assess and quantitate opioid and other substance use, withdrawal, craving, motivation for treatment, health status questionnaire, health services utilization).
- Participants receive total 32mg BUP in divided doses. After the participant has received a total of 8mg, participants will be observed for 30 minutes to ensure that there are no adverse reactions to BUP-NX. If the participant has a qualifying adverse event after the first dose (e.g., allergic reaction or other clinically significant AEs as described in Section 5.1.1), the second dose will not be given and the participant will be withdrawn from the study without receiving subsequent doses. Otherwise, the second dose of 24 mg will be administered.
- Participants will be assessed using opioid withdrawal scales (COWS, SOWS, VAS) prior to BUP administration and every 30 minutes afterward for at least 90 minutes after last dose.
- Participants will be discharged with 4 scheduled appointments, 3 research visits (days 1, 2, 3), an appointment for follow up with a BUP provider for ongoing OUD treatment, and a research follow-up phone call on Day 30, which marks the end of the study for the participant.
- In light of the health safety risks associated with the COVID-19 pandemic, interviews may be conducted remotely, rather than in-person, using an approved, secure audio or audio-video connection (e.g., telephone, Cisco Webex) from a setting offering adequate privacy. Participants will be advised that they may disconnect their video feed.

7.4.3 Intermediate Research Visits

7.4.3.1 Research Visits (In person, Days 1-3, 30-60 minutes)

- Participants will complete assessments of withdrawal, craving, and substance use in-person daily for 3 days. The visits will occur either at the ED or at other clinical research space on Bellevue/NYU campus. In light of the health safety risks associated with the COVID-19 pandemic, interviews may be conducted remotely, rather than in-person, using an approved, secure audio or audio-video connection (e.g., telephone, Cisco Webex) from a setting offering adequate privacy. Participants will be advised that they may disconnect their video feed.
- Participants will assess themselves for symptoms of opioid withdrawal using subjective scales
- At the first visit (Day 1-3) in which the participant has objective signs of withdrawal, the participant will be provided with a prescription for BUP. If the participant does not have objective signs of withdrawal by the Day 3 visit, the prescription will be written at the conclusion of that visit. The prescription will be electronically sent to the participant's pharmacy for BUP or BUP/Nx 8/2mg: 2 films/tabs taken SL daily for each day, starting immediately, with a quantity sufficient to last until the scheduled appointment for

ongoing treatment)

- Participants will be assessed for adverse events, which will be recorded and reported.

7.4.4 Final Study Visit (Phone)

Final Study Phone Check In (Day 30+/-3, 30 minutes)

- A healthcare utilization review and health questionnaire will be conducted to collect information on the type and amount of services received by participants.
- Functional outcome will be assessed using tools selected from the Study Measures.
- Attendance at follow-up treatment appointment within 1 month will be assessed by participant self- report and verified by contact with the provider.
- Participants will be assessed for adverse events, which will be recorded and reported.

At the conclusion of the study, the specifics of continued treatment will be a joint decision between the participant and the provider and will be managed by providers on a case-by-case basis. These decisions will not be reported to the study team. The novel part about this study is the induction strategy, but patients will otherwise be maintained on BUP in accordance with the standard of care. If patients wish to continue treatment, they will be connected with follow-up. The decision to continue will be a joint decision between the patient and provider.

Unscheduled Visit
If a patient is experiencing objective signs of withdrawal outside the hours of one of their research visit appointments, they may present to the Emergency Department for treatment. They will be asked to report this visit to the study team. The PI may be contacted 24 hours a day, seven days a week.

7.5 Concomitant Medications, Treatments, and Procedures

Concomitant therapy/medications will be evaluated and reviewed on an individual basis by the PI. See inclusion/exclusion criteria in *Section 6*. All concomitant prescription medications taken during study participation will be recorded on the study record in REDCap. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.5.1 Precautionary Medications, Treatments, and Procedures

Patients will be made aware of the risk of using other sedating substances such as alcohol or benzodiazepines while taking BUP, as these may increase the risk of over sedation and respiratory depression. They will also be made aware of the risks of using other opioids, as the concomitant use of BUP and full-agonist opioids will precipitate withdrawal.

7.6 Prohibited Medications, Treatments, and Procedures

Patients will be prohibited from participating in this study if they are already receiving treatment for OUD with methadone, naltrexone, or BUP, or are already prescribed other opioids for pain. They will be forbidden from initiating any of these medications during the study, except for the BUP prescribed by the researchers.

7.7 Rescue Medications, Treatments, and Procedures

The ED setting and clinical staff are well-equipped to manage all potential adverse events associated with the study. Patients/Participants may receive treatment for other medical conditions and/or ancillary treatment for symptoms of opioid withdrawal (e.g., nausea, muscle aches) or sedation as clinically indicated in accordance with standard clinical practices. All medications, treatments, and procedures will be delivered as part of the clinical care of the ED visit.

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
    - Note that the existing clinical protocol for the initiation of treatment with BUP in the Bellevue ED includes instructions for patients to return to the ED in some circumstances, including for repeat assessment, for social work or care management or referral assistance, for subsequent dose and/or prescription of BUP, for early return of withdrawal symptoms, etc. If return to the ED is for one of these reasons, it will not be considered an AE.
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

A **serious adverse event** (SAE) is any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Based on the appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Participants or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

AEs are graded according to the following scale:

Mild: An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.
Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention and/or interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

8.2.2 Relationship to Study Agent

The study uses the following AE attribution scale:

Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
Related: The AE is clearly related to the study procedures.

8.2.3 Expectedness

Dr. McCormack will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit (30 days), the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a participant that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

AEs are identified by the research coordinator or study team during study visits and phone call check-ins. After discharge, AEs are assessed at time of study follow-up visits.

All AEs and SAEs are reported according to the NYUSoM IRB's reporting guidelines.

The PI will report the following types of adverse events to the IRB and DSMB:
a. Serious AND unanticipated AND possibly, probably or definitely related events;

b. Anticipated adverse events occurring with a greater frequency than expected; and
c. Other unanticipated problems involving risks to participants or others.

These adverse events or unanticipated problems involving risks to participants or others will be reported to the DSMB, IRB, and FDA (if required) within 72 hours of it becoming known to the investigator, using the appropriate forms. The PI and DSMB will conduct a review of all adverse events upon completion of every study participant. The PI will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

8.4.2 Serious Adverse Event Reporting

See above *Section 8.4.1.*

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor 72 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 72 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 72 hours of the IR's receipt of the report of the problem from the investigator.

8.4.4 Reporting of Pregnancy

As detailed previously, pregnant women will not be included in this study. If any of the study participants become pregnant, however, it will immediately be reported to ND or IDE sponsor, study leadership, IRB, and regulatory agencies. Pregnant patients will be managed with the help of experts, and on an individualized basis. OUD treatment can be continued throughout pregnancy, but patients must be aware of the risks to the fetus, both of continuing treatment and abruptly discontinuing treatment. Participants who become pregnant during the study will be retained in the study, unless they voluntarily remove themselves.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Study Halting Rules

Administration of study agent will be halted when three grade 3 AEs determined to be "probably related" are reported to the sponsor. When the third grade 3 event is reported, enrollment screens will stop accepting new study participants. The study sponsor will inform the DSMB members within 24 hours of this occurrence and will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the study sponsor.

8.7 Safety Oversight

A Data and Safety Monitoring Board (DSMB) will be established for initial and ongoing protocol review, including data, protocol compliance, safety and efficacy data in compliance with the IRB.

Dr. Daniel Lugassy, MD, and Michael P. Bogenschutz, MD will serve as the DSMB members for this study. Dr. Lugassy is an Emergency Department physician and a toxicologist, and Dr. Bogenschutz is a Psychiatrist and addiction researcher who has extensive experience in opiate research. Dr.'s Lugassy and Bogenschutz will ensure protocol compliance and data safety, and neigher have ethical conflicts, including financial interest related to study outcome. If necessary, they will disclose any potential conflicts in writing. The board will meet at least annually, and as needed if a meeting is deemed necessary by the study team.

Day-to-day oversight of the trial is provided by the Principal Investigator (PI), Dr. McCormack. Dr. McCormack assures that informed consent is obtained prior to performing any research procedures, that all participants meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. Dr. McCormack will review all study data and any adverse events (AEs) according to protocol, and report all AEs to the DSMB chair, sponsor, and IRB.

During DSMB board meetings, Dr. McCormack and other research personnel will report on the trial status, followed by a closed session under the direction of the DSMB chairperson, during which time the investigators and research team may be present. This will be followed by an executive session restricted to DSMB members. Issues discussed may include those related to participant safety and benefit, whether the primary study question is being answered, conflict of interest, confidentiality, and ongoing study review (including AEs, SAEs, and regulatory issues). All adverse events and unanticipated problems during follow-up will be reported to the IRB, DSMB, and NIAAA. The PI will evaluate the frequency and severity of adverse events and determine if modifications to the protocol and/or consent form are required. During the review process, the DSMB will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the principal investigator, DSMB, or the NYU IRB have the authority to stop or suspend the study or require modifications. Following the DSMB meeting, recommendations will be made by the chairperson to Dr. McCormack and a final report (edited by all DSMB members) will be prepared and submitted to the NYUMC IRB. Stopping the trial due to safety concerns or interim analysis of the primary outcome are not anticipated; the study medication, BUP/NX, is FDA-approved, and no significant safety issues have arisen. DSM Plans typically include stopping rules that specify the outcome differences detected between groups during an interim analysis that can result in stopping the clinical trial. In general, stopping rules will reflect one of the following conditions: 1) there is clear evidence of harm or harmful side-effects of the treatment; 2) there is not likelihood of demonstrating treatment benefit; 3) there is overwhelming evidence of the benefit of the treatment. Again however, because we are simply using a higher dose of BUP/NX to initiate treatment, which is already FDA-approved for the indication in question, and since data from other studies do not suggest significant safety considerations, early stopping on the basis of clear benefit (yes/no) is not anticipated.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- As described in Section 8.7, Dr. McCormack will oversee the study in its entirety and ensure that human participants safety and wellbeing is protected, that all data is carefully reviewed, and that all adverse events are appropriately reported.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

The overall findings of the study will be used to assess the feasibility, acceptability, and utility of initiating a BUP loading dose in ED patients and linking patients to ongoing OUD treatment. Statistical analyses will consist of descriptive analyses for the primary outcome (proportion of participants successfully induced via loading dose), and secondary outcome measures (opioid withdrawal and craving scores, time to next BUP dose, opioid and other illicit drug use, proportion making a successful transition to an outpatient clinic). Measures of central tendancy (the mean), and the variability (standard deviation) of the study participant characteristics and for other participant-reported or objectively evaluated measures will also be calculated. Summary tabulations and measures of central tendency, variance, and other distributional properties of the obtained results will be presented. Where applicable, we will also conduct cross-tabulations and comparative analyses of variance based on selected key characteristics of the study participants (e.g., sex, age categories, baseline opioid requirement). This is a pilot study aimed at producing preliminary data which will inform future large-scale studies. Our analyses will be purely descriptive and we will not attempt to show an effect size, thus there is no power calculation for this sample size, it is based on feasibility.

Our a priori hypotheses of the potential effect of patient characteristics on outcomes will be tested in subsequent large scale studies. The outcomes obtained in the proposed pilot study will also be compared with benchmark data based on the results of our previous studies with similar patient populations and other available recent or contemporaneous research and clinical data. Adverse events recorded in the study will be reported using both quantitative tabulations and qualitative descriptions.

10.2 Measures to Minimize Bias

10.2.1 Enrollment/Randomization/Masking Procedures

This open label, single arm study does not involve any randomization or blinding. Study participants will be recruited by convenience, and participants will receive the 32mg BUP induction dose. Analysis of the study outcomes will facilitate planning of clinical protocols for treatment of OUD and future large scale studies using this novel induction approach.

11 Source Documents and Access to Source Data/Documents

All study data will be entered into REDCap, a secure, HIPAA-compliant database platform, and unique study ID's will be used to de-identify participants' data. REDCap is currently approved by NYU MCIT to store data containing PHI. Data will be stored on secure servers and/or in locked filing cabinets in a locked research office with access only to authorized study personnel as identified by the principal investigator and project manager for this study. Dr. McCormack will permit study-related audits and monitoring as required by the IRB, the sponsor, government, or any University regulatory, compliance, or quality assurance group who is authorized to review the study.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.1 Ethical Standard

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.2 Institutional Review Board

13.2.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. This protocol has been submitted with the Informed Consent Form, verbal consent script and study overview sheet. Informed written consent will be obtained prior to any study activities.

13.2.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. It will take place in the Emergency Departments of Bellevue Hospital, NYULH-Tisch, NYULH-Brooklyn, NYULH-Winthrop, NYULH-Cobble Hill. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They will be required to sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the participant's research record, which will be kept in locked filing cabinets in a locked research office with access only to authorized study personnel as identified by the PI and project manager. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the participant's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The Informed Consent Form has been submitted with this protocol. The research staff obtaining consent may be located remotely (outside of the ED) with communication occurring by telephone or IRB-approved virtual technologies (i.e., WebEx) and consent completed using a paper informed consent form or electronically captured using REDCap software. Electronically signed informed consent documents will be maintained within the REDCap data system in accordance with approved guidelines.

Any patient who is unable understand the study and provide written informed consent to participate will be excluded, and this could include anyone who has a medical, psychiatric or cognitive impairment, as well as someone who is currently too intoxicated to understand and consent to participation in the study. Dr. McCormack has extensive experience working with ED patients who have substance use disorders and enrolling them in research studies, and has developed methods of quizzing patients on the study purpose, risks, and benefits, to ensure their understanding of the study. We will assess all potential participants with exact or modified questions selected from the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC), which can be viewed at https://irb.nyspi.org/themes/doc/Literature.Jeste.DecisionalCap.IRBmbr.Dec2017.pdf. Dr. McCormack has published on the topic of including ED patients with alcohol use disorder in research, and showed the feasibility of using the UBACC to assess consent (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4530610/).

Specific questions we will ask include:

1. What is the purpose of the study that was just described to you?
2. What makes you want to consider participating in this study?
4. Do you have to be in this study if you do not want to participate?
5. If you withdraw from this study, will you still be able to receive regular treatment?
6. If you participate in this study, what are some of the things that you will be asked to do? How many times will you be asked to come back for research visits?
7. Please describe some of the risks or discomforts that people may experience if they participate in this study. (Please describe the 2 serious risks associated with the study.)
8. Please describe some of the possible benefits of this study.
9. Is it possible that being in this study will not have any benefit to you?

It is important to note that treatment with buprenorphine requires the patient to be experiencing withdrawal symptoms, so no patients who are currently under the influence of drugs will be eligible for the study. Rather, they may be re-assessed for eligibility at a later time.

13.4 Participant and Data Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI.

The following procedures have been put in place to minimize this risk. Patients will be fully informed that information collected during the study will be kept confidential and be available only to the research team. The PI will apply for an NIH Certificate of Confidentiality to encompass protocol activity and participant data and ensure against the release of confidential information. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

Data will be de-identified and unique identifiers will be used. We will use data collection and handling measures that are secure and compliant with HIPAA, Bellevue Hospital Center, and NYULH. Screening data and volunteer survey data will be entered into REDCap, a secure, HIPAA-compliant database platform. REDCap is currently approved by NYU MCIT to store data containing PHI. Data will be stored on secure servers and/or in locked filing cabinets in a locked research office with access only to authorized study personnel as identified by the principal investigator and project manager for this study.

All research assistants and others involved in the study will be required to complete appropriate IRB Human Subjects and HIPAA trainings. The principal investigator will be responsible for ensuring that all staff involved in the study understand and follow all human participants' confidentiality protection measures. Any potential breaches of confidentiality will be reported to the study PI, who will report such breaches to the IRB and any appropriate regulatory and funding agencies, and take any further corrective measures as appropriate. Study findings will be presented using only aggregate data; no publication or presentation will involve use of any individually identifying information.

13.4.1 Research Use of Stored Human Samples, Specimens, or Data

Intended Use: Data collected under this protocol may be used to study ED-based treatment of OUD using BUP. No genetic testing will be performed.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in an organized manner to ensure accurate interpretation of data. Most data will be recorded electronically, but when necessary, hard copy CRFs will be completed with black ink to ensure clarity of reproduced copies. Any changes or corrections will be indicated with a single line crossing out the original entry.

Electronic CRFs (eCRF) will used in REDCap, and any hard copy CRFs will be recorded in REDCap after the participant is enrolled. Any discrepancies between a paper and electronic CRF will be explained and captured in a progress note and maintained in the participant’s official electronic study record in REDCap.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. The principal investigator will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans must be approved by the IRB of record. All protocol deviations will be monitored for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that they do not compromise the integrity of the trial.

All protocol deviations will be recorded in the participant's study record. Dr, McCormack must be contacted immediately if an unqualified or ineligible participant is enrolled into the study.

Additionally, all research assistants and those involved in the study are responsible for reviewing the IRB of record's definition of a protocol deviation or violation and understanding which events need to be reported. Researchers must recognize that the IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

The study will be funded by the Emergency Medicine Foundation (EMF) and the NYU Clinical and Translational Science Institute (CTSI).

15.2 Costs to the Participant

Participants are not expected to face any additional costs by participating in this study. Participants will be ED patients recruited during their ED visit. They will be billed for the costs of medical care during that encounter, if the expenses would have happened even if they did not choose to participate in the study. If they have health insurance, the cost of these services will be billed to their insurance company. If their insurance does not cover these costs or they do not have insurance, the costs will be their responsibility. The study medication (BUP) will be provided as part of clinical care and including in the billing of their clinical services. All participants will be patients who are eligible and interested in receiving treatment for OUD with BUP. As such, the study medication is the same medication that they would have otherwise received during routine care of their ED visit but at a higher dose. They will not have to pay for the research urine or saliva drug screen(s), but will be responsible for any other laboratory studies that are part of routine care. Participants will be compensated for their time to complete research assessments and transportation for follow-up (see Section 15.3). Receiving BUP at the dose indicated by this study protocol (32 mg) will not impact insurance coverage for patients.

15.3 Participant Reimbursements or Payments

Payment will be provided reimbursement for participation in this study. Payment will be distributed incrementally for each follow-up treatment visit or off-site survey in which the participant participates. This population consists of a large volume of patients with OUD or other substance use disorders who do not regularly receive healthcare; without some payment and financial aid in commuting back and forth to visits, it is much more unlikely that patients will follow-up and complete the study. The total amount of compensation was carefully considered to come up with an amount that provides enough incentive for participation, but is unlikely to deceive people into participating.

$80 value will be provided at initial recruitment in the Emergency Department for study participation. Participants will receive $40 value for each in-person research visit on days 1, 2, and 3 of the study, and receive a total of $120 value for completing all three. $40 will also be provided for the follow up phone call at Month 1. A total of $240 value will be disbursed to each participant. Participants will also be provided with Metrocards or car service (Uber, Lyft) within the NYC Metropolitan area.

For methods of compensation, participants can choose either the full value on a Clincard or a smartphone with a 30-day service plan plus the additional value on a Clincard. We anticipate the cost of the phone will be approximately $5-$20, and the cost of 30-days of cellular service is $20. For example, if a participant chooses to receive a phone and 30-day service plan during the index visit, they will also receive $40-$55 on the ClinCard.

16 Study Administration

16.1 Study Leadership

The study will be led and supervised by Dr. Ryan McCormack.

17 Conflict of Interest

The investigators report no conflicts of interest.

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