Title: An Innovative Intervention for OUD Treatment

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JHM IRB - eForm A – Protocol

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1. Abstract

This application proposes to conduct a randomized, controlled clinical trial to test the efficacy and safety of the NSS-2 Bridge Device (BD) when used for the treatment of opioid withdrawal. The BD is an FDA cleared device that is currently marketed for the treatment of opioid withdrawal; preliminary evidence suggests it is effective and has a low risk for adverse effects. However, the product has not been tested against a sham control condition within the context of treating opioid withdrawal. Descriptive data provide evidence that it has effectiveness in suppressing opioid withdrawal, but there is a need to test the device under controlled conditions. In addition to testing the BD to a sham condition (SBD), the study includes a third condition – lofexidine (Lucerma). This is an FDA-approved medication for the treatment of opioid withdrawal, and this study will be the first direct comparison of two available non-mu opioid approaches that can be used to help transition patients off of opioid physical dependence. Novel mechanisms that assist in transitioning a person from physical dependence on opioids to a non-dependent state are needed – to address a patient-centered desire to live without maintenance on opioid agonist treatment (OAT), and/or to aid in the transition to antagonist treatment. Given the accumulating evidence for the efficacy of naltrexone (NTX), and especially extended release NTX, new and innovative ways to help patient stabilize on antagonist treatment are needed. The BD may serve a useful role in this process. The device is a percutaneous nerve field stimulator that has 4 electrodes placed on/near the ear, with wires to a small device that is worn behind the ear. The device targets 4 cranial nerves (V, VII, IX, and X) that have auricular branches, and it provides alternating low-grade electrical frequencies to these nerves as a means for peripheral stimulation of the specific cranial nerves. Stimulation by the device is hypothesized to provide central nervous modulation of pain paths. When used clinically, the device is worn continuously for 5 days, and reports of its use indicate that it provides relief of opioid withdrawal within approximately an hour of placement. The primary goal of this study is to demonstrate that the BD is more effective than a sham control condition in suppressing opioid withdrawal signs and symptoms, and a secondary aim is to determine its relative efficacy compared to lofexidine. Participants will be persons physically dependent on opioids, with a diagnosis of OUD, and who agree to reside on a residential unit for the study duration. At the end of the residential stay, participants will be offered oral naltrexone treatment, and the option of transition on to XR-NTX. Given the magnitude of the opioid crisis in the United States, and the need to both expand treatment options as well as mechanisms that can facilitate the transition on to antagonist treatments, the BD has the potential to have substantial impact and public health significance. In addition, expanding the treatment of OUD to effective devices can open up new thinking and approaches that are not based solely on pharmacological approaches to this devastating medical illness.

2. Objectives (include all primary and secondary objectives)

1. Determine whether the BD is more effective at suppressing opioid withdrawal when compared to a sham Bridge Device (SBD)? (Primary objective)

2. Determine whether the BD is more effective at suppressing opioid withdrawal relative to Lofexidine (Secondary objective)

3. Determine whether persons treated with BD/Placebo versus SBD/Placebo require fewer doses of symptomatic concomitant treatments? (Secondary objective)

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Novel and new approaches for the treatment of opioid use disorder (OUD) are needed

Opioid Use Disorder (OUD) is a significant public health problem. Despite the fact that pharmacotherapies have been approved for OUD, including the opioid agonists methadone and buprenorphine and the opioid antagonist naltrexone (NTX), the massive scale of the current opioid crisis and the lack of universal treatment access underlies the substantial need of the medical community to continue innovating in this area.

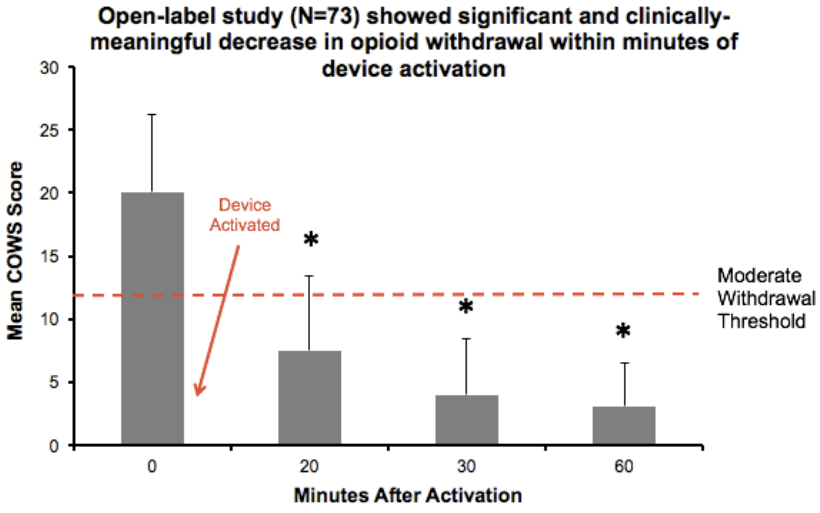
Medical devices are a new and emerging method for augmenting existing treatments or expanding treatment access. Although the medical community has embraced the use of medical devices for a wide variety of other medical conditions (e.g., degenerative joint disease, diabetes, cardiac disease), there have been relatively few devices developed for substance use disorder (SUD) treatment. The few exceptions include automated medication dispensing devices that have been developed to improve medication adherence and reduce medication diversion, and transcranial magnetic stimulation for the treatment of depression[1], which has recently led to the application of transcranial direct current stimulation to reduce cravings in patients with alcohol use disorder[2], in otherwise healthy smokers[3], and in cocaine users[4].

The NSS-2 Bridge Device (BD) is a neuromodulator medical device that has been cleared through the De Novo pathway by the FDA to reduce symptoms of opioid withdrawal. Neuromodulators send electrical impulses to specific nerves to alleviate pain or other symptoms. Several neuromodulators have been cleared for use in a variety of pain conditions, including irritable bowel syndrome and chronic pain. The BD is the first medical device and neuromodulator to be cleared for an SUD indication. Importantly, medical devices reviewed by the FDA are *cleared* (based on safety) rather than *approved* (based on efficacy), which means the BD did not need to demonstrate efficacy before it became commercially available. Although the BD was deemed safe for use, additional evidence is needed to demonstrate its efficacy relative to a placebo or a standard of care treatment. As a result, the device was not required to have a sham-controlled trial for FDA clearance and there is no active research, to our knowledge, that specifically addresses the degree to which opioid withdrawal can be treated through neuromodulation. A neuromodulator that helps bridge patients from opioid physical dependence to antagonist treatment and provides a new and cost-effective mechanism for augmenting existing OUD pharmacotherapies, improving supervised withdrawal outcomes, and expanding treatment access, would benefit the patient and the provider community and lead the way in the use of medical devices for OUD/SUD treatment.

Cranial Nerve Neuromodulation via Auricular Stimulation: The BD is believed to minimize the severity of opioid withdrawal symptoms by sending electrical impulses to the cranial nerves. Tracing studies have demonstrated that the external ear contains branches of four cranial nerves (V, VII, IX, X)[5 6]. Of particular interest are cranial nerves IX and X, which are partially responsible for regulating the sympathetic (fight or flight) and parasympathetic (rest and digest) nervous systems. Cranial nerve X (the vagus nerve) directly controls several systems of the body that are dysregulated during opioid withdrawal, including digestion, cardiovascular function, stress response, and emotion. The vagus nerve has projections to brainstem nuclei, including the nucleus tractus solitarius (NTS), which acts as a "relay station" to other areas of the brainstem including the rostral ventromedial medulla (pain), rostral ventrolateral medulla (sympathetic activity associated with cardiovascular function), and other brain levels including the

hypothalamus (learning and memory) and the amygdala (fear and anxiety). Previous studies of electrical stimulation of the external ear have exhibited neuromodulatory effects in central brain regions[7 8]. The limbic system, particularly the amygdala, is a common central link between a state of chronic pain and opioid dependence[9-13]. This brain region also has been associated with the negative emotional state during opioid withdrawal and drug craving[14]. The neuromodulatory effects of the BD on the amygdala have been demonstrated in a pre-clinical study[15]. In that study, the neuronal firing of amygdala neurons in rats was reduced by approximately 65% after 15 minutes of stimulation. Those findings supported the rapid neuromodulating effects of the BD in a clinical study[16].

A multisite, open-label retrospective chart review study was recently completed that assessed the efficacy of the BD to reduce opioid withdrawal severity in 73 outpatients who had DSM-IV opioid dependence[16]. All patients had observer (COWS) withdrawal assessment ratings collected at baseline (pre-device placement), and then at 20, 30, and 60 minutes after device application. In addition, a subset of outpatient clinics where this work was conducted recorded COWS scores at the end of the 5-day period. Patients in this study were considered successful if they transitioned on to XR-NTX at the end of the 5-day period. As shown in the figure here, the mean (SD) COWS score prior to device placement indicated participants were experiencing moderate levels of opioid withdrawal, which decreased in both a significant and clinically-meaningful way once the device was activated. Patients could receive rescue/ancillary medications during the subsequent five-day period; no subjects received medications in the first hour after placement, and during the full five-day period, no benzodiazepines, antipsychotics, or opioids were given, although 38% of participants did receive an antiemetic medication during this time. Only 33 of the 73 patients had a COWS score recorded on day 5, but for these 33, the average score was 0.6. Finally, and particularly impressive, 64 of the 73 patients (88%) successfully received a first dose of naltrexone at the end of the 5-day period. While these findings are intriguing, there are several limitations to this work. The BD was cleared by the FDA for opioid withdrawal suppression on the basis of these data, which is possible because device approval follows a different pathway than pharmacotherapy approval and is based primarily on evidence of safety rather than effectiveness for the indicated condition. There have been no randomized, controlled trials of the BD for opioid withdrawal. The saliency of placing a novel device to the head/ear and the promise that it can "fix" withdrawal has the potential to produce substantial expectancy effects, which may be conveyed by the circumstances of the treatment and trial, especially given that the device is purported to robustly resolve a distressing state (opioid withdrawal). Findings from a rigorous and controlled trial are needed to determine if the device truly works. In addition, if this study does demonstrate efficacy of the device, then there is the opportunity for devices such as this to be used to probe the biologic underpinnings of opioid use and misuse. Thus, while the preliminary data described here were sufficient for FDA clearance of the BD, and they serve as a basis for its further study, there is clearly a need to have more rigor in the work that assesses the efficacy of the BD as a treatment for opioid withdrawal symptom management.



4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

b. Study duration and number of study visits required of research participants.
c. Blinding, including justification for blinding or not blinding the trial, if applicable.
d. Justification of why participants will not receive routine care or will have current therapy stopped.
e. Justification for inclusion of a placebo or non-treatment group.
f. Definition of treatment failure or participant removal criteria.
g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Table 1. Study Overview

Study day (day of week)	Total daily morphine dose (mg)	Bridge or sham device	Lofexidine or placebo capsules
-7	60-120		
-6	120		
-5	120		
-4 naloxone challenge	120		
-3	120		
-2	120		
-1	90		
1	--	X	X
2	--	X	X
3	--	X	X
4	--	X	X
5	--	X	X
6	--		X
7	--		X
8 naloxone challenge	--		
9	--		

Preparation for discharge will occur throughout the CRU time and will include the option to transition to NTX. All participants will be referred to outpatient follow-up aftercare.

Study Overview:

This study will enroll persons with current OUD who are not currently receiving medications for OUD (MOUD). Applicants will be screened and eligible participants will be admitted to the residential Clinical Research Unit (CRU) at the Johns Hopkins Bayview Medical Center (JHBMC) for the active phase of this study. The total duration of time on the CRU is approximately 2-3 weeks. The study design uses the same general research design as our previous successful tramadol-ER randomized clinical trial. Upon admission, subjects will be stabilized for 7-11 days onto a short-acting opioid agonist. This may be morphine (30mg, SC, QID) or hydromorphone (up to 20mg, oral up to six times daily), and will undergo a precipitated withdrawal challenge using the opioid antagonist naloxone after ≥4 days of morphine/hydromorphone maintenance to ensure they are sensitive to detecting and reporting opioid withdrawal symptoms. This is a standard practice for our studies[17 18]. We propose two short-acting agonists here based as both approaches are grounded in the empirical literature and have demonstrated a good safety profile and efficacy for reducing opioid withdrawal. While we prefer morphine, national shortages of this medication have required us to add a hydromorphone option. The total number of days of morphine/hydromorphone maintenance is variable because it will allow us to schedule the first BD exposure on a weekday.

The BD and blinded study medication (capsules, described below) will begin on Study Day 1. The final dose of morphine/hydromorphone on the day preceding the start of the BD (Study Day -1) will be omitted and no additional morphine/hydromorphone will be administered from that point forward. Participants will be randomly assigned to one of three conditions: active Bridge Device with placebo medication (BD/P), sham Bridge Device with lofexidine (SBD/L), or sham Bridge Device with placebo medication (SBD/P). Participants will be informed that the device may be active or sham, and that capsules may be active medication or placebo, and that assignment is double-blind. The device will be applied on Study Day 1, once participants have a Clinical Opiate Withdrawal Scale (COWS) score of 9 or greater (high end of mild withdrawal). Our experience with this process suggests participants will achieve this score within a few of hours after their last morphine/hydromorphone dose. However, if a participant does not have a COWS score of 9+ by the end of Day 1, then they will be dropped from the study, stabilized on treatment (e.g., OAT), and transitioned into routine community-based outpatient treatment at one of our programs or affiliated treatment programs. The BD will begin on Day 1 and last for 5 days (the recommended duration of use for the device), and capsule dosing will continue through Day 7. Participants will be monitored for an additional 4 days after device removal to determine whether a resumption or rebound in withdrawal occurs.

Throughout the participant's time on the CRU, but especially over the last 2-3 days, planning for outpatient treatment will occur. Participants will undergo a second naloxone challenge after removal of the

device/capsule completion to verify lack of opioid physical dependence and will be provided access to oral naltrexone to be followed by extended release naltrexone. All participants will be given referral to and assisted with engaging in outpatient treatment following study discharge.

General Study Procedures:

Remote Consenting and Screening: During the COVID-19 crisis, participants will be consented virtually. Participants will be able to review the consent form electronically using a secure IRB compliant method, and will be able to securely sign and submit the form after they have been provided ample time to read and ask questions related to the protocol. Participants will promptly receive an electronic form of the consent and can also receive a printed version via mail, at their request. Virtual consenting will follow IRB guidelines for virtual consenting procedures and will occur prior to any data collection.

Self-report portions of the screen will be done virtually (via phone or Zoom) with study staff. For persons who do not have access to phones or when participant privacy might be challenging (e.g., for persons without stable housing), we will conduct self-report portions of the screen in a private room at the BPRU with Zoom connection to study staff in another room, to minimize participant/staff interaction. If deemed eligible based on self-report and interviewer-based questionnaires, participants will be scheduled to complete a brief in-person medical assessment consisting of a blood draw and an electrocardiogram. Participants will also complete a physical exam with a medical team member or at Patient First, an acute care center located on campus to determine medical eligibility. Medical team members may also review participant's medical history prior to determining study eligibility. Participants will also provide a urine sample to be tested for recent drug use and pregnancy (if applicable).

Description of procedures to minimize risk during the COVID-19 pandemic for in-person sessions: It is not possible to conduct a portion of the screening and the inpatient protocol remotely due to the need to collect biological measures (e.g., blood, urine) for eligibility determination and to have continuous medical supervision and care during the supervised taper. However, there are specific safety procedures that will be put into place to minimize person-to-person contact in the context of the COVID-19 pandemic. First, during all in-person sessions, all participants will be required to wear a properly fitting face surgical grade mask while in the laboratory. The exception to this policy will be when the participant is alone in their residential room at the Clinical Research Unit (CRU) with nobody else present. Facemasks which meet these requirements will be provided to participants at no cost. Second, participants will have their temperature checked using a non-invasive procedure (forehead temperature reading) and asked about potential COVID-19 symptoms upon arrival to each session and possible exposure to COVID-19. Any subject who arrives with a temperature indicative of fever or reporting symptoms indicative of COVID-19 per the JHU clinical screening algorithm will be required to return home and participation will be paused for at least 2 weeks after which a health care professional must clear a return to participation (e.g., with a negative COVID-19 test). Third, participants must adhere to the CRU policies for COVID-19 which are uploaded in the supplemental document section. This will be provided to participants at a screening visit and/or the first day of their enrollment into the residential portion of the study.

The CRU policies stipulate that participants must remain in their residential rooms unless completing study related activities that must take place in another room (i.e., electrocardiograms). In order to address issues related to isolation or boredom, participants will have access to various recreational activities in their room including video games and stationary bicycling. Participants will also be allowed to bring materials from their home including books and magazines.

Clinical Research Unit (CRU): Eligible participants must provide documentation for a negative COVID-19 test which was completed within 72 hours prior to admission to the CRU. This study will be conducted at the JHBMC Clinical Research Unit (CRU), a 10-bed residential unit. The BPRU has successfully worked with the CRU on a number of research studies, and several that involve opioid-using volunteers. . Participants who smoke tobacco products are allowed to smoke (and the CRU has a specially designed smoking room on the unit for this purpose) or be provided with nicotine replacement therapy. No medicinal cannabis use will be permitted during study enrollment.

Electrocardiogram: Electrocardiograms (ECG) will be measured at screening to determine eligibility and then again throughout the treatment portion of the study as an outcome measure. All ECGs will be reviewed by a licensed physician on the BPRU staff, regardless of the automated reading produced. ECGs that are automatically read as abnormal on the print out, or that a BPRU physician judges as abnormal or of concern, will be read by a cardiologist credentialed to read and interpret ECG tracings. However, ECGs that have a reading of "sinus bradycardia" with a heart rate equal to or greater than 55 bpm, and no other indicated abnormality will not necessitate a reading by a credentialed cardiologist.

The cardiology group at Greater Baltimore Medical Center (GBMC), who are credentialed at JHH to read ECGs, will serve as the primary readers of the BPRU's abnormal ECGs. We will provide them abnormal ECGs that are collected at screening and during the study and we will use codes rather than participant names when tracings are transmitted to the group. No PHI will be conveyed to them. As such, GBMC cardiologists would not necessarily be study investigators unless there were other reasons beyond the review of ECGs to make them such.

If an abnormal ECG is sent to the GBMC cardiology division, a copy of the resulting reading will be placed in the participant's study record (including, for example, recommendations and steps taken regarding further testing). BPRU investigators will not take any actions related to research until an official interpretation has been provided by the GBMC cardiologist

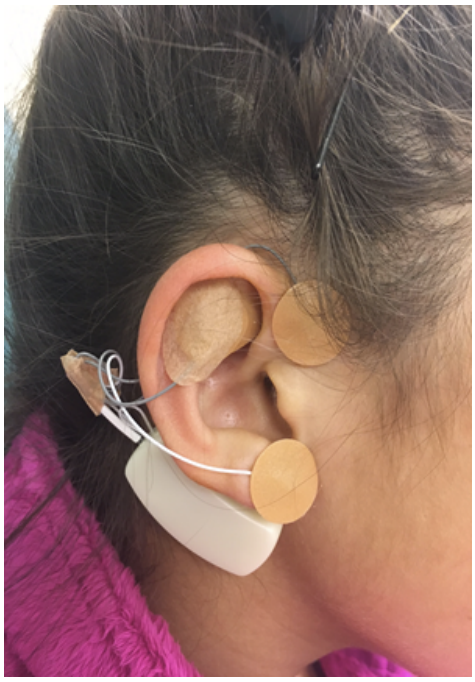
Naloxone challenge sessions: Participants will undergo two naloxone challenge sessions in this study. The first will occur ≥4 days of morphine/hydromorphone stabilization (the specific day will vary to prevent weekend challenge sessions) and the second will occur on Study Day 8 (**see Table 1**). Challenge sessions are conducted by a trained research assistant, with naloxone (0.4 mg IM) administered by a nurse. Medical staff will be available to manage any adverse events associated with the challenge. The primary outcome measure for the first session is the peak ratings score on the COWS. To be consistent with a prior BPRU study in which naloxone challenges were administered to morphine-maintained volunteers[18], and in which mean peak ratings were 7.6, absolute peak scores rather than change from baseline will be used. COWS assessments will be collected at -15 and 15, 30, 45, 60, 75, 90, 105, 120, 135 and 150 minutes relative to the time of naloxone injection (0 minutes). In addition to the COWS, other measures collected include the SOWS, visual analog scale ratings of drug effects, observer ratings of opioid effects, physiologic measures (e.g., heart rate, blood pressure, respiratory rate, temperature, pupil diameter), and psychomotor performance tasks. This standard battery of assessments has been utilized in other laboratory studies of opioid effects conducted at the BPRU[19-22]. Participants will receive a dose of morphine (30mg, SC) or hydromorphone (up to 20 mg, oral) at the end of the session to remove any persistent signs of opioid withdrawal. The second naloxone challenge session (0.4 mg IM) will occur at the end of the study (Study Day 8), and will be used to confirm the absence of residual opioid physical dependence in support of naltrexone treatment.

Randomization and stratification: Participants are randomized to 1 of the 3 conditions (BD/P, SBD/L, SBD/P). An urn randomization procedure[23] will be used, and stratification variables will be: sex, race (Caucasian/Non-Caucasian), and peak response to the naloxone challenge that occurs during the morphine/hydromorphone dosing phase (based upon a COWS peak score of <9 versus ≥9, as has been used in a prior study[17]. Urn randomization decreases the likelihood that groups are unbalanced on the stratification variables selected, which is especially relevant given that this may be viewed as a smaller sample RCT.

The Bridge Device (BD) **(see Picture below)**

The BD device is recommended for use in outpatient settings for a period of 5 days. The device manufacturer- Innovative Health Solutions - will train all staff members on proper placement of the device, prior to the start of the trial. The BD device is an ambulatory, neurological device which consists of a battery powered, externally affixed generator with 4 wire leads attached to 1 electrode/needle array and 3 single point needles. It delivers a 1-10 Hz neuromodulating signal, with a 1ms pulse width, a 3.2v

amplitude and an impulse interval of 100ms/2 sec. The generator is designed to deliver pulses periodically over a 120-hour period. The percutaneous, titanium needles on the BD are placed on the ventral and dorsal region of the ear, close to neurovascular bundles, to create a field effect in the auricle that theoretically stimulates all nerve branches. This is very different from other forms of electrical stimulation. Electroacupuncture, for example, delivers very different electrical current and requires precise placement of needles in specific "acupoints" by a trained expert and only allows for short periods of stimulation. The BD delivers alternating frequencies of stimulation that is not perceived as painful or noxious. This, combined with the programmed changes in polarity within all 4 leads, prevents nerve attenuation and allows for continued stimulation. The electrodes are placed percutaneously in the external ear with the help of a transilluminator to visualize the neurovascular bundles. Three electrodes will be placed on the ventral and one on the dorsal aspect of the ear. The electrodes are taped and secured behind the ear next to the generator itself, which is secured to the skin with adhesive.



To date, patients utilizing the BD have not reported any pain when the device is placed or for the 5 days it is worn, but will be told they may or may not feel a sensation after device placement. The electrode/needle arrays are implanted according to the individual's arterial and cranial nerve anatomy. The exact location of the implantation may vary slightly from person to person but is determined by both knowledge of auricular neuro-anatomy and visualization of the neurovascular bundles by transillumination. The points will be targeted by four-point electrical stimulation after carefully cleaning the ear. The devices are easily removed by removing the tapes and adhesives. At the end of the 5-day period a staff member will remove the device and discard it in a sharps container.

Contents of the Bridge kit: Every BD kit is packaged and consists of:

(1) An alcohol swab; (2) Prep and stay swab; (3) Round fixation plasters; (4) Fixation plasters to fasten the generator; (5) Steri-strip adhesive vial; (6) Sterile wire harness pack; (7) Generator; (8) Tweezers; (9) Surgical marker; and (10) Transilluminator

Placement details:

(1) The neurostimulator placement will be performed per BD training protocol instructions.
(2) Before the neurostimulator placement, the participant will be advised that they may or may not feel a slight pulsing sensation or a warming sensation in the ear to which the electrodes are affixed. The pulsing and warming sensation may disappear after approximately 5 minutes. If there is discomfort in the ear, the array will be slightly repositioned until the discomfort level decreases or goes away.
(3) Device placement takes approximately 5-10 minutes.
(4) A photo will be taken of the placement for record purposes (to document placement location).
(5) Post-placement, participants will be advised not to immerse the device in water as the device is water resistant but not water proof. If showering or washing their hair, it will be recommended the participant place a dry wash cloth over the area to help protect the device.

<u>Sham Bridge Device (SBD) and blinding</u>

Two-thirds of participants will be assigned to a sham Bridge Device (SBD) condition (either with lofexidine or placebo capsules). The addition of an oral medication further blinds participants to their assigned condition. The active BD does not typically produce more than a transient detectable effect if at all; some patients have reported a tapping or warming sensation. In a study of adolescent patients with abdominal pain, and who randomly received either an active or sham device, at the end of the study a substantial proportion of both groups reported believing they were on the active device, although a

higher proportion (75%) in the active group thought so relative to the sham group (46%)[24]. This may also reflect the significant efficacy found for the active condition.

As participants only receive the BD or SBD device, any slight sensation associated with the active condition will be only known to participants in this condition. Our goal is to minimize participant overlap in their time on the CRU, to further ensure there is no discussion of the experience with the device that might contribute to attempts to guess whether the person received an active or sham device. Finally, all participants will complete an end of study assessment in which they will answer questions regarding which condition assignment they believe they received (both with respect to the device as well as medication), and why they believe this.

Lofexidine (L) and its dosing

Lofexidine has been FDA-approved agent used for the treatment of opioid withdrawal. Lofexidine can produce side effects (e.g., drowsiness, lightheadedness, slowed heart rate). While there are side effects and risks associated with the use of lofexidine, it should be noted that participants are in a monitored environment (which is not necessary for use of this medication, but ensures safety in this study), and the doses being used are within the range outlined on the FDA-approved label.

All participants receive capsules 4 times daily for 7 days; the dosing schedule for lofexidine is based upon that used in the study by Gorodetzky[25] that was used to support lofexidine's approval for OUD. This includes a 5-day dosing period and subsequent 2-day dose taper, consistent with the lofexidine label recommendation. For analytic purposes, the primary outcome is assessed during the active dosing period (Days 1-5). Doses of lofexidine are overencapsulated to match placebo to active doses; the active dose is 0.72 mg four times daily for Days 1-5, for a total daily dose of 2.88 mg. (The tablet is 0.18 mg of lofexidine. The Gorodetzky study referred to these as 0.2 mg doses, of which 1.8 mg was the base of lofexidine.) Doses on Days 6 and 7 will be 1.44 and 0.72 mg, respectively. Tapering is done to decrease the risk of rebound blood pressure increases that have been noted with abrupt cessation of lofexidine. Placebo capsules will be filled with inert filler to blind staff on weight, as we have successfully done in past studies. All doses are administered by nursing staff.

Rescue and symptomatic medications

Participants will have access to our standard array of symptomatic treatments for opioid withdrawal ("PRN meds") throughout the study[17]. These will include acetaminophen (650 mg every 6 hours for pain/discomfort); antacid (30 cc every 4 hours for indigestion); hydroxyzine (50 mg every 6 hours for anxiety); ibuprofen (600 mg every 6 hours for pain/discomfort); loperamide (2 mg every 6 hours for diarrhea); milk of magnesia (30 cc once daily for constipation); ondansetron (up to 8 mg SL every 8 hours); simethicone (80 mg every 6 hours for flatulence); methocarbamol (750-1500mg PO, not exceeding 6000mg in 24 hours); promethazine (25 mg PO, not exceeding 100 mg in 24 hours; 25-50 mg IM every 6 hours as needed); dicyclomine (10-20 mg PO, not exceeding 80 mg in 24 hoaurs); and trazodone (50-150 mg at bedtime for sleep). The number of doses of PRN meds used will be tabulated each day (by medication, the total number of doses) and compared across the three groups during the 5-day study period as a secondary outcome measure. We will also explore other periods of ancillary medication use (e.g., the 4 days after the device is removed, the days prior to device placement, longer periods of time within the study). Finally, we will also examine symptomatic medication use by medication type[17].

Participant payments

Volunteers are paid for participating in this study. We use a standard daily payment schedule in which the volunteer receives the majority of the daily payment as a base pay (e.g., $50/day), and then a smaller proportion if he or she completes the study (e.g., $25/day). The base pay is given for each day the person is on the CRU, regardless of how long he or she remains in the study, but is only available on the scheduled last day of the study (and not the day they leave, if they leave early). This decreases the likelihood a person will stay for 2-3 days and then ask to leave when they have accumulated $100-150 of payments.

Measures

We will collect multidimensional assessments, encompassing self-report, observer-rated, physiological, and psychomotor/cognitive performance measures. Previous studies have demonstrated the sensitivity of these multidimensional outcome measures for detecting opioid agonist and antagonist effects (for examples see[20-22 26-28]). Assessments will be completed throughout the entire study at 0800, 1200, 1600 and 2000. The following measures will be collected:

Observer-Rated Measure: A primary outcome measure for this study is the assessment of opioid withdrawal based upon the Clinical Opioid Withdrawal Scale (COWS), a publicly-available observer-rated instrument that has been used extensively in the substance abuse treatment and research fields. The COWS will be completed by a double-blinded staff member who has been trained on its administration and scoring. We have previously used the COWS in research studies[17 29], and in earlier work we showed it to be valid for the assessment of opioid withdrawal[18].

Self-report Measures:

Subjective Opioid Withdrawal Scale (SOWS): A secondary outcome measure is the SOWS, which is used to capture the self-reported experience of opioid withdrawal. The SOWS adds to the understanding of opioid withdrawal collected via the COWS because all items in the SOWS are presented as independent (e.g., nausea, vomiting), and are also rated on the same Likert scale by the same individual[17].

Visual Analog Scales (VASs): Participants will complete the following visual analog scales (VAS) that we have used in prior opioid-related studies: "high", "drug effect", "good effects", "bad effects", "liking", "sick", "opioid withdrawal", "comfort", and "feeling normal". Each scale will be rated on a 100-point line anchored at one end with "none (0)," and at the other with "extremely (100)."

Craving Assessments: The proposed study utilizes a craving battery successfully employed in a previous study on our unit[30], and that consists of the following 100-point VASs: "How much do you want to use right now?", "How much do you want to avoid using right now?", "How much control do you feel you have over using right now", and "How much do you crave opioids right now?". These scales are considered to represent the following craving domains: (1) *Wanting* (higher scores correspond to higher craving), (2) *Avoidance* (lower scores correspond to higher craving), (3) *Control* (lower scores correspond to higher craving), and (4) *Opioid-specific Urges* (higher scores correspond to higher craving).

Risky Decision-making: If the BD decreases risky decision-making during the experience of opioid withdrawal, then this may be a further possible mechanism for efficacy beyond simple alleviation of withdrawal symptoms. Participants complete the Balloon Analogue Risk Task (BART) daily[31], in order to obtain data on the relationship between opioid withdrawal severity and risky-decision making.

Sleep Assessments: Sleep impairment is a common and disabling symptom of opioid withdrawal. The Pittsburgh Sleep Quality Index is a self-report measure that used to assess sleep quality, latency, and duration at baseline and every morning throughout the course of the study.

Physiological Measures: Heart rate, blood pressure, skin temperature, oxygen saturation, and respiratory rate are monitored and recorded throughout the time on the CRU at regular intervals. Pupil diameter will be determined from infrared measurements taken in ambient room light using a pupillometer (NeurOptics, Irvine, CA). Electrocardiograms are collected on a daily basis to assess QTc intervals.

Psychomotor/Cognitive Performance Measures: Psychomotor and cognitive performance measures can be helpful to provide another measure of the impact of withdrawal on functioning. Participants will complete: 1) *Computerized Recall (Memory) Task.* This task requires the participant to memorize an eight-digit number and then recall the digits in a finite period of time. A score is derived from the number of correct responses in ten trials. 2) *Digit Symbol Substitution Task (DSST).* The DSST is a component of the Wechsler Adult Intelligence Scale (WAIS), and is frequently used to assess psychomotor performance changes associated with medication effects. A computerized version of the DSST has been developed and shown to be sensitive to the effects of sedating drugs[32]. In this assessment, the subject is required to replicate one of nine numbered geometric figures presented on the computer screen based upon the digit presented at the bottom of the screen and using the keypad to replicate the design. Scores are the number of correct responses, the number of attempts, and the percent correct. *3) Trail-making test[33]*. In this task, the

computer screen presents a distribution of squares that contain letters and numbers, and the subject is instructed to use a mouse to connect squares following an alternating sequence of numbers and letters (e.g., 1, A, 2, B, 3, C...). A total of 25 squares are presented (A-L and 1-13), and subjects have 4 minutes to complete the task. Results are summarized for sequence errors (i.e., clicking on a number or letter out of order), and the total line length. Outcomes from a previous opioid laboratory study suggest this test may be sensitive to the potential impairing effects of higher doses of mu agonist opioids[34].

Safety and Satisfaction: Participants will complete a modified form of a side effects questionnaire used in prior BPRU trials[17]; subjects rate common side effects associated with medications (e.g., dry mouth, blurred vision, constipation, diarrhea). The form will be modified to include side effects that may be relevant to this study and the device (e.g., ear pain, tingling [paresthesias]), and that are relevant to the use of lofexidine (e.g., dizziness). In addition, spontaneous reports of adverse events are collected and coded. If participants have evidence of low blood pressure, bradycardia, or other significant adverse effects (potential side effects of lofexidine), dose decreases by omission of a capsule can occur. Decisions on this will be made by medical personnel not involved in the study as an investigator. If dose decreases do not address such issues, participants may be withdrawn from the study and encouraged and assisted to engage in routine treatment.

Blinding Questionnaire: Participants are asked at the end of the study whether they believe they were assigned to the active vs. sham device condition, and the active versus placebo medication condition (to assess blinding), and given a list of reasons for their selection (as well as an open-ended option). In addition, they are asked whether they would recommend the device and/or medication to a friend or family member undergoing withdrawal, and whether they would use the device and/or medication again if needed.

Sleep Actigraphy Measurement: Sleep quality is consequential in treatment success among individuals in treatment for OUD.(Dunn et al., 2018) To assess the impact of the BD and lofexidine on sleep quality, Participants may wear a triaxial accelerometer (Actigraph wGT3X-BT, Actigraph, LLC) on their non-dominant wrist for the entire duration of study enrollment. Wrist-worn actigraphy has been validated against PSG and provides an acceptable alternative measure of sleep continuity.

Treatment after study completion

Both the BD/SBD will be removed on Study Day 5 and all medication capsule (active/placebo) dosing will end on Study Day 7. Participants will then be monitored for an additional 4 days. Throughout the study, but especially during these final days, study staff discuss with participants post-study treatment engagement, and the risks associated with opioid overdose following discharge from the CRU.

Subjects will be encouraged to begin oral naltrexone treatment following the second naloxone challenge session (assuming there is no evidence of opioid withdrawal). If the participant agrees to oral naltrexone, it will be initiated while the person is at the CRU. Oral naltrexone (25 mg) will be administered on the first day of dosing, and then 50 mg on the following day, pending no signs of withdrawal. Prior to discharge from the CRU, participants will then be offered XR-NTX (pending evidence that oral naltrexone did not precipitate withdrawal). If a participant declines XR-NTX, but wants to continue oral naltrexone, they will be provided oral naltrexone (at an anticipated dose of 50 mg/day). A month's worth of oral naltrexone will be provided in this case. If the participant agrees to take XR-NTX , this medication will be administered once at the recommended dose (380 mg delivered intramuscularly). Study staff will also provide participants with referrals to providers/clinics that will be able to provide follow-up XR-NTX dosing every 4-weeks after initial XR-NTX administration, as it is clinically indicated. If the participant wishes to continue oral naltrexone, referral to providers/clinics that will be able to provide follow-up oral naltrexone will be made as well.

Participants may decline to take naltrexone. While we will strongly encourage them to take this medication (in oral or monthly forms), we recognize that this is the person's decision. In the event that a participant is not interested in initiating XR-NTX, study staff will provide them with a referral to ongoing OUD outpatient treatment and participants will be provided with a take-home dose of intranasal naloxone (Narcan, Adept Pharmaceuticals). As noted above, we will emphasize concerns with the risk of lower tolerance and overdose as the person leaves the CRU.

Ultimately, study staff will work with participants directly to identify substance abuse treatment clinics and providers for post-discharge care that best fits their needs. The JHBMC campus has several outpatient substance abuse treatment options available and operated by Hopkins faculty from which participants will be able to initiate treatment, as well as other local community programs.

Data Sharing with University of Pennsylvania:

Data from this study that are collected at JHU will be shared with colleagues at the University of Pennsylvania (UPenn). Data will be de-identified (not linked). Researchers at UPenn will use the dataset as part of a pooled analysis aimed at characterizing the time course of fentanyl withdrawal among individuals with opioid use disorder. These analyses are generally concordant with the original study objectives of examining features of opioid withdrawal. The pooled analysis will examine the onset, peak, and severity of fentanyl withdrawal, including comparisons between participants with and without fentanyl detected on urine drug testing. Analyses will also assess the impact of sex, drug use history, BMI, and non-opioid drug use on fentanyl withdrawal trajectories. Findings will be used to generate scientific outputs, including publication of results.

UPenn's Human Research Protection Program has determined that from their perspective this is not human subjects research based on their review, and a copy of this correspondence is included with this Change in Research. The data will include demographic information (e.g., age, gender, race, ethnicity, and BMI category), but will not include any forms of dates.

5. Inclusion/Exclusion Criteria

Inclusion:

- Age between 22 and 65 years old
- Meets DSM-5 criteria for OUD (moderate or severe) based upon MINI
- Provides a urine sample that tests positive for opioids during screening or have evidence of opioid withdrawal
- Be in good general health based on a physical examination, medical history, vital signs, and screening urine and blood tests
- No significant psychiatric illnesses besides OUD
- Seeking treatment to stop using illicit opioids
- Willing to comply with the study protocol
- Have no clinically significant chronic medical or surgical disorders or conditions that are judged by the investigators to prevent participation
- Evidence of blood pressure below 140 SBP and 90 DBP at screening OR if blood pressure is $\geq$ 140 SBP or $\geq$ 90 DBP at screening, evidence of blood pressure below 140 SBP and 90 DBP at least one week after screen and at admission
    - If participant endorses a history of hypertension, they must have evidence of normal blood pressure (< 140 SBP, < 90 DBP) at the screening and at admission.

Exclusion:

- Pregnant or breast feeding
- Receiving opioid agonist treatment
- Significant medical illness (e.g., insulin dependent diabetes)
- Significant psychiatric illness (e.g., schizophrenia)
- Use of medical cannabis
- Contraindications for use of the Bridge Device, morphine, hydromorphone, lofexidine or naloxone (e.g., hemophilia, psoriasis and other skin conditions, a cardiac pacemaker)
- Have evidence of physical dependence on alcohol or benzodiazepines that requires medical detoxification

- Hypotension
- Prolonged QTc interval on screening ECG
- Hepatic or renal impairment
- Treatment with a strong 2D6 inhibitor (e.g., paroxetine)
- Have a known allergy to any of the study medications

Have circumstances that would interfere with study participation (e.g., impending jail)

This application will then address the following questions:

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Lofexidine, naltrexone (oral, extended-release) and the NSS-2 Bridge device will be used in this study as for their FDA-approved indications and in a manner consistent with their approved labeling.

Lofexidine:

Lofexidine is a central alpha-2 adrenergic agonist that binds to receptors on adrenergic neurons. This reduces the release of norepinephrine and decreases sympathetic tone. Lofexidine is indicated for the treatment of opioid withdrawal. Including Lofexidine in the protocol will allow us to compare the efficacy of the BD to the efficacy of a currently approved medication for the treatment of opioid withdrawal. In this study, we propose prescribing it as indicated. This includes a 5-day dosing period and subsequent 2-day dose taper, consistent with the lofexidine label recommendation. Doses of Lofexidine are over-encapsulated to match placebo to active doses; the active dose is 0.72 mg four times daily for Days 1-5, for a total daily dose of 2.88 mg. Doses on Days 6 and 7 are 1.44 and 0.72 mg, respectively. Tapering is done to decrease the risk of rebound blood pressure increases that have been noted with abrupt cessation of lofexidine.

Naltrexone (oral):

Naltrexone hydrochloride is an FDA-approved medication that is approved for the indication of opioid dependence and preventing relapse following detoxification. Naltrexone hydrochloride blocks the effects of opioids through competitive binding at opioid receptors. When taken orally, the time to maximum concentration is 1 hour. On average, the elimination half-life is 4 hours. Dosing is 50 mg orally daily with initial daily dose of 25 mg/daily if unsure of risk for precipitated withdrawal. Doses of 50mg provide opioid receptor blockade for up to 24 hours. Oral naltrexone will be provided as clinically indicated after a participant completes their final naloxone challenge after discontinuation of treatment during supervised withdrawal.

Naltrexone (extended-release injection):

Naltrexone injections have the same mechanism of action as the oral formulation. Naltrexone injection is FDA approved for the indication of opioid dependence and relapse prevention following detoxification. Naltrexone concentration peaks 2 days after initial IM injection[35]. On average, the elimination half-life is 5 to 10 days. The clinically indicated dose of IM naltrexone (e.g., 380mg) will be administered prior to discharge to participants who elect to receive it after completing the study treatment phase.

Bridge Device:

The Bridge Device has been cleared by the FDA for treating opioid withdrawal and will be used for 5 days continuously. This is the period of time that is recommended by the manufacturer, Innovative Health Solutions, Inc. The device is a percutaneous nerve field stimulator that has 4 electrodes placed on/near the ear, with wires to a small device that is worn behind the ear. The device targets 4 cranial nerves (V, VII, IX, and X) that have auricular branches, and it provides alternating low-grade electrical frequencies to these nerves as a means for peripheral stimulation of the specific cranial nerves. Stimulation by the device is hypothesized to provide central nervous modulation of pain paths. Reports of its use indicate that it

provides relief of opioid withdrawal within approximately an hour of placement. The device appears to continually aid in the suppression of withdrawal throughout the duration of its application.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Morphine, hydromorphone, and naloxone will be used in this study for the purposes of suppressing emergent opioid withdrawal (morphine or hydromorphone) and eliciting a brief precipitated withdrawal to assess for opioid physical dependence (naloxone). These drugs will be used in a manner we have in previous studies, which we have found to be both safe and effective.

Morphine: Morphine is an opioid agonist and is selective at the mu receptor. Stable and standardized dosing of morphine will be provided to safely induct participants and to equate recent opioid exposure across all participants prior to randomization. When delivered subcutaneously- as proposed in this study – onset of effects occur between 10 to 30 minutes after administration and lasts from 4 to 5 hours. The dose selected for this study is consistent with doses used in previous studies conducted at the BPRU. For example, the dose of morphine used in the present study (30 mg SC four times per day, for a total daily dose of 120 mg) is in the mid-range of doses used in studies of opioid dependence that were conducted at NIDA's Addiction Research Center (ARC) in the 1970s; those studies used total daily doses as low as 30 and as high as 240 mg. This dose of morphine has been successfully used in a recent study conducted at the BPRU and was well tolerated[17 18].

Hydromorphone: Hydromorphone is a short-acting opioid agonist that is selective for the mu receptor. Unlike morphine, it is not differentially metabolized by CYP enzymes. Hydromorphone is approved in Canada for injectable opioid treatment, largely due to its high potency. We have demonstrated in prior research that hydromorphone elicits effects similar to heroin (36), which is ideal for persons who are fentanyl-exposed. For this study, we will use oral doses of hydromorphone (up to 20mg, up to six times a day). These values are based on three prior studies that used similar doses of hydromorphone oral up to six times a day to stabilize persons with opioid use disorder in the same general stabilization paradigm we are employing here (IRB315529, IRB00301337) and several other studies that have shown safety of 20mg oral hydromorphone in persons with opioid physical dependence (40-48). 10mg oral hydromorphone has the same morphine milligram equivalent as 40mg SC morphine, demonstrating equivalence across these doses. These data provide good evidence of safety for this stabilization strategy. When administered orally, hydromorphone is rapidly absorbed through the gastrointestinal tract and subjected to extensive first-pass metabolism. Exposure to hydromorphone is proportional to the dose range, with *in vivo* bioavailability of an 8mg tablet being approximately 24%. Following oral administration, peak plasma level of hydromorphone is generally attained in 30 – 60 minutes, and approximately 95% of hydromorphone is metabolized to hydromorphone-3-glucuronide via glucuronidation in the liver. There is no apparent effect of sex on the pharmacokinetics of hydromorphone

Naloxone: Naloxone is an opioid agonist with the greatest affinity for the mu receptor. It is indicated for opioid overdose reversal. Onset of effects occurs 15-20 minutes after IM injection. As demonstrated in previous work conducted at the BPRU[17], withdrawal data collected from a naloxone challenge is a sensitive measure of physical dependence which will be used for group stratification when participants are randomized to treatment conditions. We will dose 0.4 mg of IM naloxone, consistent with our previous protocols, to induce moderate levels of withdrawal.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Primary outcome variables

The period of primary study interest is the five days of device placement and capsule administration, and primary outcome analyses are based upon the Intent To Treat (ITT) sample. There are two primary outcome measures: participant retention to day five, and withdrawal severity as measured by COWS scores. We will consider using COWS scores from the first naloxone challenge session as a covariate in analyses, to decrease individual subject variability in response during the active treatment phase of the study. Retention will be evaluated as being enrolled on the final day of the active phase (study day 5), and analyzed as a dichotomous variable across groups using chi-square analyses. COWS data will be analyzed with three approaches – peak scores during the five-day period, area under the curve (AUC) for the five-day period, and an analysis of score by time. Comparisons will be made with a one-way ANOVA in the case of peak and AUC scores (i.e., the three conditions), and a repeated measures regression for the time course analyses (i.e., condition x time). Rates of missing data are expected to be very low, given the study is conducted on a residential unit under constant staff supervision and data collection. Pairwise comparisons will be assessed with Tukey's post hoc procedure.

b. Secondary outcome variables.

Secondary analyses will include both the ITT and completer groups as appropriate. Retention to study day 9 will also be evaluated using chi-squared analyses. Secondary measures of interest from the study (e.g., SOWS scores, successful completion of the study) will be analyzed following a similar approach as the primary analyses. A particular interest is the proportion of participants who successfully start on naltrexone. Subgroup analyses will also be conducted when indicated. Adverse events will be summarized by system and severity (mild, moderate, severe), and when appropriate, compared between conditions using Proc Mixed with a repeated measures factor of severity. Concomitant medication utilization and satisfaction ratings will be categorized and similarly compared across conditions.

c. Statistical plan including sample size justification and interim data analysis.

The calculation of the proposed sample size was based upon an examination of the relative proportion of patients who completed five days of opioid withdrawal treatment in relevant studies. Specifically, the derivation of the sample size was based upon work published in three papers: Miranda and Taca (2017)[16], which looked at the BD, Gorodetzky et al. (2017)[25], which looked at lofexidine and placebo, and Dunn et al. (2017)[17] which looked at clonidine (a medication that has a similar mechanism of action as lofexidine). Unfortunately, no all reports provide similar assessments of opioid withdrawal; however, we were able to derive a proportion of subjects who completed the primary study period from each of these reports. Thus, for the BD, the study by Miranda and Taca (2017) found that 87.7% of participants completed the five-day period with the device. Gorodetzky et al. (2017) found that 26.9% of their placebo group completed the five days of treatment, and 37.3% of their lofexidine group completed the five days of treatment. The dropout rate for the lofexidine group was much higher than they had expected (their expected dropout rate was 35%), and the completion rate for the Dunn et al. (2017) study clonidine group was 61.1% (similar to what Gorodetzky anticipated).

Based upon these findings, we assumed a completion rate for the five-day treatment in the present proposal of 88% for the active BD/placebo group, 27% for the sham device/placebo group, and 50% for the sham device/lofexidine group (this latter representing the midpoint between the lower rate from the Gorodetzky study and the higher rate in the Dunn study). Assuming power=0.80 and alpha=0.05, using a z-test of proportions, this suggests we will need seven subjects per group for the comparison of active BD to sham device/placebo, and 20 subjects per group for the comparison of active BD to lofexidine. While

our primary comparison is active BD to sham BD, we have decided to power the study to be able to compare active BD to active lofexidine, and target an enrollment of 20 participants per group. We realize this is a conservative approach (especially for the SBD/P condition), and have taken it due to the concern with potential variability in results from these other study findings, and our interest in also looking at withdrawal as a primary measure (which may not have the same degree of difference between groups).

d. Early stopping rules.

Volunteers in this study may choose to stop study participation at any time. Participants who demonstrate strong drug effects that are poorly tolerated may be discharged early from the study and treated outside the parameters of the protocol using routine clinical practice. All patients will be discharged with opioid overdose education, and referral to outpatient OUD treatment.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.
b. Steps taken to minimize the risks.

Bridge Device:

a. *Risks:* There are no significant risks with the use of the BD. The BD is FDA cleared, and in studies and clinical use there have been no major or worrisome minor "side effects" with its use.
b. *Steps taken to minimize the risks:* Applicants who have a contraindication to the use of the device will be excluded. These include participants with hemophilia, a cardiac pacemaker, psoriasis, or an ear condition that precludes the placement of device (e.g., local infection of a pierced ear). Participants with a hearing aid will be offered the opportunity to participate, but will have the hearing aid removed during the time of the device's placement.

Lofexidine:

a. *Risks:* Lofexidine can produce side effects such as drowsiness, dizziness, lightheadedness, a slowed heartbeat, a decrease in blood pressure, and a dry mouth.
b. *Steps taken to minimize the risks:* Participants with hepatic impairment, a prolonged QTc interval on screening ECG, and/or renal impairment will be excluded from the study, as will applicants who are being treated with a strong CYP2D6 inhibitor (such as paroxetine), as these are relative contraindications to the use of lofexidine. Blood pressure will be monitored daily while participants are on the CRU, and the dose of lofexidine will be tapered over days 6 and 7 to decrease the known risk of rebound hypertension. Participants will be in a monitored environment (which is not necessary for use of this medication, but ensures safety in this study), and the doses being used are consistent with the FDA approved label

Morphine and Hydromorphone:

a. *Risks:* In a non-physically dependent person receiving morphine or hydromorphone, there could be risk of respiratory depression, but this is unlikely given volunteers have active OUD. There is also a slight risk of injection site reaction for morphine.
b. *Steps taken to minimize the risks:* Morphine or hydromorphone will be used in this study on a short-term basis under medical staff observation and 24/7 monitoring. It will be administered at doses that have been used in prior similar studies with participants with opioid dependence and OUD.

Naloxone:

a. *Risks*: when administered to patients who are physically dependent upon opioids, naloxone will produce a reliable and predictable opioid withdrawal syndrome which can consist of nausea, muscle aches and pains, yawning, sweating, pupil dilation, minor increases in blood pressure, and runny nose/tearing. These symptoms are uncomfortable but time-limited and tolerable. There is also a slight risk of injection site reactions.

b. *Steps taken to minimize the risks*: Like morphine or hydromorphone, naloxone will be administered under nursing observation with trained research assistants present. Symptoms will be monitored closely.

Confidentiality/Disclosure of Sensitive Information:

a. *Risks:* Although staff members are highly trained to maintain participant confidentiality, there is always a risk that some of the confidential information could be revealed to people who are not involved in the research study. This could be embarrassing to the participant if the participant preferred to keep his or her study participation secret, or if sensitive information became known to an individual outside the study
b. *Steps taken to minimize the risks:* We have an extensive history of conducting research among individuals with substance use histories and have instituted several practice to prevent a breach in confidentiality from occurring. All records and data will be kept strictly confidential and will only be released outside of the research staff with written consent of the participant. Participants will be assigned a unique identifying code at the time of study enrollment to help ensure confidentiality. Data will be maintained through the use of these identifiers and no patient names will be used for data purposes. Names that are liked to identifiers will be stored in independent binders as well as password protected electronic databases. Specifically, data will be primarily recorded in REDCap. A minority of questionnaires will be collected via Qualtrics.

Opioid Withdrawal:

a. *Risks:* Participants will undergo opioid withdrawal. This is expected to be mildly uncomfortable, but not inconsistent with the experience OUD persons have in the community.
b. *Steps taken to minimize risks:* All participants will have access to symptomatic treatments for opioid withdrawal

Relapse:

a. *Risks:* The primary risk to this study is that participants could relapse in their opioid use after leaving the CRU. Relapse is an inherent feature of OUD.
b. *Steps taken to minimize risks:* We will offer and strongly encourage treatment interventions, especially oral and extended release naltrexone, as well as outpatient services, as participants are transitioned to discharge from the CRU. Volunteers will be specifically instructed about the risks of opioid overdose following withdrawal. They will also be told that this is a research study, and will be provided options of outpatient treatment that is not research, prior to the study.

c. Plan for reporting unanticipated problems or study deviations.

All study events will be monitored during weekly meetings between the study investigators and we will follow all IRB guidance and recommendations regarding the reporting of unanticipated problems of study deviations. All such problems and deviations will be documented and if they do not meet the criteria for immediate reporting, they will be submitted to the IRB as part of the continuing review (or when otherwise requested).

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Some information is collected at intake and during enrollment regarding illegal activities (especially drug use). This information is generally provided as a global report (yes/no, frequency) rather than with specific information about a given instance of criminal activity that could lead to prosecution. We do not believe this type of information m, if breached, could lead to legal consequences.

e. Financial risks to the participants.

There are no financial risks to the patient.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Participants in this study will be seeking to be medically withdrawn off of opioids, and will receive such over a prolonged period in a supervised environment (a service that is not typically provided in the community). In addition, they will be given the opportunity to start on naltrexone, and given referral and assistance in entering local treatment for on-going care.

This study will test the efficacy of a novel intervention that can be used to treat opioid withdrawal. Managing opioid withdrawal is critical for successful retention and treatment of individuals with OUD. Providing efficacious treatment will reduce morbidity and mortality associated with chronic substance use and will increase likelihood that a patient can be completely rehabilitated.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will earn $30 for the screening visit. Participants will be paid $100 per day while residing on the Clinical Research Unit, which consists of $75/day base pay and a $25/day bonus for completion of the study. Depending on the length of the morphine/hydromorphone stabilization period, participants can earn up to and between $1630 and $2030.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The participants in this study will not pay for any aspect of study participation. All study medications, residential treatment costs, and staff support is paid through the NIDA grant.

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