Sterling Achieve More. IRB

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PRINCIPAL INVESTIGATOR – APPROVAL NOTIFICATION

Date Issued:	September 25, 2019
Issued To:	Jeffrey A Craven, MD
Protocol Title:	BRIDGE Device for Symptoms of Opioid Withdrawal: A Randomized, Double-Blind, Placebo-Controlled Study
IRB ID#:	**7454-JACraven**
	Please include the IRB ID# listed above on all correspondence pertaining to this study.
Sponsor:	Innovative Health Solutions

Review Type:	Full Board
Review Determination:	Approved with Contingencies
Approval Date:	**September 24, 2019**
Contingency Verification Date (*if applicable*):	September 25, 2019
Study/Site Expiration Date:	**September 23, 2020**
Study Status Report Due:	**30 Days Prior to Expiration Date**

Approved Principal Investigator: Jeffrey A Craven, MD

Approved Site Locations:
Brightview Morgan Center
446 Morgan St.
Cincinnati, OH 45206

Please see Section A for approved study items.

Please see Section B for additional study information.

Please see Section C for Principal Investigator/Site Responsibilities.

The current Sterling IRB Membership List is available on our website, www.sterlingirb.com.

The Principal Investigator's qualifications to conduct the above referenced study were reviewed and **approved** as indicated above. If applicable, satisfaction of the Board-determined contingencies was verified by the Chairman or his/her designee on the date listed above.

Sterling IRB has approved this Principal Investigator to conduct this study at the above-listed site(s). Approval will expire on the Study Expiration Date listed above, and if the study is to continue the Principal Investigator must receive Sterling IRB approval for study continuation prior to the expiration date. The Principal Investigator should submit the **Study Status Report** not less than one month prior to the last Sterling IRB meeting preceding the expiration date (form available in Sterling IRB's web portal, SilverLink). If approval for study continuation is not obtained prior to the expiration date, the study will be considered to be in noncompliance with Federal Regulations and IRB requirements, may be suspended, and may be subject to termination.

A **final Study Status Report** will be due at the conclusion of the study (form available in SilverLink).

The Sponsor/CRO may receive a copy of all documentation issued to your site.

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SECTION A: APPROVED STUDY ITEMS

- Protocol
- * Participant Informed Consent Form and Authorization to Use and Disclose Medical Information (Version Date: September 5, 2019)
- Instructions For Use NSS-2® BRIDGE® (Part No.: 01-1017-NSS-2 / BRIDGE, Rev. No.: 003)
- Investigator's Qualifications

Study Materials:

- * Pain and Craving Symptom Survey
- * CNSVS SUBTESTS
- * Clinical Opiate Withdrawal Scale (COWS) (5M 11/11)

For approved recruitment/study materials, you may insert or change site-specific information without resubmitting to the IRB. This is not applicable to the Informed Consent Form(s).

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* For any approved items which are labeled with the **asterisk (*)** symbol, copies of these items can be found in SilverLink in the Attachments page for this submission's Event. Items not labeled with the asterisk (*) symbol will be provided by the Sponsor/CRO.

You must use the most current Informed Consent Form(s) approved by Sterling IRB for consenting participants.

End of Section A

Sterling Achieve More. IRB

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SECTION B: STUDY INFORMATION

Sterling IRB has determined that the research involves minimal risk.

End of Section B

Sterling Achieve More. IRB

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SECTION C: PRINICIPAL INVESTIGATOR / SITE RESPONSIBILITIES

The Principal Investigator is responsible for following all policies of Sterling IRB as described in the Investigator's Compliance Agreement which was attested to on the submission application. It is the Principal Investigator's responsibility to ensure this research is conducted in accordance with applicable regulations (local, state/provincial and federal) as well as any requirements established by the IRB at the time of the approval. Refer to the Investigator Handbook at www.sterlingirb.com for details of these responsibilities.

- Check all addresses (sites) and phone numbers for accuracy in the Approval Document and Informed Consent Form(s). **Let our office know ASAP if there are any inaccuracies.**
- Please note the due date listed on the Approval Document for the Study Status Report. A final Study Status Report should also be submitted once the study at your site is completed. **These reports are required by the Board and by Federal Regulations.**
- Sterling IRB forms (including English and Spanish versions of the California Experimental Subject's Bill of Rights) for use by the Principal Investigator/Site are available on our website, www.sterlingirb.com.
- Sterling IRB has developed an Investigator Handbook that outlines the responsibilities of the Principal Investigator. **The Investigator Handbook should be read by all key personnel on the research team.** It can be located on the Sterling website, www.sterlingirb.com.
- Sterling IRB requires Principal Investigators to **promptly** report all events that may constitute unanticipated problems involving risk to subjects or others and new or updated safety information relating to the study or study product. Please refer to Chapters 7 ('Reportable Events') and 10 ('Research Conflicts') of the Investigator Handbook (located on our website at www.sterlingirb.com) for additional information regarding reporting guidelines.
- Any changes to the research must be submitted in writing to Sterling IRB for review and approval prior to implementation.
- Sterling IRB should be informed immediately of any serious adverse reaction or should any unanticipated problems involving risks to the subject or others occur or should the Sponsor provide safety information.
- Local prejudices or negative attitudes in the community toward the conduct of research projects must be reported immediately.
- State/provincial or local laws (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe) pertaining to Patient/Volunteer Bill of Rights and specific state/provincial or local laws (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe) laws concerning research which affect the conduct of clinical research must be enforced.
- Non-English speaking subjects enrolled in this study must be provided with an informed consent written in their fluent language, which must be approved by Sterling IRB before use.

If you have any questions please call our office at 888-636-1062.

End of Section C / End of Document

Study Protocol

STUDY TITLE: BRIDGE Device for Symptoms of Opioid Withdrawal: A Randomized, Double-Blind, Placebo-Controlled Study.

STUDY PURPOSE

A recent retrospective study demonstrated evidence for the rapid and effective attenuation of signs and symptoms associated with opioid withdrawal using the BRIDGE device (Innovative Health Solutions, Versailles, IN, USA). While there was no control group in that study, it did show a high degree of success in treating withdrawal symptoms and transitioning patients (88%) to long-acting naltrexone (XR-NTX) (1). The BRIDGE device is a novel, non-pharmacological, non-invasive, auricular percutaneous electrical nerve field stimulator (PENFS) that is thought to significantly reduce pain and modulate the autonomic nervous system. The novelty of this device is in the use of alternating current and higher voltage stimulation over a large field in the external ear that allows access into central brain regions involved in fear and pain modulation. The purpose of the study is to prospectively evaluate the effectiveness this new, FDA-cleared device in reducing signs and symptoms of acute, opioid withdrawal compared to placebo. This will be tested with the following specific aims:

SPECIFIC AIMS/HYPOTHESIS

Aim 1: Determine the severity of opioid withdrawal symptoms in patients using the BRIDGE device versus sham (inactive device) during active withdrawal in a double-blind, randomized controlled study design. **Hypothesis**: Treatment with the BRIDGE device will have a significant and profound effect on decreasing opioid withdrawal scores compared to sham.

Aim 2: Assess improvements in pain, craving and cognition in patients using the BRIDGE device versus sham (inactive) device. **Hypothesis**: Neuromodulation with the BRIDGE device will have a significant and profound effect on decreasing pain and craving scores quickly in the two hours following application as well as the ensuing 4-5 days. It will also demonstrate improvement in memory and executive function compared to sham treatment.

BACKGROUND AND RATIONALE

Results of a retrospective study in adults going through opioid withdrawals suggest that the BRIDGE device can decrease symptoms of opioid withdrawal by over 87% within the first hour of treatment without the use of supportive medication. Pre-clinical studies in rats suggest that neurostimulation with the BRIDGE decreases neuronal activity in the central amygdala (2). The amygdala is a common central link between a state of chronic pain and opioid dependence. As this central nervous system structure is involved in pain processing activation it has been associated with fear and the negative emotional state of withdrawal from opioids and drug craving (3-5). It is therefore likely that the BRIDGE device will impact pain and symptoms associated with opioid withdrawal. It is well known that there is a high prevalence of pain in persons with OUD during acute opioid withdrawal. A recent study concluded that in many cases, pain is a major reason for patients opting out of treatment (6). Another study demonstrated that up to 37.5 % of patients drop out of therapy within the first month and the majority of those occur during the first week (7,8). Early dropout is often the result of severe and dysphoric symptoms of withdrawal. Thus, alleviating signs and symptoms of withdrawal effectively and rapidly at the initial time of engagement is likely to increase the likelihood of success of any treatment protocol. The first few hours and days of therapy are critical to get patients engaged thus willing to enter into secondary therapy with pharmacotherapy and counseling to prevent relapse. In a recent study, 29% of patients who were randomized to receive MAT with opioid antagonists dropped out of treatment and did not receive the first dose of medication (9).

Overall, it is well known that pharmacotherapy used to treat patients during withdrawal usually falls short of completely alleviating symptoms rapidly and effectively (10,11). While it is accepted that opioid agonists such as buprenorphine relieve symptoms of opioid withdrawal, the literature suggests that this reduction is not, by any means, complete or rapid. Gunderson et.al. studied 758 opioid dependent subjects in a prospective, randomized, multicenter trial (12). Subjects used either higher bioavailability formulation of buprenorphine/naloxone or generic as induction agent. COWS scores were measured at several time points (**Figure 1A**). An approximate average score of 7.5 was seen in both groups by the first hour with an average starting COWS score of 15, suggesting a 50% decrease in withdrawal symptoms. Interestingly, patients were allowed rescue medication if needed, but no specific data were given regarding supportive care. While improvement in opioid craving decreased after initiation of opioid agonist therapy, studies suggest that craving scores take at least 1 week to significantly decrease (Figure 1B) (13). Increased craving and withdrawal symptoms have been identified as negative predictors for favorable treatment outcomes in patients with substance use disorder. Therefore, improvement in craving with the BRIDGE device in patients treated with buprenorphine during the first week of therapy could significantly impact treatment outcomes and/or patient comfort.

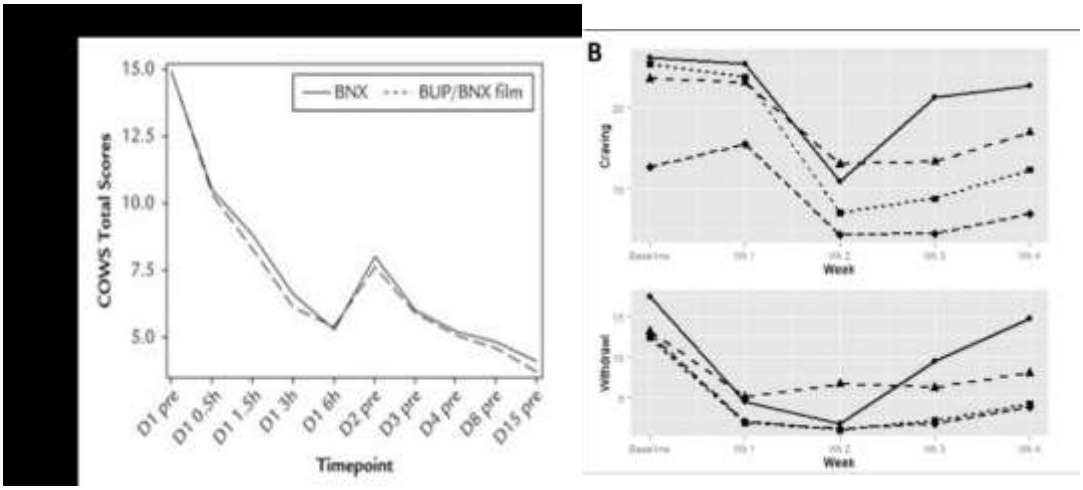

Figure 1. A) Mean time profile of total scores on the clinical opiate withdrawal scale (COWS) with buprenorphine/naloxone. B) Weekly craving and withdrawal scores after induction with buprenorphine. Craving scores do not significantly decrease until after the first week of treatment. Figure shows a subsequent increase in craving and withdrawal after tapering the doses of buprenorphine at week 2.

A separate study showing effects of buprenorphine/naloxone showed very similar results (14). That study examined buprenorphine/naloxone induction of 69 participants who self-reported primary PO use of methadone, ER-oxycodone, IR-oxycodone, or hydrocodone[4]. COWS scores were measured one hour after the initial dose of medication. The percent decreases in COWS scores in the first hour ranged from 53-58%. (Table 1).

Table 1 Participant characteristics and induction outcomes by primary PO used

Participant characteristics	ER oxycodone $n = 219$	IR oxycodone $n = 107$	Methadone $n = 41$	Hydrocodone $n = 202$
Induction outcomes				
Mean pre-dose COWS Score	12.7 (SD 3.5)	12.4 (SD 3.5)	13.0 (SD 3.6)	12.7 (SD 3.5)
Mean post-dose COWS Score	5.3 (SD 3.9)	5.8 (SD 3.9)	5.6 (SD 4.8)	5.9 (SD 4.1)

In contrast, the recently published retrospective study with the BRIDGE device resulted in an 87% reduction in opioid withdrawal symptoms within the first hour of treatment without the use of supportive medications and a 97% reduction by day 5 (1) (**Figure 2**). Although the benefits of the BRIDGE device in alleviating symptoms of

withdrawal were striking in this retrospective assessment, the placebo effect cannot be ignored. Therefore, it is important to evaluate the potential benefits of neurostimulation in patients suffering from symptoms of opioid withdrawal as they may impact patient comfort, retention in treatment, and types and doses of medication used.

Figure 2

The clinical opiate withdrawal scale (COWS) is commonly used in drug treatment protocols to assess the severity of acute withdrawal (15,16). This tool limits the possibility of feigned responses by combining subjective symptoms (GI upset, anxiety, irritability, muscle aches, nausea, restlessness, craving, chilling) with objective signs (heart rate, sweating, restlessness, pupil size, runny nose, tremors, yawning, and piloerection). Common pharmacotherapies use medications which have strong affinity for opioid receptors and gradually displace opioids from binding sites. This makes withdrawal symptoms inevitable. Other approaches such as electroacupuncture have been suggested to improve symptoms related to opioid withdrawal. Unfortunately, studies show that these techniques can have a delay of up to 2 days in demonstrating efficacy, even with the concomitant use of opioid receptor agonists (17). A delay in efficacy of any treatment in this population at the initial time of engagement is extremely undesirable.

DESIGN AND METHODS

The study will recruit a total of 50 subjects and will take place in a well-established outpatient treatment center (Brightview). Brightview is a private addiction treatment center located in Cincinnati, Ohio. The site PI at Brightview will be Dr. Jeffrey Alan Craven (MD, ABIM, ABAM DABPM), a board-certified physician in addiction medicine. Dr. Samin Rezania (PhD) will be a Co-investigator. The volume of patients treated for opioid use disorder (OUD) at this facility is sufficient for patient recruitment in this study. Dr. Craven will be responsible for patient recruitment and overseeing the entire project at Brightview. He will monitor the health of all patients in the study per standard clinical practice. Samin Rezania will be responsible for patient recruitment as well and monitor protocol adherence as well as supervise data collection, entry, and analysis.

This study will involve a double-blind, randomized, controlled trial with active BRIDGE or sham device (Figure 3). The sham device will be identical in appearance to the active device but will have no electrical current. Both providers and patients will be blinded to treatment allocation throughout the study. Participants will be 18 years or older who speak English and meet criteria for opioid use disorder based on the Diagnostic and Statistical Manual of Mental Disorders-5. Patients going through acute opioid withdrawal will be assessed for the severity of opioid withdrawal using the Clinical Opioid Withdrawal Scale (COWS). Additional demographic data will be collected at presentation including age, sex, duration of opioid misuse, types of medications or illicit drugs used as well as the presence of other medical conditions. After the severity of opioid withdrawal is established (COWS score $\geq$10), subjects will be randomized in blinded fashion. Once the patient is consented, a visual analog scale (VAS) for pain and an opioid craving scale (OCS) will be completed. Baseline cognitive function will be measured with the Stroop test using the CNS Vital Signs (CNSVS) in-office neurocognitive testing software https://www.cnsvs.com/index.html. This instrument measures executive function. The test takes approximately

4 minutes to administer and will be performed at the same intervals as COWS score, pain and craving assessments before and after device placement.

Blinding and Randomization
Patients will be randomly assigned to one of the 2 treatment groups in equal ratio, Randomization will be done centrally using a randomized block design, with blocks of 4 using the Pqantadosi Randomization software
There will be a randomization table provided to the person dispensing the devices. The unblinded, lead research coordinator will keep the data in a secure database and will not be involved in any of the patient recruitment or study procedures. All other research coordinators, investigators, and nurses involved will be blinded to group allocation. In general, the study biostatisticians and the person dispensing will be the only people un-blinded throughout the duration of the study.

Unblinding
Unblinding (or unmasking) patient's treatment assignment is only done when knowledge of the blinded treatment is necessary, for the treatment of an adverse event. Where possible patient will remain on trial and where medically feasible on assigned treatment. For all unblinding if possible, any assessors of subsequent outcomes will remain blinded. Record will be kept on unblinding and patients will be excluded from per protocol analysis but not the intent to treat analysis.

DATA MANAGEMENT

Subjects will be randomized in a 1:1 ratio to receive either active or a sham device. Randomization in blocks of 10 (5 for each treatment) will be determined using the computer program randomization.

The severity of opioid withdrawal signs and symptoms will be assessed with the COWS at several time points: 1) pre-device placement, 2) 1-hour post placement of sham or active device, 3) two hours post placement (approximately one hour after first dose of buprenorphine), 4) at subsequent follow-up in clinic on day 2 and 5) at final follow-up in clinic on day 5 prior to removal of device. The visual analogue pain and craving scale will also be administered at intervals to monitor patient comfort: 1) pre-device placement, 2) 1-hour post placement of sham or active device, 3) two hours post placement (approximately one hour after first dose of buprenorphine),4) at subsequent follow-up in clinic on day 2, 5) in clinic or remotely (via phone) on days 3 and 4, and 6) at final follow-up in clinic on day 5 prior to removal of device . Assessment of cognitive function (CNSVS) will be recorded at 1) pre-device placement, 2) 1-hour post placement of sham or active device, and 5) at final follow-up in clinic on day 5 prior to removal of device. One hour following placement of either sham or active device, the patients will be given the first dose of buprenorphine with a starting dose of 2, 4 or 8 mg at the blinded provider's discretion based on BMI, patient previous experience with BUP, patient apprehension or other factors. Adjustments to this dose will not be made for at least an hour after receiving the first dose but the providing clinician may order additional buprenorphine after one hour as indicated by initial response, previous experience, presence of precipitated clinical opioid withdrawal scale (COWS) and BMI. Subsequent adjustments will be made based on the blinded provider's discretion and patient needs and comfort as per clinic standard. Ancillary (supportive) medications to help manage signs and symptoms of opioid withdrawal will NOT be allowed for one hour after the first dose of buprenorphine. Following the first hour, symptom control medications including ibuprofen, clonidine, ondansetron, loperamide, and acetaminophen may be furnished or prescribed. A medication log will be provided to track usage of this modality. Subjects will remain blinded and keep the device on for 5 days regardless of randomization status. Subjects will be asked to return to clinic for additional induction visits based on the clinic standard of care which will be Day 2 and in some cases Days 3 & 4. In order to monitor whether neurostimulation with the BRIDGE has any added benefit for patients on outpatient opioid agonist therapy, subjects (regardless of active or placebo) will be reassessed using OCSand VAS at each subsequent visit, or remotely (via phone) when unrequired to return to clinic, during the 5-day trial.

Overall, the study will have very little deviation from the current standard of practice to treat substance use disorder (SUD), with the exception of the first hour of medical management which will be effected without

buprenorphine or symptom control medications, and the second hour during which symptom control medications will not be used. Current standard of practice in the clinical setting is to give the first dose of buprenorphine on Day 1 after initial screening, followed by a second or third dose prior to discharge home. Patients will be sent home and monitored as outpatients and asked to return to clinic within 2-5 days. The current study will not deviate from clinical practice after Day 1 with the exception of having either the BRIDGE device or sham device for 5 days. The device will be removed at the clinic visit on Day 5 and disposed of in a sharps container. If the patient cannot come back on day 5, they will be instructed to remove the device at home and bring it back at the next clinic appointment for proper disposal.

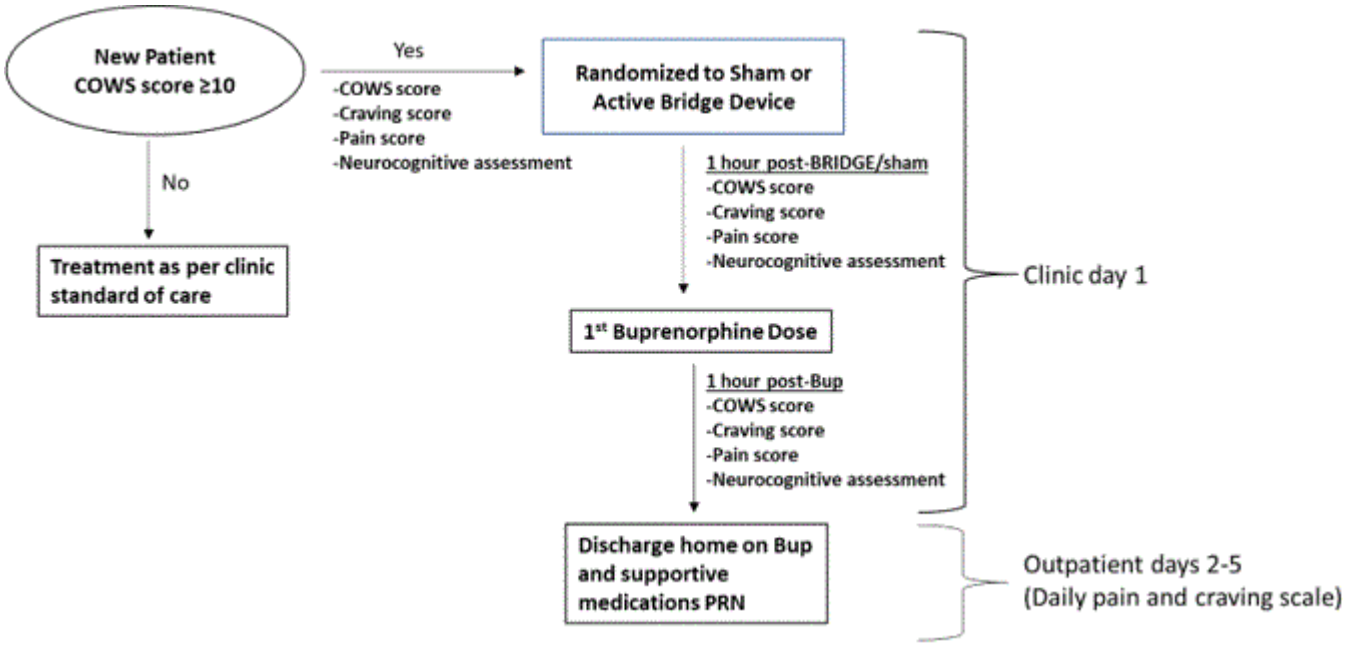

Figure 3

If at any time the patient wishes to discontinue the BRIDGE device and receive standard treatment for opioid withdrawal outside the study, he/she will be allowed to do so.

The study will involve the use of the NSS-2 BRIDGE device, an ambulatory, neurological device which consists of a battery powered, externally affixed generator with 4 wire leads: 1 double needle electrode lead and 3 single point electrode needle leads (Figure 4). The device delivers low voltage (3.2V) stimulation in alternating frequencies for a total of 5 days (around the clock). The arrays are designed to produce a field effect. The leads will be 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 aspect and one on the dorsal aspect of the ear. The electrodes will be taped and secured behind the ear next to the generator itself which is secured to the skin with adhesive. The placement of the devices is within standard of care by properly trained medical providers or physician extenders.

Figure 4

Inclusion criteria:

Participants in this study will be males and females between the ages of 18 and 60 years who are English speaking and capable of giving informed consent. Applicants must fulfill the criteria for opioid use disorder based upon the Structured Clinical Interview for DSM-5 (SCID). In addition, they must have an opioid (morphine, 6MAM, oxycodone or metabolites, hydrocodone or metabolites or fentanyl or metabolites, methadone or metabolites) positive urine immunoassay test during the screening process and have evidence of opioid withdrawal with COWS score ≥10. They must be healthy, with no significant medical illnesses (e.g., insulin dependent diabetes), and without significant psychiatric illness (e.g., schizophrenia) other than their drug dependence.

Exclusion criteria

Subjects will be excluded if they have other serious medical or psychiatric disorders or if they have a co-dependence on other substances such as alcohol or benzodiazepines. Patients who test positive for benzodiazepines will be excluded. They will also be excluded if they are suicidal or homicidal. Women will be excluded from entering the study if they are pregnant.

Subject recruitment and enrollment

Subjects presenting to the outpatient clinic at Brightview health will be identified by the attending physician and the patient will be approached for inclusion in the study by the research coordinator if they meet criteria. The principal investigator, a co-investigator or research coordinator will introduce the study to the patient during the initial clinic visit and will explain the details and purpose of the study during an informed consent discussion and obtain consent. Once the patient had enough time to consider participation, understand the risks and benefits and agree to participate, he/she will sign informed consent and HIPAA documents.

Data Collected

All data collected will be entered into a Redcap database for analysis. All collected data will be de-identified and samples will only have a unique identifier that will link the unique identifier with the patient's name.

Results of the COWS and pain VAS scores, OCS and CNSVS assessments at the respective time points will be tabulated and analyzed.

Upon completion of each patient's treatment with the device (sham or active), patients will be asked if they thought they had an active or inactive device. They will also be asked to respond to the questions: Do you want an active, functioning device to be placed prior to going home today (yes/no)? and on a 7 point Likert scale: 1) "How useful do you think the BRIDGE Device was for you overall in your treatment?" 2) "What is your impression of the effectiveness of the BRIDGE Device to treat your symptoms of withdrawal?" 3) "How satisfied are you and how the BRIDGE device worked for you?" and 4) "How likely are you to use the device again if you have symptoms of withdrawal?" Results will be tabulated and analyzed descriptively.

Analysis will also include differences in dosing of buprenorphine as well as usage of other symptom control medications and continued engagement in recovery treatment at 5- and 30-days post-device placement. If subject does not return to clinic at the 5- and 30-day scheduled appointment as dictated by clinic standard practice, a phone call will be made to assess whether the patient is still engaged in a recovery program.

DATA MANAGEMENT

GENERAL CONSIDERATIONS FOR DATA ANALYSES

In general, for demographics, baseline disease characteristics, type of opioid misused, and all safety data, continuous variables will be summarized using descriptive statistics including N, mean, median, standard deviation (SD), minimum, and maximum. For all the efficacy parameters (e.g. COWS, VAS, OCS and CNSV experience with the device, continued engagement in recovery program) the descriptive statistics will include N, mean median, standard error (SE), minimum and maximum or percentage and exact Clopper Pearson 95% confidence interval.

Definition of analysis population

Intent-to-treat (ITT) Population

The intent-to-treat (ITT) population will include every subject who is randomized to a treatment assignment (BRIDGE or Sham). The ITT population will be the primary population for all efficacy analyses and will be the basis of all sensitivity analysis.
Patients who received study medication different from that to which they are randomized will be included in the group to which they are randomized. All data will be analyzed by randomized treatment group.

Per Protocol (PP) Population
The per-protocol population will be defined as the subset of the intent-to-treat population and will include patients who meet the following criteria:

• received BRIDGE or sham as randomized
• completed first hour of double-blind treatment

Safety Population
The safety population will consist of all patients who have received at least one hour of treatment . The safety population will be used for analysis of all safety data.
Patients who received study treatment different from that to which they were randomized will be included in the group according to the treatment actually used.

All Patients
The all patients population will include any patient who was assigned a patient screening number, whether subsequently randomized or not.
This population will be used in summarizing the patients who participated in the screening period regarding their patient disposition, baseline characteristics in summary tables and listings

Data Points Requiring Special Handling
For ITT analysis, patients with multiple assessments within a scheduled visit will be included by selecting the first assessment in time within a visit. However, all data will be presented in the patient data listing.

Sub-Group Analyses
The primary and key secondary efficacy variables (i.e., COWS score, VAS pain and craving scale) and neurocognitive assessment will be summarized for the following sub-groups:
• Sham or active group
• Demographic groupings including gender age and type of opioid medication abused**.**

Patient disposition and analysis population
The number of patients enrolled will be summarized by treatment group, and a patient listing of all patients excluded from each of the analysis populations will be generated**.**

Baseline characteristics
Summary statistics will be presented for each treatment group for the following demographics and baseline characteristics: gender, age, race, weight, height, and body mass index (BMI), evaluations done**.**

Efficacy Analysis
All efficacy data will be analyzed using the ITT patient population. In addition, key efficacy analyses will be repeated using the mITT population.
Results of the COWS and pain VAS scores, OCS and CNSVS assessments at the respective time points will be tabulated and analyzed. In addition, other variables of interest below will be tabulated:
• Percent reduction in COWS, VAS for pain and craving for each patient will be calculated as percentage of baseline.
• Percent less than a three for VAS by day

• Percent of subjects needing rescue medication over first 5 days.
• Percent of subjects who achieve a COS less than 10 in the first hour, at end of first day
• Dose of buprenorphine at first day and total over first 5 days.

Primary Efficacy Variable
The primary efficacy variable is change in COWS from baseline to first hour. The two groups will be compared using a two-sided two sample t-test at an alpha of 0.001 at an interim analysis of the first 24 completing and at an alpha of 0.049 after 50 have completed.

Secondary efficacy analysis
As a secondary analysis we will examine the change over time of the COWS, pain VAS scores, OCS and CNSVS between groups using a mixed-effects model repeated measures (MMRM) analysis incorporating treatment period data up to 3 months. The effects in the model will include the baseline score, treatment groups, visit, treatment-by-visit interaction and baseline-by-visit interaction. Visit week will be treated as the repeated variable within a patient. Patient, treatment, and visit will be treated as class variables. Unstructured covariance matrix will be used initially, and additional types (e.g., auto- regression, Toeplitz, CS, etc.) will be tried to assess the robustness of the unstructured matrix. Comparison between treatments will be based on contrasts of least square treatment means at each week of interest. Based on the analysis above, least square means, standard errors, and 95% confidence intervals (CI) of treatment difference will be reported for the two groups.

Missing data
For missing data, the missing pattern will be summarized, and the subgroups investigated. Logistic regression and CART will be used to investigate the possible causes for missing data. In general, we will assume missing at random (MAR), and multiple imputations will be used for items.
To assess effects of dropouts, the dropout cohort analysis will be performed by summarizing the change of primary and secondary efficacy variables using different dropout cohorts.

REPORTING ADVERSE EVENTS AND UNANTICIPATED PROBLEMS
All safety variables (e.g., adverse events will be summarized for each assessment time (including follow-up) using descriptive statistics. Incidence of adverse events will be summarized by treatment.
Overall risks/ discomforts involved are very minimal – Rare (event rate 1% - < 5%)

Possible risks/discomforts may involve:
• Discomfort upon insertion of the electrodes for < 5 minutes - Rare (event rate 1% - < 5%)
• Discomfort at the lead placement site > 5 minutes – Rare (1 % - < 5%)
• Bleeding at the electrode site if the neurovascular bundle is penetrated - Rare (event rate 1% - < **5%)**
• Localized discomfort if the electrodes should become dislodged during the wearing of the device - Rare (event rate 1% - < 5%)
• Localized dermatitis - Rare (event rate 1% - < 5%)
• Drop in blood pressure - Rare (event rate 1% - < 5%)
• Syncope (fainting) - Rare (event rate 1% - < 5%)
• Adverse effects to supporting personnel
• Skin piercing with percutaneous needles - Rare (event rate 1 % - < 5%)

Of note, in the recently completed neurostimulation trial for functional abdominal pain disorders in adolescents, there were no serious adverse events. The rate of reported side effects was no different between the treatment and placebo groups. Of 115 subjects, n=10 (9%) reported the following side effects: ear discomfort (n=6; three treatment/three placebo), adhesive allergy (n=3; one treatment/two placebo) and syncope due to needle phobia (n=1; placebo) (18).
Safety Analysis

The Bridge Device is FDA cleared as an aid in the treatment of opioid withdrawal symptoms. It has been classified as a class II device, with minimal no adverse effects in this population. Nevertheless, caution will be taken to monitor safety in this patient population. Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to study device, all events of death, and any study specific issue of concern.

All safety variables will be summarized for each assessment time (including follow-up) by treatment group, and period using descriptive statistics. Incidence of AEs will be summarized based on body systems and preferred terms. Incidence of marked abnormal lab test results will be summarized.
All safety summary outputs will be generated using the safety population.

Exposure to Study Treatment
The following extent of exposure to study device will be summarized for each treatment group, and patient data listing will be produced:
• Overall adherence to assessment (i.e., average during the entire treatment period).
• Premature Withdrawals from the Protocol Therapy
• Patients (n,%) who prematurely withdraw from the protocol during the treatment period will be summarized separately for overall and by reason for withdrawal and will be presented in patient listing.

Adverse Events
All adverse events will be summarized for the following 3 study periods separately, and include the specified AEs:
• Screening Period: Include the AEs of which the onset date is before the start of the study device placement.
• Treatment Period: Include (a) the AEs of which onset date is on or after the first day of the study device and on or prior to five days after the last device treatment day.
• Follow-up Period: Include (a) the AEs of which onset date is more than 30 days after the last device placement; OR (b) the AEs of which onset date is during the treatment period with the end date is more than 30 days after the last dose day or is unresolved and the follow up intensity is worse than the initial intensity.

For each AE recorded, the term entered by the investigator describing the event (the “verbatim term”) will be assigned to a standardized term (the “preferred term”) based on the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Within this dictionary, all preferred terms are grouped into categories known as “system organ class” terms or “super class” terms (SCT). All data displays of AE will be performed using the preferred terms and super-class terms (also referred as Body System).
For each treatment group, the frequency of each AE preferred term will be defined as the number of patients reporting at least one occurrence of the event. The incidence rate will be calculated as the frequency count divided by the total number of patients in the population and treatment group specified. Each table will also present the overall number of patients experiencing at least one AE and the total number of adverse events reported.

In the summary table of AEs by intensity, if a patient has more than one occurrence of an event, the event with the most severe intensity will be counted. If the intensity of an adverse event is missing, then the AE will be included only in the total number of events columns, and not in the count of patients with the event by intensity.
In the summary table of AEs by relationship to trial treatment, if a patient has more than one occurrence of an event, the most closely related event will be counted. If the relationship of an adverse event is missing, then the AE will be included only in the total number of events columns, and not in the count of patients with the event by relationship.

The "listing of patients who prematurely withdraw due to adverse events" will include all AEs (not only the events leading to withdrawal) which were reported by the patients. Expected adverse events that are not serious will be reported on the Continuing Review Progress Report. Continuing Review will be performed on a 12-

month cycle, starting at the time of the protocol's initial approval. More frequent progress reports will be submitted at the request of the IRB.

Serious Adverse Events
The PI, within 24 hours, will report all serious adverse events occurring in any enrolled subjects to the IRB. Unexpected (but not serious) adverse events occurring in enrolled subjects which, in the opinion of the PI, are possibly related to participation in the study will be reported by the PI within 5 working days to the IRB. Enrollment will be discontinued after reaching 50 subjects.

Safety Monitoring Plan
All procedures will be performed by trained professionals within the standard of care under continuous medical supervision while in the outpatient clinic. Potential side effects will be documented as noted above. COWS score ratings will be filled out by nursing staff or provider as per standard of care. All patients will be carefully monitored. If any serious harm or discomfort is identified by the subjects or the study personnel, the treatment will be discontinued. Any patient with worsening or no improvement in symptoms who has a device placed during the study will be able to drop out at any time and receive standard of care medical therapy. The skin of the external ear will be carefully monitored for signs of irritation or infection. All patients will be given the option to have an active device at the end of the 5 day study period at no cost.

Safety Analysis Plan
There are no dangerous interventions related to this study.

TOTAL NUMBER OF HUMAN RESEARCH PARTICIPANTS PROPOSED FOR THIS STUDY AT THIS SITE.
A total of 50 subjects will be recruited for this study. Stopping points for the study include achieving adequate information on sufficient study subjects, unanticipated adverse events, inability to obtain enough data or patients/caregivers electing to discontinue the study.

Power Calculation for primary aim (difference in COWS scores between active and sham device).
We hypothesize that compared to sham treatment, the improvement in COWS due to the BRIDGE device will be significantly higher than the sham. Similarly, pain and craving as measured by the VAS and OCS will be reduced. Patients with the active BRIDGE device will have improved memory and executive function compared to sham as assessed by CNSVS.

The primary outcome is comparison of change from baseline of the COWS scores between active and sham device at one hour. The data will be analyzed as a randomized, placebo-controlled trial with an interim analysis when 24 patients are completed at a $P< 0.001$. We will compare the bridge device and sham using a two sided t-test of the change of COWS at one hour form baseline. Using the sample size software Pass 15 with 25 subjects in each group we will have at least 90% power at an alpha of 0.049 to detect a difference in the COWS at one hour between treatment and sham of at least .94 standard deviations(SD), In the withdrawal study we had a SD of ~6, and so if we have a similar variability we will be able to detect a difference of approximately 5.7 (1). In the paper, we found a difference of > 12 , so even allowing for a placebo effect we should have adequate power.

Period	Baseline	(1-hour after BRIDGE)	(1-hour after BUP)	Post-MAT	Post-MAT	Post-MAT	Post-MAT
Contact	**Clinic**	**Clinic**	**Clinic**	**Phone**	**Phone**	**Phone**	**Clinic**
Project Day	**1**	**1**	**1**	**2**	**3**	**4**	**5**
Informed Consent	X						
Demographics and Medical History	X						
Prior and Concomitant Medications	X						X
Vital Signs, height, weight and BMI	X						
Physical Examination	X						
Placement of BRIDGE Device or sham	X						
COWS scores	X	X	X	X			X
VAS pain and craving scale	X	X	X	X	X	X	X
Neurocognitive assessment	X	X					X
First dose of Buprenorphine		X					

DEVICE PLACEMENT PROCEDURE

Auricular Neurostimulation treatment protocol

The electrode/needle arrays are placed according to the individual's distribution of neurovascular bundles. The exact location of the placement 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 disinfecting the ear. The generator/battery will be positioned and secured behind the ear (similar to a hearing aid) and may be covered by hair. Neurostimulation in active devices will be delivered for 5 consecutive days. The device will be applied by a trained MD or APN and will be removed during the clinic visit or independently at home. The devices are easily removed by removing the tapes and adhesives.

The NSS-2 BRIDGE Surgical kit 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 (10) Transilluminator (Figure 5).

NSS-2 BRIDGE placement details:

1. A research coordinator will document the patient ID, name and the device serial number in the study database.
2. The research coordinator or provider will record baseline answers to questionnaires and will also record vital signs (temperature, heart rate and blood pressure).
3. The neurostimulator placement will be performed as directed and per BRIDGE training protocol instructions identical to prior IRB approved protocols.

4. Before device placement, the subject caretakers should be advised that some discomfort is normal at first. If the discomfort persists or worsens after a few minutes the medical provider will be notified. The patients will be advised that they may feel a slight pulsing sensation and perhaps a warming sensation in the ear to which the electrodes are affixed. The pulsing and warming sensation may disappear after approximately 5 minutes. If the discomfort level increases the offending array can be repositioned until the patient's discomfort level decreases to an acceptable level.
5. Subjects 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, placing a dry wash cloth over the area to help protect the device will be recommended. Subjects will be given a contact person (Principal investigator, Co-investigator or Research coordinator) to call if they are having any problems with the device or if it falls off.
6. The device may be removed by the patient or a caretaker if at home. If uncomfortable doing so or unable to carry out the instructions, an outpatient appointment will be made and the device will be removed by the investigators.
7. If removed at home, the patient will be asked to return the used device for proper disposal when they return the following week.

Figure 5

Data to be collected:
Consent from participants for use of these materials for research will be obtained.

Demographic Information
Data will be collected as part of the clinic visit. This includes subject's date of birth, age, sex and ethnicity. The physician assessment will also include questions about prior medical diagnoses, co-morbid symptoms and the characteristics of the current illness. Types of illicit drugs used other than opioids (benzos, alcohol, etc.), duration of drug use, underlying psychiatric disorders.
Efficacy Information

1. Clinical Opioid Withdrawal Scale (COWS) (total time 5 min)
2. Pain (11-point VAS) (total time 2 min)
3. Opioid Craving Scale (11-point scale) (total time 3 min)

   a. How much do you currently crave opiates (Range: 0–10, 0 = not at all, 10 = extremely)

   b. In the past week, please rate how strong your desire to use opiates has been when something in the environment has reminded you of opiates (examples: seeing a medication bottle, using the Internet, visiting a doctor's office, going to a place where you used to buy drugs)? (Range: 0–10, 0 = not at all, 10 = extremely)

   c. Please imagine yourself in the environment in which you previously used opiates (examples: a party, a hangout, a particular room where you live). If you were in this environment today and if it were the time

of day that you typically used opiates, what is the likelihood that you would use opiates today? (Range: 0–10, 0 = not at all, 10 = extremely)

4. CNS Vital Signs in-office neurocognitive testing with domain scores (total time 15 min) https://www.cnsvs.com/index.html
5. Four question patient questionnaires at end of study period
6. Dosing of medication assisted therapy (buprenorphine)
7. Additional (symptom control) medication log
8. Number of subjects with continued engagement in recovery treatment at 5 days post-device placement
9. Whether the patient thinks they had an active or inactive device at end of 5 days treatment

PROVISION FOR THE PROTECTION OF PRIVACY OF SUBJECTS *(confidentiality, health and financial risks*) **AND TO MAINTAIN THE CONFIDENTIALITY OF DATA**

Each subject will be assigned a unique identifying number which will be the only identifier listed on the questionnaires, device kits and data collection forms. Each subject's identifying number and related electronic data will be kept on a secured, password-protected database that provides access only to the PI and research staff. Only authorized research personnel will have access to the database. A separate secure database will have the subject identification number linked to the patient's name. The BRIDGE devices will be shipped directly from the manufacturer (Key Electronics) to the office research coordinator. The devices will be stored in a locked room in the offices. The RN or research coordinator will record that device was disposed of properly.

PROVISIONS FOR MONITORING DATA TO ENSURE THE SAFETY OF SUBJECTS; AND ADDITIONAL SAFEGUARDS TO PROTECT THE RIGHTS AND WELFARE OF SUBJECTS WHO ARE LIKELY TO BE VULNERABLE

The PI will monitor the health of all patients in the study per standard clinical practice. The PI will monitor protocol adherence and supervise data collection, entry, and analysis.

ANTICIPATED BENEFITS ASSOCIATED WITH THE PROTOCOL *(value or desired outcome / advantage)* **TO HUMAN RESEARCH PARTICIPANTS AND SOCIETY** *(medical, psychosocial, altruistic)*

Currently, pharmacological therapies are the mainstays of treatment for acute opioid withdrawal. These medications are not always effective and often have side effects. If effective, this alternative approach may revolutionize narcotic withdrawal management and have a substantial impact on health care costs, morbidity and mortality.

STOPPING POINTS THAT WOULD NOT ALLOW THE STUDY TO CONTINUE AS PROPOSED

Stopping points for the study include achieving inadequate information on sufficient study subjects, unanticipated adverse events, inability to obtain enough data or patients electing to discontinue the study.

IS THERE A DATA SAFETY MONITORING BOARD IN PLACE? WHO ARE IT'S MEMBERS? HOW OFTEN DO THEY MEET?

No data safety monitoring board will be appointed unless requested.

DESCRIBE HOW THE CONSENT AND ASSENT PROCESS WILL TAKE PLACE. INCLUDE A LIST OF APPROPRIATELY TRAINED PERSONNEL WHO WILL BE INVOLVED.

Written informed consent for participation will be obtained from the participating subjects. Consent will be obtained by a study investigator or member of the research team during the time of enrollment. Volunteers' consent will allow for accessing information collected for program evaluation/clinical purposes. Participating

subjects will have the option of having the consent document read aloud to them to facilitate understanding. Copies of signed consent documents will be given to participants.

ANTICIPATED SIGNIFICANCE OF THE PROPOSED STUDY

The key significance of this study is the identification of a successful, non-pharmacological and non-invasive therapy for the treatment of opioid withdrawal in patients with opioid use disorder. We expect to be able to show that the NSS-2 BRIDGE device effectively and rapidly alleviates symptoms of opioid withdrawal, which translates to better outcomes for patients with opioid used disorder. The study may demonstrate that the BRIDGE device augments the effects of opioid agonist therapy (buprenorphine) during the period of opioid withdrawal leading to improvement in withdrawal scores, pain scores, craving, and retention in treatment. Improvements in neurocognitive function with this type of neuromodulation if apparent would also improve the patient's ability to make decisions about his/her care and improve patient retention. With this study, we hope to lay the foundation for the application of the BRIDGE device in this patient population. If the device proves efficacious, it could extend its use throughout the addiction treatment field, leading to better patient outcomes. This is an innovative and novel treatment approach which could expand treatment options and ultimately improve patient care.

FINANCIAL RELATIONSHIPS

This is an investigator-initiated study. The Principal Investigator and Brightview will use IHS support solely for purposes of the study for which it was provided. At the completion of the study, the Principal Investigator will confirm in writing that the support has been used only to support that study. Innovative Health Solutions (IHS) has agreed to pay Brightview $150,000 for fulfilling its duties related to this study. This includes a facility fee, patient stipends, salary support for research coordinator and physician part time FTE. IHS will provide Brightview with enough devices to complete the study at no charge with a minimum of 25 active and 25 sham devices.

Patients will receive a $100 gift card to a local store to participate in the study. This will be given at the end of the study.

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