IRB Approved Template
MUST BE APPROVED
FOR SITES BEFORE USE
AS MODIFIED
Mar 08, 2022

RESEARCH SUBJECT CONSENT FORM

TITLE: Delivering Transcutaneous Auricular Neurostimulation to Improve Relapse Prevention in Opioid Use Disorder

PROTOCOL NO.: SBM-OWP-03
IRB Protocol #

SPONSOR: Spark Biomedical, Inc.

<<CF-Main Header Block - Investigator>>
INVESTIGATOR: Name
Address
City, State Zip
Country

STUDY-RELATED PHONE NUMBER(S): <<CF-Main User Defined #1>>
Phone Number
[24 hour number is required]

RESEARCH CONSENT SUMMARY

You are being asked for your consent to take part in a research study. This document provides a concise summary of this research. It describes the key information that we believe most people need to decide whether to take part in this research. Later sections of this document will provide all relevant details.

What should I know about this research?

- Someone will explain this research to you.
- Taking part in this research is voluntary. Whether you take part is up to you.
- If you don't take part, it won't be held against you.
- You can take part now and later drop out, and it won't be held against you
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

How long will I be in this research?

We expect that your taking part in this research will last 97 days and include 21 in-person study visits. This study consists of seven visits during Phase I: Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7 and 14 visits during Phase II: Day 1, Day 7, Day 14, Day 21, Day 28, Day 35, Day 42, Day 49, Day 56, Day 63, Day 70, Day 77, Day 84, and Day 90.

Why is this research being done?

The purpose of this research is to evaluate if transcutaneous auricular neurostimulation (tAN; stimulating a nerve in the ear through the skin) used with lofexidine and naltrexone can prevent relapse in individuals with opioid use disorder. The device (Sparrow Ascent tAN System) has not been cleared by the US Food and Drug Administration (FDA) for relapse prevention and is considered investigational. The device is based on the Sparrow Therapy System, which is FDA cleared for opioid withdrawal symptoms. Data from this clinical trial may be used to support the FDA clearance of the Sparrow Ascent System for use in relapse prevention.

About 168 subjects will take part in Phase I of this research and 100 subjects in Phase II.

What happens to me if I agree to take part in this research?

If you decide to take part in this research study, the general procedures include:

- Measurement of height and weight and collection of information about your medical history and the medications that you currently take.
- Your doctor will assess your level of suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS) prior to study activities. You will be asked 6 questions and the questionnaire will take around 5 minutes to complete.
- Your doctor will measure your opioid withdrawal symptoms using the Clinical Opiate Withdrawal Scale (COWS) questionnaire. The questionnaire will take around 5 minutes for your doctor to complete.
- Your doctor will measure opioid withdrawal symptoms using the Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop). You will be asked 10 questions and the questionnaire will take around 5 minutes to complete.
- Your doctor will assess your level of depression using the 9 question Patient Health Questionnaire (PHQ-9). The questionnaire will take less than 5 minutes to complete.
- Your doctor will measure your health-related quality of life using the World Health Organization Quality of Life (WHO-QOL-BREF) questionnaire. You will be asked 26 questions and the questionnaire will take around 10 minutes to complete.
- Your doctor will measure signs of post-traumatic stress disorder (PTSD) using the 20-question PTSD Checklist for DSM-5 (PCL-5). The questionnaire will take around 10 minutes to complete.
- Your doctor will assess your level of anxiety using the 7 question General Anxiety Disorder (GAD-7) questionnaire. The questionnaire will take less than 5 minutes to complete.
- Your doctor will measure your recovery capital using the Brief Assessment of Recovery Capital (BARC-10) assessment. The assessment will take less than 5 minutes to complete.
- Your doctor will measure opioid craving using the Opioid Craving Scale (OCS). You will be asked 3 questions and the questionnaire takes less than 5 minutes to complete.
- You will be asked to provide a urine sample for a urine drug screen to detect Amphetamines, Buprenorphine, Benzodiazepines, Cocaine, Ethyl Glucuronide, Fentanyl,

Synthetic Marijuana, Ecstasy, Methamphetamines, Methadone, Opiates / Morphine, Oxycodone, Cannabinoid (Marijuana), and Tramadol.

- For Phase I, you will be put into a study group by chance (like drawing straws). You have an 87.5% chance of being placed into one of the three groups with at least one active therapy/treatment and a 12.5% chance of being placed in the one group without any active therapy/treatment. You cannot choose your study group. You may not receive lofexidine, tAN therapy, or either. You will not know which group you have been placed in until the end of your enrollment in the trial.
- For Phase II, you have a 50% chance of being placed in each group. You cannot choose your study group. You may not receive tAN therapy. You will know which group you have been placed in.
- Your ear will be cleaned with alcohol and any hair will be removed to prepare for placement of the device.
- The device (Sparrow Ascent tAN System) will be placed on your ear and electrical stimulation may be delivered through the skin of your outer ear.
- You may be given up to 2.16 mg of lofexidine a day on Days 1 – 7.
- At the conclusion of Phase I, you have the option to receive a monthly naltrexone injection of up to 380 mg.

Could being in this research hurt me?

The most important risks or discomforts that you may expect from taking part in this research include:

- Dermal (skin) irritation
- Erythema (redness where device is touching the skin)
- Paresthesia (tingling, prickling or numbness)
- Allergic contact dermatitis (red, itchy rash due to allergy)
- Dermal hypersensitivity (increased skin sensitivity)
- Transient (temporary) pain or discomfort due to stimulation
- Transient pain or discomfort due to device malfunction
- Otalgia/otodynia (earache)
- Muscle twitching during stimulation
- Failure of a device component resulting in loss or decrease of therapeutic effect

Most therapy-related side effects are reversible and corrected by reprogramming or turning the system OFF or removing the Earpiece. Chronic, irreversible stimulation-related adverse events are expected to be rare.

If randomized to receive lofexidine, possible side effects of lofexidine include:

- Slow heart rate
- Hypotension
- Dizziness
- Drowsiness

- Sedation
- Dry mouth
- Low blood pressure
- Fainting

If randomized to receive naltrexone, possible side effects of naltrexone include:

- Precipitated withdrawal symptoms including body aches, fever, sweating, runny nose, sneezing, piloerection (hair stands on end), yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia.
- Increased blood pressure
- Musculoskeletal pain
- Headache
- Nasal dryness
- Nasal edema
- Nasal congestion
- Nasal inflammation
- Hepatic enzyme abnormalities
- Injection site pain
- Insomnia
- Common Cold-like symptoms
- Toothache

Additional risks include:

- You may find it difficult or tiresome to comply with the stimulation time requirements.
- The risks to pregnant women and their unborn child due to the presence of the system and the therapy provided are unknown. Women of childbearing potential must maintain adequate contraception during the study.

Will being in this research benefit me?

Anticipated benefits due to tAN alone or when used with lofexidine or naltrexone may include a reduction in symptoms associated with opioid withdrawal and prevention of relapse with the therapeutic effect potentially continuing after cessation of stimulation. Participants may experience an improvement in mood and anxiety. We cannot promise any benefits to you or others from your taking part in this research.

What other choices do I have besides taking part in this research?

Instead of being in this research, your choices may include being treated with the current standard of care for opioid use disorder generally used by your study doctor.

You can get the drugs used in this study, lofexidine and naltrexone, without being in the study. Other treatments that may assist in opiate withdrawal include methadone and buprenorphine.

DETAILED RESEARCH CONSENT

You are being invited to take part in a research study. A person who takes part in a research study is called a research subject, or research participant.

What should I know about this research?

- Someone will explain this research to you.
- This form sums up that explanation.
- Taking part in this research is voluntary. Whether you take part is up to you.
- You can choose not to take part. There will be no penalty or loss of benefits to which you are otherwise entitled.
- You can agree to take part and later change your mind. There will be no penalty or loss of benefits to which you are otherwise entitled.
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

Why is this research being done?

The purpose of this research is to evaluate whether transcutaneous auricular neurostimulation (tAN; stimulating a nerve on the ear through the skin) used with lofexidine and naltrexone can prevent relapse in individuals with Opioid Use Disorder. The device (Sparrow Ascent tAN System) has not been cleared by the US Food and Drug Administration (FDA) for relapse prevention and is considered investigational. The device is based on the Sparrow tAN System 1.0, which is FDA cleared for opioid withdrawal symptoms. Data from this clinical trial may be used to support the clearance of the Sparrow Ascent System for its use in relapse prevention.

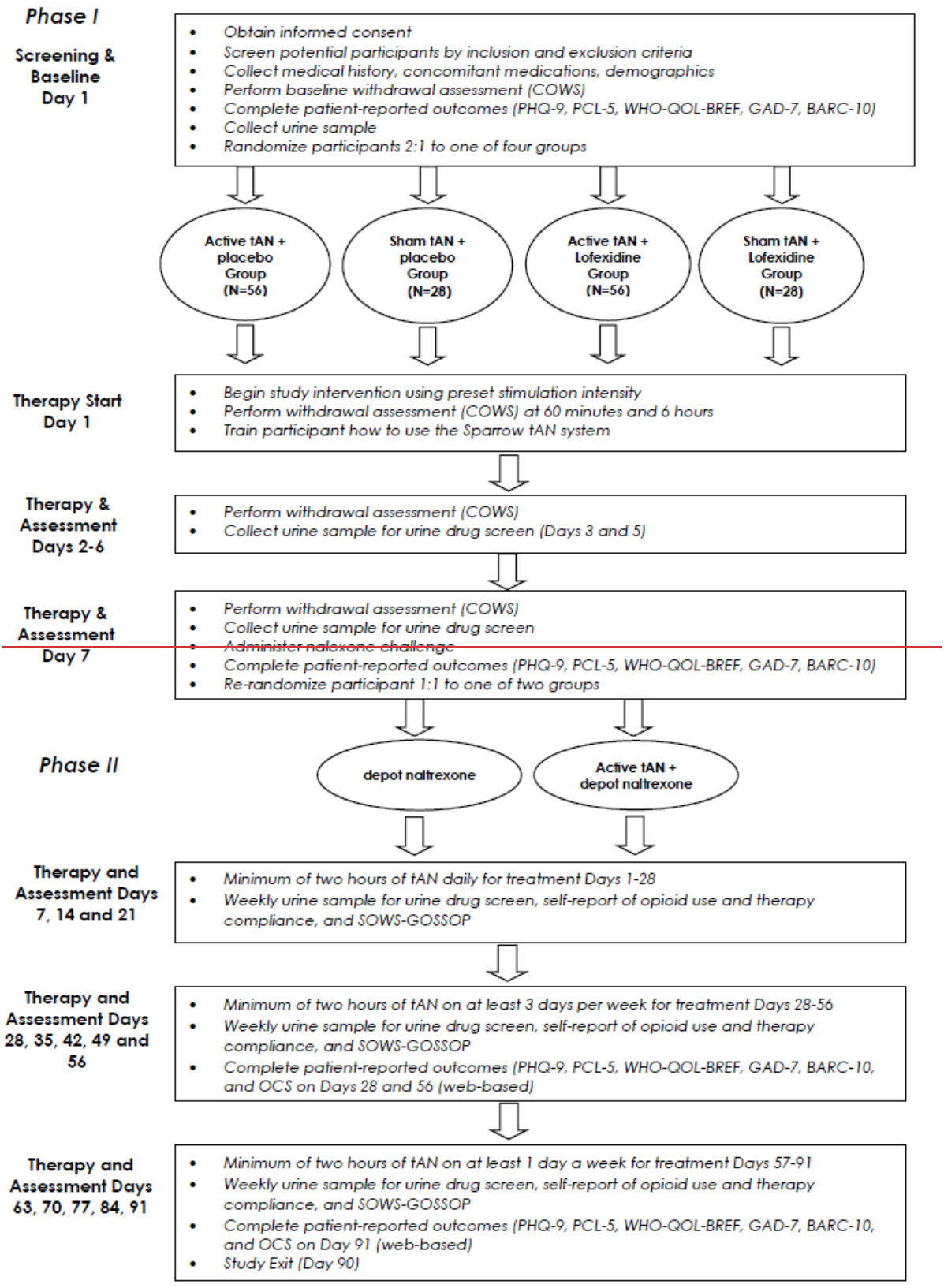
About 168 subjects will take part in Phase I of this research and 100 subjects in Phase II.

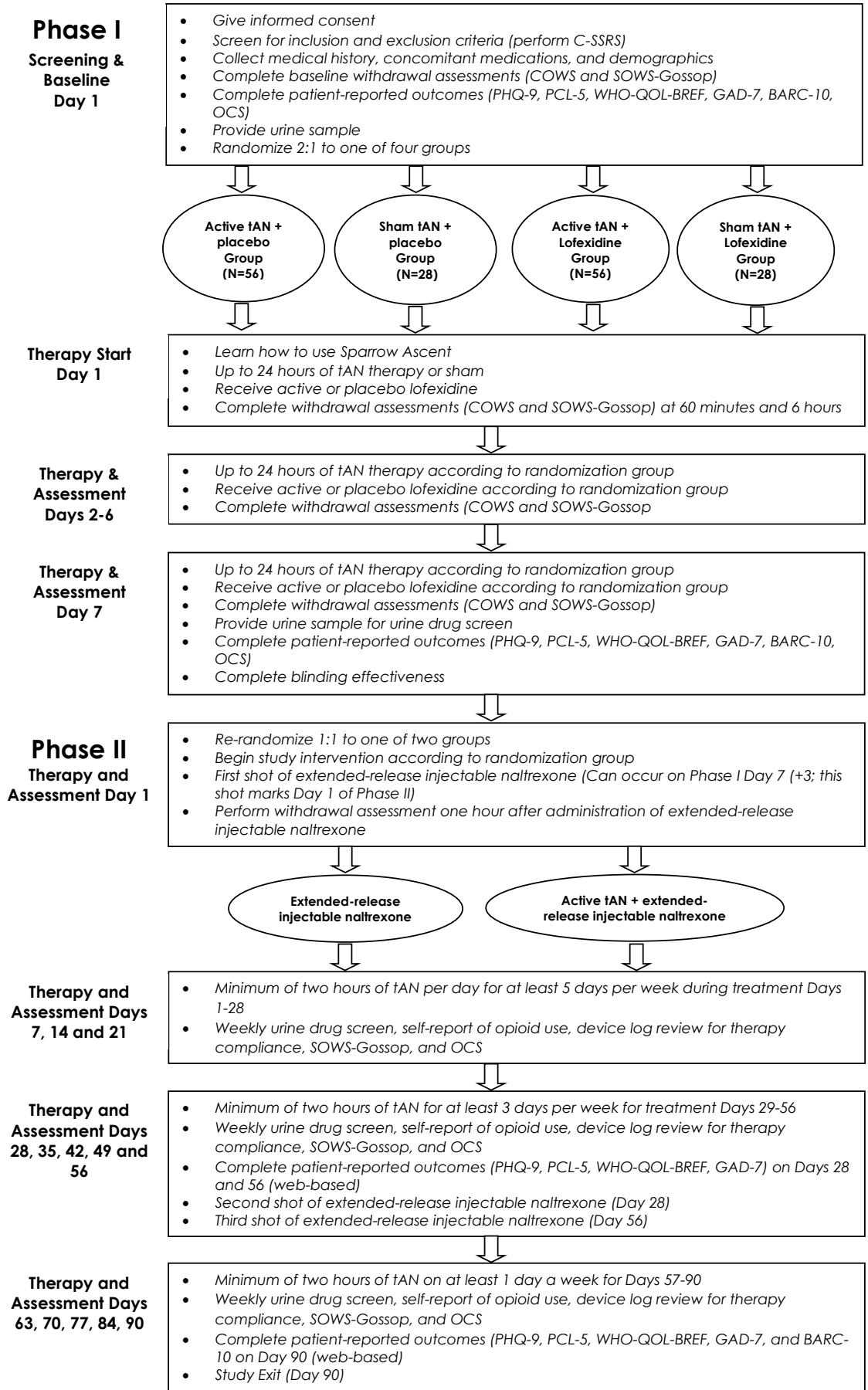
How long will I be in this research?

We expect that your taking part in this research will last 97 days and include 21 in-person study visits. This study consists of seven visits during Phase I: Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7 and 14 visits during Phase II: Day 1, Day 7, Day 14, Day 21, Day 28, Day 35, Day 42, Day 49, Day 56, Day 63, Day 70, Day 77, Day 84, and Day 90.

What happens to me if I agree to take part in this research?

The picture below shows what will happen during the study.


Phase I
Screening & Baseline Day 1
Obtain informed consent
Screen potential participants by inclusion and exclusion criteria
Collect medical history, concomitant medications, demographics
Perform baseline withdrawal assessment (COWS)
Complete patient-reported outcomes (PHQ-9, PCL-5, WHO-QOL-BREF, GAD-7, BARC-10)
Collect urine sample
Randomize participants 2:1 to one of four groups
Active tAN + placebo Group (N=56)
Sham tAN + placebo Group (N=28)
Active tAN + Lofexidine Group (N=56)
Sham tAN + Lofexidine Group (N=28)
Therapy Start Day 1
Begin study intervention using preset stimulation intensity
Perform withdrawal assessment (COWS) at 60 minutes and 6 hours
Train participant how to use the Sparrow tAN system
Therapy & Assessment Days 2-6
Perform withdrawal assessment (COWS)
Collect urine sample for urine drug screen (Days 3 and 5)
Therapy & Assessment Day 7
Perform withdrawal assessment (COWS)
Collect urine sample for urine drug screen
Administer naloxone challenge
Complete patient-reported outcomes (PHQ-9, PCL-5, WHO-QOL-BREF, GAD-7, BARC-10)
Re-randomize participant 1:1 to one of two groups
Phase II
depot naltrexone
Active tAN + depot naltrexone
Therapy and Assessment Days 7, 14 and 21
Minimum of two hours of tAN daily for treatment Days 1-28
Weekly urine sample for urine drug screen, self-report of opioid use and therapy compliance, and SOWS-GOSSOP
Therapy and Assessment Days 28, 35, 42, 49 and 56
Minimum of two hours of tAN on at least 3 days per week for treatment Days 28-56
Weekly urine sample for urine drug screen, self-report of opioid use and therapy compliance, and SOWS-GOSSOP
Complete patient-reported outcomes (PHQ-9, PCL-5, WHO-QOL-BREF, GAD-7, BARC-10, and OCS on Days 28 and 56 (web-based)
Therapy and Assessment Days 63, 70, 77, 84, 91
Minimum of two hours of tAN on at least 1 day a week for treatment Days 57-91
Weekly urine sample for urine drug screen, self-report of opioid use and therapy compliance, and SOWS-GOSSOP
Complete patient-reported outcomes (PHQ-9, PCL-5, WHO-QOL-BREF, GAD-7, BARC-10, and OCS on Day 91 (web-based)
Study Exit (Day 90)


Phase I
Screening & Baseline Day 1
Give informed consent
Screen for inclusion and exclusion criteria (perform C-SSRS)
Collect medical history, concomitant medications, and demographics
Complete baseline withdrawal assessments (COWS and SOWS-Gossop)
Complete patient-reported outcomes (PHQ-9, PCL-5, WHO-QOL-BREF, GAD-7, BARC-10, OCS)
Provide urine sample
Randomize 2:1 to one of four groups
Active tAN + placebo Group (N=56)
Sham tAN + placebo Group (N=28)
Active tAN + Lofexidine Group (N=56)
Sham tAN + Lofexidine Group (N=28)
Therapy Start Day 1
Learn how to use Sparrow Ascent
Up to 24 hours of tAN therapy or sham
Receive active or placebo lofexidine
Complete withdrawal assessments (COWS and SOWS-Gossop) at 60 minutes and 6 hours
Therapy & Assessment Days 2-6
Up to 24 hours of tAN therapy according to randomization group
Receive active or placebo lofexidine according to randomization group
Complete withdrawal assessments (COWS and SOWS-Gossop
Therapy & Assessment Day 7
Up to 24 hours of tAN therapy according to randomization group
Receive active or placebo lofexidine according to randomization group
Complete withdrawal assessments (COWS and SOWS-Gossop)
Provide urine sample for urine drug screen
Complete patient-reported outcomes (PHQ-9, PCL-5, WHO-QOL-BREF, GAD-7, BARC-10, OCS)
Complete blinding effectiveness
Phase II
Therapy and Assessment Day 1
Re-randomize 1:1 to one of two groups
Begin study intervention according to randomization group
First shot of extended-release injectable naltrexone (Can occur on Phase I Day 7 (+3; this shot marks Day 1 of Phase II)
Perform withdrawal assessment one hour after administration of extended-release injectable naltrexone
Extended-release injectable naltrexone
Active tAN + extended-release injectable naltrexone
Therapy and Assessment Days 7, 14 and 21
Minimum of two hours of tAN per day for at least 5 days per week during treatment Days 1-28
Weekly urine drug screen, self-report of opioid use, device log review for therapy compliance, SOWS-Gossop, and OCS
Therapy and Assessment Days 28, 35, 42, 49 and 56
Minimum of two hours of tAN for at least 3 days per week for treatment Days 29-56
Weekly urine drug screen, self-report of opioid use, device log review for therapy compliance, SOWS-Gossop, and OCS
Complete patient-reported outcomes (PHQ-9, PCL-5, WHO-QOL-BREF, GAD-7) on Days 28 and 56 (web-based)
Second shot of extended-release injectable naltrexone (Day 28)
Third shot of extended-release injectable naltrexone (Day 56)
Therapy and Assessment Days 63, 70, 77, 84, 90
Minimum of two hours of tAN on at least 1 day a week for Days 57-90
Weekly urine drug screen, self-report of opioid use, device log review for therapy compliance, SOWS-Gossop, and OCS
Complete patient-reported outcomes (PHQ-9, PCL-5, WHO-QOL-BREF, GAD-7, and BARC-10 on Day 90 (web-based)
Study Exit (Day 90)

Phase I: Acute Detox Treatment

Baseline

After signing this Informed Consent form, the first step will be for your doctor to ask you some questions to see whether you qualify to be included in the study. The following will happen during the prescreening and baseline assessment at the residential detox center:

- Measurement of height and weight and collection of information about your medical history and the medications that you currently take.
- Your doctor will assess your level of suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS) prior to study activities. You will be asked 6 questions and the questionnaire will take around 5 minutes to complete.
- Your doctor will measure your opioid withdrawal symptoms using the Clinical Opiate Withdrawal Scale (COWS) questionnaire. The questionnaire will take around 5 minutes for your doctor to complete.
- Your doctor will measure opioid withdrawal symptoms using the Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop). You will be asked 10 questions and the questionnaire will take around 5 minutes to complete.
- Your doctor will assess your level of depression using the 9 question Patient Health Questionnaire (PHQ-9). The questionnaire will take less than 5 minutes to complete.
- Your doctor will measure your health-related quality of life using the World Health Organization Quality of Life (WHO-QOL-BREF) questionnaire. You will be asked 26 questions and the questionnaire will take around 10 minutes to complete.
- Your doctor will measure signs of post-traumatic stress disorder (PTSD) using the 20-question PTSD Checklist for DSM-5 (PCL-5). The questionnaire will take around 10 minutes to complete.
- Your doctor will assess your level of anxiety using the 7 question General Anxiety Disorder (GAD-7) questionnaire. The questionnaire will take less than 5 minutes to complete.
- Your doctor will measure your recovery capital using the Brief Assessment of Recovery Capital (BARC-10) assessment. The assessment will take less than 5 minutes to complete.
- Your doctor will measure opioid craving using the Opioid Craving Scale (OCS). You will be asked 3 questions and the questionnaire takes less than 5 minutes to complete.
- You will be asked to provide a urine sample for a urine drug screen to detect Amphetamines, Buprenorphine, Benzodiazepines, Cocaine, Ethyl Glucuronide, Fentanyl, Synthetic Marijuana, Ecstasy, Methamphetamines, Methadone, Opiates / Morphine, Oxycodone, Cannabinoid (Marijuana), and Tramadol.
- Your ear will be cleaned with alcohol and any hair will be removed to prepare for placement of the device.

The device is a system that consists of a Patient Controller and a disposable flexible earpiece (see Figure 1). The Patient Controller produces the electrical stimulation which is delivered through the disposable flexible earpiece. The Patient Controller and the earpiece are connected by a cable.

Figure 1. Sparrow Ascent (A) Earpiece, (B) Cable, and (C) Patient Controller

The device stimulation intensity will be adjusted so that the therapy is comfortable for you. The Patient Controller is portable and is easy to carry around.

Randomization
For Phase I, you will be put into a study group by chance (like drawing straws). You have an 87.5% chance of being placed into one of the three groups with at least one active therapy/ treatment and a 12.5% chance of being placed in the one group without any active therapy/ treatment. You cannot choose your study group. You may not receive lofexidine, tAN therapy, or either. You will not know which group you have been placed in until the end of your enrollment in the trial.

Therapy Start (Day 1)
Your ear will be cleaned with alcohol and any hair will be removed to prepare for placement of the device on your left or right ear. If you are assigned to a group who will receive active tAN, stimulation will be delivered through the skin of your outer ear up to 24 hours a day on Days 1 –

7. If placed in the active tAN plus lofexidine group, you may be given up to 2.16 mg of lofexidine a day, on Days 1 – 7. You will receive a matching placebo (sugar) pill that is inert (inactive) but is identical in appearance (size, shape, color, etc.) to the lofexidine tablet if placed in the active tAN plus placebo group.

If you are placed in a sham tAN group, the earpiece will be applied and the cable will be connected to the Patient Controller, but stimulation will not be turned on. If assigned to the sham tAN plus lofexidine group, you may be given up to 2.16 mg of lofexidine a day on Days 1 – 7. You will receive a matching placebo (sugar) pill that is inert (inactive) but is identical in appearance (size, shape, color, etc.) to the lofexidine tablet if placed in the sham tAN plus placebo group.

Your doctor will measure your opioid withdrawal symptoms using the COWS and SOWS-Gossop at 60 minutes and 6 hours after start of therapy. You will be trained on how to use the device including how to adjust the intensity of the stimulation.

Therapy and Assessment Days 2 - 6
You will use the study device for up to 24 hours per day and receive up to 2.16 mg of either active or placebo lofexidine, depending on your study group placement. Your doctor will measure your opioid withdrawal symptoms using the COWS and SOWS-Gossop once a day on Days 2 – 6. You will be monitored for any adverse events (side effects) and any medication changes will be recorded.

Therapy and Assessment Day 7
On the last day of Phase I, your doctor will measure your opioid withdrawal symptoms using the COWS and SOWS-Gossop and you will also be asked to complete six questionnaires to determine levels of depression, PTSD, anxiety, quality of life, recovery capital, and opioid cravings. You will also be asked to provide a urine sample for a urine drug screen. You will be monitored for any adverse events (side effects) and any medication changes will be recorded.

If you complete Phase I (acute detox treatment) and are eligible to transition to extended-release injectable naltrexone treatment, you will be considered for inclusion in Phase II of the study. If you do not qualify or decline participation in Phase II, you will be exited from the study and unblinded to your assigned Phase I treatment group.

<u>Phase II: Long-Term Follow-up</u>

Randomization
If you agree to participate in Phase II, you have a 50% chance of being placed into one of two groups: 1) extended-release injectable naltrexone alone or 2) active tAN + extended-release injectable naltrexone. You cannot choose your study group. You may not receive tAN therapy. You will know which group you have been placed in. All participants in Phase II will be given a monthly naltrexone injection of up to 380 mg.

Therapy Start (Day 1)
You will receive your first shot of extended-release injectable naltrexone and complete a withdrawal assessment (COWS or SOWS-Gossop) one hour after the injection. If you are placed in the active tAN + extended-release injectable naltrexone treatment group, you will be provided with a device and instructed to use the therapy according to the specified frequencies:

- Month 1 (Days 1 – 28): a minimum of 2 hours per day at least 5 days a week
- Month 2 (Days 29 – 56): a minimum of 2 hours per day at least 3 days a week
- Month 3 (Days 57 – 90): a minimum of 2 hours per day at least 1 day per week

Therapy and Assessment Days 7, 14, and 21
You will return to the clinic to answer questions about opioid use and therapy use once a week on Days 7, 14, and 21 of Phase II. You will also be asked to complete the Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop) and the Opioid Craving Scale (OCS) to measure protracted (lingering) opioid withdrawal symptoms and levels of opioid cravings at these visits. You will be asked to provide a urine sample for a urine drug screen to detect Amphetamines, Buprenorphine, Benzodiazepines, Cocaine, Ethyl Glucuronide, Fentanyl, Synthetic Marijuana, Ecstasy, Methamphetamines, Methadone, Opiates / Morphine, Oxycodone, Cannabinoid (Marijuana), and Tramadol. You will be monitored for any adverse events (side effects), medication changes will be recorded and the amount of time you used therapy will be taken from the device.

Therapy and Assessment Days 28, 35, 42, 49, and 56
You will return to the clinic on Days 28, Day 35, Day 42, Day 49, and Day 56 to answer questions about opioid use and therapy use. You will also be asked to complete the Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop) and the Opioid Craving Scale (OCS) to measure protracted (lingering) opioid withdrawal symptoms and levels of opioid cravings at these visits. You will be asked to provide a urine sample for a urine drug screen. You will be monitored for any adverse events (side effects), medication changes will be recorded, and the amount of time you used therapy will be taken from the device.

Additionally, on Days 28 and 56, you will be asked to complete four questionnaires to measure levels of depression, PTSD, quality of life, and anxiety. These questionnaires may be completed online, outside of the clinic. You will also receive the second and third injections of extended-release injectable naltrexone on Days 28 and 56, respectively.

Therapy and Assessment Days 63, 70, 77, 84, 90
You will return to the clinic on Day 63, Day 70, Day 77, Day 84, and Day 90 to answer questions about opioid use and therapy use. You will also be asked to complete the Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop) and the Opioid Craving Scale (OCS) to measure protracted (lingering) opioid withdrawal symptoms and levels of opioid cravings at these visits. You will be asked to provide a urine sample for a urine drug screen. You will be monitored for any adverse events (side effects), medication changes will be recorded and the amount of time you used therapy will be taken from the device.

Additionally, on Day 90, you will be asked to complete five questionnaires to measure levels of depression, PTSD, quality of life, anxiety, and recovery capital. These questionnaires may be completed online, outside of the clinic. You will return the device to the clinical site and will exit the study on Day 90.

Follow-Up by Telephone or Email
You may be contacted by push notification, phone call, and/or email as needed to discuss any issues with the device that come up, to see if you have relapsed (e.g., due to missed visit), or have had any adverse events (side effects) or medication changes.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible for:

- Abstaining from sexual relations or using adequate contraception for the duration of the study if you are a woman of childbearing potential
- Stopping use of opioids prior to starting therapy (only applicable to participants not in withdrawal; still taking opioids)
- Abstaining from using any opioid-based medications during the study
- Using the device when required by the study protocol
- Following the instructions provided by the study team and giving them any new information about new medications, new medical issues, etc.
- Promptly reporting any side effects to the study team

Could being in this research hurt me?

The most important risks or discomforts that you may expect from taking part in this research include:

- Dermal (skin) irritation
- Erythema (redness where device is touching the skin)
- Paresthesia (tingling, prickling or numbness)
- Allergic contact dermatitis (red, itchy rash due to allergy)
- Dermal hypersensitivity (increased skin sensitivity)
- Transient (temporary) pain or discomfort due to stimulation
- Transient pain or discomfort due to device malfunction
- Otalgia/otodynia (earache)

- Muscle twitching during stimulation
- Failure of a device component resulting in loss or decrease of therapeutic effect

Most therapy-related side effects are reversible and corrected by reprogramming or turning the system OFF or removing the earpiece. Chronic, irreversible stimulation-related adverse events are expected to be rare.

If randomized to the lofexidine group, possible side effects of use of lofexidine include:

- Slow heart rate
- Hypotension
- Dizziness
- Drowsiness
- Sedation
- Dry mouth
- Low blood pressure
- Fainting

If randomized to the naltrexone group, possible side effects of use of naltrexone include:

- Precipitated withdrawal symptoms including body aches, fever, sweating, runny nose, sneezing, piloerection (hair standing on end), yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia.
- Increased blood pressure
- Musculoskeletal pain
- Headache
- Nasal dryness
- Nasal edema
- Nasal congestion
- Nasal inflammation
- Hepatic enzyme abnormalities
- Injection site pain
- Insomnia
- Common Cold-like symptoms
- Toothache

Additional risks include:

- You may find it difficult or tiresome to comply with the stimulation time requirements.
- The risks to pregnant women and their unborn child due to the presence of the system and the therapy provided are unknown. Women of childbearing potential must maintain adequate contraception during the study.

There may be unknown risks to you in this study.

Will it cost me money to take part in this research?

The study devices and lofexidine will be provided to you at no cost. However, in some cases, insurance does not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay. Ask your study doctor to discuss the coverage options available.

Will being in this research benefit me?

Anticipated benefits due to tAN alone or when used with lofexidine or naltrexone may include a reduction in symptoms associated with opioid withdrawal and prevention of relapse with the therapeutic effect potentially continuing after cessation of stimulation. Participants may experience an improvement in mood and anxiety. We cannot promise any benefits to you or others from your taking part in this research.

What other choices do I have besides taking part in this research?

Instead of being in this research, your choices may include being treated with the current standard of care for opioid use disorder generally used by your study doctor.

What happens to the information collected for this research?

Your private information and your medical record will be shared with individuals and organizations that conduct or watch over this research, including:

- The research sponsor
- People who work with the research sponsor<<CF-Main SMO Company 1>><<CF-Main Affiliated IN Language 1>>
- Government agencies, such as the Food and Drug Administration
- The Institutional Review Board (IRB) that reviewed this research

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

We protect your information from disclosure to others to the extent required by law. We cannot promise complete secrecy.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Data or specimens collected in this research might be deidentified and used for future research or distributed to another investigator for future research without your consent.

Who can answer my questions about this research?

If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number listed above on the first page.

This research is being overseen by WCG IRB. An IRB is a group of people who perform independent review of research studies. You may talk to them at 855-818-2289 or researchquestions@wcgirb.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

What if I am injured because of taking part in this research?

If you are injured or get sick because of being in this research, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance may be billed for this treatment. The sponsor will pay any charges that are not covered by insurance policy or the government, provided the injury was not due to your underlying illness or condition and was not caused by you or some other third party. No other payment is routinely available from the study doctor or sponsor.

Can I be removed from this research without my approval?

The person in charge of this research can remove you from this research without your approval. Possible reasons for removal include:

- It is in your best interest
- You have a side effect that requires stopping the research
- You need a treatment not allowed in this research
- You become pregnant
- The research is canceled by the FDA or the sponsor
- You are unable to use the device
- You are unable to keep your scheduled appointments

We will tell you about any new information that may affect your health, welfare, or choice to stay in this research.

What happens if I agree to be in this research, but I change my mind later?

If you decide to leave this research, contact the research team so that the investigator can take back the device and complete the necessary paperwork.

If you decide to leave the research early, there may be risks with this decision. These may include return of opioid withdrawal symptoms or relapse.

Will I be paid for taking part in this research?

<<CF-Main Payment for Part. Paragraph>>You will be paid for taking part in this research study. Discuss the details of payment with the Research team.

<<CF-Main Financial Disclosure>>

Statement of Consent:

Your signature documents your consent to take part in this research.

Signature of adult subject capable of consent	Date
Signature of person obtaining consent	Date

<<CF-Main California HIPAA>>

****For Sites in California****

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits.

Who may use and give out information about you?
The study doctor and the study staff. [They may also share the research information with [enter SMO company name], an agent for the study doctor. delete if the site does not have an SMO]

Who might get this information?
The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- The institution where the research is being done,
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- Institutional Review Board (IRB)

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to make sure that the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
This permission will be good until December 31, 2070.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Authorization:
I have been given the information about the use and disclosure of my health information for this research study. My questions have been answered.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

AUTHORIZATION SIGNATURE:

_____ _____

Signature of Subject **Date**