NCT04901481

THERANOVA, LLC

Clinical Research Protocol

PILOT EVALUATION OF THE EMPOWER NEUROMODULATION SYSTEM FOR ANXIETY TREATMENT

Protocol Number:	CRD-12-1396-01
Version Date:	October 26, 2021
Investigational Product:	Empower Neuromodulation System
IND/IDE Number:	N/A, nonsignificant risk study
Development Phase:	Feasibility
Sponsor:	TheraNova, LLC 101 Mississippi St. San Francisco, CA 94107
Funding Organization:	NIH-NCCIH
Principal Investigator:	Name: Lauren Edwards, MD Address: 985575 Nebraska Medical Center Omaha, NE 68198-5575 Telephone: [redacted] E-mail: [redacted]
Coordinating Center:	Not applicable

Approval:

PI or Sponsor Signature (Name and Title) *Date*

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is participant to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Participant to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing TheraNova, LLC with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: CRD-12-1396-01

Protocol Title: Pilot evaluation of the Empower Neuromodulation System in GAD Patients

Protocol Date: October 26, 2021

_____ _____

Investigator Signature *Date*

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Print Name and Title

Site Name _____

Address _____

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Phone Number _____

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PROTOCOL SYNOPSIS

TITLE	Pilot evaluation of the Empower Neuromodulation System in GAD Patients
SPONSOR	TheraNova, LLC
FUNDING ORGANIZATION	NIH-NCCIH
NUMBER OF SITES	One (1)
STUDY DESIGN	This is a double-blinded (study participant and clinician assessor), sham-controlled pilot study.
INVESTIGATIONAL DEVICE	Empower Neuromodulation System
INDICATIONS FOR USE/PATIENT POPULATION	The Empower Neuromodulation System is intended to provide transcutaneous electrical nerve stimulation to reduce anxiety. The indicated population is adults who are diagnosed with generalized anxiety disorder (GAD).
PRIMARY OBJECTIVES	The primary study objectives of this pilot study are to evaluate the feasibility and acceptability of the Empower Neuromodulation System as a daily therapy for GAD. Feasibility will be evaluated via treatment adherence (% treatment sessions completed out of the total possible) and acceptability will be evaluated via usability as assessed by the System Usability Scale (SUS) questionnaire.
SECONDARY OBJECTIVES	The secondary study objectives are to evaluate additional endpoints for feasibility (effective nerve stimulation) and acceptability (overall satisfaction with treatment) as well as endpoints for safety (device-related adverse events), effectiveness (anxiety, medication use, depression, PTSD, sleep quality, quality of life) and blinding to treatment group (blinding assessment).
NUMBER OF PARTICIPANTS	Up to 60 (our enrollment target for the intent-to-treat population is 30 participants total, so n=60 includes up to 50% screen fails).
PARTICIPANT SELECTION CRITERIA	<u>Inclusion Criteria</u>: 1. ≥19 years old 2. Current diagnosis of GAD per DSM-5 via M.I.N.I. assessment by clinician 3. HAM-A ≥18 4. Negative urine pregnancy test at screening (females only) 5. Able to provide informed consent 6. Capable and willing to follow all study-related procedures

	Exclusion Criteria: 1. Has current (past 30 days) psychotic or bipolar disorder, homicidal ideation, psychiatric hospitalization, or moderate/severe SUDs per clinician assessment via M.I.N.I. 2. HAM-D ≥18 3. PCL-5 ≥34 4. Exhibits suicidal intent as confirmed on the Columbia-Suicide Severity Rating Scale-Revised (C-SSRS-R) with a "Yes" response to question 4 or question 5 or to question 6 in the past 3 months. 5. Changes in psychoactive medications in the past 30 days (including but not limited to psychotropic medications, thyroid hormone medication, steroids), with the exception of benzodiazepines 6. If regularly taking benzodiazepines, has had changes in benzodiazepine dosing in the past 30 days or average use >2 days per week 7. Psychotherapy was initiated or discontinued in the past 30 days or psychotherapy modality was changes in the past 30 days 8. Has a history of epilepsy or a seizure disorder 9. Has been diagnosed with peripheral nerve damage of the arm or hand or has numbness or tingling in the arm or hand at least weekly 10. Is currently pregnant or breastfeeding, has been pregnant within the past 6 months or intends to become pregnant during the study period 11. Currently has an active implant and/or an electrical or neurostimulator device, including but not limited to cardiac pacemaker or defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, sacral stimulator, bone growth stimulator, or cochlear implant 12. Has an electrically conductive metal object (e.g. jewelry) that cannot be removed from [redacted] and will directly contact the gel electrodes of the Empower Neuromodulation System at either anatomic location 13. Has an open incision, wound, scar, active infection or otherwise compromised skin at the [redacted] and will directly contact the gel electrodes of the Empower Neuromodulation System at either anatomic location 14. Does not have daily access to an electrical outlet for charging the investigational device and associated smartphone 15. Has used of an investigational drug/device therapy within the past four weeks 16. Unable to provide informed written consent 17. Has any medical condition that would, in the opinion of the investigator, make the participant ineligible

TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Transcutaneous electrical nerve stimulation with the Empower Neuromodulation System. [redacted]
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Transcutaneous electrical nerve stimulation with the Empower Neuromodulation System. [redacted]
DURATION OF PARTICIPANT PARTICIPATION AND DURATION OF STUDY	Each participant will be in the study for up to 57 days: **Screening:** up to 7 days **Study participation:** up to 50 days The total duration of the study is expected to be 9 months.
STUDY PROCEDURES	The study will include three clinic visits and twice daily self-administered treatment sessions at home over the 6-week study. All visits can be conducted by secure video call if the COVID-19 pandemic prevents in-person visits and Visit 2 can be conducted by phone. The visits are the following: 1) Enrollment clinic visit (Day 1), 2) Mid-study clinic visit or phone/video call (Day 15 ± 7 days), and 3) Study completion clinic visit (Day 43 ± 7 days). At Visit 1 (enrollment), the participant will first provide informed consent and be screened (screening includes clinician-administered M.I.N.I., C-SSRS-R, HAM-A, and HAM-D and participant-reported PCL-5). The warnings and contraindications as noted in the Instructions for Use (IFU) will also be discussed with the participant. If the participant meets all enrollment criteria, the participant will complete surveys (GAD-Q-IV, PHQ-9, PSQI, and SF-12). The participant will then be randomized to the active or sham treatment group (1:1, [redacted] and trained on device and app use, which includes training on how to self-administer a treatment session with the Empower Neuromodulation System. The participant will then self-administer a treatment session and answer all pre- and post-treatment session survey questions on the Empower app. During this initial treatment session, the participant will, under investigator supervision, adjust the

	stimulation intensity to a perceptible, yet comfortable level. After the session is completed, the clinical research staff will ask the participant about potential adverse events (AEs) through open-ended questioning. The participant will then be given an Empower system, supplies (skin electrodes, batteries, chargers), and the IFU to take home with him/her for self-administering treatment sessions at home. At Visit 2 (mid-study visit), the participant will be asked about potential AEs through open-ended questioning and will be assessed for suicidal intent via the C-SSRS-R. The participant will also complete the blinding assessment. This visit may be conducted by phone. At Visit 3 (study completion), the participant will undergo clinician-administered assessments (C-SSRS-R, HAM-A, and HAM-D, and complete surveys (PCL-5, GAD-Q-IV, PHQ-9, PSQI, and SF-12). The clinical research staff will ask about potential AEs that may have occurred during the study through open-ended questioning. The participant will also complete the blinding assessment, usability survey (system usability scale (SUS) questionnaire), and Study Completion Questionnaire.
PRIMARY ENDPOINTS	• Feasibility: Treatment adherence (% of treatment sessions completed out of the total possible) for each treatment group • Acceptability: System usability scale (SUS) score for each treatment group

SECONDARY ENDPOINTS	• Feasibility: For each treatment group, the percentage of treatment sessions that provide effective nerve stimulation as assessed via participant-reported confirmation of tingling sensation
	• Acceptability: For each treatment group, the overall satisfaction with treatment (via 100-mm VAS)
	• Effectiveness:
	  • Effect of treatment group on change in clinician-assessed anxiety severity (via Hamilton Anxiety Rating Scale (HAM-A))
	  • Effect of treatment group on change in weekly participant-reported anxiety severity (via Beck Anxiety Inventory (BAI)
	  • Effect of treatment group on change in participant-reported GAD symptoms (via GAD-Q-IV)
	  • Effect of treatment group on change in daily self-reports for anxiety severity (via 100-mm VAS)
	  • Effect of treatment group on change in self-reports of anxiety severity immediately after vs. before treatment (via 100-mm VAS)
	  • Effect of treatment group on change in daily self-reports for anxiety interference with daily living (via (100-mm VAS)

	• Effect of treatment group on medication use (via self-reports) • Effect of treatment group on change in clinician-assessed depression severity (via HAM-D) • Effect of treatment group on change in participant-reported depression severity (via PHQ-9) • Effect of treatment group on change in participant-reported PTSD severity (via PCL-5) • Effect of treatment group on change in sleep quality (via PSQI survey) • Effect of treatment group on change in quality of life (via SF-12 survey) • Blinding: For each treatment group, the blinding index and 95% confidence interval (via Bang et al.[26] blinding assessment method)
SAFETY EVALUATIONS	Incidence of adverse events and device-related adverse events
STATISTICS	The primary endpoints are feasibility and acceptability of the Empower Neuromodulation System as a daily therapy for GAD. Feasibility will be evaluated via treatment adherence, and acceptability will be evaluated via usability as assessed by the SUS questionnaire. Feasibility: We will calculate adherence (treatment sessions administered as a percentage of total possible) for each participant. We will consider a treatment session to be completed if at least 20 minutes of the session was administered. We will also compare adherence between the active and sham treatment groups (t-test). Acceptability: We will compare SUS scores for the active and sham treatment groups (t-test), and compare each against the average (SUS≥68) and excellent (SUS≥80) benchmarks.[27]
RATIONALE FOR NUMBER OF PARTICIPANTS	As a pilot study, our primary goal is to demonstrate feasibility for GAD treatment. Accordingly, the study sample size is based on similar pilot GAD studies in the literature. For two rTMS studies, each treatment arm had 12-25 participants, with an average of 15 participants.[28, 29] To be consistent with these studies, we will enroll 15 participants per treatment arm, for a total of 30 participants.

1 BACKGROUND

TheraNova has developed the Empower Neuromodulation System, a portable, safe, easy-to-use neuromodulation device that stimulates the [redacted] nerve to enable a convenient and non-pharmaceutical therapy for generalized anxiety disorder (GAD). The overall goal of this study is to conduct a 6-week pilot investigation into the feasibility and acceptability of the Empower Neuromodulation System in GAD patients. Safety and effectiveness endpoints will also be evaluated as secondary endpoints.

1.1 Overview of GAD and GAD treatment

Anxiety disorders are the most common type of psychiatric disorder.[30] Approximately 32% of Americans experience an anxiety disorder at some point in their lives.[2] With this high prevalence, it is no surprise that the estimated annual economic burden of anxiety disorders in 1998 was $63 billion,[31] and the cost is likely higher today. Characterized by excessive anxiety and worry for at least 6 months, generalized anxiety disorder (GAD) is one of the most common anxiety disorders,[1, 2] affecting 2.9% (~6.4 million) of American adults each year.[2] GAD is often a chronic, recurring condition[3-5] that is associated with decreased psychosocial functioning and quality of life as well as increased disability days.[1, 6] GAD is also costly to treat, with medical costs that are 33% higher than other anxiety disorders.[1, 6] Furthermore, GAD is often comorbid with major depressive disorder (MDD), which, in turn, negatively affects remission from both GAD and MDD.[4, 5] Importantly, recent weekly GAD-2 surveys by the U.S. Census Bureau have indicated that the prevalence of GAD may be sharply increasing as a result of the COVID-19 pandemic. In July 2020 surveys, 36% of American adults had symptoms of GAD vs. 8% before the pandemic.[32] Taken together, there is an urgent need for comprehensive therapies that effectively treat anxiety disorders, in general, and GAD, in particular.

Current guidelines for treatment of GAD include medication, cognitive behavioral therapy (CBT), or both.[5, 7-10] Most medications show moderate initial efficacy, but benefits often decrease over time.[9] Benzodiazepines (BZs), which are $GABA_A$ receptor agonists,[11] are the most effective for treating GAD (Hedges' g (effect size) of ~0.50; where g=0.2, 0.5, and 0.8 are generally considered small, moderate, and large effect sizes, respectively).[5, 7-10] However, guidelines recommend only prescribing BZs for short-term use due to the potential to develop tolerance and dependence.[7, 8] Recommended medications for long-term use include antidepressants (selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)), which are also recommended for other anxiety disorders.[7] However, SSRIs and SNRIs have only modest effectiveness for treating GAD (Hedges' g=0.33-0.36).[3-5] Also, these medications take several weeks to reach maximum efficacy and have common, undesirable side effects, including headaches, nausea, agitation, difficulty sleeping, and sexual dysfunction, which substantially impact medication adherence and discontinuation.[5] As a non-pharmaceutical treatment, CBT has distinct advantages for patient acceptability, but CBT also has modest effectiveness (Hedges' g=0.3-0.5).[12-14] Taken together, GAD remission rates are relatively low for current first-line therapies.

1.2 Neuromodulation as a Treatment for GAD

[redacted]

[redacted]

[redacted]

1.3 Prior Investigations with the Empower Neuromodulation System

The Empower Neuromodulation System has been used in four prior investigations. All studies have been designated nonsignificant risk (NSR) or minimal risk by the approving IRB, and no device-related adverse events have been reported in any of the studies:

- [redacted]"Study to optimize and validate the treatment parameters for the Empower Neuromodulation System" (CRD-12-1154*; approved by Salus IRB; study has been completed*). [redacted]
- [redacted]"Pilot evaluation of the Empower Neuromodulation System in AUD Patients" (*#18-26539; approved by the University of California San Francisco (UCSF) IRB; study has been completed)*. [redacted]

[redacted]

3. "Use of a wearable neuromodulation device to reduce opioid craving in Veterans with chronic pain" (*IRB # 19-27491; approved by the UCSF IRB; study is ongoing)*.

[redacted]

[redacted] "Pilot evaluation of the Empower Neuromodulation System in OUD patients" (*IRB # 19-28297; approved by the UCSF IRB; study is ongoing*

[redacted]

2 RISK / BENEFIT ASSESSMENT

Transcutaneous electrical nerve stimulation (TENS) devices, such as the Empower Neuromodulation System, are non-invasive, generally considered safe (non-significant risk), and are commonly used to relieve neuropathic pain or achieve neuromodulation. Many TENS devices are available over-the-counter, demonstrating their established safety profile.

2.1 Potential Risks

Most of the potential risks to the participant are generally low. Risks include, but are not limited to:

Likely

- A sensation of tickling, tingling, burning, pricking or numbness of the skin along the stimulated nerve (paresthesia, generally known as the feeling of "pins and needles" or of a limb "falling asleep")
- Spasms/twitching of arm and hand muscles
- Involuntary contraction of muscles (tetany) during stimulation on the hand or arm of stimulation application
- Mild discomfort or pain at or near the stimulation site or along the course of the stimulated nerve

Less Likely

- Skin irritation, redness or inflammation at or near the stimulation site (temporary)
- Skin reaction or hypersensitivity to the electrode gel
- Moderate-to-high discomfort or pain (including a throbbing pain) at or near the stimulation site or along the course of the stimulated nerve
- Numbness of fingers (temporary)
- Nausea
- Headache

Rare

- Possible interactions with other electrical and/or neurostimulator device, including but not limited to cardiac pacemaker or defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, sacral stimulator, bone growth stimulator, or cochlear implant.

The likely and less likely risks are considered to be minimal and are addressed in the protocol and consent form. Per the exclusion criteria, to reduce participant risks, we will exclude all participants who have an implanted electrical or neurostimulator device.

2.2 Potential Benefits

As discussed above in Sections 1.2 and 1.3, based on previous acupuncture studies in the literature and our preliminary study in AUD patients, stimulation of [redacted] nerves has the potential to provide anxiolytic effects. This potential benefit from a non-pharmaceutical treatment could provide a valuable therapy option to improve outcomes in the treatment of anxiety disorders, in general, and GAD, in particular.

2.3 Conclusion of the Risk-Benefit Assessment

Based on the established safety profile of TENS devices and the potential benefits to reducing anxiety for GAD patients, we believe that the benefits outweigh the risks in this study.

3 STUDY OBJECTIVES

3.1 Primary Objectives

The primary study objectives of this pilot study are to evaluate the feasibility and acceptability of the Empower Neuromodulation System as a daily therapy for GAD. Feasibility will be evaluated via treatment adherence (% treatment sessions completed out of the total possible) and acceptability will be evaluated via usability as assessed by the System Usability Scale (SUS) questionnaire.

3.2 Secondary Objectives

The secondary study objectives are the following:

- Feasibility: Evaluate the feasibility of the Empower Neuromodulation System treatment via its ability to provide effective nerve stimulation (via participant-reported tingling sensation, a direct indication of effective nerve stimulation)
- Acceptability: Evaluate the acceptability of the Empower Neuromodulation System treatment via overall satisfaction with treatment (via 100-mm VAS)
- Safety: Evaluate the safety of the Empower Neuromodulation System treatment via device-related adverse events
- Effectiveness: Evaluate the effectiveness of the Empower Neuromodulation System treatment for (all endpoints assessed for active vs. sham groups):
    - Reducing clinician-assessed anxiety severity (via Hamilton Anxiety Rating Scale (HAM-A))
    - Reducing participant-reported anxiety severity (via Beck Anxiety Inventory (BAI), Generalized Anxiety Disorder Questionnaire-IV (GAD-Q-IV), daily self-reports for anxiety severity (100-mm VAS), and pre- and post-treatment self-reports of anxiety severity (100-mm VAS))
    - Reducing participant-reported anxiety interference with daily living (via daily self-reports for anxiety interference with daily living (via 100-mm VAS)
    - Reducing medication use (via self-reports)
    - Reducing clinician-assessed depression severity (via Hamilton Depression Rating Scale (HAM-D))
    - Reducing participant-reported depression severity (via Patient Health Questionnaire-9 (PHQ-9))
    - Reducing participant-reported post-traumatic stress disorder (PTSD) severity (via PTSD Checklist-5 (PCL-5))
    - Improving sleep quality (via Pittsburg Sleep Quality Index (PSQI) survey)
    - Improving quality of life (via SF-12 survey)
- Blinding: Evaluate if the active and sham treatments are well-blinded per the blinding assessment

4 STUDY DESIGN

4.1 Sponsor

TheraNova, LLC
101 Mississippi St.
San Francisco, CA 94107
Phone: 415-926-8616

4.2 Sponsor Contact

[redacted]

4.3 Sites

This is a single site study:
University of Nebraska Medical Center and Nebraska Medicine
985575 Nebraska Medical Center
Omaha, NE 68198-5575

4.4 Study Overview

This is a single site, sham-controlled, double-blinded trial. The overall study goal is to evaluate the feasibility and acceptability of the Empower Neuromodulation System as a daily therapy for GAD patients. The total duration of participant participation will be six weeks (**Fig. 2**), and the total duration of the study is expected to be 9 months. Screening data will be reviewed to determine participant eligibility. Participants who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to be randomized.

At enrollment, participants will be randomized (1:1) to either the active treatment arm [redacted] or the sham treatment arm [redacted] Participants and clinician assessors will be blinded. For each enrollee's 6-week participation in the study, the participant will be instructed to self-administer [redacted] and complete daily surveys (self-reports on anxiety levels, medication use, and skin tingling felt during treatment) on the Empower app (on the provided smartphone). Weekly, the participant will be prompted to complete the BAI survey

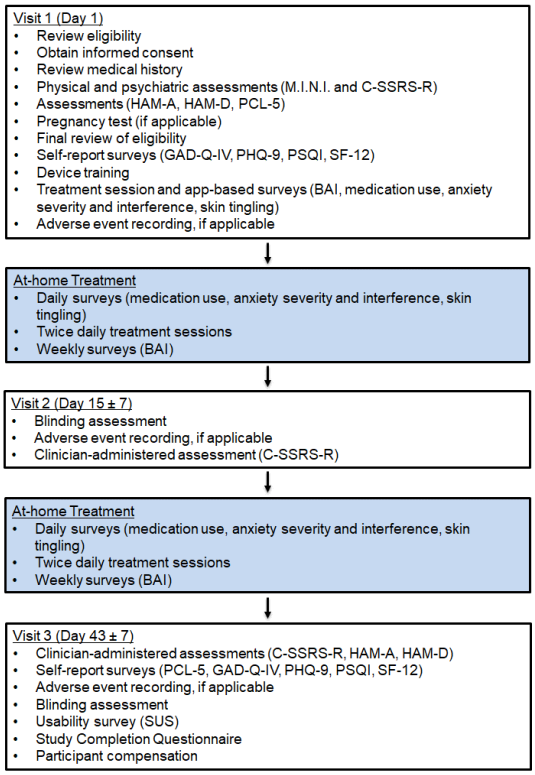

Figure 2. Study outline. This 6-week study will include three study visits. For the duration of the study, participants will self-administer twice daily treatment sessions at home with the Empower Neuromodulation System and complete daily and weekly surveys. At Visits 1 and 2, clinician assessments will be administered and participants will complete surveys. The study completion visit will also include a usability survey and Study Completion Questionnaire.

on the Empower app. At the enrollment visit (Visit 1) and the final study visit (Visit 3), the participant will be assessed by one of the study clinicians for anxiety (HAM-A) and depression (HAM-D). At these study visits, the participant will also complete the following surveys on paper or electronically: PCL-5 GAD-Q-IV, PHQ-9, PSQI, and SF-12. At all clinic visits, the participant will be assessed for suicidality via the Columbia-Suicide Severity Rating Scale-Revised (C-SSRS-R).

Once enrolled and trained on device and app use, the participant will be instructed to conduct treatment sessions and complete surveys [redacted] The Empower Neuromodulation System (which includes a smartphone with

Empower app) will be loaned to each participant for the duration of his/her participation in the study.

The study will include three visits (all visits can be conducted by secure video call if the COVID-19 pandemic prevents in-person visits and Visit 2 can be conducted by phone):

1) Enrollment clinic visit (Day 1),

2) Mid-study clinic visit or phone/video call (Day 15 ± 7 days), and

3) Study completion clinic visit (Day 43 ± 7 days).

At Visit 1 (enrollment), the participant will first provide informed consent and be screened (screening includes clinician-administered M.I.N.I., C-SSRS-R, HAM-A, and HAM-D and participant-reported PCL-5). The warnings and contraindications as noted in the Instructions for Use (IFU) will also be discussed with the participant. If the participant meets all enrollment criteria, the participant will complete surveys (GAD-Q-IV, PHQ-9, PSQI, and SF-12). The participant will then be randomized to the active or sham treatment [redacted] and trained on device and app use, which includes training on how to self-administer a treatment session with the Empower Neuromodulation System. If the subject is randomized to the active treatment group [redacted] The participant will then self-administer a treatment session and answer all pre- and post-treatment session survey questions on the Empower app. During this initial treatment session, the participant will, under investigator supervision, adjust the stimulation intensity to a perceptible, yet tolerable level. After the session is completed, the clinical research staff will ask the participant about potential adverse events (AEs) via open-ended questioning. The participant will then be given an Empower system, supplies (skin electrodes, batteries, chargers), and the IFU to take home with him/her for self-administering treatment sessions at home.

At Visit 2 (mid-study visit), the participant will be asked about potential AEs via open-ended questioning, and the participant will be assessed for suicidality via the C-SSRS-R. The participant will also complete the blinding assessment. This visit may be conducted by phone.

At Visit 3 (study completion), the participant will undergo clinician-administered assessments (C-SSRS-R, HAM-A, and HAM-D) and complete surveys (PCL-5, GAD-Q-IV, PHQ-9, PSQI, and SF-12). The clinical research staff will ask about potential AEs that may have occurred during the study. This will be done via open-ended questioning. The participant will also complete the blinding assessment, usability survey (system usability scale (SUS) questionnaire), and Study Completion Questionnaire, with surveys completed on paper or electronically.

The Empower app automatically logs participant adherence to the treatment session regimen. For each treatment session, the app will record time/date of treatment and the duration of treatment. This data (de-identified, only includes the participant's study ID

number and Empower controller MAC address) will be uploaded automatically to the sponsor's password-protected cloud server for remote compliance monitoring.

5 CRITERIA FOR EVALUATION

5.1 Primary Endpoints

The co-primary endpoints will be feasibility and acceptability of the Empower Neuromodulation System as a daily therapy for GAD. Feasibility will be evaluated via treatment adherence (% treatment sessions completed out of the total possible) and acceptability will be evaluated via usability as assessed by the System Usability Scale (SUS) questionnaire. As part of this study, it is critical to identify an appropriate sham treatment prior to initiating a follow-on pivotal study, so all feasibility and acceptability endpoints will be evaluated for [redacted] treatments in this study. The effect of treatment group on these co-primary endpoints will also be evaluated.

5.2 Secondary Endpoints

The following secondary endpoints will be evaluated:

- Feasibility: For each treatment group, the percentage of treatment sessions that provide effective nerve stimulation as assessed via participant-reported confirmation of tingling sensation
- Acceptability: For each treatment group, the overall satisfaction with treatment (via 100-mm VAS)
- Effectiveness:
    - Effect of treatment group on change in clinician-assessed anxiety severity (via HAM-A)
    - Effect of treatment group on change in weekly participant-reported anxiety severity (via BAI)
    - Effect of treatment group on change in participant-reported GAD symptoms (via GAD-Q-IV)
    - Effect of treatment group on change in daily self-reports for anxiety severity (via 100-mm VAS)
    - Effect of treatment group on change in self-reports of anxiety severity immediately after vs. before treatment (via 100-mm VAS)
    - Effect of treatment group on change in daily self-reports for anxiety interference with daily living (via (100-mm VAS)
    - Effect of treatment group on medication use (via self-reports)
    - Effect of treatment group on change in clinician-assessed depression severity (via HAM-D)
    - Effect of treatment group on change in participant-reported depression severity (via PHQ-9)
    - Effect of treatment group on change in participant-reported PTSD severity (via PCL-5)
    - Effect of treatment group on change in sleep quality (via PSQI survey)

  - Effect of treatment group on change in quality of life (via SF-12 survey)
- Blinding: For each treatment group, the blinding index and 95% confidence interval (via Bang et al.[26] blinding assessment method)

All of these secondary endpoints provide valuable information on the effectiveness of the Empower Neuromodulation System for GAD treatment as well as the acceptability to the intended patient population.

5.3 Safety Evaluations

Safety evaluations will include the incidence and severity of device-related AEs and the incidence and severity of SAEs (regardless of relationship to the device).

6 PARTICIPANT SELECTION

6.1 Study Population

The study population is adults with generalized anxiety disorder (GAD). Participants who meet all of the inclusion and none of the exclusion criteria will be eligible to be randomized for full participation in the study.

6.2 Inclusion Criteria

1. ≥19 years old
2. Current diagnosis of GAD per DSM-5 via M.I.N.I. assessment by clinician
3. HAM-A ≥18
4. Negative urine pregnancy test at screening (females only)
5. Able to provide informed consent
6. Capable and willing to follow all study-related procedures

6.3 Exclusion Criteria

1. Has current (past 30 days) psychotic or bipolar disorder, homicidal ideation, psychiatric hospitalization, or moderate/severe SUDs per clinician assessment via M.I.N.I.
2. HAM-D ≥18
3. PCL-5 ≥34
4. Exhibits suicidal intent as confirmed on the Columbia-Suicide Severity Rating Scale-Revised (C-SSRS-R) with a "Yes" response to question 4 or question 5, or to question 6 in the past 3 months.
5. Changes in psychoactive medications in the past 30 days (including but not limited to psychotropic medications, thyroid hormone medication, steroids), with the exception of benzodiazepines
6. If regularly taking benzodiazepines, has had changes in benzodiazepine dosing in the past 30 days or average use >2 days per week
7. Psychotherapy was initiated or discontinued in the past 30 days or psychotherapy modality was changes in the past 30 days
8. Has a history of epilepsy or a seizure disorder

9. Has been diagnosed with peripheral nerve damage of the arm or hand or has numbness or tingling in the arm or hand at least weekly
10. Is currently pregnant or breastfeeding, has been pregnant within the past 6 months or intends to become pregnant during the study period
11. Currently has an active implant and/or an electrical or neurostimulator device, including but not limited to cardiac pacemaker or defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, sacral stimulator, bone growth stimulator, or cochlear implant
12. Has an electrically conductive metal object (e.g. jewelry) that cannot be removed from [redacted] and will directly contact the gel electrodes of the Empower Neuromodulation System at either anatomic location
13. Has an open incision, wound, scar, active infection or otherwise compromised skin at the [redacted] and will directly contact the gel electrodes of the Empower Neuromodulation System at either anatomic location
14. Does not have daily access to an electrical outlet for charging the investigational device and associated smartphone
15. Has used of an investigational drug/device therapy within the past four weeks
16. Unable to provide informed written consent
17. Has any medical condition that would, in the opinion of the investigator, make the participant ineligible

7 CONCURRENT MEDICATIONS

Each participant should be maintained on the same psychotropic/psychoactive medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

As outlined in the inclusion criteria, at the time of enrollment, participants may be taking scheduled antianxiety, psychotropic, or psychoactive medications (>30 days on a stable dose preceding enrollment) or benzodiazepines (≤2 days per week). Participants may also be in psychotherapy as long as no changes have been made in psychotherapy in the 30 days preceding study enrollment. Only treatments and medications noted in the exclusion criteria described above will be considered a protocol violation. All other medications are allowed.

8 STUDY PROCEDURES

8.1 Method of Assigning Participants to Treatment Groups

This is a randomized, controlled study. At enrollment participants will be randomized (1:1, [redacted] to the active or sham treatment group. Men and women will be randomized separately to ensure that the distribution of men and women in the active and sham arms are consistent. Women account for approximately 64% of American adults with GAD.[46] Thus, to ensure that we enroll a study cohort that is both representative of the American patient population and provides a sufficient sample size of both sexes to

exploratorily evaluate sex as a biological variable, we will enroll a maximum of 21 women and a maximum of 12 men.

Participants will also be randomized for the body side that they should apply stimulation to first [redacted]

8.2 Investigational Device

8.2.1 Device Description

The investigational device is called the Empower Neuromodulation System (**Fig. 3**).

8.2.2 Device Description

[redacted]

8.2.3 Intended Use

The Empower Neuromodulation System is intended to provide transcutaneous electrical nerve stimulation to reduce anxiety.

8.2.4 Technical Specifications

[redacted]

8.2.5 User Interface

[redacted]

8.2.6 Participant-Contacting Materials

8.2.6.1 Gel Electrodes

[redacted]

[redacted]

8.2.6.2 Controller

[redacted]

8.3 Measures of Compliance

The device keeps a log of when the participant administers a treatment session and the duration of each session. This data is transmitted to the smartphone via Bluetooth at the end of each treatment session. [redacted]

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the participant. Assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Screening. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race, ethnicity) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent psychological history (e.g. depression, PTSD, etc.), and information regarding underlying diseases will be recorded at Screening.

9.1.4 Physical Examination

An abbreviated physical examination as needed to determine eligibility (specifically for evaluating the exclusion criteria for jewelry that cannot be removed and open wounds at the [redacted] will be performed by a study clinician at Screening. Site staff will also measure [redacted] participants randomized to the active treatment group.

9.1.5 Psychiatric Examination

An abbreviated psychiatric examination as needed to determine eligibility will be performed by either the investigator or qualified staff (MD, NP, or PhD) at screening. The Mini-International Neuropsychiatric Interview (M.I.N.I.) will be used to evaluate the DSM-5 criteria for GAD and other psychiatric disorders that are in the inclusion and exclusion criteria. The Columbia-Suicide Severity Rating Scale-Revised (C-SSRS-R) will be used to evaluate suicidality risk at each clinical visit.

9.1.6 Medical chart review

The participant will be asked about the following, and if available, the participant's medical chart will also be reviewed to determine if the participant has been diagnosed with any of the following:

- Epilepsy or seizure disorder
- Peripheral neuropathy or nerve damage of the upper extremities

The participant will be asked about the following, and if available, the participant's medical chart will be reviewed to determine if the participant has any of the following:

- Has used an investigational drug or device within the past four weeks
- Has implanted electrical and/or neurostimulator device (e.g. pacemaker, defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, sacral stimulator, bone growth stimulator, or cochlear implant)

9.1.7 Surveys

Throughout the study, the participant will provide responses and complete surveys that cover medication use, skin tingling during treatment, anxiety, depression, sleep quality, and quality of life. Daily surveys (medication use, skin tingling during treatment, anxiety

severity and interference with daily living) and weekly surveys (BAI) will be completed on the Empower app. Surveys will be completed at the same time as Empower treatment (the participant will be guided by the app as to when each survey is to be completed). Surveys conducted at Visits 1 and 3 (GAD-Q-IV, PHQ-9, PSQI, and SF-12) will be completed electronically or on paper. At each clinic visit, the participant will complete the daily and weekly surveys if they have not been completed for that day/week. At the final clinic visit, the participant will also complete the following electronic or paper-based surveys: usability survey (SUS), rating of overall satisfaction with treatment (100-mm VAS), blinding assessment, and a Final Study Questionnaire that includes questions regarding feedback on device features, device comfort and tolerability, and marketing questions.

9.1.7.1 Daily Surveys

The daily survey questions will be completed on the Empower app and include questions about non-scheduled anxiety medication use (e.g. benzodiazepine dose taken over the past 24 hours and day/time of last dose), anxiety severity over the past 24 hours, anxiety interference with daily life over the past 24 hours, and anxiety severity at the present time. For anxiety severity, the participant will be asked to rate it on a 100-point visual analog scale (VAS) [0=”No anxiety at all” through 100=”Severe Anxiety”]. For anxiety interference with daily life, the participant will be asked to rate it on a 100-point visual analog scale (VAS) [0=”Not at all” through 100=”Extreme”].

The app will guide the participant to complete the daily survey prior to self-administering the first treatment session of each calendar day. Immediately after the session, the participant will also be asked about anxiety severity at the present time and if a tingling sensation was felt on the skin at the site of stimulation application to confirm effective nerve stimulation.

9.1.7.2 Weekly Surveys

The weekly surveys (BAI) will be completed on the Empower app. The app will guide the participant to complete the weekly survey prior to self-administering the first treatment session of each calendar week.

9.1.7.3 Surveys only at Visits 1 and 3

Surveys conducted at Visits 1 and 3 (GAD-Q-IV, PHQ-9, PSQI, and SF-12) will be completed electronically or on paper. At Visit 3, the participant will also complete the following electronic or paper-based surveys: usability survey (SUS), rating of overall satisfaction with treatment (100-mm VAS), blinding assessment, and a Final Study Questionnaire that includes questions regarding feedback on device features, device comfort and tolerability, and marketing questions.

9.1.8 Treatment Session

[redacted]

[redacted]

9.1.9 Treatment regimen reminders sent to participants via text message

[redacted]

[redacted]

9.1.10 Contact with participants who are not adhering to the treatment regimen

[redacted]

the clinical site research staff will contact the participant and request that they comply with the study procedures.

9.1.11 Adverse Events

Information regarding occurrence of AEs and serious AEs (SAEs) will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study device and procedures will be recorded on the case report form (CRF).

If the participant's skin becomes too irritated to comfortably carry out the treatment sessions, the participant will be instructed to refrain from administering a treatment session until the skin is no longer irritated.

9.1.12 Suicidality Evaluation

The C-SSRS-R will be used to evaluate suicidality risk at each clinic visit. If a participant exhibits suicidality or is determined to be at risk for harm to self/others by the clinician, the participant will be referred to his/her current mental health provider or primary care provider and will be provided information on community resources. In the event of acute suicidality, as confirmed on the C-SSRS-R with a "Yes" response to question 4 or question 5, or to question 6 in the past 3 months, the participant will be referred to the emergency department or psychiatric emergency services and withdrawn from the study.

9.1.13 Participant Compensation

Participants will be compensated a nominal amount for their time and expenses associated with the study. Each participant will be compensated $100 for the screening/enrollment visit (Visit 1), $100 each for the remaining two visits (Visits 2 and 3), and a bonus of $25 for returning the study equipment (Empower controller and smartphone), for a total compensation of up to $325 per participant. Compensation at Visits 2 and 3 includes compensation for the time and effort of conducting twice daily treatment sessions at home during the study.

9.2 Clinical Laboratory Measurements

9.2.1 Pregnancy Test

A urine pregnancy test will be obtained from female participants at the screening visit.

10 EVALUATIONS BY VISIT

10.1 Visit 1 (Day 1)

1. Review the study with the participant and obtain written informed consent and HIPAA authorization and assent
2. Assign the participant a unique screening number
3. Record demographics data
4. Record medical history
5. Record concomitant medications
6. Perform an abbreviated physical examination
7. Perform an abbreviated psychiatric examination, including M.I.N.I. and C-SSRS-R
8. Collect urine sample and perform a urine pregnancy test, if applicable
9. Perform clinician-administered assessments (HAM-A and HAM-D) and participant-reported survey (PCL-5)
10. Final review of eligibility
11. Complete self-report surveys (GAD-Q-IV, PHQ-9, PSQI, SF-12)
12. Randomize participant
13. Train participant on Empower device, smartphone, and app.
14. Self-administer a treatment session and complete app-based surveys (BAI, medication use, anxiety severity and interference, skin tingling)
15. Record adverse events, if applicable
16. Schedule participant for Visit 2 in 14 days

10.2 Visit 2 (Day 15 ± 7)

1. Complete blinding assessment
2. Record adverse events, if applicable
3. Perform assessment of suicidality (C-SSRS-R)
4. Schedule participant for Visit 3 in 28 days

10.3 Visit 3 (Day 43 ± 7)

1. Perform clinician-administered assessments (C-SSRS-R, HAM-A, HAM-D)
2. Complete self-report surveys (PCL-5, GAD-Q-IV, PHQ-9, PSQI, SF-12)
3. Record adverse events, if applicable
4. Complete blinding assessment, usability survey, and Study Completion Questionnaire
5. Return of all device and study materials
6. Participant reimbursement

10.4 Early Withdrawal Visit

1. Perform clinician-administered assessments (C-SSRS-R, HAM-A, HAM-D)
2. Complete self-report surveys (PCL-5, GAD-Q-IV, PHQ-9, PSQI, SF-12)
3. Record adverse events, if applicable
4. Complete blinding assessment, usability survey, and Study Completion Questionnaire
5. Return of all device and study materials
6. Participant reimbursement

11 ADVERSE EXPERIENCE REPORTING, DOCUMENTATION, AND MONITORING

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these regardless of relationship to participation in the study.

11.1.2 Unanticipated Problem (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems (UPs) involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

11.1.3 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any AE that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the study participant at immediate risk of death from the event as it occurred)

- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect.

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

Unanticipated problems will be recorded in the data collection system throughout the study.

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

11.3 Characteristics of an Adverse Event

11.3.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

11.3.2 Expectedness of SAEs

The Study PI and Independent Safety Monitors will be responsible for determining whether an SAE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

11.3.3 Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL.

11.4 Reporting Procedures

AEs will be monitored at frequent intervals during the study. Study participants will be monitored during the study at each clinic visit for expected and unexpected AEs related to the Empower Neuromodulation System. The Site PI or research coordinator will probe, via discussion with the participant, for the occurrence of AEs during each participant visit and record the information in the AE case report form (CRF). AEs will be described by duration (start and stop dates), severity, outcome, treatment and relation to study device, or if unrelated, the cause.

During the study, site clinical research personnel will note any change in the participant's symptoms (anxiety, depression, etc.) and the occurrence and nature of any AEs. Important clinical information that comes to light during study participation will be communicated by research coordinators to the study PI in real time.

The study investigator (either the Site PI, Dr. Lauren Edwards, or, in her absence, the Site co-investigator, Dr. Justin Weeks) will review each participant's safety at each study visit.

- Moderate and severe AEs reported by participants will be reviewed on the same day as they are reported by the study participant. Mild AEs reported by participants will be reviewed within 72 hours of being reported by the study participant.

- Adverse effect assessment will be done by the research coordinators and discussed with the Site PI on a daily basis, immediately after these AEs are reported by the participant to the study coordinator.

The Site PI, if not immediately present at the time of adverse effect data collection, will be contacted in real time by the study coordinator by phone, pager, or text message, so that AEs can be discussed with the Site PI.

At least every 6 months, the Site PI will report to the independent monitoring committee and study sponsor the assessment of the potential relatedness of each AE to protocol procedure, studied disease state, and study device via the CRF. For each AE recorded on the AE CRF, the PI will make an assessment of seriousness, severity, and causality.

The PI will follow all unresolved AEs until the event has resolved to baseline grade or better, the event is assessed as stable by the PI, new therapy is initiated, the participant is lost to follow-up, the participant withdraws consent, or until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

Every effort will be made to follow all SAEs considered to be related to study procedures until a final outcome can be reported. During the study period, resolution of AEs (with dates) will be documented on the AE CRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the AE CRF.

In the event that an SAE or death occurs, the event will be reported by the Site PI within 48 hours after she first learns of the event to the sponsor and the reviewing IRB per the UNMC IRB reporting requirements. The initial report of an SAE must be made by phone as well as by email. The sponsor will immediately conduct an evaluation of the SAE(s) and report the results of the evaluation to FDA and NCCIH within 5 working days after first receives notice of the SAE(s).

The Site PI must report any UPs within the same timeframe. The Site PI must report any protocol deviations or violations to the sponsor within 7 days of PI awareness. The Site PI must also submit all reports to the UNMC IRB in accordance with the institutional policies.

11.4.1 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of the UP report form. To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, Independent Safety Monitors, and sponsor (who will then report to the funding agency, NCCIH) within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Independent Safety Monitors, and sponsor (who will then report to the funding agency, NCCIH) within 14 days of the investigator becoming aware of the problem.

11.4.2 AE Reporting

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Safety Monitors, IRB, and sponsor (who will then report to the funding agency, NCCIH).

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the Independent Safety Monitors, IRB, and sponsor (who will then report to the funding agency, NCCIH) within 48 hours of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 7 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor, IRB, and sponsor (who will then report to the funding agency, NCCIH) within 7 days.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE

summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitors Report will state that all AEs have been reviewed.

11.4.3 Reporting of Pregnancy

Due to the unknown effects of transcutaneous electrical nerve stimulation (TENS) on a fetus or breastfeeding infant whose mother is receiving TENS treatment, an exclusion criterion for this study is: "Currently pregnant or breastfeeding, has been pregnant within the past 6 months or intends to become pregnant during the study period." If a study participant becomes pregnant during study participation, she will be instructed to discontinue treatment, return the study materials, and will continue to be followed up for safety monitoring. This will be reported by the Site PI to the IRB, and sponsor (who will then report to the funding agency, NCCIH) within 5 days.

11.5 Halting Rules

The study will be stopped if, in the judgment of the Site PI, there are sufficient safety concerns that arise during the conduct of the study that would indicate that participants are being harmed by the study interventions, e.g., multiple SAEs that are judged to be related to study interventions. Subsequent review of serious, unexpected, and related AEs by the Independent Safety Monitors, IRB, sponsor, or FDA or relevant local regulatory authorities may also result in suspension of further study interventions/administration of study product. The FDA and study sponsor retain the authority to suspend additional enrollment and study interventions/administration of study product for the entire study, as applicable.

12 DISCONTINUATION AND REPLACEMENT OF PARTICIPANTS

12.1 Early Discontinuation of Study

A participant may be discontinued from study at any time if the participant, the investigator, or the Sponsor feels that it is not in the participant's best interest to continue. The following is a list of possible reasons for study discontinuation:

- Participant withdrawal of consent (or assent)
- The PI believes it is in the best interest of the participant to withdraw from the study. This could be due to worsening anxiety or depression symptoms, suicidal or homicidal ideation, or for other reasons that the PI determines warrant it being in the participant's best interest to discontinue study participation
- Participant is not compliant with study procedures, including not administering at least one treatment session per two week period
- AE that in the opinion of the investigator would be in the best interest of the participant to discontinue study participation
- Protocol violation requiring discontinuation of study participation
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a participant is withdrawn from the study due to an AE, the participant will be followed and treated by the PI until the abnormal parameter or symptom has resolved or stabilized. All participants who discontinue study participation should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures. All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the investigator to provide a reason for participant withdrawals. The reason for the participant's withdrawal from the study will be specified in the participant's source documents. Refer to Section 10 for early withdrawal procedures.

12.3 Withdrawal of Participants from the Study

If a participant who does not meet enrollment criteria is enrolled, the study sponsor will be contacted. In such cases, the PI will provide information on the participant´s anticipated benefit or current benefit from being enrolled in the study or continuing to receive study interventions. In addition, the PI will discontinue participants from the study in the following circumstances:

- The PI decides that the participant should be withdrawn from the study due to an SAE judged to be due to study interventions.
- The participant or his or her medical provider requests withdrawal of the participant from the study.
- The PI stops the participant's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- Per C-SSRS-R assessment at a clinic visit, the participant exhibits acute suicidality, as confirmed on the C-SSRS-R with a "Yes" response to question 4 or question 5, or to question 6 in the past 3 months
- The participant is not compliant with study procedures, including not administering at least one treatment session per two week period. Exceptions may be made after discussions with the PI, with sponsor's approval.
- The participant has not been in contact with the research staff for at least two weeks after at least three research staff attempts for contact. Exceptions may be made after discussions with the PI, with sponsor's approval.
- In the clinical judgment of the investigator, the participant's clinical condition worsens substantially and it is felt to be in the participant's best interest to obtain alternative treatment including, but not limited to, additionally psychotherapy, pharmacotherapy, hospitalization, etc.
- The participant's skin becomes too irritated to comfortably carry out the treatment sessions, and after refraining from administering a treatment session until the skin is no longer irritated, the irritation returns upon administering another treatment session.

When a participant withdraws before completing the study, the reason for withdrawal will be documented in the CRF and in the source document.

Participants who discontinue study participation early (i.e., they withdraw prior to Visit 3) should have an early discontinuation visit. Refer to Section 10 for early withdrawal procedures. Participants who withdraw after Visit 1 but prior to Visit 3 should be encouraged to come in for a final visit (and the procedures to be followed would include those listed in Section 10).

12.4 Replacement of Participants

Participants who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the participant, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, participant safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a participant.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 DATA SAFETY MONITORING

14.1 Independent Monitoring Committee

The Independent Monitoring Committee (IMC) for this study will be comprised of up to three Independent Safety Monitors. The monitors will not be associated with this research project and will be required to work independently of the Site PI Lauren Edwards, MD, or sponsor representative (and NCCIH grant PI), Michael Jaasma, PhD. No member of the Committee will be allowed to have collaborated or co-published with the grant PI or Site PI within the past three years. They will be qualified to review the patient safety data generated by this study because of their unique expertise.

14.2 Safety Review Plan

Study progress and safety will be reviewed monthly (and more frequently if needed) by the PO. Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Independent Safety Monitors semi-annually. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for

dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Safety Monitors and will be forwarded to the sponsor (who will submit to the funding agency, NCCIH).

14.3 Study Report Outline for the Independent Safety Monitors (Interim or Annual Reports)

The study team will generate Study Reports for the Independent Safety Monitors and will provide information on the following study parameters: enrollment status, subject status, demographics, adverse events, serious adverse events, deaths, unanticipated problems, any laboratory findings for tests conducted based on adverse events. Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population.

14.4 Submission of On-Site Monitoring/Audit and Inspection Reports

The IMC and sponsor (who will then submit to the funding agency, NCCIH) will receive copies of all study monitoring/audit or inspection reports within 14 day of PI receipt. Any FDA inspection report will be submitted to the IRB, IMC, and the sponsor (who will then submit to the funding agency, NCCIH).

14.5 Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

15 STATISTICAL METHODS AND CONSIDERATIONS

15.1 Data Sets Analyzed

All eligible patients who receive at least one stimulation session with the study device (the Safety Population) will be included in the safety analysis.

15.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: race, gender, age, primary antianxiety medication currently taking, and primary psychotherapy treatment currently participating in.

15.3 Analysis of Primary Endpoint

The primary endpoints will be feasibility and acceptability of the Empower Neuromodulation System as a daily therapy for GAD. Feasibility will be evaluated via

treatment adherence, and acceptability will be evaluated via usability as assessed by the SUS questionnaire.

Feasibility: We will calculate adherence (treatment sessions administered as a percentage of total possible) for each participant. We will consider a treatment session to be completed if at least 20 minutes of the session was administered. We will also compare adherence between the active and sham treatment groups (t-test).

Acceptability: We will compare SUS scores for the active and sham treatment groups (t-test), and compare each against the average (SUS≥68) and excellent (SUS≥80) benchmarks.[27]

15.4 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed via the methods described below. Unless otherwise noted, for daily and weekly metrics, we will use a random-intercept linear mixed model with restricted maximum likelihood to compare results between the active and sham treatment groups. As a secondary analysis for each of these endpoints, we will evaluate the correlations for duration since last benzodiazepine dose and dose amount vs. the endpoint. If this relationship is significant for an endpoint, we will include time since last dose in our statistical analysis.

Feasibility: Effective nerve stimulation: We will calculate effective nerve stimulation (treatment sessions that elicit skin tingling as a percentage of total treatment sessions) for each participant. We will also compare effective nerve stimulation between the active and sham treatment groups (t-test).

Acceptability: Overall satisfaction with treatment: We will compare overall satisfaction with treatment scores between the active and sham treatment groups (t-test).

Safety: We will tabulate AEs across all participants. This will include tabulating the number of participants for whom the event occurred, the rate of occurrence, and the severity and relationship to the study device.

Effectiveness: Change in HAM-A score: We will compare the change in HAM-A score between the active and sham treatment groups (t-test).

Effectiveness: Change in GAD-Q-IV score: We will compare the change in GAD-Q-IV score between the active and sham treatment groups (t-test).

Effectiveness: Change in BAI score: We will compare the change in BAI score between the active and sham treatment groups (mixed models).

Effectiveness: Change in daily anxiety severity self-report: We will compare the change in daily anxiety severity scores between the active and sham treatment groups (mixed models).

Effectiveness: Change in daily anxiety interference self-report: We will compare the change in daily anxiety interference scores between the active and sham treatment groups (mixed models).

Effectiveness: Change in anxiety severity self-report as an immediate result of treatment: We will compare the short-term effect of Empower treatment on anxiety severity score (% change for post-treatment score vs. pre-treatment score) (repeated measures ANOVA with Tukey correction, active vs. sham treatment group).

Effectiveness: Medication use: We will calculate average benzodiazepine use per week. We will compare medication use between the active and sham treatment groups (mixed models).

Effectiveness: Change in HAM-D score: We will compare the change in HAM-D score between the active and sham treatment groups (t-test).

Effectiveness: Change in PHQ-9 score: We will compare the change in PHQ-9 score between the active and sham treatment groups (t-test).

Effectiveness: Change in PCL-5 score: We will compare the change in PCL-5 score between the active and sham treatment groups (t-test).

Effectiveness: Change in PSQI score: We will compare the change in PSQI score between the active and sham treatment groups (t-test).

Effectiveness: Change in SF-12 score: We will compare the change in SF-12 score between the active and sham treatment groups (t-test).

Blinding: We will statistically assess blinding for the active and sham treatment groups using the blinding index from Bang et al.[26]

15.5 Randomization and Sample Size

At enrollment, participants will be randomized (1:1, [redacted] stratified by sex) to the active or sham stimulation. Participants will also be randomized for the body side that they should apply stimulation to first (right vs. left, 1:1 simple randomization). Men and women will be randomized separately.

As a pilot study, our primary goal is to demonstrate feasibility for GAD treatment. Accordingly, the study sample size is based on similar pilot GAD studies in the literature. For two rTMS studies, each treatment arm had 12-25 participants, with an average of 15 participants.[28, 29] To be consistent with these studies, we will enroll 15 participants per treatment arm, for a total of 30 participants.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

Study personnel will enter data from source documents corresponding to a participant's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Participants will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a participant study ID number.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

16.2 Data Management Responsibilities

The study staff are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

The PI is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the PI, Co-I, or CRC. A copy of the CRF will remain at the PI's site at the completion of the study.

16.3 Database Protection

This study will use an electronic database and on-paper surveys and CRFs. The electronic database will be secured with password protection. The informatics manager will receive only coded information that is entered into the database under those identification numbers. Electronic communication with outside collaborators will involve only unidentifiable information. The database incorporates an electronic audit trail to show change(s) to data after original entry including the date/time and user making the change. For all paper-based study records will be kept in a locked filing cabinet. Code sheets linking a participant's name to the participant's study identification number will be stored separately in another locked filing cabinet or on a password-protected computer.

16.4 Source Document Protection

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept

in a locked filing cabinet or on a password-protected computer or server. Code sheets linking a participant's name to a participant study identification number will be stored separately in another locked filing cabinet or on a password-protected computer.

All study data collected on an electronic CRF will be entered into a validated database. The database is safeguarded against unauthorized access by established security procedures. Throughout the study, device use data (i.e. frequency and duration of use, stimulation intensity used in a treatment session) and daily survey data will be upload by the smartphone's cellular data plan to a cloud-based, password-protected, secure server (Amazon Web Services). This data will also be stored securely on a password-protected server maintained by the sponsor at the sponsor's facility. Note that data files transmitted to and saved on the password-protected cloud server and the sponsor's server will be de-identified. These files will only include the participant's study ID number and Empower controller MAC address.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.5 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

16.6 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each participant must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that participant. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the study has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.7 Schedule and Content of Reports

The study team will generate Study Reports for the Independent Monitors and will provide information on the following study parameters: enrollment status, subject status, demographics, adverse events, serious adverse events, deaths, unanticipated problems, any laboratory findings for tests conducted based on adverse events. A Final Study Report will

also be generated after study completion. The Final Study Report will include analysis of adverse events, primary and secondary endpoints, blinding to treatment group, and participant qualitative feedback on the Empower Neuromodulation System that is collected via a questionnaire.

16.8 Monitoring

The sponsor's QA Reviewer will review de-identified source documents and data collected at least quarterly. This includes review of subject screening and enrollment logs, informed consent forms of enrolled subjects, critical data used to evaluate eligibility criteria of enrolled subjects, CRFs used to log study visits and treatments, documented AEs and SAEs, and protocol deviations. If any errors are identified, the QA Reviewer will notify site study personnel to resolve the error or errors. Corrective action will also be taken to prevent a similar error from occurring again. This could include such steps as re-training of site staff or double-data entry. The frequency of all quality assurance/quality control checks is incorporated into Table below.

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitors
Status of all enrolled subjects, as of date of reporting	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitors
Data entry quality control checks on 50% of charts	Quarterly	Internal QA Reviewer
Adherence data regarding study visits and intervention	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitors
AEs and rates (including out-of-range lab values)	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitors
	Annually	NCCIH, FDA (If Applicable)
SAEs (unexpected and related)	Per occurrence	PI, Independent Monitors NIH/NCCIH, FDA (if applicable)
SAEs (expected or unrelated)	Per Occurrence	PI, Internal QA Reviewer
	Annually	Independent Monitors, NIH/NCCIH
Unanticipated Problems	Monthly	PI, Internal QA Reviewer
	Per Policy	IRB, FDA (if applicable)

16.9 Participant Confidentiality

In order to maintain participant confidentiality, only a participant study ID number will identify all study participants on CRFs and other documentation submitted to the study monitor or Sponsor. For text messaging of study notifications to participants, the participant

phone number will be stored with the participant ID number, which will be stored within a password-protected server.

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to subjects.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked filing cabinet or on a password-protected computer. Code sheets linking a patient's name to a patient identification number will be stored separately in another locked filing cabinet or on a password-protected computer. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

17.1 Non-Significant Risk Determination for the Study

Given the well-established safety profile of TENS devices and the fact that the Empower Neuromodulation System controller, which provides the electrical stimulation, is powered by a single 9-volt battery, we believe that this study qualifies as a non-significant risk (NSR) study. In further support of a NSR determination, the Empower Neuromodulation System has been used in four prior or ongoing investigations that were all determined to be NSR or minimal risk studies (see Section 1.3). These studies are pilot investigations in similar patient populations (alcohol use disorder, opioid use disorder, and chronic pain). In addition, in these four studies, no device-related AEs has occurred. Given the similarities of the current study with that of past studies with this device, we believe the current study should also be granted an NSR determination.

Furthermore, this study with the Empower Neuromodulation System can be designated a NSR study per FDA guidance provided in "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors - Significant Risk and Non-significant Risk Medical Device Studies". The NSR determination can be made from answering "no" to the following four questions from the FDA guidance document for determining Significant Risk:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a participant; → No, this device is not an implant.
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a participant; →No, this device is not intended for supporting or sustaining human life.
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a participant; → No, this is a feasibility study, so in this study this device is not used in the diagnosis, curing, mitigating or treating of disease.
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a participant; → No, this device does not present a potential for serious risk to the health, safety, or welfare of participants.

17.2 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor and approved by the PI prior to submission. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB is notified within five working days.

17.3 Institutional Review Board (IRB)

The protocol and consent form will be reviewed and approved by the UNMC IRB prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB's unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.4 Informed Consent

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Participants (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each participant prior to entering the participant into the trial. Information should be given in both oral and written form and participants must be given ample opportunity to inquire about details of the study. Because it is unknown if transcutaneous electrical nerve stimulation can affect a fetus, women of child-bearing age will be advised about the importance of using at least one form of contraception during study participation. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. To complete the informed consent process at the end of study participation, study staff will inform the subject when his/her participation has come to an end and will document this in the study record.

17.5 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.6 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of participants.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to participants or others.
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/participants.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. STUDY VISITS

	VISIT 1 (Day 1)	VISIT 2 (Day 15 ± 7)	VISIT 3 (Day 43 ± 7)
Informed consent	**X**		
Assign unique screening number	**X**		
Demographic information	**X**		
Medical history	**X**		
Record concomitant medications	**X**		
Abbreviated physical exam	**X**		
Psychiatric exam, including M.I.N.I	**X**		
C-SSRS-R	**X**	**X**	**X**
Perform clinician-administered assessments (HAM-A, HAM-D)	**X**		**X**
Pregnancy test (if applicable)	**X**		
Eligibility review	**X**		
Randomization	**X**		
Complete self-report surveys (PCL-5, GAD-Q-IV, PHQ-9, PSQI, SF-12)	**X**		**X**
Device and App Training	**X**		
Treatment Administration	**X**		
Complete app-based surveys (BAI, medication use, anxiety severity and interference, skin tingling)	**X**		
Adverse event reporting	**X**	**X**	**X**
Blinding assessment		**X**	**X**
Complete usability survey and Study Completion Questionnaire			**X**
Participant compensation			**X**

APPENDIX 2. REFERENCES CITED

https://www.nimh.nih.gov/health/publications/generalized-anxiety-disorder-gad/index.shtml

[redacted]

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