A Randomized, Phase II, Open-Label Study Evaluating the Nu-V3 Cranial Nerve Stimulation Treatment Device in Patients with Chronic Pain, Anxiety, Depression, and/or Sleeplessness

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Protocol Signature Page

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Protocol Amendment 1.6: April 20, 2022

By signing below, the Investigator attests that they will adhere to the protocol and Informed Consent Form and report, to the Study Sponsor and the IRB, any adverse device or participant study event.

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1.0 Introduction

1.1 Background

Research evidence has shown that the symptoms of chronic pain, anxiety, depression, and sleeplessness, or any combination of these symptoms are prevalent among patient populations with chronic medical conditions, particularly inflammatory arthritis (Psoriatic Arthritis, Rheumatoid Arthritis), Fibromyalgia, anxiety disorders (PTSD, Generalized Anxiety Disorder), Depression, Chronic Pain conditions (neuropathy, chronic neck and back pain, Osteoarthritis, TMJ Syndrome), and sleep disorders. Patients with one of these chronic conditions often have clusters of one or more of these four symptoms (pain, anxiety, depression, and/or sleeplessness).

These patient populations have a need for an innovative treatment approach to address these symptoms, as they often occur simultaneously. By addressing all possible combinations of these symptoms in an individual patient or population, significant improvements in patients' health and health outcomes can be achieved.

Globally, the lifetime prevalence of anxiety disorders from a 2013 meta-analysis was 7.3% (4.8-10.9%) and ranged from 5.3% (3.5-8.1%) in African cultures to 10.4% (7.0-15.5%) in Euro/Anglo cultures.[1] These statistics translate into 1 out of 13, and 1 out of 10 people affected globally and in North America, respectively. In the United States alone, anxiety affects about 18% of the population or 40 million adults aged 18 and older at cost of more than $42 billion a year in 1990.[2,3]

In a separate systematic review on depression, the global prevalence of major depressive disorder was 4.7% (4.4-5.0%).[4] In 2015, over 16 million adults aged 18 or older have been estimated to have had at least one major depressive episode in the prior year, representing 6.7% of all U.S. adults.[5]

Insomnia is a global public health issue and is believed to affect approximately 30-35% of the global population.[6,7] Poor sleep has been associated with decreased immunity, depression, anxiety, poorer quality of life, obesity, increased pain, occupational errors, absenteeism from work, and motor vehicle crashes.[7,8]

The prevalence of chronic pain, like all the previous conditions discussed, is highly variable among subgroups in population and by indication. It is estimated that approximately 20% of the adult European population suffers from chronic pain.[9] Similarly, approximately 17.6% (about 40 million) of US adults experience severe levels of pain along with over 11.2% (25.3 million) of adults suffering from daily pain for the prior 3 months at an annual estimated cost of approximately $560-$635 billion.[10,11]

Given the high prevalence of conditions associated with chronic pain, anxiety, depression, and/or sleeplessness (CPADS), the associated economic burden, and lack of safe and cost-effective therapies, interest and research is expanding into the field of neuromodulation therapies, including TENS devices, to meet this need.

The Nu-V3 device is not considered to be a Transcutaneous Electrical Nerve Stimulation (TENS) device. TENS devices are applied only in the area of the body directly related to the pain. The Nu-V3 device is placed on the auricular (ear) area and utilizes a non-invasive electrical micro-signal to access the cranial nerves via three small electro-gel pads. There are no TENS devices currently approved or cleared by the FDA that qualify as being substantially equivalent.

Under further research pertaining to accessing the cranial nerves, in particular the vagus nerve, we discovered that there are a variety of Vagal Nerve Stimulators available. However, none are non-invasive and small enough to be attached to the ear while stimulating multiple cranial nerves in the auricular area.

In summary, while Nu-V3 is technically a transcutaneous device, the mechanism for mitigation of symptoms (chronic pain, anxiety, depression, and sleeplessness) is unique by TENS standards for the following reasons:

A. TENS is typically placed in the general area where the pain exists. Nu-V3 is placed only in the auricular area (on the ear) and accesses the cranial nerves as the mechanism for relief.
B. TENS devices are known to stimulate muscular tissue and nerves in the area where pain exists, creating vasodilation (increased blood flow) and thereby the possibility of temporary relief. Nu-V3, by accessing the cranial nerves (specifically the vagus nerve) non-invasively, acts to stimulate the body's natural enkephalins and elevate blood flow, and may result in the balancing or rebalancing of the Autonomic Nervous System (ANS).[12-18]
C. By accessing the cranial nerves in the manner described above, the effect may be cumulative and residual and offer the patient immediate, intermediate, and longer lasting relief from their symptoms.

In part, the purpose of this clinical study is to demonstrate the effect of the device upon the four specific symptoms of chronic pain, anxiety, depression, and sleeplessness. Any one or combination of these symptoms may result in Autonomic Nervous System dysfunction.

1.2 Device Description

The Nu-V3 device is a miniaturized, wearable, microchip-controlled, cranial nerve stimulation treatment device which delivers pulsed micro-signals over a period of 14 days. The Nu-V3 device provides a continuous flow of intermittent, low frequency electrical pulses to the ear's specific cranial nerve endings. The Nu-V3 device is a patent pended, non-invasive transcutaneous stimulating device which offers useful features to the patient and clinical professional. The Nu-V3 device control features are set by the manufacturer and prevent patient misuse of the device.

Three miniature, non-invasive, electro-gel pads are utilized to deliver a micro signal at 1

Hz in a square plus minus waveform, which cycles on and off every three hours to provide a resting period and prevent adaption to the stimulation. The device is powered by three (No.10) zinc air batteries at 1.4 volts each (4.2 volts in total), to provide the required stimulation for up to 14 days. The low frequency, reliability of the zinc air batteries and consistency of the micro-signal through the eight-pin micro-chip technology, provides consistent and equivalent stimulation energy regardless of individual skin impedance.

1.3 Non-significant Risk Medical Device Study

The FDA considers other microcurrent transcutaneous devices (such as TENS devices) as nonsignificant risk devices for medical device studies.[19] The Nu-V3 device used in this study reflects an investigational device that meets the definition of a nonsignificant risk device per review of the IRB.

2.0 STUDY OBJECTIVE

The objective of this research study is to collect data which demonstrates the ability of the Nu-V3 device to offer relief from one or more of the following symptoms: chronic pain, anxiety, depression, and/or sleeplessness.

3.0 STUDY PARTICIPANT SELECTION CRITERIA

3.1 Inclusion Criteria

- Participant is at least 18 years of age
- Participant presents with one or more of the following symptoms: chronic pain, anxiety, depression, and/or sleeplessness
- Participants must score greater than or equal to a 5/10 for their primary symptom score on the Baseline Symptom Questionnaire
- Patient's chosen primary symptom must have an available accrual slot for the participant. If patient scores greater than or equal to a 5/10 for a second symptom, they can be selected to accrue to another symptom slot.
- Participant has signed the Informed Consent Form

3.2 Exclusion Criteria

- Participants with a hearing aid
- Participants with a pacemaker
- Participants with irregular heart rate or a heart rate lower than 60 beats per minute (bradycardia)
- Have had a transplant within the last 2 years
- Have had a heart attack or cardiac bypass surgery within the last 12 months
- Patients with complaints of dizziness or lightheadedness within the last 3 months
- Women who are pregnant

- Participants with Diabetic Retinopathy
- Current ear infection
- SBP < 100 and/or DBP < 60
- History of uncontrolled bipolar disorder within the last 12 months
- History of uncontrolled seizures within the last 12 months
- History of aneurysms
- History of syncope within the last 12 months
- Participants that have had a TIA or stroke within the last 12 months
- Participants with health problems deemed at risk for the study by the Principal Investigator
- Participants with any changes to Pain/Anxiety/Depression/Sleeplessness medications within last 60 days (participants that do not meet this medication-change washout period may be delayed until 60-day period is met)
- Participants that are currently under adjudication process for disability support, VA or other

4.0 STUDY PROTOCOL

The Nu-V3 Clinical Study is a randomized, open-label study using the Nu-V3 cranial nerve stimulation treatment device in patients with chronic pain, anxiety, depression, and/or sleeplessness. Study participants are those who have signed the informed consent form, met the inclusion and exclusion criteria, and are enrolled in the study at one of multiple sites.

Subjects randomized to receive the Nu-V3 treatment will undergo the following regimen:

- At the baseline visit, patients will be asked to complete study questionnaires (Appendix 11) regarding all of the following symptoms: chronic pain, anxiety, depression, and/or sleeplessness, as well as their quality of life, active medications, medical history, and demographical information. The subject's primary symptom of concern will also be notated at baseline, for later assessment of continuation after week 12.
- At each subsequent visit, patients will be asked to complete study questionnaires regarding all the following symptoms: chronic pain, anxiety, depression, and/or sleeplessness, as well as their activity level and quality of life.
- The sessions will begin with the Nu-V3 device being clipped on the ear and three small pads (non-invasive) adhered to the surface of the ear. Each Nu-V3 device lasts for up to 28 days with a change in the pads approximately 7 days into the treatment.
- Each session takes approximately 15-20 minutes. The placement of the device takes approximately 5 minutes, and the remaining time is spent verifying ePRO form completion, and evaluating the patient for all device effects.
- The Nu-V3 device is mobile and is worn externally on the left ear 24 hours a day during treatment, fitting comfortably behind the ear. An electrical signal is sent to

the external ear through coated wire leads attached to the device and adhesive pads which attach to three sites on the ear.
- Participants should be able to perform their typical day-to-day activities while wearing the device. They may shower while wearing the Nu-V3 device, if they do not get the device wet and use the small disposable ear covers that are provided for them.
- In the event the Nu-V3 gel pads are inadvertently removed or the device comes off, the participant will contact the site coordinator. The participant is encouraged to adjust the device placement as needed for comfort.
- Patients should not change their existing forms of treatment or medications without discussion with the study investigator.

Subjects randomized to the observation control arm of the study will undergo the following regimen:

- At the baseline visit, patients will be asked to complete study questionnaires (Appendix 11) regarding all the following symptoms: chronic pain, anxiety, depression, and/or sleeplessness, as well as their quality of life, active medications, medical history, and demographical information. The subject's primary symptom of concern will also be notated at baseline.
- At each subsequent visit, patients will be asked to complete study questionnaires regarding all the following symptoms: chronic pain, anxiety, depression, and/or sleeplessness, as well as their activity level and quality of life.
- Patients should not change their existing forms of treatment or medications without discussion with the study investigator.
- At completion of 12 weeks of standard of care treatment post study enrollment, observation (control arm) subjects will be offered a crossover into the treatment arm of the study for an additional 24 weeks.

Sample size
For this Phase II study, a total of 100-200 subjects will be randomized 1:1 to either the Nu-V3 treatment arm or to the observation treatment arm (SOC, control).

Recruitment
Participants are enrolled into relevant symptom cohorts based on their chronic pain, anxiety, depression, and/or sleeplessness symptom presentation at baseline and treated with the Nu-V3 device for 24 weeks.

Analyses
Interim analysis of reported data will be based on baseline symptom cohort and conducted at 6, 12, 18, and 24 weeks during this time. The participant will be evaluated after the initial 12-week treatment period to assess for further therapeutic need. Upon having three consecutive weeks of mean symptom reduction of ≥70% via patient reported numerical scales, the participant will continue as described in the study assessments table, but without device therapy. Then if the participant's primary

symptom score increases at any time by ≥20%, they may again continue device therapy until week 24, as depicted in section 4.1.

Study subjects randomized to the observation arm will be offered the opportunity to cross-over to the Nu-V3 study treatment arm upon completion of the initial 12-week observation study period.

4.1 Phase II Study Assessment Tables

Initial Study Assessments Table

*Evaluations are completed weekly, every 7 days ±3 days

Nu-V3 Treatment Arm Evaluation*	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Informed Consent	x											
Inclusion and Exclusion[1]	x											
Patient Registration[1]	x											
Medications Form[1]	x			x				x				x
Patient Onboarding and Orientation[2]	x											
In office assessment	x	x	x	x	x	x	x	x	x	x	x	x
New Device Placed[3]	x				x				x			
Pad Replaced[3]		x	x	x		x	x	x		x	x	x
Treatment Forms[1]	x	x	x	x	x	x	x	x	x	x	x	x
No Device												
HRV Assessment (optional)[4]	x	x	x	x	x	x	x	x	x	x	x	x
ePRO Questionnaires[5]	x	x	x	x	x	x	x	x	x	x	x	x
Patients' Global Impression of Change ePRO form (PGIC)[5]		x	x	x	x	x	x	x	x	x	x	x
Providers' Global Impression of Change ePRO form (PGIC)[1]		x		x		x		x		x		x
Optional Patient Media Testimony[6]	x	x		x				x				x

1. Inclusion/Exclusion, Registration, Medications, Treatment, and Providers' PGIC forms to be completed by site via online module.
2. Patient Onboarding and Orientation includes introductory demographics form, Nu-V3 patient training video
3. Upon having three consecutive weeks of primary symptom reduction of ≥70% via patient reported numerical scales from baseline, the participant will have reached symptom response plateau and will continue as described in the study assessments table, but without device therapy. Then if the participant's primary symptom score increases at any time by ≥20% from the symptom response plateau, they may again continue device therapy until week 24.
4. (Optional) HRV assessment will be conducted before the first treatment and again 15-20 minutes following the first treatment. The HRV assessment will also be conducted prior to each weekly treatment. This assessment is applicable to participating sites per the clinical trial agreement. Contact the clinical trial manager for Information.
5. ePRO questionnaires completed on patient's mobile device: DQ-9 (baseline), PTB-7, PEG, GAD-7, PHQ-9, PROMIS 4a, PGIC
6. If patient consents to media testimony, site will collect via study collection process.

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Study Assessments Table

*Evaluations are completed weekly, every 7 days ±3 days

Nu-V3

Nu-V3 Treatment Arm Evaluation*	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24
Medications Form[1]				x				x				x
In office assessment	x	x		x	x		x	x		x	x	x
New Device Placed[2]	x			x			x			x		
Pad Replaced[2]		x			x			x			x	
Treatment Forms[1]	x	x		x	x		x	x		x	x	
No Device			x			x			x			x
HRV Assessment (optional)[3]	x	x		x	x		x	x		x	x	
ePRO Questionnaires[4]	x	x	x	x	x	x	x	x	x	x	x	x
Patients' Global Impression of Change ePRO form (PGIC)[4]	x	x	x	x	x	x	x	x	x	x	x	x
Providers' Global Impression of Change ePRO form (PGIC)[1]		x			x			x		x	x	
Optional Patient Media Testimony[5]	x	x		x				x				x

1. Providers' PGIC form, Medications and Treatment forms to be completed by site via online module.
2. Upon having three consecutive weeks of mean symptom reduction of ≥70% via patient reported numerical scales, the participant will continue as described in the study assessments table, but without device therapy. Then if the participant's primary symptom score increases at any time by ≥20%, they may again continue device therapy until week 24.
3. (Optional) HRV assessment before the first treatment and again 15-20 minutes following the first treatment. HRV assessment will also be conducted prior to each weekly treatment. This assessment is applicable to participating sites per the clinical trial agreement. Contact the clinical trial manager for Information.
4. ePRO questionnaires completed on patient's mobile device: DQ-9 (baseline), PTB-7, PEG, GAD-7, PHQ-9, PROMIS 4a, PGIC
5. If patient consents to media testimony, site will collect via study collection process.

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Control Study Assessments Table

*Evaluations are completed weekly, every 7 days ±3 days

Nu-V3

Control Arm Evaluation*	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Informed Consent	x											
Inclusion and Exclusion[1]	x											
Patient Registration[1]	x											
Medications Form[1]	x			x				x				x
Patient Onboarding and Orientation[2]	x											
In office assessment	x			x				x				x
No Device	x	x	x	x	x	x	x	x	X	x	x	x
ePRO Questionnaires[3]	x			x				x				x
Patients' Global Impression of Change ePRO form (PGIC)[3]				x				x				x

1. Inclusion/Exclusion, Registration, Medications, Treatment, and Providers' PGIC forms to be completed by site via online module.
2. Patient Onboarding and Orientation includes introductory demographics form, Nu-V3 patient training video
3. ePRO questionnaires completed on patient's mobile device: DQ-9 (baseline), PTB-7, PEG, GAD-7, PHQ-9, PROMIS 4a, PGIC

5.0 DATA COLLECTION AND RETENTION

The study endpoints data will be collected from each participant's study questionnaires. The data will be collected electronically via the patient's own device and uploaded to an electronic data capture system. The data will be used to measure whether the Nu-V3 device provides participants with a reduction in participants' chronic pain, anxiety, depression, and/or sleeplessness.

The data analysis will include baseline data for each participant's questionnaire prior to beginning treatment with the Nu-V3 device. Longitudinal data will consist of participant's weekly questionnaires measuring chronic pain, anxiety, depression, and sleeplessness during the treatment phase. The final data collection will be completed by participants at the end of the treatment with the Nu-V3 device and will measure chronic pain, anxiety, depression, and sleeplessness.

The Principal Investigator at each site will be responsible for recording, collecting, and storing the research participant's study data. The written records will be stored in a secure location. Only the Principal Investigator or designated study staff will have access to the study records and all electronic files will be password protected. The Principal Investigator will also maintain adequate records for the study including:

- all correspondence with the IRB and Sponsor
- other pertinent data related to the study

All records are to be retained by the Principal Investigator for a period of three (3) years following the closure of the study. Following study closure, the Principal Investigator shall inform Nu-Life of the location of study records and storage changes (i.e., the Principal Investigator leaves the institution where the study was conducted). In such cases, the study records may be transferred to another institution, investigator, or to Nu-Life upon written agreement between the Principal Investigator and Nu-Life.

6.0 DATA DISCLOSURE AND SUBJECT CONFIDENTIALITY

Medical record confidentiality and data protection will be maintained at every visit. Subject medical information obtained because of this study is considered confidential and disclosure to third parties, other than those noted below, is prohibited. Data generated during this study is to be available for inspection on request by the FDA or other government regulatory agency auditors, the Sponsor's authorized representatives, and the IRB.

7.0 ADVERSE EVENT(S)

Subjects will be evaluated for safety if they have received any study treatment. Adverse event assessments will be continuous during the 24-week trial (see section 4.1). During

treatment visits, toxicity assessments should be done in person. Once subjects reach symptom stabilization and are not actively receiving device therapy, follow-up either in person or documented via telephone call, is acceptable. Adverse events and will be graded according to the NIH-CTCAE version 5.0.

Potential unanticipated problems require prompt reporting to the central IRB and study sponsor. These problems potentially place subjects or others at greater risk of physical or psychological harm than was previously recognized, and warrant consideration of substantive changes in the protocol or informed consent process or other action to protect the safety, welfare, or rights of participants. The central IRB must be notified within 5 calendar days of the event and the study sponsor within 24 hours. The completed IRB Unanticipated Problem Form (Appendix 7) must be received by the central IRB within 10 calendar days of the event to avoid a major deviation.

Unanticipated problems are defined as those problems which alter the risks to subjects or others. This includes any study suspensions or holds. This form will be used to report any problem that is unforeseen or involves risk. One form will be used per event or problem.

8.0 STUDY ENDPOINT and DATA ANALYSIS

8.1 Primary Endpoints: Primary endpoints consisted of the following:

Safety: At screening/baseline, a medical history will be obtained to capture relevant underlying conditions. The screening/baseline examinations will include BP, and HR. Baseline signs and symptoms are those that are assessed within 14 days prior to week 1 treatment.

Concomitant medications will be collected from within 14 days prior to enrollment through the study treatment period and maintenance period (see Study Assessments Table section 4.1).

The primary safety endpoint is the occurrence of reported unanticipated problems involving risk to subjects or others (“UPIRTSOs”). These UPIRTSOs are defined as those problems which alter the risks to subjects or others. This includes any study suspensions or holds. The primary safety endpoint analyses will be based on a risk-benefit conclusion.

Effectiveness: There are four instruments measuring participant’s symptoms of chronic pain, anxiety, depression, and sleeplessness. The primary effectiveness endpoint is a statistically significant reduction in one or more of measures of: chronic pain, anxiety, depression, or sleeplessness between baseline and 12 or 24 weeks after initiating treatment.

The null hypothesis to disprove is that there is no statistically significant reduction from baseline to 12 or 24 weeks in mean chronic pain, anxiety,

depression, or sleeplessness symptom severity scores using the Nu-V3 device compared with the usual care cohort.

The instruments used in this study are:

Chronic Pain – Pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G) (PEG Scale),
The PEG is a three-item instrument that measures pain intensity (one item) and pain interference (two items). Each item is valued from 0 (no pain/interference) to 10 (as bad as you can imagine). The instrument score is calculated as the average of the three item values.

Anxiety - Generalized Anxiety Disorder 7-item (GAD-7)
The GAD-7 is a seven-item instrument that measures respondents' symptoms of anxiety. Each item is scored on a four-point Likert scale, and values range from 0 ("Not at all") to 3 ("Nearly every day".) Items are summed to determine the instrument's score. Values of 10 or higher have been associated with moderate anxiety, while values of 15 or higher have been associated with severe anxiety.

Depression - Patient Health Questionnaire (PHQ-9)
The PHQ-9 is a nine-item instrument that measures depression-related symptoms and functional impairment. Each item is scored on a four-point Likert scale and values range from 0 ("Not bothered at all") to 3 ("Bothered nearly every day.") The items' values are summed to determine the instrument's score. PHQ-9 values of 10 and 15 represent moderate and moderately severe depression respectively.

Sleeplessness - PROMIS short form 4a
This eight item instrument measures sleep disturbance and sleep-related impairment.

8.2 Secondary Endpoints: Secondary endpoints consisted of the following:

Effectiveness: There are two secondary effectiveness endpoints:

1. In the Nu-V3 device treatment arm, the study will report the mean time from treatment initiation to reduction of symptoms of at least 30% in any of the four domains of symptom measurement.
2. In both the Nu-V3 device treatment arm and the observation arm, the study will report the mean percentage change in symptoms severity from initiation to 12 and 24 weeks for each instrument.

Additional secondary endpoints of this study are:

- Mean improvement in quality of life measured with Patient's Global Impression of Change (PGIC) between the treatment and usual care arm, and

- Mean improvement in activities of daily living via Perceived Treatment Benefit Form (PTB-6) between the treatment and usual care arm.

8.3 Sub-Analyses: Sub-Analyses consist of the following:

The study has several sub-analyses. They include:

- The mean number of weeks that chronic pain, anxiety, depression, and sleeplessness response are achieved and sustained, without utilization of another device or change in other treatments, during the full 24-week intervention in the Nu-V3 device treatment arm.

- The mean number of weeks to initial benefit from Nu-V3 device use in the Nu-V3 device treatment arm. Benefit is defined as a reduction of at least 30% of symptoms in at least one of chronic pain, anxiety, depression, or sleeplessness.

- **The device's comfort-of-use, and patient's perceived treatment benefit** in the Nu-V3 device treatment arm**.**

9.0 STUDY MONITORING

Nu-Life will monitor the study according to good clinical practice. Monitoring will begin upon enrollment of the first 5 patients at the site and will continue every 8 weeks until completion of the study. The Principal Investigator will work with a representative from Nu-Life to ensure the study is conducted according to this protocol and that all study matters are properly communicated.

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Appendix 1: Study Process Maps

Figure 1- Baseline Visit

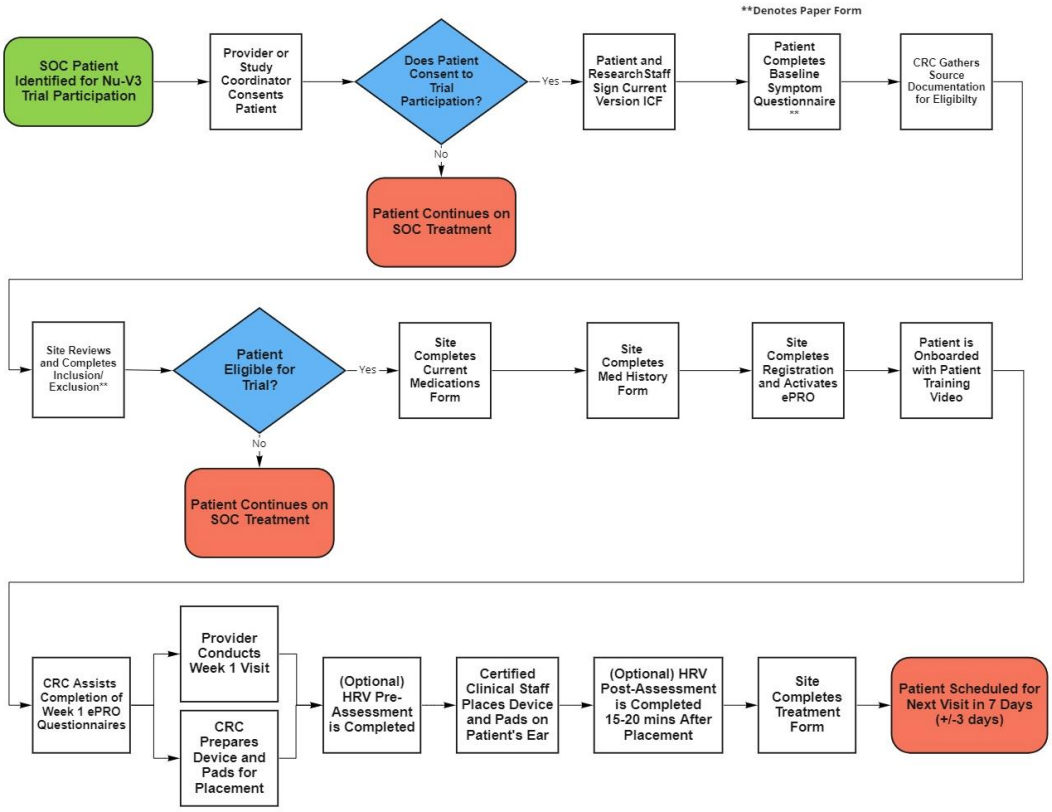
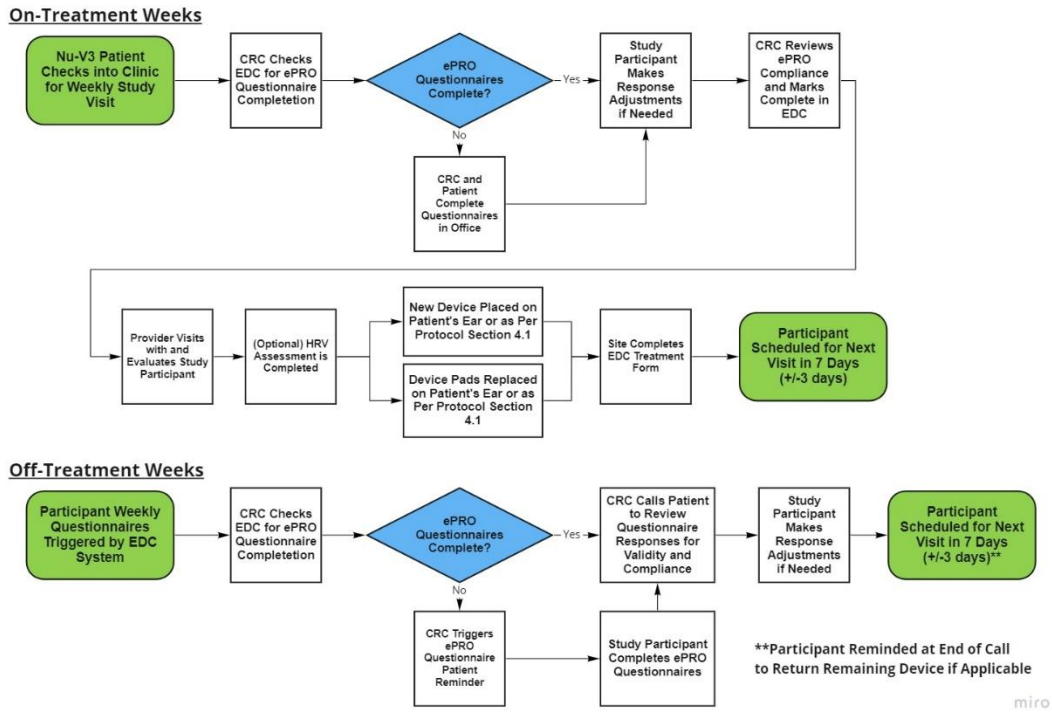


Figure 2- Weekly Visits



Appendix 2: Eligibility Checklist

SCREENING AND ELIGIBILITY CHECKLIST

A Randomized, Phase II, Open-Label Study Evaluating the Nu-V3 Cranial Nerve Stimulation Treatment Device in Patients with Chronic Pain, Anxiety, Depression, and/or Sleeplessness

Subject Initials:
Subject Identification Number:
Date of Consent:

STATEMENT OF ELIGIBILITY:

This subject is ☐eligible / ☐ineligible for participation in the study.

Investigator Signature:_____Date:_____

Printed Name:_____

INCLUSION CRITERIA (all questions should be answered YES – If question is answered No, subject is not eligible for participation)

Yes	No	
☐	☐	Participant is at least 18 years of age
☐	☐	Participant presents with one or more of the following symptoms: chronic pain, anxiety, depression, and/or sleeplessness
☐	☐	Participant must score greater than or equal to a 5/10 for their primary symptom on the Baseline Symptom Questionnaire
☐	☐	Study cohort must have an available accrual slot for the participant respective of their primary symptom
☐	☐	Participant has signed the Informed Consent Form

If any of the above boxes are checked "No", the subject does not meet eligibility criteria

EXCLUSION CRITERIA (all questions should be answered No – If question is answered Yes, subject is not eligible for participation)

Yes	No	
☐	☐	Participants with a hearing aid
☐	☐	Participants with a pacemaker
☐	☐	Participants with an irregular heart rate or a heart rate lower than 60 beats per minute (bradycardia)
☐	☐	Have had a transplant within the last 2 years
☐	☐	Have had a heart attack or cardiac bypass surgery within the last 12 months
☐	☐	Patients with complaints of dizziness or lightheadedness within the last 3 months
☐	☐	Women who are pregnant
☐	☐	Participants with Diabetic Retinopathy
☐	☐	Current Ear infection
☐	☐	SBP < 100 and/or DBP < 60
☐	☐	History of uncontrolled bipolar disorder within the last 12 months
☐	☐	History of uncontrolled seizures within the last 12 months
☐	☐	History of aneurysms
☐	☐	History of syncope within the last 12 months
☐	☐	Participants who have had a TIA or stroke within the last 12 months
☐	☐	Participants with health problems deemed at risk for the study by the Principal Investigator
☐	☐	Participants with any changes to Pain/Anxiety/Depression/Sleeplessness medications within last 60 days (participants that do not meet this medication change washout period may be delayed until 60-day period is met)
☐	☐	Participants that are currently under adjudication process for disability support, VA or other

If any of the above boxes are checked "Yes", the subject does not meet eligibility criteria

Appendix 3: IRB Unanticipated Problem Form

Nu-Life Solutions
Miniaturized Wearable Medical Technology - Nu-V3

Nu-V3

Nu-V3 Unanticipated Problem Form

Nu-V3 Version 1.0 Version Date:: 07/Nov/2017	☐ Initial Report: / / dd / mmm / yyyy	☐ Follow-up No. ____ / / dd / mmm / yyyy	☐ Follow-up No. ____ / / dd / mmm / yyyy

Investigator Name:	Site:	Subject #:

DEMOGRAPHICS

Gender	Date of Birth	Height	Weight
☐ Female ☐ Male	/ / dd / mmm / yyyy	____ ☐ in ☐ cm	____ ☐ lbs ☐ kg

ADVERSE EVENT INFORMATION

SAE Term *(diagnosis preferred over signs/symptoms)*:

Onset Date	Serious Criteria *(select all that apply)*	CTCAE Grade	Outcome
/ / dd / mmm / yyyy **Stop Date** / / DD / MON / YYYY	☐ Requires/prolongs inpatient hospitalization[a] ☐ Life-threatening ☐ Persistent or significant disability/incapacity ☐ Congenital Anomaly/Birth Defect ☐ Important medical event ☐ Death[b]	☐ Grade 1 - Mild ☐ Grade 2 -Moderate ☐ Grade 3 - Severe ☐ Grade 4 - Life-threatening ☐ Grade 5 - Fatal	☐ Ongoing ☐ Resolved ☐ Resolved w/ sequelae[c] ☐ Fatal

[a]**Hospitalization:** **Date of Admission** / / dd / mmm / yyyy **Date of Discharge** / / dd / mmm / yyyy

[b]**Death:**
Date of death / / dd / mmm / yyyy
Was autopsy completed? ☐ Yes ☐ No If yes, please forward report.
Is death certificate available? ☐ Yes ☐ No If yes, please forward.

[c]**Describe sequelae:**

STUDY DEVICE INFORMATION

Study Device		Date of First Use	Date of Last Use before SAE Onset	Relationship to Device	Action taken with Device
Nu-V3 ☐ N/A Serial#_____	____	/ / dd / mmm / yyyy	/ / dd / mmm / yyyy	☐ Related ☐ Unrelated	☐ None ☐ Dose Reduced ☐ Interrupted ☐ Discontinued

Possible Cause of SAE other than Study Device *(select all that apply)*:
☐ Concurrent condition ☐ Concurrent medication ☐ Other, specify: ____
Condition term Medication name

Nu-V3 Version 1.0 Version Date:: 07/Nov/2017	Site Name:	Subject #:

Nu-V3 Treatment Modifications:
If action taken = interrupted or discontinued, did event stop once device was stopped? ☐ Yes ☐ No

If action taken = interrupted, did event recur once device was restarted? ☐ Yes ☐ No

RELEVANT LABORATORY/DIAGNOSTIC TESTS ☐ None

Test Name	Date dd/mmm/yyyy	Results/Value	Unit	Normal Range

RELEVANT CONCOMITANT MEDICATIONS ☐ None

Medication	Start Date dd/mmm/yyyy	Stop Date or Ongoing dd/mmm/yyyy	Dose & Unit	Frequency	Route	Indication
		or ☐ Ongoing				
		or ☐ Ongoing				
		or ☐ Ongoing				
		or ☐ Ongoing				

RELEVANT MEDICAL HISTORY ☐ None

Diagnosis	Start Date dd/mmm/yyyy	Stop Date or Ongoing dd/mmm/yyyy
		or ☐ Ongoing
		or ☐ Ongoing
		or ☐ Ongoing
		or ☐ Ongoing

NARRATIVE SUMMARY

Describe the event in detail from onset through resolution. Include rationale for causality and any interventions given.

REPORTER INFORMATION

Investigator Name:	Phone:	Email address:
Reporter Name:	Phone:	Email address:

INVESTIGATOR SIGNATURE VERIFIES THAT EVENT HAS BEEN REVIEWED AND INVESTIGATOR CONCURS WITH THIS REPORT.
I, the undersigned investigator, attest that I have reviewed this SAE Report. *NOTE: Sign and date.*

Signature:	Date:
Signature:	Date:
Signature:	Date:

SAE report may be emailed to Nu-Life Solutions Executive Medical Team
Email: esiebeneck@nu-lifesolutions.com

Appendix 4: Adverse Event Form

Subject ID_____ Date (dd/mmm/yyyy): _____/_____/_____

Nu-Life Solutions
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Adverse Events Form

1. **Has the participant experienced any adverse events?**

   ____No (end of form)
   ____Yes (update log below)

2. **Adverse Event Log (CTCAE 5.0)**

Grade 1=Mild Grade 2=Moderate Grade 3=Severe Grade 4=Life-threatening Grade 5=Death
Attribution Grading: A=unrelated B=unlikely C=possibly D=probably E=definitely

Event Name	SAE?	Grade	Attribution	Start Date (dd/mmm/yyyy)	End Date (dd/mmm/yyyy)	Treatment held or withdrawn?
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			
	y / n		A B C D E			

Appendix 5: Medical History Form

Subject ID_____ Date (dd/mmm/yyyy): _____/_____/_____

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Medical History Form

Please answer the following questions about your past and current medical history.

1. Do you have a history of any significant medical problems or chronic disease requiring a physician's care?
   ☐ Yes *(If Yes, please list below)* ☐ No

Medical Problem	Date of Diagnosis (dd/mmm/yyyy)	Are you having trouble with this problem now?
	/ /	☐ Yes ☐ No
	/ /	☐ Yes ☐ No
	/ /	☐ Yes ☐ No
	/ /	☐ Yes ☐ No
	/ /	☐ Yes ☐ No
	/ /	☐ Yes ☐ No
	/ /	☐ Yes ☐ No
	/ /	☐ Yes ☐ No
	/ /	☐ Yes ☐ No

2. Have you had trouble with or sought medical attention for (please include even if stated in Question 1).

Irregular Heart Rate	☐ Yes ☐ No	
Cardiac Arrhythmia	☐ Yes ☐ No	
Heart Disease	☐ Yes ☐ No	

Subject ID_____ Date (dd/mmm/yyyy): _____/_____/_____

Chest Pain	☐ Yes ☐ No	
Heart Attack	☐ Yes ☐ No	
Heart Murmur	☐ Yes ☐ No	
Dizziness/ Lightheadedness	☐ Yes ☐ No	
Diabetic Retinopathy	☐ Yes ☐ No	
Bradycardia	☐ Yes ☐ No	
Epilepsy, Seizures, or Convulsions	☐ Yes ☐ No	
Aneurysms	☐ Yes ☐ No	
Syncope	☐ Yes ☐ No	
TIA or Stroke	☐ Yes ☐ No	
Drugs or Alcohol	☐ Yes ☐ No	

3. Have you had trouble with or sought medical attention for (please include even if stated in Question 1).

High Blood Pressure	☐ Yes ☐ No	
Head Injury	☐ Yes ☐ No	
Chronic Neck or Back Pain	☐ Yes ☐ No	
Hypothyroidism	☐ Yes ☐ No	☐ Stable ☐ Unstable
Hyperthyroidism	☐ Yes ☐ No	☐ Stable ☐ Unstable
Rheumatoid Arthritis	☐ Yes ☐ No	
Inflammatory Arthritis	☐ Yes ☐ No	
Psoriatic Arthritis	☐ Yes ☐ No	

Subject ID_____ Date (dd/mmm/yyyy): _____/_____/_____

Irritable Bowel Syndrome	☐ Yes ☐ No	
Neuropathy	☐ Yes ☐ No	☐ Motor ☐ Sensory
Headaches	☐ Yes ☐ No	☐ Tension ☐ Migraine

4. FEMALES ONLY; *if male, skip to Question #5.*
   a. Are you pregnant, or trying to become pregnant? ☐ Yes ☐ No
   b. Are you using birth control? ☐ Yes ☐ No
   c. If 'Yes', describe:

5. Have you had any surgery in the past three months? ☐ Yes ☐ No
   If 'Yes', describe:

6. Have you ever been hospitalized for psychiatric reasons? ☐ Yes ☐ No

7. Have you ever been diagnosed with any of the following disorders?

Depression	☐ Yes ☐ No	☐ Less than 3 months ago ☐ 3-12 months ago ☐ Greater than 1 year ago
Bipolar Disorder	☐ Yes ☐ No	☐ Less than 3 months ago ☐ 3-12 months ago ☐ Greater than 1 year ago
Panic Disorder	☐ Yes ☐ No	☐ Less than 3 months ago ☐ 3-12 months ago ☐ Greater than 1 year ago
Phobia	☐ Yes ☐ No	☐ Less than 3 months ago ☐ 3-12 months ago ☐ Greater than 1 year ago

Subject ID_____ Date (dd/mmm/yyyy): _____/_____/_____

PTSD	☐ Yes ☐ No	☐ Less than 3 months ago ☐ 3-12 months ago ☐ Greater than 1 year ago
Obsessive Compulsive Disorder	☐ Yes ☐ No	☐ Less than 3 months ago ☐ 3-12 months ago ☐ Greater than 1 year ago
General Anxiety Disorder	☐ Yes ☐ No	☐ Less than 3 months ago ☐ 3-12 months ago ☐ Greater than 1 year ago
Schizophrenia	☐ Yes ☐ No	☐ Less than 3 months ago ☐ 3-12 months ago ☐ Greater than 1 year ago
Schizo-Affective Disorder	☐ Yes ☐ No	☐ Less than 3 months ago ☐ 3-12 months ago ☐ Greater than 1 year ago

9. Have you ever been given any medications for emotional problems, such as anti-depressant, anti-anxiety or anti-psychotic medications? ☐ Yes ☐ No

Appendix 6: Treatment Form

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Weekly Treatment Form

Subject ID_____ Date (dd/mmm/yyyy): _____/_____/_____

1. Device Serial Number: _____

2. Was the device placed on the participant's left ear?

   ☐ Yes ☐ No If no, reason why: _____

Appendix 7: Medications and Standard of Care Treatment Form

Subject ID_____ Date (DD/MMM/YYYY): _____/_____/_____

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Medications and Standard of Care Treatment Form

Please record all medications and other standard of care treatments related to any of the study indications, chronic pain, anxiety, depression, or sleeplessness. Include any treatments, supplements, and alternative holistic therapies.

1. Have the participant's medications changed?

   ____ No (continue to other treatments section)
   ____ Yes (update the medications log below)

2. Medications Log – *Include any medications, herbal/non-herbal supplements, or medical marijuana used in the treatment of symptoms for chronic pain, anxiety, depression, or sleeplessness.*

Med Name	Dose	Unit	Frequency	Start Date (dd/mmm/yyyy)	End Date (dd/mmm/yyyy)	Indication

3. Treatment Log - *Include any treatments related to symptom relief for chronic pain, anxiety, sleeplessness, or depression.*

Examples include but are not limited to:

- Aromatherapy
- Acupuncture
- Cryotherapy
- Meditation
- Tai Chi

Therapy Name	Start Date (dd/mmm/yyyy)	End Date (dd/mmm/yyyy)	Indication

Appendix 8: ePRO Questionnaires

DATE: _____ Device/Pad serial #_____
Week # _____ Subject ID _____

Complete Patient ePRO Questionnaire Packet

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Form DQ-7: Patient Demographics

Subject ID

_____

Date (dd/mmm/yyyy):

_____/_____/_____

Age

What is your age? _____

Sex at Birth

____Male
____Female
____Other
____Choose not to answer

Marital Status

____Single
____Married
____Divorced
____Widowed

Primary Language?

Self-Description (please choose one):

____Arabic
____Bengali
____English
____French
____German
____Hindi/Urdu
____Japanese
____Mandarin
____Portuguese
____Punjabi
____Russian
____Spanish
____Other

Race/Ethnicity

Self-Description (please choose one):

____ American Indian
____ Asian-American/Oriental/Pacific Islander
____ Asian East Indian
____ Black/African-American
____ Mexican-America/Chicano
____ Puerto-Rican
____ Other Hispanic
____ White/Caucasian
____ Other

Education History

What is the highest degree or level of school you have completed? *If currently enrolled, highest degree received.*

____No schooling completed
____Nursery school to 8th grade
____Some high school, no diploma
____High school graduate, diploma or GED
____Some college credit, no degree
____Trade/technical/vocational training
____Associate degree
____Bachelor's degree
____Master's degree
____Professional degree
____Doctorate degree

Service Status

Are you now, or have you ever served as a member of the armed forces?

____Yes, I am a military veteran
____Yes, I am an active duty member
____No, I have never served in the armed forces

Are you a First Responder (firefighter, EMS, law enforcement, etc)?

____Yes, I am current or former First Responder
____No, I have never been a First Responder

PEG: A Three-Item Scale Assessing Pain Intensity and Interference

Subject ID: _____ **Date (dd/mmm/yyyy):** _____/_____/_____

PEG: A Three-Item Scale Assessing Pain Intensity and Interference

1. **What number best describes your pain on average in the past week?**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

2. **What number best describes how, during the past week, pain has interfered with your enjoyment of life?**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

3. **What number best describes how, during the past week, pain has interfered with your general activity?**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

From Krebs et al., 2009.

GAD-7 - Generalized Anxiety Disorder 7-item Scale

Subject ID: _____ **Date (dd/mmm/yyyy):** _____/_____/_____

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

Source: Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. *Arch Intern Med.* 2006;166:1092-1097.

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PHQ-9- Patient Health Questionnaire

Subject ID: _____ **Date (dd/mmm/yyyy):** _____/_____/_____

Over the last *2 weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
	add columns	+	+	

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

PROMIS Item Bank v1.0 - Sleep Disturbance - Short Form 4a

Subject ID: _____ **Date (dd/mmm/yyyy):** _____/_____/_____

	In the past 7 days…	Very poor	Poor	Fair	Good	Very good
1	My sleep quality was	☐	☐	☐	☐	☐
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
2	My sleep was refreshing.	☐	☐	☐	☐	☐
3	I had a problem with my sleep.....	☐	☐	☐	☐	☐
4	I had difficulty falling asleep	☐	☐	☐	☐	☐

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PATIENTS' GLOBAL IMPRESSION OF CHANGE (PGIC) SCALE

Subject ID: _____ **Date (dd/mmm/yyyy):** _____/_____/_____

Chief Complaint (Presenting Problem): _____

Since beginning treatment at this clinic, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS, and OVERALL QUALITY OF LIFE, related to your painful condition? Please circle the number below, that matches your degree of change since beginning care at this clinic for the above stated chief complaint.

No change	Almost the same	A little better	Somewhat better	Moderately better	Better	A great deal better
1	2	3	4	5	6	7

Explanation:

1 = No change (or condition has got worse)
2 = Almost the same, hardly any change at all
3 = A little better, but no noticeable change
4 = Somewhat better, but the change has not made any real difference
5 = Moderately better, and a slight but noticeable change
6 = Better, and a definite improvement that has made a real and worthwhile difference
7 = A great deal better, and a considerable improvement that has made all the difference

Patient's signature: _____

NOTE TO HEALTH CARE PROVIDER

A significant, favorable change is a score of 5-7
No significant change is a 1-4 response.
Note, this a dichotomous scale (5-7 = yes; 1-4 = no).
A 2-point change is significant from their last reported score.

Reference: Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. Journal of Manipulative Physiological Therapeutics (IMPT) 2004;27:26-35.

Subject ID_____ Date (DD/MMM/YYYY): _____/_____/_____

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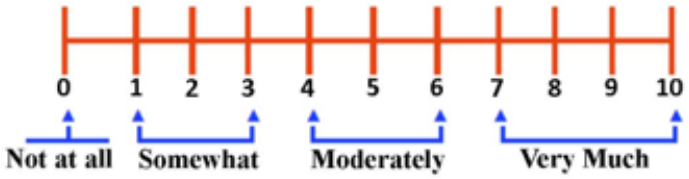
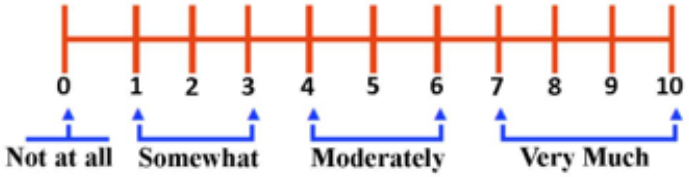
Form PTB-6: Patient's Perceived Treatment Benefit

1. On a scale of 0-10, how much benefit do you feel you have received from the Nu-V3 treatment in helping your symptoms?



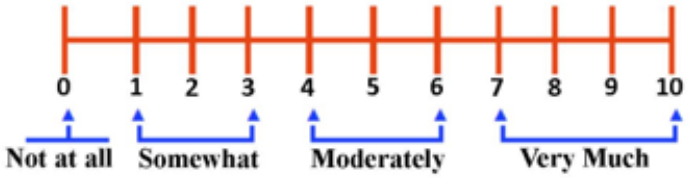
2. On a scale of 0-10, how much has your daily activity level improved?



3. Do you feel that your as needed medications have decreased from using the device?

_____Yes
_____No

4. How comfortable was the Nu-V3 Device to wear?



5. Have you had any major discomfort from the device?

_____Yes; please continue to question 6
_____No

6. If yes to question 5, did adjusting the device correct the discomfort?

_____Yes
_____No

Nu-Life Solutions
Version Date: March 2, 2022

Appendix 9: Baseline Symptom Questionnaire

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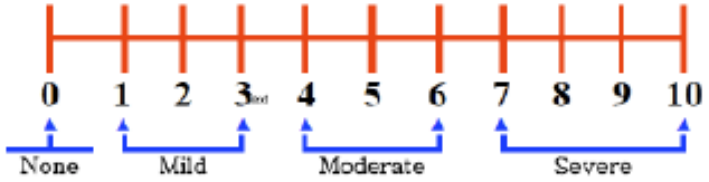
Baseline Symptom Questionnaire

Please choose your primary symptom: (circle only one)

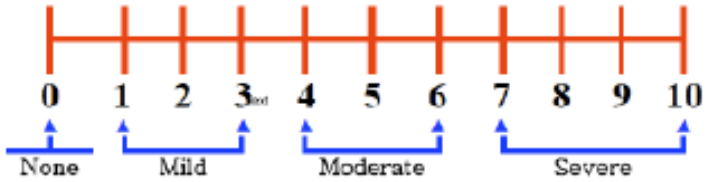
a. Chronic Pain b. Anxiety c. Depression d. Sleeplessness

Please rate your **primary symptom** over the last 30 days:

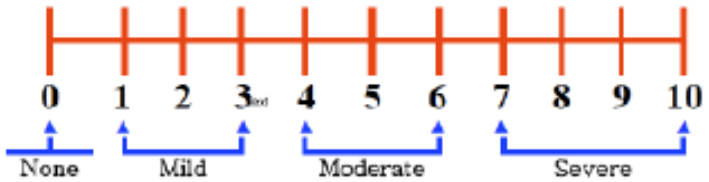
Pain Level:



Anxiety Level:



Depression Level:



Sleep Interruption Level: