A Phase I Prospective, Single-Arm, Open-Label, Multi-Center Study Using the Nu-V3 Cranial Nerve Stimulation Treatment Device in Patients with Pain, Anxiety, Depression, and/or Sleeplessness

PROTOCOL NUMBER: Nu-V3 PROTOCOL NO. 1

INVESTIGATIONAL PHASE: Phase I

VERSION: 1.2

DE NOVO NUMBER:

INVESTIGATIONAL DEVICE: Nu-V3

ORIGINAL PROTOCOL ISSUE DATE:

VERSION DATE: December 14, 2017

STUDY SPONSOR: Nu-Life Solutions
310 W. Michigan
Indianapolis, IN 46202

STUDY CONTACTS:

Medical Monitor	Biostatistician	Clinical Trial Manager
Brad Doebbeling (317)941-6709 bdoebbeling@nu-lifesolutions.com	Name Here Phone Here Email Here	Eric T. Siebeneck (317)941-6709 esiebeneck@nu-lifesolutions.com

Sponsor Protocol Signature:

Protocol Signature Page

A Phase I Prospective, Single-Arm, Open-Label, Multi-Center Study Using the Nu-V3 Cranial Nerve Stimulation Treatment Device in Patients with Pain, Anxiety, Depression, and/or Sleeplessness

Protocol Amendment 1: December 14, 2017

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.

Investigator Name: _____

Title: _____

Address: _____

Address: _____

Address: _____

Phone: _____

Facsimile: _____

Signature: _____

Date: _____

Table of Contents

1.0 Introduction

1.1 Background

Research evidence has shown that the symptoms of pain, anxiety, depression, and sleeplessness, or any combination of these symptoms are prevalent in 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 (anxiety, depression, pain and 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, significantly improved outcomes can be achieved.

Globally, the lifetime prevalence of anxiety disorders from a 2013 meta-analyses 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 This translates 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 age 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 by population and other factors. It is estimated that approximately 20% of the adult European population has 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 pain, anxiety, depression, and/or sleeplessness (PADS), 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 (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 results and relief.

For the reasons cited above, Nu-Life will be submitting Nu-V3 for FDA clearance under De Novo 513(f)(2), as a new and unique technology. In part, the purpose of this clinical study is to demonstrate the effect upon the four specific symptoms of pain, anxiety, depression and sleeplessness, as 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: pain, anxiety, depression, and/or sleeplessness. The objective is to demonstrate the effectiveness of Nu-V3 for any or all of the four symptoms listed.

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: pain, depression, anxiety, and/or sleeplessness
- Participant is capable of understanding the use and maintenance of the device
- Participant is capable and agreeing to participate in the ongoing assessment
- Participant has signed the Informed Consent Form
- Participant can commit to follow all protocol study timepoints

3.2 Exclusion Criteria

- 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
- History of substance abuse, including prescription drugs, 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 prospective, single-arm, open-label, multi-center study using the Nu-V3 cranial nerve stimulation treatment device in patients with pain, anxiety, depression, and/or sleeplessness.

For this Phase I study, a total of 50-100 patients at multiple centers will be registered for study participation. 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. Enrolled participants are stratified based on their pain, anxiety, depression, and/or sleeplessness symptom presentation at baseline and treated with the Nu-V3 device for 8 weeks, then observed for an additional 4 weeks. Interim analysis of reported data will be based on baseline stratifications and conducted at 4, 8, and 12 weeks during this time. Post study, participants will be given the chance to continue with an optional maintenance treatment with the Nu-V3 device per a 2-weeks on, 2-weeks off schedule, for an additional 12 weeks, with an 8-week observation.

Subjects enrolled onto the Nu-V3 Clinical Trial 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: pain, anxiety, depression, and/or sleeplessness, as well as their quality of life, active medications, medical history, and demographical information.
- At each subsequent visit, patients will be asked to complete study questionnaires regarding all the following symptoms: 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 placed on the left ear and three small pads (non-invasive) being placed on the ear. Each Nu-V3 device

lasts for up to 14 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, provided that they do not get the device wet and use the small disposable ear covers that are provided for them.
- Patients should not change their existing forms of treatment or medications without discussion with the investigator.
- Nu-Life reserves the right to capture video, photographs and written testimonials from patients with written permission. In the event subjects elect to participate in any or all of these activities, they will be asked to sign a waiver giving exclusive rights to Nu-Life for the materials gathered from the patient, such as video, photographs and written testimonials. Their participation in this study is not dependent upon their willingness to provide these testimonial materials.

4.1 Phase I Study Assessment Tables

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

Study Treatment Assessments Table

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

Nu-V3

Evaluation*	Study Treatment									
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9-11	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
New Device Placed	x		x		x		x			
Pad Replaced		x		x		x		x		
Treatment Forms[1]	x	x	x	x	x	x	x	x		
No Device									x	x
ePRO Questionnaires[3]	x	x	x	x	x	x	x	x	x	x
Patients' Global Impression of Change ePRO form (PGIC)[3]		x	x	x	x	x	x	x		x
Providers' Global Impression of Change ePRO form (PGIC)		x	x	x	x	x	x	x		x
Family Global Impression of Change ePRO form (PGIC)		x	x	x	x	x	x	x		x
Optional Patient Media Testimony	x			x				x		x

1. Inclusion/Exclusion, Registration, Medications, Treatment forms to be completed by site coordinator 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
4. If patient consents to media testimony, site will collect via study collection process every 4 weeks.

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

Post Study Intervention Assessments Table
*Evaluations are completed weekly, every 7 days ±3 days

Nu-V3

Evaluation*	Optional Maintenance Therapy										Long Term Follow Up					
	Week 13	Week 14	Week 15-16	Week 17	Week 18	Week 19-20	Week 21	Week 22	Week 23	Week 24	Week 25	Week 26	Week 27-28	Week 29	Weeks 30-31	Week 32
Medications Form[1]				x			x			x		x		x		x
In office assessment	x	x		x	x		x	x								
New Device Placed	x			x			x									
Pad Replaced		x			x			x								
Treatment Forms[1]	x	x		x	x		x	x								
No Device			x			x			x	x	x	x	x	x	x	x
ePRO Questionnaires[3]	x	x		x	x		x	x	x	x		x		x		x
Patients' Global Impression of Change ePRO form (PGIC)[3]	x	x		x	x		x	x				X				X
Providers' Global Impression of Change ePRO form (PGIC)		x			x			x				X				X
Family Global Impression of Change ePRO form (PGIC)		x			x			x				X				X
Optional Patient Media Testimony		x			x			x				x				X

1. Inclusion/Exclusion, Registration, Medications, Treatment forms to be completed by site coordinator 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
4. If patient consents to media testimony, site will collect via study collection process every 4 weeks.

4.2 Protocol Deviations

In the event the Nu-V3 device is inadvertently removed or the device comes off, the participant will contact the Principal Investigator. The Principal Investigator will determine the appropriate course of action to be taken.

If the study participant is unable to wear the device on their left ear, the study participant will be allowed to wear the device on their right ear, which will result in a minor study deviation. Left-ear deviations could be due to discomfort, sleep position, pain at the local site, or infection. A lack of significant improvement by the end of week 4, per the Principal Investigator's discretion, can also result in a deviation from left-ear placement.

Device placement should be recorded on the study treatment form within the electronic data capture system.

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. Only patient data from the stratified indication(s) will be used for analysis of symptom response. The data will be used to demonstrate that the Nu-V3 device provides participants with relief of the symptoms of pain, depression, anxiety and/or sleeplessness. The data analysis will include comparative data for each participant's questionnaire prior to beginning treatment with the Nu-V3 device, the participant's weekly questionnaires during

treatment and the questionnaire completed at the end of the treatment with the Nu-V3 device.

Interim analyses of available data will be regularly submitted to the FDA for review.

The Principal Investigator at each site will be responsible for recording, collecting, and storing the research participant's study data. The written records must 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 seven (7) 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 as a result 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)

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 in order 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: 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: The primary effectiveness endpoints are an overall change in median reported symptoms of pain, anxiety, depression, and/or sleeplessness via numeric rating scales at 8 weeks. This primary effectiveness is measured by median reported symptom changes in pain, anxiety, depression, and/or sleeplessness for respective stratified populations via the following validated tools: Pain - Pain Intensity and Interference (PEG_Scale), Anxiety - Generalized Anxiety Disorder 7-item (GAD-7) scale, Depression - Patient Health Questionnaire (PHQ-9), Sleeplessness - PROMIS short form 4a, and overall improvement of quality of life (QOL) - Patient's Global Impression of Change (PGIC).

The hypothesis-driven criterion of effectiveness is to show that there is a statistically significant reduction in the median reported pain, anxiety, depression, and/or sleeplessness levels of patients using the Nu-V3 device. The second criterion is intended to show that there is a statistically significant improvement in reported quality of life and perceived treatment benefit, secondary to overall reported symptom reductions of pain, anxiety, depression, and/or sleeplessness.

8.2 Secondary Endpoints: Secondary endpoints consisted of the following:

Effectiveness: The secondary effectiveness endpoint is an overall change in median reported symptoms of pain, anxiety, depression, and/or sleeplessness for respective stratified populations via numeric rating scales at 4, 8, and 12 weeks. This is measured via the following validated tools: Pain – Pain Intensity and Interference (PEG_Scale), Anxiety - Generalized Anxiety Disorder 7-item (GAD-7) scale, Depression - Patient Health Questionnaire (PHQ-9), Sleeplessness - PROMIS short form 4a, and overall improvement of quality of life- Patient's Global Impression of Change (PGIC).

The patient's perceived treatment benefit and device comfort information will be captured via the non-validated tool, Perceived Treatment Benefit Form (PTB-7). This effectiveness tool will measure median levels of reported perceived treatment benefit and device comfort.

The hypothesis-driven criterion is to show that there is a statistically significant reduction in the median reported pain, anxiety, depression, and/or sleeplessness levels of patients using the Nu-V3 device at weeks 4, 8, and 12. The second criterion is intended to show that there is a statistically significant improvement in reported quality of life and perceived treatment benefit secondary to overall reported symptom reduction of pain, anxiety, depression, and/or sleeplessness at weeks 4, 8, and 12.

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

The sub-analyses endpoints consist of the mean number of weeks that pain, anxiety, depression, and sleeplessness response are achieved and sustained, without utilization of another device, during the 8-week intervention. In addition, study sub-analyses also include the mean number of weeks to initial benefit from Nu-V3 device use, and the mean medication dosage reduction of short acting pain, anxiolytics, and/or insomnia. The device's comfort-of-use, and patient's perceived treatment benefit will also be captured for sub-analyses.

9.0 STUDY MONITORING

Nu-Life will monitor the study according to good clinical practice. 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.

10.0 REFERENCES CITED

1. Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol Med. 2013 May;43(5):897-910.
2. *National Institutes of Health*. U.S. Department of Health and Human Services, n.d. Web. 25 Jan. 2017.
3. Greenberg PE, Sisitsky T, Kessler RC, et al. The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry. 1999 Jul;60(7):427-35.
4. Ferrari, A.J., Somerville, A.J., Baxter, A.J., Norman, R., Patten, S.B., Vos, T. and Whiteford, H.A. (2013) 'Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature', *Psychological Medicine*, 43(3), pp. 471–481.
5. Center for Behavioral Health Statistics and Quality. (2016). *Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health* (HHS Publication No. SMA 16-4984, NSDUH Series H-51). Retrieved from http://www.samhsa.gov/data/
6. PharmaPoint: Insomnia - Global Drug Forecast and Market Analysis to 2023. Feb-2015

7. Roth T. Insomnia: Definition, Prevalence, Etiology, and Consequences. *Journal of Clinical Sleep Medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2007;3(5 Suppl):S7-S10.

8. Mai E, Buysse DJ. Insomnia: Prevalence, Impact, Pathogenesis, Differential Diagnosis, and Evaluation. *Sleep medicine clinics*. 2008;3(2):167-174.

9. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006 May;10(4):287-333.

10. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *Journal of Pain.* 2015;16(8):769-780.

11. "2 Pain as a Public Health Challenge." Institute of Medicine. 2011. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press

12. Ueno N et al. Innervation of the external ear in humans and musk shrew. Nihon Jibiinkoka Gakkao Kaiho. 1993 Feb;92(2):212-8. Japanese

13. He W, Wang X, Shi H, et al. Auricular Acupuncture and Vagal Regulation. Evidence-based Complementary and Alternative Medicine : eCAM. 2012;2012:786839. doi:10.1155/2012/786839

14. Jean-Pierre Barral and Alain Croibier, Chapter 25 - Ear, In Manual Therapy for the Cranial Nerves, Churchill Livingstone, Edinburgh, 2009, Pages 227-238, ISBN 9780702031007, https://doi.org/10.1016/B978-0-7020-3100-7.50028-8.

15. Torsten Liem, Chapter 17 - The organ of hearing and balance, In Cranial Osteopathy (Second Edition), Churchill Livingstone, Edinburgh, 2004, Pages 605-633, ISBN 9780443074998, https://doi.org/10.1016/B978-044307499-8.50024-7.

16. Terry Oleson, 2 - Theoretical Perspectives of Auriculotherapy, In Auriculotherapy Manual (Fourth Edition), Churchill Livingstone, Saint Louis, 2014, Pages 25-86, ISBN 9780702035722, https://doi.org/10.1016/B978-0-7020-3572-2.00002-1.

17. Review of the Uses of Vagal Nerve Stimulation in Chronic Pain Management. Chakravarthy K, Chaudhry H, Williams K, Christo PJ. Curr Pain Headache Rep. 2015 Dec;19(12):54. doi: 10.1007/s11916-015-0528-6. Review.

18. Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex—linking immunity and metabolism. Nature reviews Endocrinology. 2012;8(12):743-754. doi:10.1038/nrendo.2012.189.

19. Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors~~,~~: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health (CDRH), January 2006, http://www.fda.gov/downloads/Regulatory Information/Guidances/UCM126418.pdf

Appendix 1: Informed Consent

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

Name and Clinic Number
Patient ID Sticker Here

Approval Date:

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: A Phase I Prospective, Single-arm, Open-Label, Multi-Center Study Using the Nu-V3 Cranial Nerve Stimulation Treatment Device in Patients with Pain, Anxiety, Depression, and/or Sleeplessness

IRB#:

Principal Investigator:

Study Number: Nu-V3

Sponsor: Nu-Life Solutions

Protocol Number: Nu-V3 PROTOCOL NO. 1

This Informed Consent Form is for adults 18 years and older who suffer from the symptoms of pain, anxiety, depression, and/or sleeplessness.

Please read this information carefully. It tells you important things about this trial. A member of our research team will talk to you about taking part in this research study. If at any time you have any questions, please ask to stop and go through the information for further explanation. If you have questions later, you can always ask your study coordinator, the study doctor, or the staff.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- If you choose to participate, you are free to change your mind at any time.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- If you choose not to participate or discontinue your participation, your decision won't change the access to medical care you receive now or in the future.

You will be given a copy of the full Informed Consent Form.

CONTACT INFORMATION

You can contact...	At...	If you have questions about...
Principal Investigator:	**Phone:** **Address:**	• Study tests and procedures • Research-related injuries or emergencies • Any research-related concerns or complaints • Withdrawing from the research study • Materials you receive • Research-related appointments
Institutional Review Board (IRB)	**Phone:** **Address:**	• Rights of a research participant
Clinical Trial Manager Eric Siebeneck, MS	Phone (7a-7p MST): **Address:**	• Issues with accessing your mobile questionnaires

Introduction:

The Nu-V3 device is a miniaturized, lightweight, non-invasive, non-pharmaceutical device used for the possible relief of one or more of the following symptoms: pain, anxiety, depression and/or sleeplessness.

A research study is being conducted to determine the effectiveness of the Nu-V3 device to offer possible relief from pain, anxiety, depression, and/or sleeplessness. You are being asked whether you want to be in a research study because you have one or more of these symptoms. The Nu-V3 device is investigational, which means that it has not been approved by the Food and Drug Administration (FDA) or any other agency and is currently being studied. The device is similar to other devices such as a TENS machine, but differs in treatment, delivery, and patient experience.

Being in this study does not replace your regular medical care. So, it is important that you understand the difference between the regular care you get from your doctor and the research study. If you are currently receiving any treatment for your pain, anxiety, depression, and/or sleeplessness, you will continue to take this medication as prescribed by your doctor.

In this document, you will see the terms "medication", "treatment", and "treatment period"; these are terms used in research studies and are not meant to indicate that you will be receiving medical treatment for any condition. These terms apply to the investigational study device (Nu-V3 device) and parts of the study where you will be receiving this investigational device.

Type of Research Intervention:

This is an open-label study, which means that you will know that you are receiving active treatment. Every person taking part in the research will receive the device, there are no placebos or dummy devices (which contain no active treatment).

This study involves the use of the Nu-V3 device, which clips onto the ear and has three adhesive gel pads (like small round band aids) which are placed on the external ear. The device is worn continually for two weeks with a change of the pads after the first week. The device is about 1.25 inches by 0.5 inches and weighs about .20 ounces. The total number of devices used will depend on the stage of the study. The device creates a transcutaneous electrical stimulation of the vagus and other cranial nerves. This is thought to increase your autonomic nervous system stimulation, which may have a positive effect on your symptoms.

Total Number of Participants:

About 50-100 individuals will be enrolled in the study at multiple sites. You will be in the study for about 12 weeks. You will visit the study center weekly for 8 weeks, then you will have a follow up phone call weekly for another 3 weeks. At the 12th week, you will visit the study center for an evaluation, and will be offered the opportunity to continue treatment with an

optional maintenance period. This optional maintenance period will last another 12 weeks and will consist of a 2-weeks on, 2-weeks off treatment, followed by an 8 week observation period.

In order to be eligible to take part in this research you will need to:

- be at least 18 years of age
- have one or more of the following symptoms: pain, anxiety, depression, and/ or sleeplessness
- be capable of understanding the use and maintenance of the device
- be capable of and agree to participate in the ongoing assessment
- agree to voluntarily participate and sign the Informed Consent Form
- be willing to commit to follow all protocol study timepoints and instructions

You will not be able to take part in the research if you:

- have a pacemaker
- have an irregular heart rate or a heart rate lower than 60 beats per minute (bradycardia)
- had a transplant within the last 2 years
- had a heart attack or cardiac bypass surgery within the last 12 months
- have a history of substance abuse, including prescription drugs within the last 12 months
- had complaints of dizziness or lightheadedness within the last 3 months
- have Diabetic Retinopathy (high blood sugar levels cause damage to blood vessels in the retina)
- have a current ear infection
- have a systolic blood pressure less than 100 and/or a diastolic blood pressure less than 60
- have a history of uncontrolled bipolar disorder within the last 12 months
- have a history of uncontrolled seizures within the last 12 months
- have a history of aneurysms (a weakness in the wall of your artery)
- have a history of syncope (fainting) within the last 12 months
- had a Transient Ischemic Attack (a mini-stroke) or stroke within the last 12 months
- have health problems that the study doctor thinks will put you at risk to take part in the research
- have had any changes to pain/anxiety/depression/sleeplessness medications within the last 60 days
- are currently undergoing the process of applying for disability support from any source

If you are a woman who is pregnant, you cannot take part in this research.

Please attest to the following if you are female:

I am not pregnant, nor am I trying to become pregnant

☐ **Yes** ☐ **No**

I am actively using birth control

☐ **Yes** ☐ **No**

Procedures and Instructions:

- Prior to the study, you will be asked to complete study questionnaires regarding all of the following symptoms: pain, anxiety, depression, and/or sleeplessness, as well as your quality of life, active medications, medical history, and demographical information.
- At each subsequent visit, you will be asked to complete study questionnaires regarding all the following symptoms: pain, anxiety, depression, and/or sleeplessness, as well as your quality of life.
- Each session will begin with the Nu-V3 device being placed on your left ear and three small pads (non-invasive) being placed on three areas of the ear. Each Nu-V3 device you receive stays on your ear for approximately 14 days, with a change of pads after approximately 7 days.
- Each session takes approximately 15 – 20 minutes. The placement of the device takes approximately 5 minutes, while the remaining time is spent verifying mobile questionnaire completion and checking for any immediate effects from the device.
- The Nu-V3 device is mobile, fits comfortably behind your left ear and is worn for 24 hours a day during treatment. An electrical signal is sent to your external ear through coated wire leads attached to the device and adhesive pads which attach to three sites on your ear.
- You should be able to perform your typical day-to-day activities while wearing the device. You may shower while wearing the Nu-V3 device, provided that you do not get the device wet and use the small disposable ear covers that are provided for you.
- You should not make changes to your existing treatment or medications without discussion with your medical provider.
- Nu-Life reserves the right to capture video, photographs and written testimonials from you with written permission. It may be possible to tell your identity from the videos, photography and testimonials. It is optional for you to take part in these activities. In the event that you elect to participate in any or all of these activities, you will be asked to sign a waiver (a separate permission form) giving exclusive rights to Nu-Life for the materials gathered from you, such as video, photographs and written testimonials. Your participation in this study is not dependent upon your willingness to provide these testimonial materials. Please ask your study doctor or study staff to explain the use of

these photographs, videos or testimonials before you make a decision whether to agree to take part in this optional part of the research.

Do you know why we are asking you to take part in this study?
☐ **Yes** ☐ **No**

Do you know what the study is about?
☐ **Yes** ☐ **No**

Alternative Procedures or Treatment:

Your alternative to study participation is to continue standard of care treatment and NOT participate. This research study does not offer alternative procedures or treatment. Your doctor will continue to monitor your medical care according to the current clinical standards of care.

Will I be compensated for participating in this study?

You will not be compensated for participation in this study.

What are the costs to me for participating in this study?

There will be no direct study costs for your participation in this study. All study visits, tests and procedures will be billed to you per a typical standard of care maintenance visit.

Voluntary Participation:

Your participation in this research is entirely voluntary. It is your choice whether to participate or not.

Side Effects:

Dizziness: When the Nu-V3 device is first placed on your ear, you may experience a slight dizziness – caused by the stimulation of the ear nerves - and/or a mild headache. For this reason, you will be asked to wait for 10-15 minutes following the placement of the Nu-V3 device to check for any side effects and ensure they are resolved before you leave the clinic.

Discomfort: If the device becomes uncomfortable, you may move the device (not the gel pads) along the ear, following discussion with the Investigator. If any severe side effects occur, such as a rash, you may simply remove it and report this event to your study doctor.

Risks:

There is a risk that you may not receive any benefit from the Nu-V3 device, or it may take a number of weeks to see any benefit. There is a risk that benefits received from the Nu-V3

device may not be long lasting. By stimulating the cranial nerves and the autonomic nervous system, there may be side effects that you are not expecting.

There is a risk that you may develop an allergic reaction to the pads. If you develop a rash, skin irritation or swelling, please remove the pads and contact your study doctor. There may be risks for participating in this research that are currently unknown.

Benefits:

If you participate in this research study, you may or may not experience an improvement in your symptoms. Your participation will help advance the technology of the Nu-V3 device for others who are suffering. Your participation is likely to help the Sponsor refine the device so it may help others in the future.

Notification of Significant New Findings:

During the course of the study, we may learn new information which could be important to you. This includes information that might cause you to withdraw from the study. You will be notified as soon as possible if such information becomes available.

In the event of a Nu-V3 device related injury:

In the event that the Nu-V3 device causes an injury, even though all instructions have been followed and cautions considered, your insurance will be billed for the medical treatment and the study Sponsor will pay for the costs not covered by your insurance. The sponsor will only pay for reasonable costs and only if the Nu-V3 device has been used in accordance with the study protocol and any other instructions provided by the Sponsor.

Confidentiality:

Your personal information collected from this study will be kept confidential to the extent permitted by law. Your personal identity will be protected by assigning an identification number to you. We cannot guarantee absolute confidentiality. By signing this document, you give permission to access your medical records, including after withdrawal from the study, for data verification purposes.

Information about you collected during the research will be available to

- the researchers and study staff involved in the study
- Nu-Life Solutions, the sponsor of this study or those who work for or represent the sponsor
- the clinicians treating you
- The U.S. Food and Drug Administration (FDA)
- Aspire Independent Review Board (IRB)/ Western IRB

The results from the study, including laboratory tests, may be published for scientific purposes, but your identity will be kept confidential.

In the rare event that your information is required to be disclosed by law to another entity, privacy laws may not apply, and neither the Sponsor nor Aspire/ Western IRB can protect your information.

A description of this clinical trial will be available on http://www.clinicaltrials.gov as required by U.S. Law. This website will not include personally identifiable information. You can search this website at any time.

Do you understand the procedures that will be used to ensure your information remains confidential?

☐ **Yes** ☐ **No**

Right to Refuse or Withdraw:

You do not have to sign this form, but if you do not, you cannot take part in this research study. You do not have to take part in this research study. You may decide to stop at any time. You should tell the Principal Investigator if you decide to stop and you will be advised whether any additional assessments may need to be done for your safety.

In addition, the Principal Investigator, the study sponsor, or [**study site**] may stop you from taking part in this study at any time: if it is in your best interest, if you don't follow the study procedures, or if the study is stopped.

If you cancel your permission to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you during your study involvement may continue to be used.

If you choose not to take part or if you withdraw from this study, it will not harm your relationship with your doctors or with [**study site**].

Who to Contact:

For questions, concerns or complaints or information about the study or a research-related injury, contact the Principal Investigator at the number listed on page 2 of this document.

For questions about your rights as a study participant, please contact the Institutional Review Board (IRB) at the number listed on page 2 of this document.

For issues, questions, or concerns related to your mobile study questionnaires, please contact the Clinical Trial Manager at the number listed on page 2 of this document.

What if I experience an Adverse (Bad) Event related to my study participation?
If you need emergency care:

- Go to your nearest hospital or emergency room right away or call 911 for help. It is important you tell the doctors at the hospital or emergency room that you are participating in a research study. If possible, take a copy of this Informed Consent Form with you. Neither Nu-Life, nor the study site, have an emergency room or provide emergency care.

- Call the study doctor as soon as you can. They will need to know that you are hurt or ill. Call the Principal Investigator using the contact information provided to you on page 2 of this document (Contact hours 24 hours a day, 7 days a week).

If you do not need emergency care:

- Contact the Principal Investigator and your Primary Care Physician or go to an urgent care facility. It is important that you tell your Primary Care Physician or the urgent care Facility that you are participating in a research study. If possible, take a copy of this Informed Consent Form with you.

The sponsor and Principal Investigator will determine whether the adverse event is related to your study participation.

What if the device inadvertently comes off during my treatment?
In the event the Nu-V3 device is inadvertently removed or comes off, the participant should contact the Principal Investigator. The Principal Investigator will determine the appropriate course of action to be taken.

Enrollment and Permission Signatures

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it, and any questions I have asked have been answered to my satisfaction.

I consent voluntarily to participate as a participant in this research. I have been told that I can change my mind later if I want to. I will be given a signed and dated copy of this agreement. By signing this consent form, I am not giving up any of my legal rights.

_____/____/_____:_____AM/PM
Printed Name of Subject Date Time

_____
Signature of Subject

If this consent form is read to the subject because the subject is unable to read the form, or unable to physically sign the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement on behalf of the subject:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. The subject freely consented to be in the research study.

_____/____/_____:_____AM/PM
Printed Name of Impartial Witness Date Time

_____
Signature of Impartial Witness

Name and Clinic Number
Patient ID Sticker Here

Approval Date:

Statement by the researcher/person taking consent:

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant

_____/____/_____:_____AM/PM
Printed Name of Person Obtaining Consent Date Time

_____
Signature of Person Obtaining Consent

[Optional] Consent to Continued Maintenance and Observation Beyond Initial 12 Weeks:

If you have completed the initial 12-Week treatment period, and would like to continue receiving therapy, you are eligible to continue treatment with the Nu-V3 device. We will provide you with any new information including risks, discomforts, or new alternative treatments that might affect whether you wish to continue to be in the study.

I freely accept to continue my participation in this study:

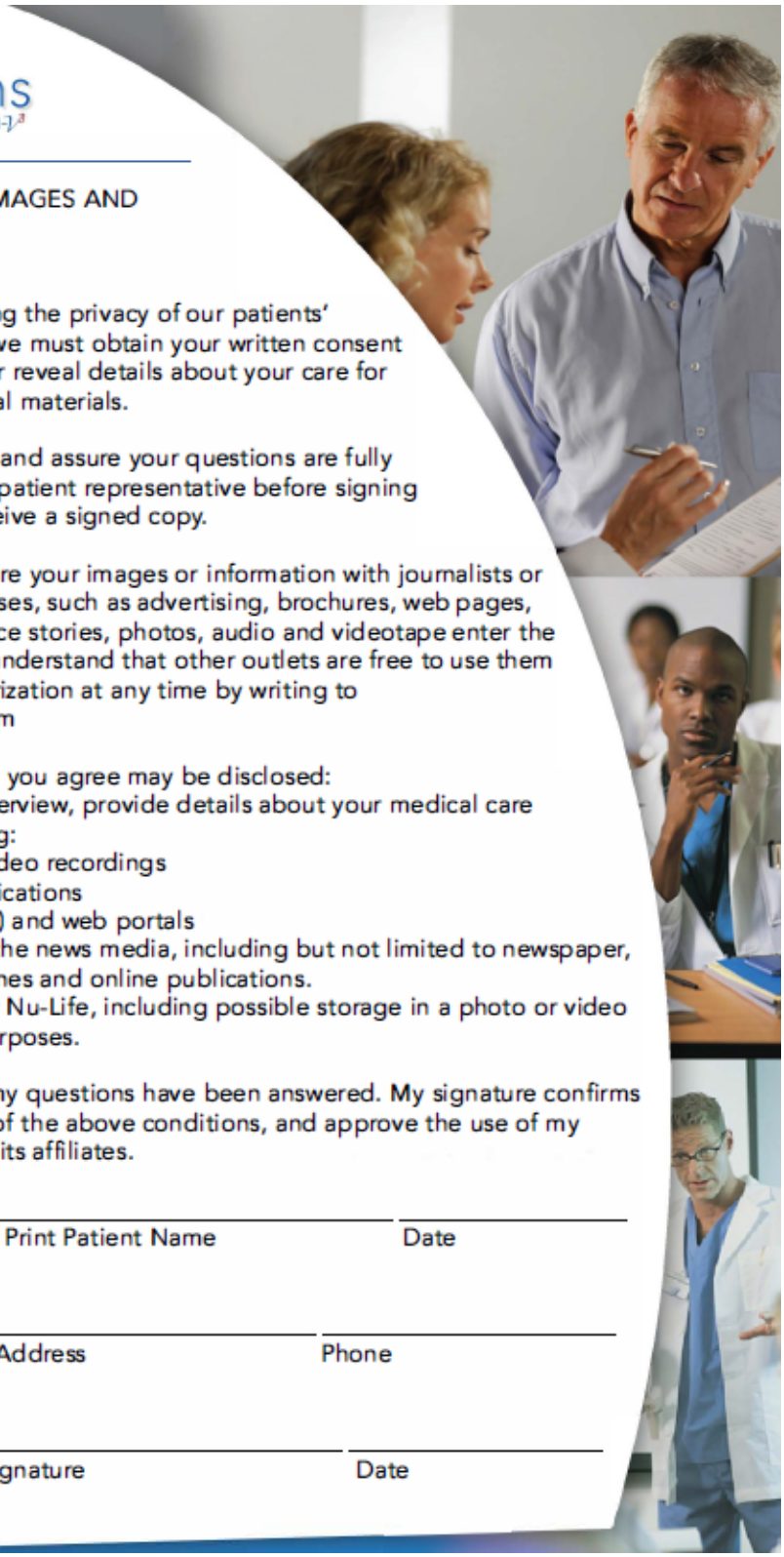
Signature of Participant _____ Date:_____

Signature of person obtaining re-consent _____ Date:_____

Signature of Investigator/Physician _____ Date:_____

Appendix 2: Media Testimony Consent

Nu-Life Solutions
Miniaturized Wearable Medical Technology · Nu-J



PATIENT PERMISSION TO USE IMAGES AND MEDICAL INFORMATION

Nu-Life is committed to protecting the privacy of our patients' medical information. That's why we must obtain your written consent before we can photograph you or reveal details about your care for use in news stories or promotional materials.

Please review the following facts and assure your questions are fully answered by a Nu-Life or facility patient representative before signing this form. You are entitled to receive a signed copy.

A Nu-Life representative may share your images or information with journalists or the public for promotional purposes, such as advertising, brochures, web pages, publications or news stories. Once stories, photos, audio and videotape enter the public domain, it's important to understand that other outlets are free to use them too. You may revoke your authorization at any time by writing to Patient.Info@Nu-LifeSolutions.com

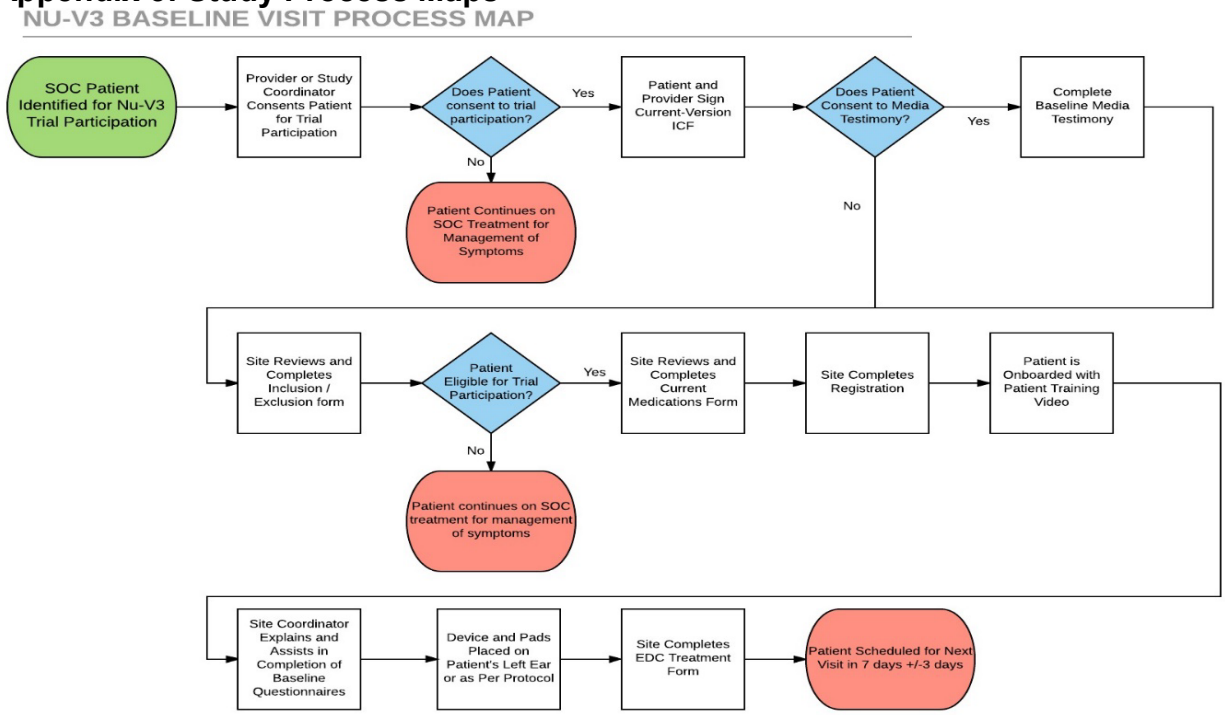
Please check specific information you agree may be disclosed:
You agree to participate in an interview, provide details about your medical care and/or participate in the following:

_____ Photographs, audio or video recordings
_____ Nu-Life brochure or publications
_____ Nu-Life/Nu-V3 web site(s) and web portals
_____ Nu-V3-related stories in the news media, including but not limited to newspaper, television, radio, magazines and online publications.
_____ Marketing/advertising by Nu-Life, including possible storage in a photo or video archive for future promotional purposes.

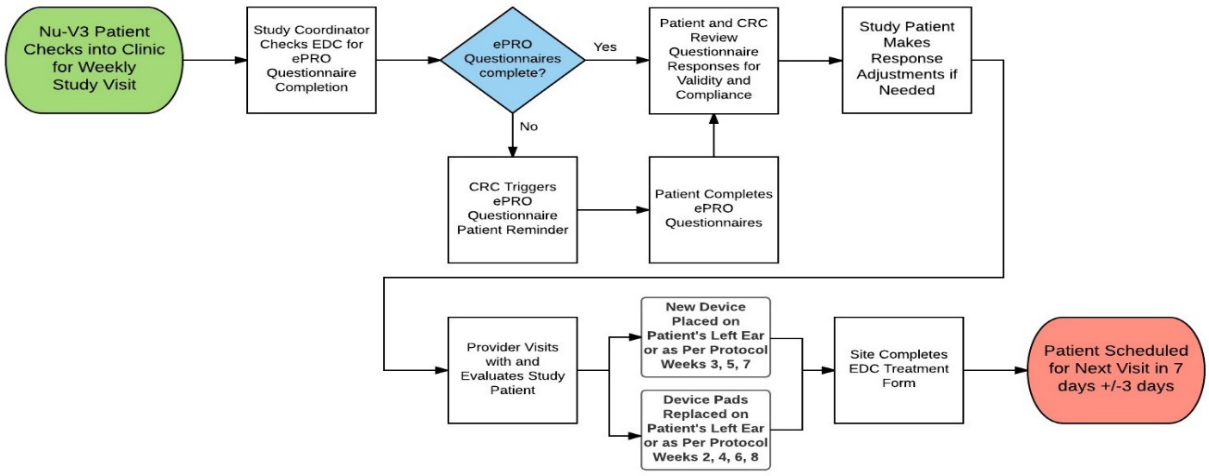
I have read this form, and all of my questions have been answered. My signature confirms that I understand and accept all of the above conditions, and approve the use of my images by Nu-Life Solutions and its affiliates.

_____	_____	_____
Signature (Patient or Guardian)	Print Patient Name	Date
_____	_____	_____
Relationship to Patient	Email Address	Phone
_____	_____	_____
Print Nu-Life Rep's Name	Signature	Date

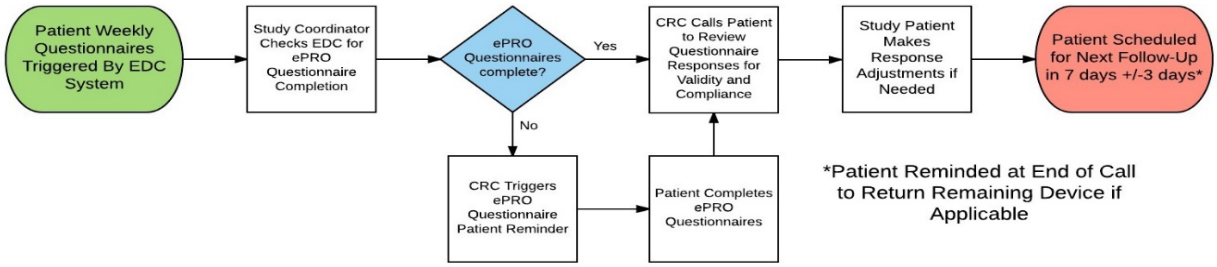
Appendix 3: Study Process Maps



Weeks 2-8



Weeks 9-12



Appendix 4: Eligibility Checklist

Nu-Life Solutions
Miniaturized Wearable Medical Technology · Nu-^{3}

NU-V3 Protocol No. 1

SCREENING AND ELIGIBILITY CHECKLIST

A Single-Arm, Phase I Study to Evaluate the Efficacy of the Nu-V3 Device for Patients with Pain, Anxiety, Depression, 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: pain, anxiety, depression, and/or sleeplessness
☐	☐	Participant is capable of understanding the use and maintenance of the device
☐	☐	Participant is capable and agreeing to participate in the ongoing assessment
☐	☐	Participant has signed the Informed Consent Form
☐	☐	Participant can commit to follow all protocol study time-points

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 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
☐	☐	History of substance abuse, including prescription drugs, 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

Instructions for Use

For proper placement of the pads, identify the shortest wire lead (Pad #1) and place the pad on the lobe perpendicular to the tragus. Then place Pad #2 in the concha, preferably below the crus helix and behind the anti-tragus. Finishing with the longest wire lead (Pad #3), place the pad in the triangular fossa.

1 Prepare the Patient's Ear

Clean the area where the device and pads will be placed with the alcohol prep pads. Allow to dry for 60 seconds.

2 Place the Device

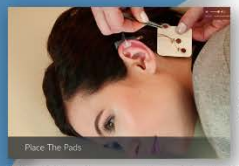
PADS™ refers to the lightweight, non-invasive electro-gel pad assembly developed exclusively by Nu-Life Solutions for Nu-V3.

Carefully place the device behind the ear as shown. Adjust placement and clip for comfort.

3 Connect the PADS™ Assembly

Connect the PADS™ assembly to the device by inserting the pin into the connection port of the device.

4 Place each pad of the PADS™ Assembly



Carefully place each pad in the locations as indicated on the placement guide above. Place each pad on the flattest part of each position. Tweezers (included) may be helpful in placing the pads.

5 Place the Protective Covers

Once each pad is in place, remove a protective cover from its backing and place directly over each pad.

6 Use and Care Instructions

Once the device and all pads have been placed, instruct the patient on the use and care of the device for the time he or she will be wearing it and be sure they have the instructions to take with them.

Preparing the Device

Step 1: Remove the device and PADS™ assembly from the packaging.

The **Nu-V3 Device and Packaging**

Step 2: Gently remove the PADS™ assembly from its pouch.

Step 3: Remove the protective cover from the device tray and activate the batteries by pulling off the yellow tabs.

Note: The device is equipped with a miniature LED light, which begins to flash shortly after the batteries are activated. This helps to ensure the device is operating as intended. The device is in active stimulation mode for 3 hours and off for 3 hours. The LED flashes once per second in active mode and once every 10 seconds in off mode.

Step 4: Be sure the LED is flashing. Assemble the top and bottom of the device.

Items Supplied:
Nu-V3 Device with non-activated batteries
PADS™ Assembly
Alcohol Prep Pad
Instruction for Use & Safety Instructions
Ear Covers

Nu-Life Products, Inc
Manufacturing and Supply of Nu-V3

Important: Before applying the device, read all use and safety instructions on the reverse side.

Appendix 6: Use and Care Instructions (Patient)

Nu-Life Products, Inc
Manufacturing and Supply of Nu-V3

Indianapolis, Indiana
www.Nu-V3/Patient.info

Nu-V3

Use and Care Instructions

Consult instructions for use For Single Use Only

SAFETY INSTRUCTIONS
These safety instructions are an integral part of the Nu-V3 and the therapy provided by the device and as such, must be followed closely to ensure the proper use of the device and safety of the treatment. These instructions for use and safety instructions are to be read and observed in full by every user. Treatment Provider and patient are both responsible for educating themselves and following these instructions and the proper use of the device as described in these instructions. Non-observance of the warnings and safety instructions may lead to injuries, infections or serious harm to the user and others.

The exclusive PADS™ assembly is only intended for single use. The re-use of single-use products represents a possible risk for the patient or user. Never place the exclusive gel pads on any location other than the auricular (ear) area, especially the eyes. It is important that all used devices and PADS™ assemblies are not reused in any way and that the device and PADS™ assembly is removed by the treatment provider or returned to the treatment provider by the patient or user.

Use of the device in the immediate vicinity of short-wave, or RF devices can be a cause of interference and should be avoided. The serial number for the Nu-V3 device is located on the packing for each device. These serial numbers are kept on file with the manufacturer and should be kept by the treatment provider and filed with the patient's reports on a regular basis.

Absolute Contraindications
- History of dizziness or lightheadedness within the last 30 days
- Current ear infection
- Heart rate lower than 60 beats per minute (bradycardia)
- SBP < 100 and/or DBP < 60
- Heart attack within the last 12 months
- Cardiac bypass surgery within the last 12 months
- History of uncontrolled seizures
- Aneurysms
- History of an organ transplant within the last 2 years
- Pregnancy
- Diabetic Retinopathy
- Uncontrolled Bipolar Disorder within last 12 months

Relative Contraindications
The following should be discussed with the patient's physician before use.
- Patients with a pacemaker
- History of syncope within the last 12 months
- History of TIA or stroke within the last 12 months
- Need for obtaining an MRI during the time the device in in place

Because the gel pads are non-invasive and use a specialized electro-gel to transmit the stimulation signal from the device to the nerves, the patient may or may not feel a gentle pulsing. This pulsing may diminish or stop as the body gets used to the stimulation. This is normal and is not an indication that the device is not working. The device is water resistant but not waterproof. When showering, patient should use the clear ear covers supplied with the device to ensure that the device stays dry. Do not allow the device to come in direct contact with water. Direct contact with water may result in the malfunction of the device.

TECHNOLOGY DATA
Appliance: Non-invasive, Pulsed Stimulation Device Type description: Nu-V3 Device Power supply: 3 X 1.4 V batteries (Type AC 10E)
Output: (Load impedance range 1k-10k8) max. 3.8V, Impulse interval 500ms, Impulse width 5ms, (1Hz / 5 ms / bipolar), max duration of treatment 14 x 24 hours.
Classification: Class II (FDA) Duty Type: approx. 3h duty / 3h at rest (periodic duty) Weight incl. battery: .20 oz. Dimensions: 1.25 in x .5 in.

Form G1IN001

The Nu-V3 Device

For professional use only

Remarks
The stimulation received from the Nu-V3 device is controlled by a state-of-the-art micro-chip that creates a square, plus-minus wave, and turns itself off and on automatically every three (3) hours. This allows for an alternating stimulation and rest period.

About the Nu-V3 Device and Accessories:
- The Nu-V3 device is a miniature microchip controlled nerve stimulation therapy device.
- The Nu-V3 device kit also includes an assembly consisting of three wires with non-invasive, exclusive electro gel PADS™.
- The Nu-V3 device is placed on the ear as indicated in the illustrations in this document.
- The device transmits low-frequency electric pulses.

Recommendations on Indications for Use:

IMPORTANT: These Indications for Use are to be considered as a part of a physician's recommendation.
Acute pain and chronic pain, anxiety, depression and sleeplessness

TSA Security Information:
If traveling, the patient may keep this safety information available for TSA, or other airport safety organizations, should they inquire about the safety features of Nu-V3.

Appendix 7: 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 8: Medical History Form

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

Nu-Life Solutions
Miniaturized Wearable Medical Technology · Nu-^{3}

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 9: Treatment Form

Nu-Life Solutions
Miniaturized Wearable Medical Technology · Nu-J

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: _____

Nu-Life Solutions
Version Date: October 30, 2017

Page 1 of 1

Appendix 10: Medications Form

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

Nu-Life Solutions
Miniaturized Wearable Medical Technology · Nu-1³

Medications Form

1. Have the participant's medications changed?

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

2. Medications Log

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

Nu-Life Solutions
Version Date: November 7, 2017

Page 1 of 1

Appendix 11: ePRO Questionnaires

Nu-Life Solutions
Miniaturized Wearable Medical Technology · Nu-^{4}

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

Complete Patient ePRO Questionnaire Packet

Version Date: 07/Nov/2017
Approval Date:

Nu-Life Solutions
Miniaturized Wearable Medical Technology · Nu-1³

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

Nu-Life Solutions
Version Date: November 7, 2017

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.

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

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 Inern Med.* 2006;166:1092-1097.

Nu-Life Solutions
Miniaturized Wearable Medical Technology · Nu-^{4}

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 _____

Nu-Life Solutions
Version Date: 07/Nov/2017

Page 1 of 1

Nu-Life Solutions
Miniaturized Wearable Medical Technology · Nu-[4]

PROMIS Item Bank v1.0 - Sleep Distrubance - 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.....	☐	☐	☐	☐	☐

Nu-Life Solutions
Miniaturized Wearable Medical Technology · Nu-T

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.

Nu-Life Solutions
Version Date: November 7, 2017

Page 1 of 1

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

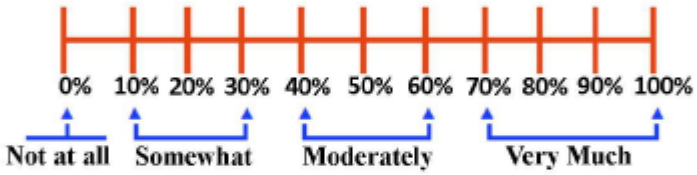
Nu-Life Solutions
Miniaturized Wearable Medical Technology · Nu-^{3}

Form PTB-7: Patient's Perceived Treatment Benefit

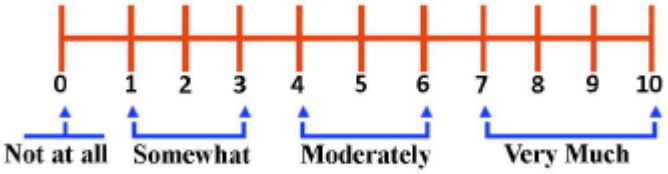
For ***initial assessment*** of all symptoms, please rate your **average symptom score** *prior* to any treatment (i.e. over the last 30 days)

For any assessment ***after treatment has been initiated***, please rate your ***global average symptom score since your last treatment***

1. On a scale of 0-100%, how much benefit do you feel you have received from the Nu-V3 treatment in helping your symptoms?



2. How comfortable was the Nu-V3 device to wear?



3. Have you had any major discomfort from the device that has necessitated you to adjust the device placement?

_____Yes
_____No

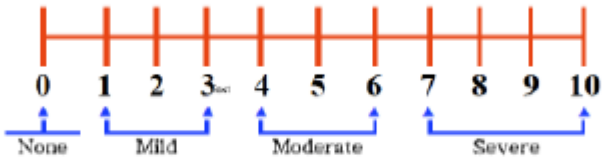
Subject ID_____ Date (dd/mmm/yyyy): _____/_____/_____

For ***initial assessment*** of all symptoms, please rate your **average symptom score** *prior* to any treatment (i.e. over the last 30 days)

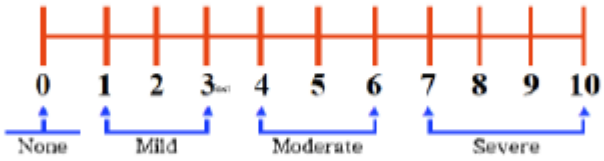
For any assessment ***after treatment has been initiated***, please rate your ***global average symptom score since your last treatment***

4. Please rate your pain, anxiety, depression, and/or sleeplessness on a 0-10 scale:

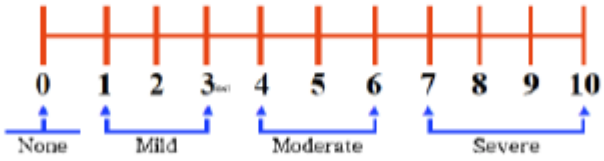
Pain Level:



Anxiety Level:



Depression Level:



Sleeplessness Level: