TITLE PAGE

Full protocol title: Addressing Disparities in Neuromodulation for Rehabilitation: A Mixed Methods Approach to Optimize Access for Underrepresented Racial Minorities

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1) Protocol Title

Addressing Disparities in Neuromodulation for Rehabilitation: A Mixed Methods Approach to Optimize Access for Underrepresented Racial Minorities

2) IRB Review History*

Approved (ID 20230154)

3) Objectives*

We will develop culturally sensitive videos for video-enhanced informed consent (VE-IC) with neuromodulation techniques (i.e., vagus nerve [taVNS] and transcranial magnetic [rTMS] stimulation techniques). We will use these videos in a mixed method study design to examine factors that influence the interest or aversion to participate in neurostimulation research in URM with persistent pain. Findings will provide insight on modifiable factors and recruitment/retention strategies to optimize racial minority representation in neurostimulation research. The videos and data from this project will be used in our future research on neurostimulation, and they will be made available for use by others. This study is part of a larger research agenda designed to inform the development of personalized pain relief programs based on using patient preferences and a mechanistic understanding of the interventions to integrate neurostimulation interventions into multimodal care for persistent pain.

Aim 1: Development of culturally sensitive videos for enhance informed consent with neurostimulation and determination of factors that influence minority interest in participating in neurostimulation research. *We hypothesize that participants will have greater interest in participation and expectations for pain relief with the modality for which they received VE-IC in comparison to modalities without VE-IC.*

Aim 2: Examination of the influence that video enhanced informed consent has on expectations with taVNS and on treatment intended effects. *We hypothesize that individuals who had VE-IC for taVNS will demonstrate greater expectations for pain relief and greater changes in heart rate variability (HRV).*

Aim 3: Explore the intended effects of taVNS in people with neuropathic pain. The sample consent form and brochure for taVNS will not specify the exact location on the ear for active taVNS. Thus, participants in the TMS video only group will be sufficiently naïve for participation in a single blinded crossover design. Half of the TMS-only group will receive active taVNS in visit 2, the other half will receive sham taVNS in visit 2, and they will crossover for visit 3 (table 1). *We hypothesize that there will be a greater increase in HRV and SICI with active taVNS than with sham taVNS.*

4) Background*

Noninvasive neurostimulation techniques show promise for improving chronic pain management.[1-3] Underrepresented racial minorities (URM) are at greater risk than non-minority individuals for persistent pain conditions[4-6]; however, recruiting URM for adequate representation in neurostimulation research remains an unmet challenge. Improving recruitment of URM participants in neurostimulation research

is critical to enhancing our understanding of factors that influence outcomes with these modalities and to maximize the generalizability of research findings to a diverse population.

Traditional consent forms have been criticized for being too long and difficult to understand, and these consent forms may be a barrier to URM participation in research, as limited literacy disproportionately affects URM and the text heavy format may foster distrust. Video-enhanced informed consent (VE-IC) has been recommended to improve recruitment of URM in cancer and cardiovascular trials; however, VE-IC has not been studied in neuromodulation research.

5) Inclusion and Exclusion Criteria*

We anticipate that most participants in this study will have chronic pain associated with chemotherapy induced peripheral neuropathy (CIPN); however, we will recruit Black and Hispanic people with chronic neuropathic pain of any etiology (e.g., diabetic neuropathy and radiculopathy) to optimize the rapid recruitment of these URM.

Inclusion Criteria: 1) between the ages of 18-80 years; 2) neuropathic pain lasting longer than 3 months (i.e., complaint of sensation of burning, stabbing or pressing pain, shooting or shock like pain, or paresthesias); 3) Neuropathic Pain Symptom Inventory score ≥10. 4) self identifies as Black or Hispanic

Exclusion Criteria: 1) any unstable medical condition or medical contraindication to moderate physical exertion (e.g., unstable angina or cardiac arrythmia), 2) pregnancy, 3) currently taking Buprenorphine or recently stopped taking (within 1 month), 4) presence of cognitive impairment or language barrier that impairs full autonomy in the consent process or in the ability to participate in detailed interviews, 5) implants in the head or neck, cochlear implants, or pacemaker, 6) head or neck metastasis or recent ear trauma, 7) history of seizures.

6) Study-Wide Recruitment Methods*

All recruitment will be in accordance with the Health Insurance Portability and Accountability Act (HIPAA), by the SCCC Protocol Review and Monitoring Committee and by the UM Department of Physical Therapy Research Leadership Team.

Black and Hispanic patients with persistent pain will be recruited for a 2-phased mixed methods study. Flyers will be placed in Uhealth clinics (Uhealth Physical Therapy, Uhealth Advanced Pain Management Center, and Sylvester Comprehensive Cancer Center) to recruit patients with neuropathic pain. In addition, the patient census of specific UHealth clinics (i.e., Dr. Peter Hosein's medical oncology clinic, the Sylvester Posner Lymphema Clinic, and the Uhealth Pain Physical Therapy Clinic) will be used for recruitment. *Physicians will be informing participants first about the study before a member of the study team will be contacting patients.* Telephone numbers and/or emails of potential participants and they will be called to screen for inclusion. Patients who provide verbal consent to be

contacted for research purposes will be called by one of the research assistants.

The Sylvester Behavioral and Community-Based Research (BCSR) Shared Resource will be used to assist with recruitment of patients with chemotherapy induced peripheral neuropathy (CIPN).

7) Study Design

Primary Purpose: Other. This study will utilize principles of community-based participatory research to develop and test educational materials for consenting people to neurostimulation research.
Study Phase: N/A
Interventional Study Model: Parallel
Number of Arms: 2
Masking: Subject only
Allocation: Randomized
Enrollment: 28

8) Study Timelines*

Each participant will complete 3 visits for a total of ~10 hours, and it is expected that the visits are completed within 1-2 weeks of each other. Thus, participants will be enrolled for less than 3 weeks on average.

9) Study Endpoints*

Primary Outcome Measure Title: Change in Heart Rate Variability (HRV)

Primary Outcome Measure Description: HRV will be measured with an H10 chest strap device (Polar, Finland)

Primary Outcome Measure Timeframe: at visits 2 and 3, Baseline (15 minutes pre taVNS application) to 15 minutes post 1 hour application of taVNS

Secondary Outcome Measure Title: Change in EXPECT questionnaire scores

Secondary Outcome Measure Description: scores ranging from 0-40 with higher scores representing greater expectations for pain relief

Secondary Outcome Measure Timeframe: at visits 2 and 3, Baseline (pre taVNS application) and repeated post 1 hour application of taVNS

10) Arms and Interventions

All participants will be educated on both neurostimulation modalities (taVNS and TMS). This study will include 2 arms. Group 1 will receive a supplemental video on taVNS, in addition to consent forms and brochures describing both modalities.

Group 2 will only receive the consent forms and brochures describing both modalities. While all participants will provide important feedback on consent forms and brochures for both modalities, Group 1 will provide additional feedback specific to the taVNS video they watched.

We will assess the impact of the taVNS video (by comparing Group 1 to Group 2) on participant expectations and intended effects with a single 60-minute bout of taVNS.

11) Procedures Involved*

Black and Hispanic patients with persistent pain will be recruited for a 2-phased mixed methods study. All data collection will take place at the Lynn Rehabilitation Center. In the first phase, participants will be educated on two neurostimulation modalities (taVNS and TMS). Educational materials will include 1:1 discussion of a typical consent form for each modality, a brief (2 page) description with pictures for each modality, and the brief video for taVNS for those randomly allocated to Group 1. *The development of these educational resources is a primary objective of this project, and the first few months will be spent consulting with experts to develop these educational resources and to produce the videos.*

Structured interviews and questionnaires will be used to examine participants interest in participating in research for each of the modalities, gather their feedback on each educational tool, and to determine factors that influence their interest. This first phase will take place in a single session, and the session is anticipated to take ~2 hours to complete. Participants will be given the choice to complete this first visit in person or via Zoom in order to decrease participation burden. For the second phase, all participants will receive active taVNS, but only Group 2 will receive both active and sham taVNS in a randomized crossover design. All participants will first complete a pretrial assessment battery, followed by a 60-minute trial of taVNS applied with continuous monitoring of HRV during quiet sitting, and then concluded with a posttrial assessment. The second phase will be completed in two sessions that are anticipated to last ~4 hours each. In summary, participants will complete 3 visits for a total of ~10 hours to complete the study.

	Visit 1	Visit 2	Visit 3
taVNS video (n=12)	Education and baseline	Active taVNS	1-wk follow up
Brochures only (n=12) 6 participants	Education and baseline	Active taVNS	Sham taVNS
6 participants	Education and baseline	Sham taVNS	Active taVNS

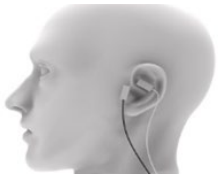
A detailed description of each procedure is provided below:

EXPECT questionnaire[7]: The EXPECT is a 4-item questionnaire that assesses expectations for pain improvement. Each of the 4 items is scored on an 11-point scale, with 0 being no change and 10 representing complete relief. It is anticipated that this questionnaire will take less than 5 minutes to complete.

Heart rate variability (HRV): HRV will be measured with an H10 chest strap device (Polar, Finland) and will serve as the primary endpoint for response to taVNS in Aim 2. Participants will wear the chest strap continuously throughout the application of taVNS.

taVNS: A portable taVNS Stimulator (Soterix Medical, Woodbridge, NJ) will be used with flexible hydrogel electrodes to administer taVNS at the cymba concha (Figure 2), using monophasic pulses (pulse width:500 μs; frequency 10 Hz), and delivered up to 200% of the perception threshold, but kept below the pain threshold, for 60 minutes. This device is approved for research purposes, and these parameters have been shown to maximize cardiovagal response with taVNS.[8] Participants will be quiet sitting in a comfortable chair during the application of taVNS.

Figure 2. taVNS electrode application



Please see the Risks to Subjects section for procedures performed to lessen the probability or magnitude of risks.

12) Data Management*

The principal investigator will be responsible for all data management and analyses. A research assistant will assist with data entry and qualitative data coding. All quantitative data will be entered and stored in the University of Miami REDCap system. NVivo 12 software (QSR International, United States) will be used for qualitative data management and analyses, and SPSS version 28 (IBM, United States) will be used for quantitative analyses (i.e., descriptive statistics).

13) Provisions to Monitor the Data to Ensure the Safety of Subjects*

Safety information will be collected during the taVNS trial study visit for this research and entered into Velos for tracking. All adverse effects will be reported to the study team, the IRB, and to the SCCC Data & Safety Monitoring Committee. All research activities will be stopped in the case

of a single serious adverse reaction (i.e., seizure) or if 3 or more minor adverse reactions (e.g., skin irritation from electrodes) are observed. A corrective plan (e.g. change in TMS or taVNS protocol) must be approved by the study team, IRB, and SCCC Data & Safety Monitoring Committee before research activities can be resumed.

The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

14) Community-Based Participatory Research*

Prior to initiating research activities, a 4-member community advisory board (CAB) will be assembled, consisting of 2 people from each ethnicity (non-Hispanic African American and Hispanic), and the CAB will meet 4 times over the course of the year to provide general feedback on the project design, plan, and progress, including feedback on video scripts, final video products, and video dissemination plan. At least 1 person from each ethnic group on the CAB must have chronic pain ($n \geq 2$).

15) Sharing of Results with Subjects*

NA

16) Setting

Participants will be recruited from Sylvester Comprehensive Cancer Center, UHealth Physical Therapy, and from the UHealth Advanced Pain Management Clinic.

The research procedures will be conducted at the Lynn Rehabilitation Center for The Miami Project to Cure Paralysis at UHealth/Jackson Memorial. The Christine E. Lynn Rehabilitation Center for The Miami Project to Cure Paralysis at UHealth/Jackson Memorial was designed from scratch to be one of the country's elite facilities for patients recovering from traumatic brain injury, spinal cord injury, cancer treatment, and other complex conditions. The stunning 250,000-square-foot, nine-story structure opened in 2020, and it houses 80 inpatient beds and features world-class amenities and next-generation rehabilitative technology. Every aspect of the facility underscores a focus on comprehensive care. The building's layout ensures that clinical care and research share space, so that patients and families see the scientists who are developing treatments, and researchers interact with real people who need the results of their work—a constant reminder of the way Lynn Rehabilitation Center integrates academic study with the day-to-day treatment of patients.

Dr. Wong's Clinical Pain Research Lab is located in the Lynn Rehabilitation Center. His dedicated lab space is equipped with a PC, laptop, secured internet access, filing cabinets, office and medical supplies, and research equipment and supplies.

A community advisory board will be formed to provide feedback and guidance on the videos produced as part of this research. Please see details in the Community-Based Participatory Research section.*

17) Resources Available

Research Team:

Marlon Wong, DPT, PhD
Principal Investigator
Dr. Marlon Wong is an Associate Professor of Clinical at the University of Miami Miller School of Medicine within the Department of Physical Therapy. Dr. Wong has extensive research and clinical experience in the assessment and management of neuropathic pain in a variety of patient populations. As the PI, he will provide expertise and oversee the execution of the aims outlined in this research project. He will develop and conduct the methodology, data collection, data analysis, and manuscript preparation. Dr. Wong has over 20 years of clinical experience using electrical stimulation for pain management. In addition, he attended a weeklong intensive training on advanced noninvasive neurostimulation techniques (i.e., taVNS and TMS) through the National Center of Neuromodulation for Rehabilitation. Dr. Wong will dedicate .2 FTE to this project (8 hrs per week), in order to complete the work in the described timeline.

Lisa McTeague, PhD
Mentor/Collaborator
Dr. McTeague is a clinical psychologist and an Associate Professor in the Brain Stimulation Laboratory of the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina. Dr. McTeague is an expert in neurostimulation techniques, specifically in taVNS and TMS, and she serves as faculty in the National Center of Neuromodulation for Rehabilitation at the Medical University of South Carolina (MUSC). She has over ten years of experience working with these modalities to develop innovative assessment and treatment methods to renormalize neural networks and restore behavior related to anxiety and mood disorders and trauma exposure. Her current work is purposefully transdiagnostic and significantly applicable to pain research. She will provide expertise and mentorship on neurostimulation research and heart rate variability. Dr. Wong will spend a week at Dr. McTeague's lab in MUSC to complete intensive training in paired-pulse TMS procedures prior to initiating research activities. Dr. McTeague will only have access to de-identified information.

Eva Widerstrom-Noga, PhD, DDS
Mentor/Collaborator
Dr. Widerstrom-Noga is a Professor of Neurological Surgery and Rehabilitation Medicine at UM, and she is the Principal Investigator of the Clinical Pain Research Laboratory of The Miami Project to Cure Paralysis. She is an expert in pain assessment and pain classification, and cross-disciplinary clinical pain research (pain physiology and pain psychology), with three decades of experience in the field. Her research involves both qualitative and quantitative pain methodologies in persons with chronic pain after neurotrauma. She will provide expertise and mentorship on pain and mixed methods research.

Frank Penedo, PhD
Mentor/Collaborator

Dr. Penedo is a Professor of Psychology and Medicine and Center Associate Director for Cancer Survivorship and Translational Behavioral Sciences at the UM SCCC. He has over 20 years' experience as a clinical health psychologist with a focus on psycho-oncology, and he is an expert in evaluating the impact of sociocultural, biobehavioral, psychosocial determinants of health outcomes in cancer survivors. Dr. Penedo's work also involves translational research evaluating the impact of symptom and toxicities monitoring and management in ambulatory oncology, the patient reported outcomes (PROs) in survivorship care, precision oncology, and phase-1 trials, as well as the implementation of culturally adapted treatments delivered within health systems. He will provide mentorship on cancer trials and patient centered research in cancer populations.

Melissa Tovin, PhD, PT
Mentor/Collaborator
Dr. Tovin is a Professor of Physical Therapy at Nova Southeastern University. She is an expert in both qualitative and mixed methods research with over 20 years' experience. Dr. Tovin will provide expertise and mentorship in the application of qualitative and mixed methods research methodology. Dr. Tovin will only have access to de-identified information.

Peter Hosein, MD
Collaborator
Dr. Hosein is an Associate Professor of Medicine and the Co-leader of the Gastrointestinal Cancers SDG at the UM SCCC. Dr. Hosein has over 12 years' experience as a medical oncologist, and he is an expert on gastrointestinal cancers having participated in numerous phase I, II, and III trials. Dr. Hosein will recruit patients with CIPN for this study and will monitor the data to ensure the safety of participants.

18) Prior Approvals

Approval will be obtained from the National Center of Neuromodulation for Rehabilitation (subcontract funding agency) and from NIH (parent funding agency) prior to commencing the research.

19) Confidentiality

Confidentiality will be maintained by assigning participant identification numbers at the beginning of the study. All data will be identified using these ID numbers. The personal information included as data will consist of the gender, age, race, ethnicity, and cancer type and treatment. This information will be kept in a locked file cabinet and stored in a password-protected digital file on the encrypted database at the University of Miami Physical Therapy Department located at 5915 Ponce De Leon Blvd, Plumer Building 1st Floor, Miami, FL 33146. Signed consent forms will be kept in a master file in a locked file cabinet. Only the principal investigator and research assistant will have access to participant's personal information and data.

20) Provisions to Protect the Privacy Interests of Subjects

Participants will only interact directly with their respective Uhealth providers for recruitment (i.e., a Uhealth provider who already has access to the patient census would contact the patient for study recruitment, and the data collection will be

performed by investigators who are members of the Uhealth clinical team). Thus, the intrusiveness of participation is minimized.

Only IRB approved research team members will have access to study records. Overall study results will not be shared with study participants, individually. Confidentiality will be maintained by assigning subject identification numbers at the beginning of the study. All data will be identified using these ID numbers. This information will be kept in a locked file cabinet and stored in a password-protected digital file on the encrypted database in the office of the PI in the University of Miami Department of Physical Therapy located at 5915 Ponce de Leon Boulevard, 2nd Floor, Coral Gables, FL 33146. Signed consent forms will be kept in a master file in a locked file cabinet. Only the principal investigator and research assistant will have access to subject's personal information and data.

21) Compensation for Research-Related Injury

Compensation will not be provided for research-related injury. Funds to compensate participants for pain, expenses, lost wages, and other damages caused by injury are not available. However, treatment will be available in most cases and their insurance may be billed or participants will have to pay.

22) Economic Burden to Subjects

There are no direct costs associated with participating in this study. However, transportation and parking may be an economic burden on some participants. Participants will be paid $250 to compensate them for the economic and time burden ($50 upon completion of visit 1 and $200 for completion of visit 2).

23) Consent Process

We will follow SOP: Informed Consent Process for Research (HRP-090). The consent process will begin with the phone screening. If they provide verbal consent to the phone screening and are deemed eligible for the study, then they will be invited to the Lynn Center. At the Lynn Center, they will be educated on the study and provided with a written consent form to review and sign. The consent form and all research documents will be available in English and Spanish. Several of the research team members are bilingual and each participant will be consented in-person in the language which they are most comfortable. Potential participants will have the opportunity to consult with family members or others and will have all questions addressed by the PI or other members of the study team. Potential participants will be briefed on their rights as a research subject, including their right to withdraw at any time with no negative consequences.

The study procedures will be reviewed with each participant at each phase of the study (i.e., taVNS and TMS procedures will be reviewed after completion of the mixed methods phase and prior to initiating the trial phase) and verbal consent will be re-obtained to ensure ongoing consent.

Each time that the verbal consent is obtained, it will be reiterated to the patient that they may choose to withdraw from the study at any time.

Non-English-Speaking Subjects

All study documents will be available in English and Spanish. A bilingual study team member will be present at all times to answer any questions and to ensure that Spanish speaking participants fully understand. As noted previously, each participant will be consented in-person in the language which they are most comfortable.

e-Consent

Verbal consent for participation will first be obtained via a phone call or in-person. During this phone call or in-person contact, eligibility will be determined by the research team at SCCC-Behavioral Community-Based Research Shared Resource department and documented in Ripple for recruitment tracking purposes only. Following verbal consent for participation, the participant will be scheduled for either a virtual or in-person consent meeting, depending on their format preferences. The consent form and all research documents will be available in English, Spanish, and Haitian-Creole and the consent process will be conducted in their preferred language.

Remote consent will also be used for participants who prefer to conduct all screening and interviews via Zoom. Once a qualified person expresses their willingness to participate, the staff will contact the person via Zoom, to explain the research study to the participant and answer any questions that may arise, and to proceed to remotely Consent patient via RedCap.

The CTSI e-Consent Template will be used for both remote and in-person consent. We will send a copy of the consent document to the participant a few days before the discussion in order to allow them to read, develop a list of questions, and discuss the research with family or friends. A printed copy will be provided to in-person participants. We will arrange a Zoom meeting that includes the person obtaining consent, the participant, and any additional people requested by the participant (e.g., relative, friend). During the meeting we will review and explain the information in the consent document, answer any questions the participant has about the study, ask the participant questions about the study to confirm their comprehension, and ask the participant if they consent to participate. If the participant agrees, then they will be asked to sign and date the consent document electronically. Then we will explain to the participant that they will receive a copy of the signed documents via email.

24) Process to Document Consent in Writing

Consent will be documented in writing prior to initiating onsite data collection. Please see the attached consent form.

25) **Drugs or Devices**

The Soterix taVNS device is approved for research purposes, and it is being used in this study as intended. The device will be stored and used in our lab at the Lynn Rehabilitation Center, and it will only be used on study participants and administered only by authorized investigators. Our lab space is not a shared space and remains locked at all times when not in use. No patient care takes place in the lab space.

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