RANDOMIZED, DOUBLE-BLINDED, CONTROLLED TRIAL OF EARLY-INTERVENTION TENS FOR THE REDUCTION OF THE PREVALENCE AND SEVERITY OF CHRONIC NEUROPATHIC PAIN DURING THE FIRST YEAR AFTER SPINAL CORD INJURY

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1) **Protocol Title**

Randomized, double-blinded, controlled trial of early-intervention TENS for the reduction of the prevalence and severity of chronic neuropathic pain during the first year after spinal cord injury (SCI)

2) **Objectives***

The primary objectives of our site-specific project are to test a non-invasive, non-pharmacologic, inexpensive intervention (i.e., transcutaneous electrical nerve stimulation; TENS) to prevent the development and reduce the severity of chronic neuropathic pain in the first year post-spinal cord injury (SCI) (Aim 1), and to increase the understanding of the time-course of the development of chronic neuropathic pain and the factors that increase the risk for neuropathic pain onset or worsening by longitudinally tracking pain symptoms, somatosensory function, and key injury-related and psychosocial factors during the first 12 months post-SCI (Aim 2).

Aim 1: *Assess the effectiveness of preemptive/early-intervention TENS therapy to decrease the risk of developing chronic neuropathic pain, and to reduce the severity of neuropathic pain, following SCI.*

Hypothesis 1a: Enhanced somatosensory stimulation using TENS within preserved dermatomes at or above the neurological level of injury will reduce the prevalence and severity of chronic neuropathic pain at 12 months post-injury when compared with neuropathic pain in those who receive Sham TENS.

Hypothesis 1b: Subjects for whom TENS effectively reduces evoked pain sensations (i.e., increased pain thresholds and/or decreased ratings of perceived intensity of noxious suprathreshold stimuli) at, and including three levels below, the level of injury after an 8-week TENS treatment protocol will be less likely to report chronic neuropathic pain

symptoms at 12 months post-injury than subjects for whom TENS does not reduce evoked pain sensations.

Aim 2: *Evaluate demographic, psychological, and physiological characteristics that are potential risk factors for the development and severity of chronic neuropathic pain at 12 months post-injury.*

Hypothesis 2a (Demographic predictors): Increased age and Hispanic/Latino background will be positively associated with increased presence and severity of chronic neuropathic pain at 12 months post-injury.

Hypothesis 2b (Psychological predictors): Greater levels of pain catastrophizing and depressive symptoms, and lower levels of resilience measured at baseline will be positively associated with increased presence and severity of chronic neuropathic pain at 12 months post-injury.

Hypothesis 2c (Physiological predictors): Sensitivity to evoked pain in the dermatomes at, and including the three levels below, the LOI after SCI will be associated with the presence and severity of chronic neuropathic pain at 12 months post-injury.

Completion of the aims outlined above will advance knowledge regarding the potential of a non-invasive, non-pharmacologic, inexpensive therapy (i.e., TENS) for the prevention or reduction of chronic neuropathic pain after SCI, and will lead to a greater understanding of the factors linked to chronic pain after SCI. This information has the potential to directly impact individuals with SCI by reducing pain and thus improving long-term outcomes and quality of life.

3) **Background***

In order to orient the reader, a brief introduction to the topic of pain is presented first, along with definitions and explanations of some of the terminology used throughout (**Box 1**).

Box 1: Pain definitions and notes

- Allodynia: pain due to a stimulus that does not normally provoke pain. Allodynia involves a change in the quality of a sensation – the original modality (e.g., tactile, thermal) is normally nonpainful, but is now evoking a sensation of pain.
- Dorsal column-medial lemniscus system (DC-MLS): the major ascending pathway for information about innocuous tactile/mechanical and proprioceptive stimulation. Information from Aβ fibers (which are activated by vibratory or pressure stimuli) in the periphery travel to the dorsal region of the spinal cord and ascend to the brainstem, thalamus, and cortex via the DC-MLS.
- Hyperalgesia: increased pain from a stimulus that normally provokes pain. Hyperalgesia does not involve a change in quality of a sensation, but, instead involves a heightened sensation of pain from a stimulus that typically evokes a less painful sensation.
- Neuropathic pain: pain caused by a lesion or disease of the somatosensory nervous system; typified by "burning," and "electric" spontaneous pain, and may include allodynic or hyperalgesic responsiveness
- Nociceptive pain: pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
- Spinothalamic tract (STT): the major ascending pathway for information about pain and temperature. Information from Aδ and C fibers (which are activated by noxious stimuli) in the periphery travel to an anterior region of the spinal cord and ascend to brainstem, thalamus, and cortex via the spinothalamic tract.

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." [1] *Acute pain* is time-limited by the inciting injury or disease and serves a protective function, while *chronic pain* is a persistent pain experience that outlasts the inciting injury and is thought to have limited biologic utility.[2] In some studies "chronic pain" is defined as pain persisting for at least three months, and in other studies is defined as pain persisting for at least six months. For the purpose of this proposal, we operationally define chronic neuropathic pain as neuropathic pain that has persisted for three months or more.

Pain taxonomies typically differentiate between two main types of pain: nociceptive and neuropathic. *Nociceptive pain* is pain that occurs in the intact nervous system and arises from normal activation of nociceptors, while *neuropathic pain* is defined as pain due to a nerve lesion. Neuropathic pain symptoms feature spontaneous pain (pain without stimulation) that is frequently described as burning, pricking, or electric-shock-like[3] and that occurs in an area affected by a lesion of the somatosensory nervous system which results in negative (i.e.,

increased thresholds to tactile or thermal stimuli) and/or positive sensory signs (i.e., allodynia or hyperalgesia)[4] (See Box 1 for definitions.). In those with traumatic SCI, a lesion of the nervous system is present that can affect the spinothalamic tract (STT) and/or the dorsal column-medial lemniscus system (DC-MLS). Lesions to the somatosensory system can be investigated using quantitative sensory testing, to assess DC-MLS dysfunction (responses to innocuous tactile stimuli) and STT dysfunction (responses to thermal or noxious stimuli). It has been suggested that a better understanding of the impact of SCI on these pathways and the interactions between them may be key to understanding risk factors for neuropathic pain after SCI. [5-8]

Significance of the problem

Chronic pain is one of the most common and debilitating long-term secondary consequences of SCI, [9-12] with approximately 70% of injured individuals reporting persistent neuropathic and/or nociceptive pain that can worsen over the months and years after injury.[13-16] Chronic pain significantly contributes to increased psychological distress and decreased participation in rehabilitation programs, social activities, and employment.[13, 17-20]

While the mechanisms for many nociceptive pain syndromes are often straight-forward, the mechanisms involved in neuropathic pain associated with SCI are less well characterized, at least partly contributing to the paucity of effective treatment options for this type of pain.[3] *Because chronic neuropathic pain has been reported to occur in approximately 50% to 75% of individuals with SCI,[5, 21, 22] is associated with significant impairment in quality of life, [23] and its presence and severity typically do not decrease with time or pharmacologic treatment,[15, 16, 24-26] neuropathic pain represents a significant problem that deserves further study in order to provide new, more effective interventions.*

Background and rationale

Early intervention with TENS may help prevent the development of neuropathic pain. (Aim 1)

TENS has been used for the treatment of acute and chronic musculoskeletal pain conditions for decades, but evidence supporting its use for treating neuropathic pain is relatively recent.[3, 27] Two types of TENS have traditionally been used: high frequency (typically > 50Hz), low intensity (below motor contraction and pain threshold) TENS, and low frequency (< 10Hz), high intensity (may produce motor contractions but is below pain threshold) TENS. Both types have

been shown to be effective for reducing some types of pain, but the mechanisms by which they exert their effects partly differ.[28] Evidence suggests that high frequency, low intensity TENS works primarily via activation of Aβ fibers, producing an inhibitory effect on nociceptive fiber-evoked responses within the dorsal column – medial lemniscal system (DC-MLS) (i.e., via "Gate control" mechanisms in the spinal cord[29]), but also via supra-spinal descending inhibitory mechanisms. [28, 30] Low frequency, high intensity TENS is often referred to as "acupuncture-like" TENS and has been associated primarily with activation of Aδ and C fibers within the spinothalamic tract (STT) resulting in supra-spinal descending inhibition of pain,[31] including via opioidergic mechanisms.[32] (In the proposed trial, we will use both low- and high-frequency TENS stimulation within a treatment session to engage these multiple mechanisms of pain inhibition.)

Despite survey studies indicating that the majority of individuals with SCI and pain have tried non-pharmacologic interventions, including TENS, [25, 26, 33, 34] few clinical trials have tested the effectiveness of TENS for diagnosed neuropathic pain specifically in persons with SCI. [35, 36] Celik et al. reported significant decreases in neuropathic pain after a 10-day trial of low-frequency, high intensity TENS in 33 participants[36] while a study by Norrbrink did not find significant decreases after two weeks of either high frequency, low intensity or low frequency, high intensity TENS in 24 people (although 25% of subjects requested to continue TENS treatment after the study was concluded).[35] The greater effectiveness of TENS in the Celik et al. study[36] may be related to the fact that subjects were more recently injured (2 to 27 months post-SCI) than were those in the Norrbrink study[35] (average of 6.8 years post-SCI).

Evidence from trials of TENS as a preventative therapy for pain in other patient populations supports the idea that early-intervention may be an effective approach to hinder the potentially irreversible changes in the nociceptive system that occur during the first few months after a SCI. Several studies have shown that intra- or post-operative TENS can reduce the severity of post-surgical pain when compared to placebo.[37-39] With regards to neuropathic pain, a recent study using TENS treatment initiated during acute herpes zoster, suggested that TENS may prevent later development of painful post-herpetic neuralgia. [40] *Because neuropathic pain associated with SCI often does not develop until at least a few months after the injury, [5, 15] there is a window of opportunity to prevent the acute hyperactivity of spinal nerves believed to be partially*

responsible for central sensitization associated with the onset and maintenance of chronic neuropathic pain.[41, 42]

Animal studies provide evidence for the potential beneficial effects of early-intervention TENS: The same neurochemicals that are dysregulated after SCI-induced neuropathic pain can be returned to normal levels with TENS treatment. Allodynic and hyperalgesic responses in rodent models have been associated with decreased GABAergic[43] and serotonergic function,[44] and increased glutamate[45] and pro-inflammatory cytokines after SCI.[46] Changes in the opposite direction in levels of these same nociceptive mediators have been shown to occur with TENS therapy[27]: TENS has been shown to increase GABA, [47] serotonin, [48] and blood-flow and rate of healing after surgical incision,[49] and to decrease glutamate in the dorsal horn[50] and inflammatory cytokines in the area of injury.[49] Additionally, in an animal model of neuropathic pain due to sciatic nerve injury, TENS delivered soon after injury was able to decrease the incidence of pain-like behaviors, [47, 51, 52] and to maintain levels of proinflammatory cytokines and opioid receptors to those comparable to uninjured animals.[52] *These findings suggest that TENS can be used to decrease the central barrage of injury-induced nociceptive hyperactivity, via peripheral and central mechanisms, thus potentially preventing the central sensitization that results in chronic neuropathic pain after SCI.*

It has recently been suggested that early, preemptive treatment using gabapentin or selective serotonin re-uptake inhibitors should be undertaken in patients with SCI to reduce neuronal hyperexcitability and neuropathic pain.[5] *TENS, however, provides a less expensive, non-invasive treatment with a better side-effect profile and fewer contraindications than these pharmacologic agents, and a clinical trial of TENS during the pre-chronic phase of SCI is warranted based on its ability to mediate endogenous substances linked to spontaneous and evoked activity within SCI-affected nociceptive pathways, and to increase activation in brain areas associated with descending pain-inhibitory pathways.*[53]

Demographic, psychological, and physiological factors that may help identify those at risk for developing neuropathic pain (Aim 2)

The investigation of whether particular subgroups of people with SCI are more at-risk for developing neuropathic pain can guide resource allocation, and the longitudinal assessment of

covariation among psychological, physiological, and pain characteristics after SCI will provide needed information with regard to optimal time points for preventive treatment.

Age, and Race as risk factors for neuropathic pain (Demographic risk factors)

Increasing age and minority status have generally been found to increase the presence and severity of various chronic pain conditions.[54, 55] Support for a relationship between older age and chronic pain status in those with SCI has also been reported, [56] but whether this age-pain relationship differs depending on the type of chronic pain (neuropathic or nociceptive) has received little attention. Similarly, differences in pain severity between Whites/Caucasians with SCI and non-White patients with SCI have been documented,[57, 58] but whether race influences the presence and severity specifically of neuropathic pain after SCI is not clear. Additionally, because of imbalanced frequencies of subjects across different racial and ethnic groups, these studies have simply compared Whites to non-Whites, pooling all minority groups together as though they were one homogenous group. The diversity of the South Florida community allows for a relatively more balanced representation of persons with SCI across minority and non-minority groups (i.e., 37% Black/African American; 34% Hispanic; 53% White, in our previous spinal cord injury subject samples). Thus, comparison among minority groups will be possible. Indeed, results from our center (see "Preliminary data," below) suggest greater rates of the *presence of chronic nociceptive pain in Black/African Americans*, and *greater rates of the presence of chronic neuropathic pain in persons with a Latino or Hispanic background*.[59]

Pain catastrophizing, depressive symptoms, and low resilience as risk factors for neuropathic pain (Psychological risk factors):

Because pain is defined as a "sensory and *emotional* experience," [1] it is not surprising that psychosocial factors, including pain coping style, depression, and resilience characteristics, have been linked to pain intensity and impact.[60-67] Some studies have looked at these factors and their relationship to pain specifically in persons with SCI,[8, 68] but: 1) whether these psychological factors predict pain development and severity *differentially* for neuropathic pain and nociceptive pain after SCI; and 2) the covariance of these factors with specific types of pain (neuropathic, nociceptive) *across time* during the first year after SCI have not been well documented in SCI. Thus, we will collect assessments of depression, pain catastrophizing, and resilience at baseline

to determine their predictive ability for the presence and severity of neuropathic pain at 12 months post-injury (Hypothesis 2b). In addition, we will also collect these assessments at three other time points (approximately 4-6 months and 12 months post-injury), in order to explore the time-course of changes in these variables and their interrelationships with pain during the first year post-injury.

STT and DC-MLS dysfunction as risk factors for neuropathic pain (Physiologic risk factors):

Investigations examining the relationship between the presence of chronic neuropathic pain and injury severity (i.e., complete vs. incomplete) [15, 21, 69-71] or radiologic evidence of the extent of damage to the spinal cord[72] have generally reported negative findings. These investigations were unable to link severity or location of the spinal cord lesion to neuropathic pain, suggesting that these factors are only marginally related to the presence of neuropathic pain, or that these measurement tools are *too crude* to reveal an association.

Several studies have used more sensitive quantitative sensory testing (QST) techniques to identify the potential contributions of STT and DC-MLS damage to the presence and severity of chronic neuropathic pain after SCI.[6-8, 69, 73-76] Although results across these studies seem to suggest that lower levels of impairment within the STT are linked to increased severity of neuropathic pain,[6, 7, 74] the cross-sectional nature of the data does not provide insight with regards to whether STT dysfunction is the cause, or result, of chronic neuropathic pain after SCI.

A few recent studies have approached this question by investigating longitudinal changes in somatosensory function and pain after SCI.[5, 21, 42, 76] Of these studies, only one has used QST techniques to track STT and DC-MLS function across time after SCI in 30 subjects,[42] while the others utilized less sensitive bedside sensory exams.[5, 21, 76] Although details of the results from these studies differ, overall findings generally point to early post-injury sensitivity to evoked pain (pin prick or cool stimulus) as a predictor for the later development of neuropathic pain,[5, 21, 42, 76] though the QST study additionally reported a relationship between higher thermal detection thresholds (i.e., *decreased* sensitivity to detecting non-painful changes in temperature) and development of neuropathic pain.[42]

Thus, by undertaking the proposed study, we will substantially advance the 'state of the art' by evaluating the contribution of STT function and DC-MLS function to neuropathic pain via

prospective, longitudinal tracking, using sensitive measurement techniques (QST) in a large sample (n = 98) of subjects with SCI.

Greater knowledge regarding the factors that increase the risk for neuropathic pain after SCI will assist with identifying patients to target with early intervention and increased clinical monitoring of neuropathic pain. Implementing preemptive strategies, particularly those with little or no contraindications and side effects, such as will be examined in the proposed project (TENS), will be particularly important for those at risk for chronic neuropathic pain.

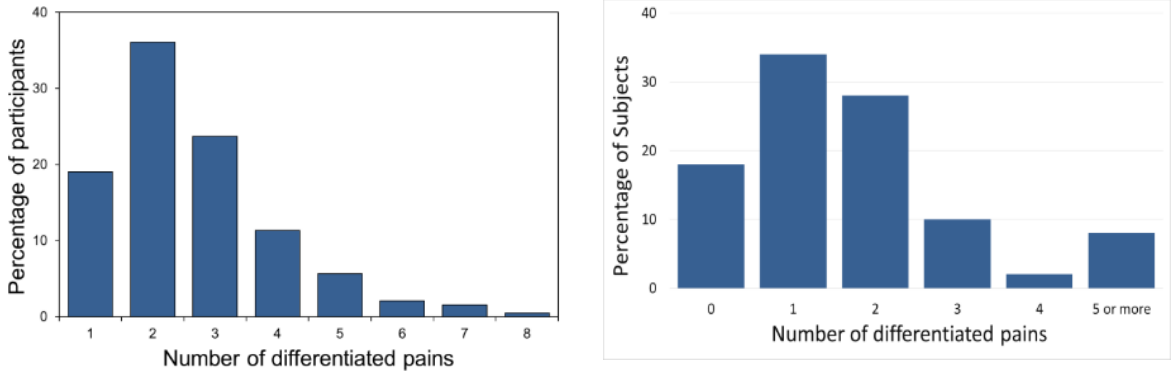
Preliminary data

Previous work by the PI and Co-investigators supports the feasibility of the project with regards to subject recruitment, study personnel training and expertise, and methodologies to be used.

Neuropathic pain characteristics and diagnosis in persons with SCI: Evaluation of pain characteristics in persons with chronic SCI and pain by investigators in our group has shown that: 1) persons with SCI can differentiate between pain types (i.e., nociceptive pain and neuropathic pain) that they experience, and that the majority of those with chronic pain report having more than one pain (that varies based on location, sensory quality, and/or temporal pattern) [**Figure 1**]; 2) neuropathic pains tend to be more bothersome than non-neuropathic pain types (for those who have more than one pain) [**Figure 2**]; and 3) minority status may be related to the prevalence of different pain types [**Figure 3**].

Figure 1: The majority of subjects with traumatic SCI and pain report having *at least* two different chronic pain conditions.

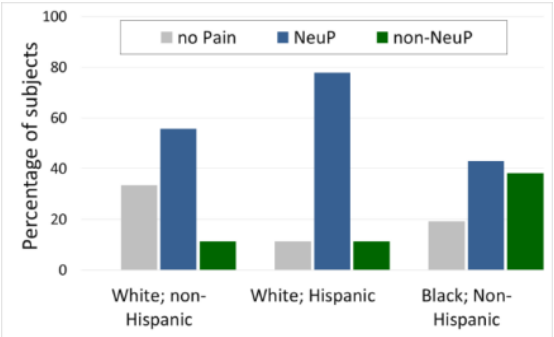
(a) **(b)**



(a) Results based on in-person interviews with 194 subjects with chronic traumatic SCI (at least 1 year

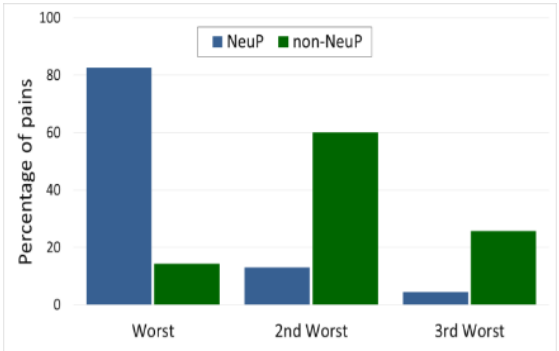
post-injury) and chronic pain (at least 6 months post duration).[77] **(b)** Results based on phone interviews with 50 chronic traumatic SCI patients.[59]

Figure 2: Persons with Hispanic/Latino background reported more neuropathic pains, while Black/African Americans reported more nociceptive pains.



Results from 50 people with chronic SCI (white, non-Hispanic = 9; white, Hispanic = 18; black, non-Hispanic = 21) who completed a phone survey using screening tools for neuropathic pain (SCIPI, ISCIPBDS).[59]

Figure 3: Persons with SCI and pain identify neuropathic pains as worse than non-neuropathic pains.



Data is from 29 subjects with chronic traumatic SCI who differentiated at least 2 pains. Neuropathic pain was more likely to be labeled as their worst pain than non-neuropathic pain ($p < 0.05$).[59]

We have recently presented data[59] from a phone survey in people with chronic traumatic SCI (between 1 and 4 years post-injury) in which we used the International Spinal Cord Injury Pain Basic Dataset, version 2.0 (ISCIPBDS2), which was developed by a team headed by Dr. Widerström-Noga,[78, 79] and the Spinal Cord Injury Pain Inventory (SCIPI[80]), to identify pains that were likely to be neuropathic in nature. Of the 50 subjects interviewed, 41 (82%) reported having a persistent pain problem (at least 3 months in duration), and for 30 (60%) respondents, at least one of their pains was identified as neuropathic (based on location of the pain at- or below-the neurologically-determined level-of-injury and a SCIPI score of ≥ 2). This percentage is similar to a recent prospective study in the literature which found 59% of its participants had neuropathic pain at one year post-SCI.[21]

Relationships between Neuropathic pain and somatosensory function (quantitative sensory testing; QST)

We have utilized a number of psychophysical techniques to investigate the association between both DC-MLS- and STT-mediated function and the severity of chronic Neuropathic pain after SCI. We have shown (**Table 1**) that the test-retest reliability of threshold measures across most somatosensory submodalities in subjects

with SCI is substantial, and comparable, or superior to, the reliability of these measures in nondisabled control subjects. Hot and cold pain thresholds are more variable over time, but are still significantly related. Thus, these measures are appropriate for assessing changes in sensory function across time, as proposed in this application. Several publications from our studies have linked heightened evoked pain sensitivity at- and below-the LOI (as measured with QST techniques including pain thresholds) and greater severity of chronic neuropathic pain symptoms, in participants with chronic SCI.[6, 8, 74,] **Figure 4** shows that, in test sites in body areas where neuropathic pain symptoms were present, lower pain thresholds (i.e., increased pain sensitivity) were associated with more severe neuropathic pain scores.

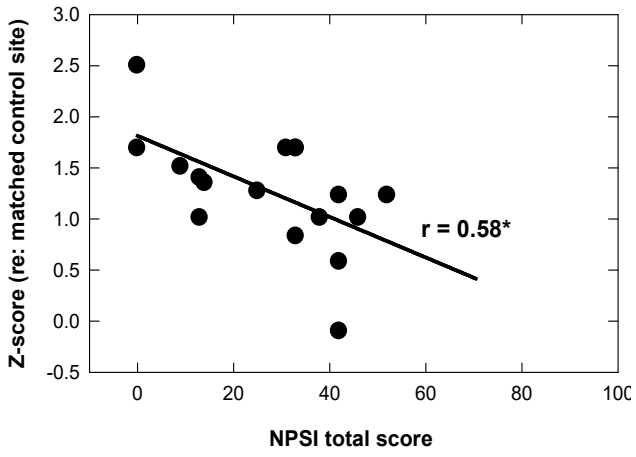
Table 1: Test-retest reliability for thresholds in persons with SCI and NeuP compared to thresholds in nondisabled control subjects

Modality	SCI		Nondisabled	
	ICC (95% CI)	# total test sites	ICC (95% CI)	# total test sites
Log MDT	0.84 (0.75-0.90)	56	0.63 (0.45-0.76)	58
Log VDT	0.90 (0.84-0.94)	67	0.86 (0.79-0.91)	80
Log CDT	0.90 (0.83-0.94)	55	0.68 (0.54-0.78)	80
Log WDT	0.95 (0.91-0.97)	50	0.70 (0.57-0.80)	79
CPT	0.50 (0.28-0.67)	56	0.49 (0.31-0.64)	80
HPT	0.50 (0.28-0.66)	62	0.68 (0.55-0.79)	79

MDT = mechanical detection threshold; VDT = vibration detection threshold; CDT = cool detection threshold; WDT = warm detection threshold; CPT = cold pain threshold; HPT = hot pain threshold

Thus, previous work by the study investigators demonstrates that the study is feasible and that they have the skills and tools necessary to perform the proposed study. Results from this body of work support the rationale of the proposed site-specific study.

Figure 4: Pain threshold is negatively related to severity of NeuP in those with SCI



Subjects with SCI and NeuP (n = 22) completed sensory testing at sites within the area affected by NeuP. Thresholds were also obtained in control subjects at the same test sites on the body and used to calculate z-scores for the thresholds obtained in those with SCI. Subjects with less loss of pain sensation (z-scores close to 0) had significantly higher NPSI scores than those with greater loss of pain sensation (higher z-scores).[74] (Z-scores reflect the degree to which thresholds in participants with SCI vary from the distribution of thresholds obtained in nondisabled control subjects, and allow for comparison of measures obtained at different locations on the body.)

4) Inclusion and Exclusion Criteria*

Inclusion criteria:

- Age ≥ 18;
- Traumatic spinal cord injury;
- Date of injury occurring within four months of study enrollment.

Exclusion criteria:

- More than four months since date of injury;
- Contraindications for the study intervention, transcutaneous electrical nerve stimulation (TENS),[88] including:
    - Implanted electronic device such as a pacemaker;
    - Cardiovascular problems;
    - Pregnancy;
    - Epilepsy;
    - Cancer;
- Persons with a spinal cord injury at the C2 level, as placement of TENS electrodes on the neck is not recommended;
- Cognitive dysfunction which limits the ability of the participant to adequately understand procedures and risks.
- Prisoners

- Pregnant Women

Special populations:

- Adults unable to consent: excluded from study
- Individuals -who are not yet adults: individuals who are less than 18 years old will be excluded from the study
- Pregnant women: Women who are known to be pregnant will not be recruited into the study. A pregnancy test will be administered to females prior to enrollment in TENS (or sham) treatment. Women who become pregnant before or during the 8-week TENS treatment period will be discontinued from the study. Women who become pregnant after the 8-week TENS treatment portion of the study will continue to be enrolled, and followed according to protocol guidelines (no information will be collected specifically on the pregnancy or fetus).
- Prisoners: excluded from study
- Neonates: not applicable

5) Number of Subjects*

This is a single-site study and 98 potential participants with newly-acquired spinal cord injuries will be enrolled. See section 22, for more information.

6) Study-Wide Recruitment Methods*

This is not a multi-center study. See section 21.

7) Study Timelines*

It is anticipated that subjects will be enrolled in the study for 12 months (see **Figure 5**, in section 10, below, for procedures timeline).

It is anticipated that enrollment of subjects will occur between November 1, 2016 and January 1, 2022. This enrollment end date is 12-months prior to the end of the funding cycle for this grant, which will allow for complete follow-up of all subjects before study termination.

The estimated date for the investigators to complete this study is October, 2022.

8) Study Endpoints*

The primary study endpoints/outcomes are: 1.) the percentage of subjects who develop chronic neuropathic pain at the 12-month post-spinal cord injury time point (as defined by a score of ≥2 on the Spinal Cord Injury Pain Inventory (SCIPI), a self-report scale of symptoms); and 2.) the severity of chronic neuropathic pain (as measured by a self-report rating of neuropathic pain symptoms) measured at the 12-month post-spinal cord injury time point. The secondary study endpoints/outcomes include other aspects of pain symptoms and physical and emotional function. All outcomes and other variables are listed in **Table 2** and described in detail below, within the "Procedures Involved" section.

Safety endpoints include frequency and severity of adverse events and increased likelihood of developing chronic pain due to TENS treatment. Please see section 13: "Provisions to monitor the data to ensure the safety of subjects," describes the monitoring of the safety endpoints.

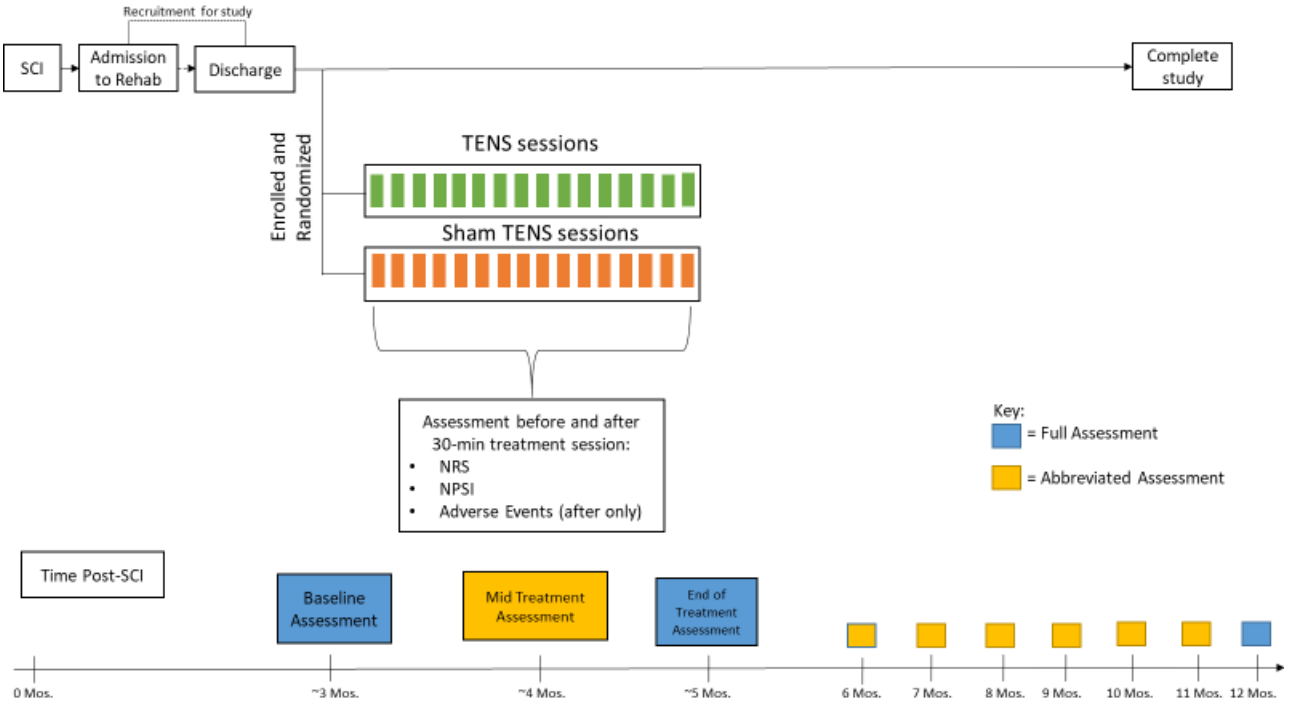
9) Procedures Involved*

Overview:

The primary study design will be a randomized, double-blinded, controlled trial of early intervention TENS compared to Sham TENS, with longitudinal tracking of signs and symptoms of NeuP, as well as symptoms and severity of non-neuropathic pains, pain impact, and psychological function, for 12 months post-SCI. **Figure 5** diagrams the study procedures, subject flow, and assessment time points.

Patients will be eligible for recruitment into the study as soon as they have been admitted to the SCI inpatient rehabilitation unit at UM/JMH/Lynn Rehabilitation Center (see Section 21 for full recruitment procedures). Treatment TENS or Sham TENS sessions (see "Randomization procedures," below) will be initiated within four months post-injury (with four weeks post-injury as the target, if feasible).

Figure 5: Timeline of subject participation and study procedures



* Note the above diagram depicts the anticipated average time course of study procedures across subjects. Due to varying times between injury and admission to/discharge from inpatient SCI rehabilitation, not all subjects will begin participation in the study precisely at the two-month post-injury timepoint.

Subjects will be enrolled and randomized regardless of whether they have NeuP symptoms at initial assessment. Because approximately 25% of SCI patients who report chronic neuropathic pain at 1 year post-injury had initial neuropathic pain symptoms at 1 month post- injury, [21] initiating treatment at four weeks post-injury will capture approximately 75% of patients before their neuropathic pain symptoms manifest. In those patients who do have neuropathic pain symptoms at the baseline assessment, we will be able to test the ability of TENS to interfere with the transition from acute to chronic neuropathic pain, by comparing the decrease in severity of neuropathic pain symptoms from baseline to 12 months post-injury between the two study groups (Treatment TENS vs Sham TENS).

Once baseline assessments are completed, treatment will be administered twice a week, for 30 minutes each session, for 8 weeks.

Assessments of primary and secondary outcome measures will occur at the time points

diagramed in **Figure 5**. Details regarding the specific assessment tools and measures to be used are described below and listed in **Table 2**. The primary outcome variables for Aim 1 (Spinal Cord Injury Pain Instrument (SCIPI)[80] score of ≥ 2, and Neuropathic Pain Symptom Inventory score[89]) will be collected during each scheduled assessment (full and abbreviated assessments), with additional outcome measures recorded less frequently (during full assessment sessions only: 4 times during the study).

Randomization and blinding procedures:

A blocked randomization procedure will be used, so that for each eight patients enrolled, four will be allocated to TENS and four to Sham TENS. A computer-generated random assignment sequence will only be accessible to the study staff member responsible for delivering TENS treatments. The PI of the study, the researchers evaluating pain diagnoses, and the research subject will not be informed of the treatment allocation assigned. All subjects will be told that they may or may not feel the stimulation from the TENS unit during treatment sessions due to the parameters of the study. The stimulation parameters of the TENS unit will not be visible to the subject, so that subjects will not obviously know to which study group they were randomized.

Treatment procedures:

(a) *TENS device:* The TENS 7000 Dual Channel battery-powered digital stimulator (Roscoe Medical, Ohio, USA) will be used. This device provides for adjustable frequency/pulse rate, pulse width, and amplitude, as well as recording of session data (settings and duration of treatment session). The TENS 7000 device has two channels. Each channel will be connected to two self-stick square electrodes (thus, a total of 4 electrode pads will be used) with dimensions of 2 inches by 2 inches. New electrode pads will be used for each treatment session.

(b) *TENS parameters:* A combination of high frequency stimulation (postulated to induce activity in Aß fibers and related DC-MLS pathways which can block pain via the Gate Control)[28, 30, 90] and low frequency stimulation (postulated to activate Aδ fibers, and associated STT pathways, resulting in supraspinal descending modulation of pain[28, 31]) will be used. Combinations of high and low frequency TENS has been suggested to obtain optimal benefit for neuropathic pain.[47] Based on Celik et al.[36] and Norrbrink et al.,[35] who performed TENS in persons with chronic SCI and chronic neuropathic pain, we have set the following stimulation

parameters for high frequency TENS: 80Hz pulse frequency, 200μsec pulse duration; and for low frequency TENS: 4Hz pulse frequency, 200μsec pulse duration. Slight adjustments to frequency and pulse duration may be made based on subject preference or new information from the literature. Subjects will receive 15 mins of high frequency TENS immediately followed by 15 mins of low frequency TENS, for a total of 30 minutes of TENS during each treatment session. The starting frequency (high or low) will be randomized for the first session, and then the order will be alternated with each subsequent session.

Intensity of stimulation will be set for each subject in the TENS group based on individualized perceptual level, so that the amplitude is above perception threshold and just below pain threshold, as this dose of stimulation amplitude is often effective and has been recommended.[91] Amplitude level will be adjusted at the beginning of low frequency TENS stimulation and again at the beginning of high frequency TENS for each session based on individual sensitivity, to account for potential adaptation effects across sessions. These parameter values will be recorded for use as possible covariates in statistical analyses. Each stimulation session will last for 30 minutes, as has been previously used for TENS in SCI patients,[35, 36] and as has been recommended by Bennett et al.[91]

(c) Electrode placement: Surface electrodes are typically placed in the area overlapping the pain. However, because persons with SCI may have reduced or absent sensory function in these areas due to their injury, and, because the goal of the study is to *prevent* pain (i.e., the majority of our subjects will not have developed any area of neuropathic pain when they are initially enrolled in the study) we will place electrodes according to neurological level of injury, so that the location of all electrodes fall within the dermatome of the level of injury or the dermatome just above the level of injury, as described in Norrbrink's study,[35] in order for stimulation to occur in a location where normal sensation is present.[88] Two electrodes from one channel will be placed paraspinally at the level of injury. The other channel's two electrodes will be placed at distal aspects within the same dermatome (at the level of injury) except for subjects who do not have appropriate skin locations available (e.g., due to presence of skin lesions/damage, or levels of injury with limited accessible skin surface area). Both stimulation channels will be set with the same stimulation parameters. If adjustments are needed to positioning of the electrodes outside of the prescribed area (at the level of injury or one dermatome above the level of injury), consideration of best placement will be discussed among the research and clinical study team on

a case-by case basis.

(d) *Sham TENS parameters:* Electrode placement for subjects randomized to Sham TENS will be based on their level of injury as described above for those in the TENS group. At the beginning of each session, the stimulus will be turned up until the subject just reports sensation (as with the TENS group), but then will be adjusted down so that no electrical stimulus is delivered.

Data collected / Assessments performed:

(a) Assessment procedures: **Table 2** lists measures that will be collected during full and abbreviated assessments, as well as before and after each TENS session. Full assessment sessions will occur at three time points: baseline (prior to treatment initiation); termination of the 8-week treatment protocol; and 12 months post-injury. The full assessment protocol will require approximately 180 minutes to complete and may be completed in multiple sessions due to participant availability. An abbreviated assessment protocol will be administered at the 4-week treatment time point (i.e., halfway through the full series of treatment sessions), and over the phone each month after treatment has ended, until the 12-month post-injury time point. The abbreviate assessment will require 30 minutes to complete. In addition, numerical ratings of pain and the Neuropathic Pain Symptom Inventory[89] will be assessed before and immediately after each 30-minute TENS session. (It is expected that, for most patients, pain ratings will be "0," as many will not have developed neuropathic pain symptoms in the first few months after injury when TENS is being administered. Collection of this information is important in order to insure that TENS is not related to any increase in pain symptoms during treatment.) Adverse events/ side effects will also be captured at the end of each TENS session. The assessment schedule is depicted by the blue and yellow boxes at the bottom of **Figure 5**.

Table 2: List of assessment tools to be used

Assessment domain	Assessment	Full assessment	Abbreviated assessment	Treatment sessions
Pain classification	SCIPI, and ISCIPBDS2	X	X	
Pain intensity and symptoms	NRS for pain	X	X	X
	ISCIPBDS2	X	X	

	ISCIPEDS ["pain symptoms" subset]	X		
	NPSI	X	X	X
	sf-MPQ-2	X		
Maladaptive pain coping	PCS	X		
Sensory function	ASIA sensory scores*	X		
	QST	X		
Emotional function	PHQ-9*	X	X	
	SCI-QOL Resilience scale – short form *	X	X	
Treatments	Frequency, dose, effectiveness (from ISCIPEDS)	X	X	
Adverse events	Incidence and severity			X
Time required (minutes)		120	30	5

* measures/assessments that overlap with national database Form I/II
** assessments that will only be carried out at 12-months post-injury

(b) *Assessment tools: C*opies of all instruments to be used are uploaded within the eProst UM-IRB application for this study.

i. Pain classification:

- The Spinal Cord Injury Pain Instrument (SCIPI)[80] will be used to identify pains that are likely to be neuropathic in nature. This four-item questionnaire has shown sensitivity and specificity of 78% and 73%, respectively, for diagnosing neuropathic pain when using a cutoff score of ≥ 2 on this scale.[80] The pain classification definitions and guideline presented within the International SCI Pain Basic Data Set 2 (ISCIPBDS2) will also be used to assist with classification of pain type.
  This assessment will be used as the primary outcome measure for Aim 1, indicating the presence or absence of neuropathic pain at each follow-up time point.

ii. Pain intensity and symptoms:

Based on differentiated pains, as reported by the study subject, the intensity of each pain will be rated using a 0 – 10 numerical rating scale (NRS), with 0 being equal to "no pain" and 10 being equivalent to "pain as bad as you can imagine." Subjects will be asked to "Rate your pain by indicating the number that best describes your pain on average over the past 24 hours," "over the past week," and "over the past 3 months."

This scale, including the phrasing of the anchors and the recall time points, has been suggested as a primary
endpoint for chronic pain clinical trials.[92] *Changes in pain intensity for neuropathic pains will be calculated across the assessment time points to measure the effectiveness of TENS treatment for those who present with neuropathic pain at baseline [Aim 1], and to assess correlations among pain severity and demographic and psychological factors [Aim 2].*

- We will use the components of the International SCI Pain Basic Data Set, version 2.0 (ISCIPBDS2),[79] to record the presence of pain, the interference of pain on activities of daily living, mood, and sleep, locations of pains, intensity of pain, the onset of the pain condition, and whether treatments are currently being used for the pain condition. The guidelines provided in the ISCIPBDS2 regarding diagnosis of pain will be used to classify each pain condition a subject reports. For each research subject at each full assessment session (baseline, end of treatment, and 12 months post-injury), two experienced SCI pain researchers (Drs. Felix and Widerström-Noga) will evaluate the characteristics of each pain a subject has to make a determination of diagnosis. These characteristics will be taken from the ISCIPBDS2 and the International SCIPEDS questions and other assessments regarding pain characteristics (e.g., location relative to LOI, quality of pain) and sensory testing results (see "Quantitative Sensory Testing" section, below). If the two assessors differ with regard to diagnosis, review of data and evaluations will be discussed by the assessors and consensus will be reached. *These pain classifications will be used to compare with NeuP classification identified by a SCIPI score of ≥2, and to evaluate relationships between different pain types and other variables measured [Aims 2].*
- We will use selected components from the newly-published International SCI Pain Extended Data Set (ISCIPEDS),[93] to record temporal characteristics of the pain ("How long does your pain usually last?", and "When during the day is the pain most intense?"), as well as treatments the subject is using for pain ("treatments" section of the ISCI Pain Extended Data Set). For each treatment the subject can respond with regard to whether he/she is currently using the treatment, how often, the dose, and adverse effects, and his/her global impression of change[94] *Responses to the treatment*

section will be used as a supplemental assessment of pain severity [92][Aim 1]. Lower doses of pain treatments suggest lower pain severity, while higher doses suggest a greater need for pain relief/ higher pain severity.

- The Neuropathic Pain Symptom Inventory (NPSI)[89] will be used to quantify the severity of neuropathic pain-specific characteristics. This questionnaire has been validated and used in a number of patient populations with various neuropathic pain conditions[89, 95-98] including those with SCI.[8, 74] A total NPSI score will be calculated as an indication of the severity of neuropathic pain.[89] This questionnaire should be distinguished from the SCIPI, which is also used for neuropathic pain, but is intended as a dichotomous *diagnostic screening tool* for neuropathic pain in SCI, whereas the NPSI is intended as an ordinal *measure of neuropathic pain severity*. *For those subjects with neuropathic pain symptoms at entry into the study, the NPSI total score will be used to determine whether a reduction in neuropathic pain severity is present after TENS treatment, and during longitudinal follow-up [Aim 1]. This measure will also be used to examine associations between neuropathic pain severity and demographic and psychosocial factors [Aim 2].*
- We will also capture specific information about the presence and severity of different qualities of the pain experience for each pain location the subject describes using the short-form McGill Pain Questionnaire 2 (SF-MPQ2)[99] as secondary outcome measures of sensory and affective components of pain. The SF-MPQ2 is a revised version of the SF-MPQ[100] to include both qualities of pain associated with nociceptive pain types and those associated with neuropathic pain types. Desirable psychometric properties of the SF-MPQ2 have been documented in a number of pain patient populations.[99, 101-103] *Responses to specific pain qualities will assist with pain diagnosis, and total scores and subscale scores of "continuous pain," "intermittent pain," "neuropathic pain," and "affective descriptors" will be used in secondary analyses of TENS effectiveness [Aim 1] and relationships with other outcomes of interest [Aims 2].*

iii. Maladaptive pain coping:

- The Pain Catastrophizing Scale (PCS)[104] measures the degree to which individuals engage in a maladaptive pain coping style that is characterized by exaggerated and ruminating negative cognitions and emotions during painful situations. The PCS has demonstrated high validity and reliability.[105] *Measures obtained from the PCS will be used to prospectively track its potential as a pre-disposing factor for the development of chronic pain after SCI [Aim 2].*

iv. Sensory function:

- Quantitative sensory testing (QST) techniques will be used as reliable and sensitive measures of STT and SC-MLS function[74, 106, 107] in areas above, at, and below the neurological level of injury using a TSA-II device (Medoc, Ltd). Measures of vibratory, warm, and cool detection thresholds, hot and cold pain thresholds, and temporal summation of thermal pain will be recorded during full assessment sessions. *The longitudinal tracking of these measures will allow for the assessment of: 1) whether use of TENS early after injury that alters STT and/or DC-MLS function is related to the effectiveness of TENS on measures of chronic neuropathic pain at 12 months post-injury [Aim1];and 2) the predictability of chronic neuropathic pain based on specific somatosensory sensitivity measures* (i.e., thresholds to innocuous tactile and thermal stimuli; thresholds to noxious stimuli; pain ratings for suprathreshold pain stimuli) *[Aim 2].* These measures and device (TSA-II) have been previously used by our group to investigate associations between sensory function and chronic pain across cohorts of subjects with chronic SCI[7,8, 74, , 108] and have been used in many other chronic pain populations to examine mechanisms, diagnoses, and relationship to analgesic response.[109-111]
- A neurological examination utilizing the International Standards for Neurological Classification of Spinal Cord Injury[112] will be obtained from the medical record if available. The sensory/motor scores for each dermatome/myotome will be recorded, as well as the neurological level of injury and American Spinal Injury Association Impairment Scale. *These variables will be used as bedside assessments of sensory function for comparison with QST measures and for their potential predictive ability for the later development of chronic neuropathic pain [Aim 2].*

v. Emotional function:

- The Patient Health Questionnaire 9 (PHQ-9)[113] will be used to assess depression symptom severity. It is a 9-item questionnaire based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Revised (DSM-IVR)[114] criteria for major depression and that has been validated across a number of patient populations,[113, 115] including SCI.[116]
- The SCI –QOL Resilience scale has been developed and calibrated specifically for those with SCIs [117] and is included in follow-up interviews for the SCIMS national database. *This measure will be used for the assessment of resilience as a potential mediating factor for the development and trajectory of pain following SCI [Aim 2].*

vi. Medications:

- While it is not feasible to restrict medication usage throughout the participant's enrollment in a longitudinal study, recording of medications at baseline and changes in medications and dosages across time will be recorded at each study time point as suggested for pain clinical trials.[118] *Use of medications traditionally prescribed for analgesic purposes will serve as a secondary outcome measure for the presence and severity of pain[92] [Aim 1].*

vii. Adverse events:

- Information regarding side effects/ adverse events that are temporally related to the treatment protocol will be collected from all participants. A questionnaire will be administered after all treatment sessions to prompt subjects to report new or increased symptoms and discomfort experienced during the TENS stimulation period. If the subject reports any symptoms, he/she will be asked to indicate the duration of the symptom, the severity, and the associated distress.[92] These records will be used to address any potential safety concerns and compare the frequency and severity of events across Treatment TENS and Sham TENS groups.

10) **Data and Specimen Banking***

No specimens will be collected in this study. Data that is collected on paper will be stored securely in a locked cabinet in a locked office that is accessible only to study staff as described in

section 26: Confidentiality. Electronic data will be collected and stored on a secure server within the University of Miami network, with access limited only to those personnel listed on the IRB application for this study.

11) **Data Management***

Power / sample size:

Based on a total sample size of 98 subjects, and an estimated 15% drop-out rate, we expect that approximately 82 subjects will complete the study (i.e., 41 subjects per treatment arm). Based on previous work,[21, 59] we project that 60% of subjects in the Sham TENS (control) group will have at- or below-level neuropathic pain at the 12 month follow-up time point. Thus, with 41 subjects in each group, $\alpha = 0.05$, power of at least 80%, and an analysis based on a two-sided Z-test (for group difference in proportion of subjects with neuropathic pain) for *Hypothesis 1a*, we will be able to detect at least a 50% reduction in the rate of subjects with chronic neuropathic pain in the TENS treatment group compared to the Sham group at 12 months post-SCI (i.e., Sham TENS = 60% with neuropathic pain; Treatment TENS = 30% neuropathic pain).

For t-test analyses assessing differences between groups (Sham vs. Treatment) using continuous variables (e.g.,NRS, NPSI), 41 subjects in each group will allow for detection of a medium-to-large effect size (i.e., Cohen's $d = 0.6$) with α set at 0.05 and power of 0.80. Paired correlations will also be used for additional analyses (*Aim 2*). For correlations within group ($n = 41$), with power set at 0.80 and $\alpha = 0.05$, we will be able to detect a medium-to-large effect size (i.e., Cohen's $f^2 = 0.20$), and we will be able to detect a small-to-medium effect size for across-group analyses ($n = 82$; Cohen's $f^2 = 0.10$).

Data analysis plan:

Descriptive evaluations of the data will be performed for all variables to check the integrity of the data and to verify the underlying assumptions of the statistical tests that are planned. If necessary, and as appropriate, data will be transformed prior to any parametric analyses, or non-parametric techniques will be used with untransformed data. Statistical analyses will use two-tailed tests and an a-priori α of 0.05.

In addition to direct tests of hypotheses (described in detail below), descriptive analyses and graphical representations (e.g., spaghetti plots) of data will be used to describe longitudinal

characteristics of clinical pain, somatosensory function, and other physical and psychological outcomes across the 12-month timeline of study participation.

Hypothesis 1a:

The primary statistical analysis, to test the effectiveness of prophylactic TENS for neuropathic pain after SCI will be via a two-proportion z test, comparing the percentage of subjects in the TENS treatment group who are "positive" for neuropathic pain at 12 months post-injury to the percentage of subjects in the Sham TENS group who are positive for neuropathic pain at 12 months post-injury. Subjects who score a 2 or more on the SCIPI for a pain located at or below their neurological level of injury at the 12 month follow-up time point will be considered positive for neuropathic pain. Subjects who do not have a pain at- or-below the level of injury or a score of 2 or more on the SCIPI will be considered negative for neuropathic pain. For those subjects who have neuropathic pain symptoms early after injury (i.e., prior to entering the study), a "positive" result for neuropathic pain will be defined as having neuropathic pain that is moderate or greater (rated at least a 4 out of 10) at the 12 month follow-up assessment.

Additional analyses will be conducted using secondary outcomes collected at the 12-month time point: 1) comparison of pain severity (using the NRS and NPSI scores) between the groups (This analysis will be especially important if the primary analysis does not show a difference in rates of the presence of neuropathic pain at 12 months.); 2) comparison of use of analgesics between groups; and 3) comparison of response to pain interference questions from the ISCIPBDS2. General linear model analyses will be used, with TENS group (Treatment vs. Sham) as a categorical predictor of these secondary outcome measures.

Separate analyses for at-level neuropathic pain and below-level neuropathic pain, as well as nociceptive pains, will also be conducted to examine whether TENS differentially impacts their development or severity. Additional analyses will be conducted, using the diagnosis of each pain type according to ISCIPBDS guidelines, as determined and agreed upon by our study staff pain experts, as a confirmation of the primary neuropathic pain metric (SCIPI $\geq$ 2).

Hypothesis 1b:

To investigate factors that may be related to patient responsiveness to TENS as a preventive treatment for chronic neuropathic pain, we will assess correlations between changes in evoked pain (before and after TENS treatments) and the presence and severity of neuropathic pain

symptoms at the 12 month post-injury time point. It is anticipated that those who show reduced sensitivity to noxious stimuli after TENS treatments will exhibit a lower risk for chronic neuropathic pain. A repeated measures regression analysis, including appropriate covariates (e.g., demographic and injury-related factors, concomitant treatments, amplitude setting of TENS treatments), will assess whether changes in evoked pain sensitivity will be a significant predictor of neuropathic pain at 12 months post-injury in the TENS treatment group.

Hypotheses 2a, 2b, and 2c:

Chi square analyses, t-tests, and correlations across all subjects (with TENS group assignment as a covariate) will be used to separately examine whether demographic variables (age and minority status), psychological characteristics (pain catastrophizing, depressive symptoms severity, and levels of resilience), and measures of evoked pain sensitivity (pain thresholds and ratings of suprathreshold noxious stimuli) measured at baseline can predict the presence and severity of chronic neuropathic pain at 12 months post-SCI. Separate sub-analyses will also be conducted with regard to the impact of these factors on pains with different diagnostic categories (nociceptive pain, neuropathic pain).

Data security / Quality control:

All research personnel will complete and maintain trainings regarding privacy and data security as required. All personnel will receive training regarding all study procedures as required for their role, as assigned and overseen by the PI, to insure data quality and integrity of the science.

Data for the study will be recorded on paper, using the most-updated and approved study forms. These paper documents will be stored in locked file cabinets in rooms 3.156 and 3.153B of the Christine E. Lynn Rehabilitation Center (1611 NW 12th Ave., Miami, FL 33136). This room is locked and is accessible only by those who have been given card access. These paper documents will be stored for at least 3 years after the final termination of the grant.

Data from the paper documents will be entered into a password protected electronic database that will receive periodic and thorough data quality checks through established procedures. This

electronic file will not contain any personally-identifiable information, and will be maintained for at least 3 years after the final termination of the grant.

The PI will assign access to rooms, filing cabinets, and electronic files as necessary for completion of the study.

As this is a single site study, all data will remain on the University of Miami medical school campus, with access under the control of the PI.

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

Safety endpoints include frequency and severity of adverse events and increased likelihood of developing chronic pain due to TENS treatment. It is anticipated that only infrequent and mild adverse events (e.g., temporary skin irritation from surface electrode adhesive, brief mild pain during initial adjustment of TENS stimulation amplitude) will occur. These events will be handled on an individual basis and may be cause for the PI to discontinue participation of a subject who may be especially sensitive to the study treatment. If these mild adverse events are recorded at higher than expected frequency (i.e., greater than 10% of treatment sessions) or if an unexpected or moderate-severe adverse event occurs, the PI will re-evaluate the treatment parameters and adjust accordingly. All events will be reported to the IRB according to regulations.

Preliminary analyses will be performed after each group of 20 subjects completes the study to determine the efficacy of the treatment by comparing the primary endpoints between the two study groups (TENS and sham TENS). More frequent analyses will be performed if warranted. If these preliminary analyses at any point provide overwhelming support that the experimental intervention (TENS) reduces the development of chronic neuropathic pain or has a substantial clinically meaningful reduction in the severity of chronic neuropathic pain present, then the PI will pursue a change in protocol to provide the active TENS treatment to all available participants. Conversely, if the preliminary analyses reveal that the active TENS treatment puts patients at higher risk for pain or other undesirable outcomes, the PI will seek to terminate the intervention, but continue follow-up on enrolled participants.

13) **Withdrawal of Subjects***

Subjects will be withdrawn from the research without their consent if the PI or other study staff, including trained clinicians, determine that the subject may experience adverse events of greater than mild severity and of greater than 10% frequency. If the TENS stimulation is not tolerated after adjustment of electrode location and/or after reduction of stimulus amplitude, then the subject will be withdrawn from the study and will receive no further treatments.

Participants who either self-withdraw from treatment or who are withdrawn by the PI or study staff from the treatment portion of the study, will continue to be followed during all time points after the treatment sessions have terminated, unless the participant does not want to participate in follow-up session for the study.

14) **Risks to Subjects***

TENS therapy poses minimal risks to patients, as outlined below.

a. Skin irritation: Persons undergoing TENS treatment may experience minor skin irritation as a result of the electrode placement.

b. Painful or unpleasant sensory sensations: TENS may evoke painful or unpleasant sensations for a brief period of time while the appropriate intensity level is being determined.

c. Emotional upset: Persons with disability may become upset at having questions asked about their disability and the pain conditions associated with their SCI.

Use of the TSA-II device also poses risks:

d. Thermal pain testing can result in sensations that are unpleasant and which may lead to short-lived, mild-to-moderate anxiety and discomfort. Temporary mild redness around the area tested may occur but will be short-lasting.

To minimize the specific risks outlined above, the following procedures will be in place:

a. Electrode skin irritation can be reduced by cleaning the skin before electrode placement. The risk of this occurring is low. Electrodes will not be placed near

open wounds. The treatment and control groups will be monitored by the research staff continually throughout each treatment session.

b. The research assistant or other research staff responsible for delivering the TENS treatments will be present during the entire 30 minute treatment session so that if discomfort occurs, the stimulus level can easily be reduced or the TENS electrodes can be removed, and summon one of the study physicians if evaluation is needed.

c. During questionnaires, participants will be reminded that they can refuse to answer any questions that they feel are emotionally upsetting. If a participant indicates that he or she has suicidal ideations, the psychologist will be notified immediately. The risk frequency is low and the severity of mild to moderate, although all of the subjects will have already consented to participate in data collection from the SCIMS, and therefore would have already answered similar questions.

d. The PI will be responsible for administering testing using the TSA-II and for training any other study staff who will perform assessments with this device. She has 17 years of experience with the equipment that will be utilized in the proposed study (TSA-II; Medoc, Ltd.), including 12 years of experience using the equipment to test individuals with spinal cord injuries. The TSA-II has cut-off temperature values (0ºC, 50ºC) that are built-in limitations of the equipment. This prevents the machine from delivering stimuli that could potentially cause tissue damage. The short duration of stimulus presentations in this study (up to a maximum of 5 seconds per trial) will also limit any lasting effects of noxious stimulation. Temperatures in the ranges to be presented in the proposed study have been used by our laboratory for several years, including in individuals with spinal cord injury, with no adverse events other than nonpainful slight reddening of the skin that lasted for approximately 60 minutes. In addition, any severe anxiety or discomfort reported by the subject will be grounds for termination of the study session.

15) Potential Benefits to Subjects*

The primary benefit of this interventional study is the potential reduction or elimination of chronic neuropathic pain in subjects randomized to the TENS treatment arm. There is no anticipated benefit for subjects randomized to the sham TENS arm. In addition, no direct benefit can be promised to those in the TENS treatment group, as this is an experimental intervention for prevention of neuropathic pain in this patient group.

16) Vulnerable Populations*

No vulnerable populations will be recruited or enrolled in the study.

17) Sharing of Results with Subjects*

Results of the study assessments will not be routinely disclosed to research subjects. However, study staff will discuss results with those subjects who specifically ask for information from their assessments.

For those subjects who screen positive for mild or moderate depressive symptoms (scores between 5 and 14 on the PHQ-9 assessment), study staff will provide them with this information and give them contact information to make an appointment with a psychologist at UM or JMH. In addition, for those subjects who score greater than moderate depression or who endorse the question "Thoughts that you would be better off dead or hurting yourself in some way," the PI will contact the SCI psychologist on duty, or another staff psychologist, to discuss results and request immediate clinical follow-up.

18) Setting

- Activities related to recruitment and access to medical records may occur at the Jackson Rehabilitation Hospital/Lynn Rehabilitation Center, during the participant's inpatient rehabilitation stay.
- Data collection (quantitative sensory testing and questionnaire completion) and TENS intervention sessions will occur within the Department of Physical Medicine & Rehabilitation at the Lynn Rehabilitation Center (rooms 3.153a, 3.153b, 3.154, 3.155, or 3.156)).

- Due to the frequency of TENS sessions (twice per week) during the treatment period, some of these sessions may take place in the participant's home. If necessary to promote compliance, the research staff member will travel to the participant's place of residence to administer TENS, if the participant approves of this arrangement.

- Data storage, administrative, and data analysis activities will occur in the offices of the PI, collaborators, and study staff within the Department of Physical Medicine & Rehabilitation at the Lynn Rehabilitation Center (rooms 3.153a, 3.153b, 3.154, 3.155, or 3.156).

19) **Resources Available**

The training and experience of our core project faculty and staff, as well as other key personnel involved in the research project, are appropriate for the oversight and performance of the study, as described below:

Elizabeth R. Felix, Ph.D., PI; Research Assistant Professor, Department of PM&R, University of Miami:

Dr. Felix holds joint appointments as Research Associate Professor within the Department of PM&R at the UMMSM and as Research Health Scientist within the Miami VA Healthcare System, and has researched pain in human subjects for almost 20 years, with an emphasis on pain in spinal cord injury patients for the past 16 years. She has investigated the potential somatosensory system mechanisms associated with chronic neuropathic pain after spinal cord injury (using the devices (TSA-II sensory analyser, and TENS devices) proposed for the current study); the psychometric properties of measurement questionnaires and scales for chronic pain; and the potential predictors of the development and severity of chronic pain after spinal cord injury, including the contributions of various psychosocial factors and injury characteristics. She has recent experience as PI of funded studies on pain in spinal cord injury, including one clinical intervention trial. Dr. Felix will provide oversight of all aspects of the study.

Other co-investigators are included on the project that fulfill several roles: clinical experts in SCI and in pain management, and research experts in SCI and in pain measurement and

assessment. The study staff also includes a research coordinator, study nurse, and other research assistants. All staff that will participate in conducting the study, including recruitment, data collection, data review, etc., and their associated duties, are listed within the IRB application in eProst. Regularly-scheduled meetings will be held with all study staff in order to insure that all are up-to-date on study procedures, training, and oversight efforts.

Financial resources for this work, including study staff effort, device procurement, subject payments, and miscellaneous supplies are provided for as appropriate via grant funding obtained by the PI.

20) **Prior Approvals**

In addition to UM IRB approval, review by Jackson Memorial Hospital will be obtained prior to commencing the study.

21) **Recruitment Methods**

Potential participants for this study will be recruited through the JMH inpatient SCI rehabilitation services. All subjects who are at least 18 years of age and who are admitted to the Jackson Rehabilitation Hospital/Lynn Rehabilitation Center with a traumatic spinal cord injury will be assessed for eligibility. Using the inclusion and exclusion criteria provided above, the inpatient SCI rehabilitation physician (Dr. Kevin Dalal) will access Jackson electronic medical record information for this purpose. If the patient meets criteria, the study physician will approach the patient and ask if he/she would agree to have a study team member talk to them about the study for possible enrollment.

All those who agree will be approached in person or over the phone by a research staff member for possible enrollment within 4 months of their injury. Patients who express interest in the study will be informed in detail of the procedures and timeline of the study. The research staff member will then review the informed consent document with the participant, including potential risks and benefits of the study, and assurance that their refusal to be a part of the study, or to withdraw from the study, will not influence their clinical services at UM/JMH. Any questions the patient has will be answered by the study staff member or referred to the PI and/or study physicians for further discussion with the patient. (See section #27 for full consenting procedures.)

Cash and check payments will be made to subjects based on completion of each treatment and assessment portion of the study: 1) $25 will be paid for each treatment session attended; 2) $150 will be paid for each full assessment session completed (partial payment, in the amount of $75, may be paid if the participant completes only the questionnaire portion of this visit, but does not complete the sensory assessment portion); 3) $25 will be paid for each brief assessment session completed; and 4) a $50 bonus will be conferred at the end of the study for subjects who complete 90% or more of study treatments, visits, and phone assessments. Up to a total of $1075 at completion of the study is available for each subject. Cash payments will be given to the subject immediately after each treatment session and in-person assessment session. Check payments may be made via mail for phone assessment if payment in person is not feasible.

22) **Local Number of Subjects**

We anticipate that, over the 5 year recruitment period (Jan 2017 – January 2022), approximately 175 patients with new traumatic spinal cord injuries admitted to Jackson Rehabilitation Hospital/Lynn Rehabilitation Center will be eligible for the study. Of these, we estimate that approximately 98 subjects will consent to enter the study. We will not enroll more than 98 subjects without prior approval by the IRB.

23) **Confidentiality**

This is a single-site study. All investigators and study staff involved in this study will protect the participant's personal and medical information by removing his or her name and other identifiable information (e.g., birth date, address) from any forms where it is not necessary. A study identification number will be assigned to the study subject's records and his or her name and other personal information will only be accessed when necessary for follow-up contact. All study forms will be secured in a locked file cabinet in a locked room that is accessible only to research staff members (Lynn Rehabilitation Center (rooms 3.153b and 3.156)). Any information related to this study that will be saved on electronic files will be password protected so that only certified study staff members can access these files.

No specimens will be collected in this study.

24) Provisions to Protect the Privacy Interests of Subjects

For recruitment purposes, the study team physician(s) will access information from medical records to assess eligibility for the study. These source documents will not be retained – the information confirming inclusion and exclusion criteria will be noted in the study records/documents.

After documented consent is obtained, and HIPAA form is signed, appropriate study staff, as appointed by the PI, will be permitted access to medical records to re-confirm eligibility.

During the initial consenting procedures, subjects will be ensured that they do not have to fully complete all questions, if they are not comfortable answering, and may still participate in the study. Subjects will be reminded of this throughout assessment sessions as needed. Research staff will make every effort to provide a friendly atmosphere and assurances of privacy and confidentiality in any way possible. Paper documents for data collection will only include assigned subject ID numbers, that cannot be easily linked to subject identity. A password-protected log of subject ID numbers associated with subject identity and contact information will be maintained only until all activities of the study are completed.

All study-related interviews or completion of questionnaires and assessments will be conducted in private areas where others will not be able to see or hear participant responses, and study staff will not discuss personal information with other study staff members unless they are in a private location where others cannot hear. Patients' study-related information will not be discussed or disclosed to anyone that is not a part of the research study unless indicated by law.

25) Compensation for Research-Related Injury

Injury due to research participation is not expected. Funds are not available for research-related injury and would need to be covered by the patient or the patient's insurance.

26) Economic Burden to Subjects

We anticipate minimal, if any, expenses to be incurred by the subject. Only the time that will be required for coming in for treatment and assessment sessions may produce an economic burden to subjects, if it requires that they take unpaid leave from work to participate. The research grant under which this study is funded includes a budget amount

for subject payment (as outlined above), and for transportation costs which will include public, private, and parking expenses as needed.

27) Consent Process

Patients who express interest in the study will be informed in detail of the procedures and timeline of the study, and study payments for time, as well as coverage of travel expenses for necessary study visits. If the patient is interested in the study, he/she will undergo the full consent process. Consent will occur in private office or lab space associated with the study at UM. We will follow HRP-090 with regard to UM SOP for the informed consent process.

There will not be a required waiting period instituted between informing the potential subject and obtaining written consent, but, if the subject requests, he/she will be given a copy of the consent form for consideration and re-approached at another time to assess his/her desire to participate.

The research staff member will review the informed consent document with the participant, including potential risks and benefits of the study, and assurance that their refusal to be a part of the study, or to withdraw from the study, will not influence their clinical services at UM/JMH. Any questions the patient has will be answered by the study staff member or referred to the PI for further discussion with the patient.

Non-English Speaking Subjects

At the present time, only those comfortable communicating in English will be enrolled in the study, due to the fact that many of the evaluation questionnaires are only available in English or have not been validated for use in non-English speaking persons. Based on our previous studies, we anticipate this only affecting a very small proportion of the potential eligible patients.

28) Process to Document Consent in Writing

The subject's consent to participate in this research study will be documented in writing according to standard UM IRB SOP (HRP-091).

29) **Drugs or Devices**

The study will make use of two devices, neither of which is an investigational device:

1. TENS 7000 (Roscoe Medical; Ohio). This device is a commercially available device used to deliver transcutaneous electrical nerve stimulation via surface electrodes for the relief of pain. It will be used in accordance with its approved labeling. Based on the FDA 510(k) for this device, the TENS 7000 is "intended for use for (1) Symptomatic relief and management of chronic (long term) intractable pain and (2) adjunctive treatment in the management of post surgical and post traumatic pain problems."

   This research is not intended to be reported to the FDA in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the device.

   This research is not intended to support a change in the advertising for the device.

   This research does not involve a route of administration, dose, or other factor that significantly increases the risk associated with use of the device.

   Storage of the devices and the self-stick electrodes will be in the offices of the research staff (Lynn Rehabilitation Center (rooms 3.153b, 3.154, or 3.156), 1611 NW 12th Ave., Miami, FL 33136.) when not being used for study subject treatment sessions. These rooms are secured with key cards and have filing cabinets with key locks in which the devices and associated supplies will be kept. When they are removed for use during treatment sessions, they will be in the possession of research study staff. All such devices will be labeled with ownership information, including PI name, research coordinator name, and contact information.

2. Thermo-Sensory Analyzer II (TSA-II; Medoc Ltd.; Israel). This device will be used for the longitudinal assessment of tactile and thermal sensory and pain thresholds. This device is not being tested as an intervention, nor for the purpose of altering labeling or advertising of the device. It is being used as an assessment tool only, and in accordance with all labeling by the manufacturer (Medoc Ltd.). The TSA-II has been used in our lab in multiple studies, and by other labs around the world, for research in human subjects. For the current study, we will use the vibration and

thermal testing apparatus to quantitatively assess tactile, thermal, and pain thresholds in subjects during the full assessment sessions (4 times during the 12-month enrollment). The TSA-II is a precise, computer-controlled device which delivers calibrated thermal stimuli as programmed through the associated software. The device and laptop used to run the equipment are mounted to a mobile cart for easy transport to any location. The TSA-II has been used extensively in human subjects' research, including studies in spinal cord injury patient populations, and the PI has over ten years previous experience using this equipment for the evaluation of somatosensory function in patient groups and control subjects.

Storage of the TSA-II will be in the offices of the research staff (Lynn Rehabilitation Center (rooms 3.153b, 3.154, or 3.156), 1611 NW 12th Ave., Miami, FL 33136). These rooms are secured with key cards that are only accessible to research staff, under the supervision of the PI. Access to controlling the device is obtained via the laptop/software program which requires a password to access. The device will be labeled with ownership information, including PI name, research coordinator name, and contact information.

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