FAST

Fibromyalgia Activity Study with TENS

STUDY PROTOCOL

August 2011
Revised:
October 2011
June 2012
July 2013
June 2014
September 2014
December 2014
July 2015
September 2015
February 2016

Study Rationale

The American College of Rheumatology (ACR) classifies fibromyalgia as a clinical syndrome defined by chronic widespread muscular pain and tenderness [65]. The cause of fibromyalgia is unknown, but people with fibromyalgia show sensitization of central nervous system pain pathways, measured by lower pain thresholds, enhanced temporal summation, and reduced diffuse noxious inhibitory controls (DNIC)[27;53;56]. Pain associated with fibromyalgia interferes with daily function, work, and social activities resulting in a decreased quality of life [3]. In addition people with fibromyalgia have a significant amount fatigue and a fear of movement [8]. These two associated factors further contribute to the reduction in physical function and quality of life (see Figure 1). Thus, one of the main treatments for patients with fibromyalgia must focus on pain relief to allow the person to function more independently both at home and at work. The reduction in pain would reduce fatigue and fear of movement that ultimately results in increased physical function and quality of life. Transcutaneous electrical nerve stimulation (TENS) is a modality used by health professionals that delivers electrical stimulation through the skin for pain control. Basic science studies, from the PIs laboratory, show that TENS activates descending inhibitory pathways from the midbrain and brainstem to inhibit excitability of nociceptive neurons in the spinal cord [10; 25; 34; 51]. Thus, is the ideal intervention to control pain in people with fibromyalgia since it reduces central excitability and increases inhibition.

Although TENS is effective for several pain conditions such as osteoarthritis, chronic musculoskeletal pain, and postoperative pain [6;22;41], its effectiveness in treatment of people with fibromyalgia is virtually unknown. Furthermore, there is a general thought among clinicians that since fibromyalgia pain is widespread, TENS would be ineffective in this population. To initially test if TENS was effective in decreasing the pain associated with fibromyalgia we performed a preliminary study examining the effectiveness of a single treatment with high frequency TENS. The group receiving active TENS showed a reduction in resting pain and pain during movement compared with placebo. There were also improvements in measures of function in the active TENS group with a greater increase in distance walked in the 6 minute walk test (by 221 feet) as compared to a decrease in distance (-100 feet) for placebo. TENS also increased pressure pain thresholds (by 20%) during DNIC when compared to virtually no change for placebo TENS (1%). Thus, TENS may decrease pain associated with fibromyalgia by increasing central inhibition and decreasing central excitability. This decrease in pain is expected to increase function and improve quality of life.

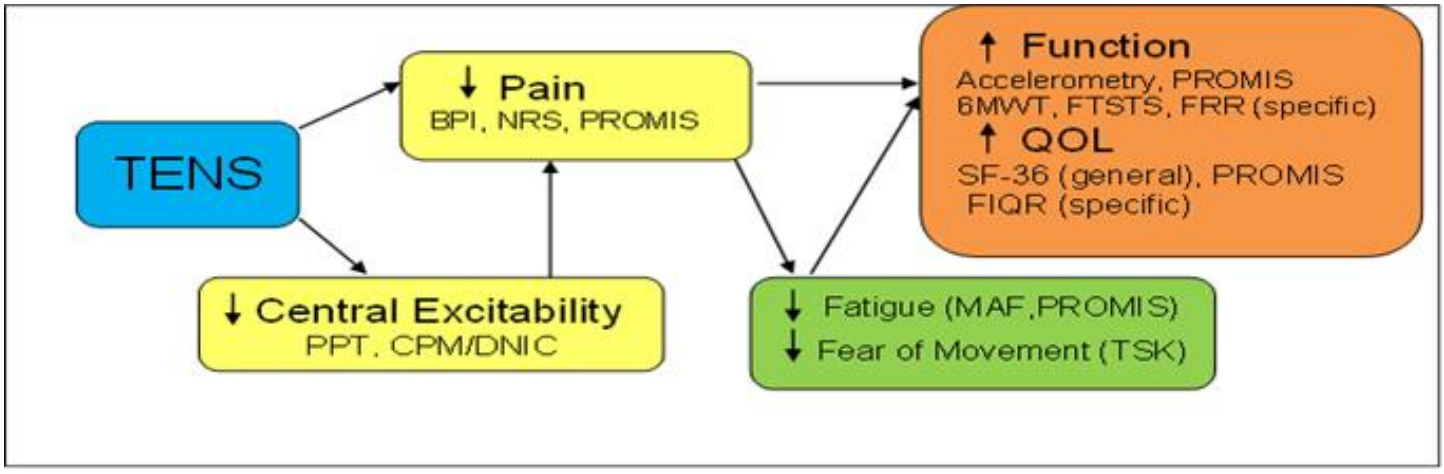

Figure 1: Conceptual Model for TENS effects

Hypothesis

We hypothesize that application of Transcutaneous Electrical Nerve Stimulation (TENS) to patients with fibromyalgia will reduce resting and movement-related pain and reduce central excitability by restoring diffuse noxious inhibitory controls (DNIC), and that this decrease in pain and/or central excitability will reduce fatigue and fear of movement, thereby improving function and quality of life (see Figure 1).

Aims

Aim #1: The primary aim of the study is to test the effectiveness of repeated TENS use on movement-related pain in people with fibromyalgia with random assignment to three treatments: standard care, placebo TENS and active
Aim #2: A secondary aim will test if pain reduction by TENs results in a concomitant decrease in fatigue and fear of movement, and an increase in function and quality of life. Outcome measures will include physical function by directly assessing daily activity with an accelerometer, as well as performing specific functional tasks
Aim #3: To determine if active TENS alters pain processing in women with fibromyalgia and if improvement in clinical symptoms correlates with normalization of pain processing physiology. We will evaluate change in these physiologic parameters in responders versus non-responders as assessed clinically.

Aim #4: To determine if PROMIS is a useful instrument for assessing outcome for fibromyalgia by comparing to the revised version of the fibromyalgia impact questionnaire (FIQ-R).

Healthy Control Aims:

Aims:

Physically active women with fibromyalgia will have a similar phenotype (pain thresholds and conditioned pain modulation) and cytokine profile to physical active women without pain; conversely sedentary women with fibromyalgia will have a similar phenotype and cytokine release profile to sedentary women without pain.

Aim #5 will perform quantitative sensory testing to profile excitability and central inhibition in individuals with fibromyalgia and healthy controls; both sedentary and physically active individuals will be recruited in each cohort.

Aim #6 will examine for cytokine release profiles in immune cells (monocytes) from the sedentary and physically active individuals with and without fibromyalgia.

Study Synopsis

Protocol Title	Fibromyalgia Activity Study with TENS (Transcutaneous Electrical Nerve Stimulation)
Protocol Number	
Name of Sponsor	Funded by NIH NIAMS Performed at University of Iowa, Vanderbilt University
Investigational Product	TENS (Transcutaneous Electrical Nerve Stimulation) TENS is a non-pharmacological agent which delivers electrical stimulation by a battery operated device via electrodes placed on the skin. TENS is considered to be a safe, inexpensive and non-invasive modality used to treat a variety of acute and chronic pain conditions.
Phase of Development	Phase II Clinical Trial
Purpose of Study	The primary aim of the study is to test the effect of the long-term use of TENS on movement-related pain as measured by a numeric rating scale (NRS) during six minute walk test (6MWT) in women with fibromyalgia with random assignment to three treatments: standard care (No TENS), placebo TENS and active TENS.
Indication	Women with Fibromyalgia, ages 18-70
Number of Centers	The study will be conducted at 2 study sites: University of Iowa and the Vanderbilt University
Study Duration	5 years
Objectives	**Aim #1:** The primary aim of the study is to test the effectiveness of repeated TENS use on movement-related pain in people with fibromyalgia with random assignment to three treatments: standard care, placebo TENS and active **Aim #2:** A secondary aim will test if pain reduction by TENs results in a concomitant decrease in fatigue and fear of movement, and an increase in function and quality of life. Outcome measures will include physical function by directly assessing daily activity with an accelerometer, as well as performing specific functional tasks **Aim #3:** To determine if active TENS alters pain processing in women with fibromyalgia and if improvement in clinical symptoms correlates with normalization of pain processing physiology. We will evaluate change in these physiologic parameters in responders versus non-responders as assessed clinically. **Aim #4:** To determine if PROMIS is a useful instrument for assessing outcome for fibromyalgia by comparing to the revised version of the fibromyalgia impact questionnaire (FIQ-R).
Study Design	This is a phase II randomized, double-blind, placebo controlled multi-center clinical trial. The initial phase of the study will randomly allocate subjects to receive active TENS, placebo TENS or standard care (No TENS). After participating in the 1 month random assignment, all subjects will receive active TENS for 1 month. The subjects will make 4 visits to the clinic.

Subject Population	Females with fibromyalgia.
Inclusion Criteria	• Participants will be 18 to 70 years of age • Women may participate in the study • Diagnosis of Fibromyalgia by 1990 ACR criteria • History of cervical or lumbar pain with fibromyalgia (this is expected in all patients since axial pain is required for diagnosis) • Current stable treatment regimen for the last 4 weeks and projected stable treatment regimen for the next 2 months. • English speaking
Exclusion Criteria	• Current or history of cardiovascular, pulmonary, neurological, endocrine, or renal disease that would preclude the involvement in the study. • TENS use in the last 5 years • Pacemaker • Uncontrolled blood pressure or diabetes • Neuropathic pain condition • Systemic autoimmune disorder (Lupus, PMR, RA, Psoriatic arthritis) • Spinal fusion – cervical or lumbar • Metal implants in the spine • Severe skin allergy to adhesive • Allergy to nickel • Pain less than 4 • Pregnancy • Epilepsy • Change in or new drug or treatment program within the last month or in the next 2months, i.e. must have a stable treatment plan • Unstable medical or psychiatric condition which in the opinion of the investigator could compromise the subject's welfare or confound the study results
Planned Sample Size	Final sample size of 264 subjects divided into 88 subjects per group. We will recruit 316 subjects based on a 20% projected attrition.
Randomization	Patients will be randomly allocated on the second visit after a re-assessment of eligibility. We will use a permuted block schedule, stratified by site. The randomization schedule will be implemented using SAS v9.2 PROC PLAN, creating blocks of size 6 for each of the strata factors.
Study Device Dosage and Administration	FDA Summary of Empi Select TENS Unit: TENS is a non-pharmacological agent which delivers electrical stimulation by a battery operated device via electrodes placed on the skin. TENS is considered to be a safe, inexpensive and non-invasive modality used to treat a variety of acute and chronic pain conditions**.** **510(k) Summary for 300 PV Complete Electrotherapy Systems** **1. Manufacturer** Empi 599 Cardigan Road St. Paul, Minnesota 55126-4099

	Contact Person: John Bum Telephone: (651) 415-9000 Date Prepared: April 2, 2002 **2. Device Name** Proprietary Name: 300 PV Complete Electrotherapy System Common/Usual Name: Electrical Muscle and Nerve Stimulator Classification Names: Powered Muscle Stimulator, Transcutaneous Nerve Stimulator, interferential Current Stimulator, External Neuromuscular Functional Stimulator **3. TENS Parameters: Active and Placebo Units** • TENS Frequency – 10 to100 Hz, SMP mode • TENS Pulse Width - 200 µs • TENS Intensity - Maximal tolerable intensity • Duration: 2 h per day during activity. The 2 h may be broken into smaller segments of time with a minimum of 30 minutes. • Administration - Daily • TENS Location: TENS electrode on the skin will be a 4 x 7 butterfly electrode to the cervical and lumbar region. • Placebo TENS Unit - The placebo TENS unit will deliver current for 45s ramping to 0 in the last 15s.
Study Summary	This is a phase II randomized, double-blind, placebo controlled multi-center clinical trial involving a device, TENS, to assess the efficacy of TENS on pain with movement over a 1 month period in subjects with fibromyalgia. After participating in the 1 month random assignment, all subjects will receive active TENS for 1 month. Subjects will receive a phone call weekly from the study coordinator regarding progress. • Screening: Telephone screen for eligibility for the study • Assessor – performs baseline and all testing except TENS allocation and TENS home instruction. The assessor is blinded to TENS treatment. • TENS Allocator – performs TENS allocation, home instructions and questions regarding TENS
Demographic and Outcome Measures	• Consent • Health History/Demographic • Vital Signs • Confirmation of ACR 1990 Criteria for FM/Tender Point Exam • 2010 ACR Criteria • NRS Rest Pain, Rest Fatigue, Movement Pain, Movement Fatigue • BPI • PROMIS • FIQR • SF-36 • MAF • TSK • IPAQ • PSQI • PSEQ • PCS

	• Global Impression of Change • Accelerometry (Actigraph • 6MWT • STS • FR • PPT • CPM • TENS
Criteria for Evaluation	Primary Efficacy Endpoint: • Pain with movement (NRS) during 6MWT Secondary Efficacy Endpoints: • Health History/Demographics • Vital Signs • Confirmation of ACR 1990 Criteria for FM/Tender Point Exam • 2010 ACR Criteria • NRS Rest Pain, Rest Fatigue, Movement Pain, Movement Fatigue • BPI • PROMIS • FIQR • SF-36 • MAF • TSK • IPAQ • PSQI • PSEQ • PCS • Global Impression of Change • Accelerometry • 6MWT • STS • FR • PPT • CPM • TENS • Blinding
Statistical Methods	• Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, standard error, median, first and third quartiles, and minimum and maximum). • Categorical variables will be described with counts and percentages. The endpoints (VAS, BPI, PPT,CPM, and 6MWT, STS, FR and accelerometry measures) will be treated as continuous variables as well as scores from questionnaires (FIQR, SF-36, MAF, and TSK, PROMIS). • Changes from initial measurement to one month after randomization will be calculated for each of these endpoints. Changes in outcomes and percent changes in outcomes will be treated as continuous variables and will be summarized with descriptive statistics. Outcomes will be summarized by visit, as change from initial measurement, and percent

	change from initial measurement. Continuous endpoints may also be categorized into discrete variables when appropriate. Shift tables may be utilized to investigate shifts in outcome categories from baseline to one month after randomization. SAS v9.2 or higher will be used for all analyses and a significance level of 0.05 will be used for all statistical tests. In the case that endpoints are found to be non-normal, appropriate transformations will be employed and non-parametric tests may be used •
Statistical Methods Aim #1- #4	**Aim #1:** The primary endpoint of Aim #1 is the change (visit 3- visit 2) in pain scores during movement. In order to evaluate the effectiveness of long-term use of TENS (Aim 1), the primary analysis will be the comparison of change in pain (with movement for those randomized to either active TENS, placebo TENS, or standard of care). The comparison of the change (visit 3 – visit 2) in pain for the three groups will be made using linear mixed model analysis for repeated measures with treatment group, time (visit2 and visit3), and treatment group*time interaction as the fixed effects. The test for the treatment group*time interaction effect corresponds to the test comparing mean change among the groups. Post-hoc pairwise comparison of mean change between groups will performed by test of mean contrasts estimated from the fitted linear mixed model with p-values adjusted using Bonferonni's method to account for the number of tests performed (i.e. 3 tests for all pairwise comparisons). It is expected that the randomization will lessen the need for covariate-adjusted analyses. However, in the event that adjusted analyses are necessary, a secondary comparison of the change in endpoints for the three groups will be made by expanding the linear mixed model to include covariates. Potential confounders include age, race, ethnicity, educational attainment, marital status, TENS dose/intensity, change in opioid status, medication intake and use of rescue medications. While every effort will be made to follow-up with patients, preliminary data suggests that approximately 10% of the patients will not return for follow-up. The ITT analysis will be performed using all available data for all randomized participants. In the presence of missing data, under the assumption of missing at random (MAR), linear mixed model analysis which can handle incompletely observed subjects and uses a likelihood estimation method will provide correct likelihoods and lead to valid estimates (ref1). However, since the data under analysis cannot distinguish if data is MAR or it it is missing not at random (MNAR), sensitivity analysis will also be performed using pattern mixture models. Multiple imputations will be used for sensitivity analysis by imputing from a non-random pattern mixture model (ref2). Furthermore, based on previous work, it is expected that approximately 5% of subjects randomized to active TENS may not receive a full dose of active TENS because they did not achieve the adequate intensity dose. In the primary ITT analysis, these patients will be included as randomized. However, as an additional analysis a modified ITT (mITT) analysis will be conducted. This analysis will utilize an ITT principle in terms of randomization but will be limited to those who achieved at least one adequate intensity dose. (ref1) Molenberghs G. and Kenward MG (2007) Missing Data in Clinical Studies. John Wiley & Sons Ltd, West Sussex, England.

(ref2) Carpenter J and Kenward MG (2013) Multiple Imputation and its Application. John Wiley & Sons Ltd, West Sussex, England.

Aim #2: The primary endpoint of Aim #2 is the change (visit 3 – visit 1) in fear of movement scores. Secondary endpoints for this aim include changes in function, fatigue, resting pain, function, use of rescue analgesic medications, and quality of life. Additionally physical function measures will be determined using accelerometer data and data obtained during a course of specific functional tasks. Rescue analgesic medications will be recorded as number and dose of medications, indicators for increases or decreases in frequency or dose, and any utilization. Comparisons between the randomized groups for these outcomes will be performed as described in Aim 1. Additional analyses, using the change in fatigue, fear of movement, function, quality of life and resting pain measures as dependent variables in linear regression models, associations between these outcomes and changes in pain values will be investigated.

Aim #3: The primary endpoints of Aim #3 are the change (visit 3 – visit 2) in PPT and DNIC/CPM for those who complete one month of active TENS. After one month of active TENS, participants will be clinically evaluated and classified as responders or non-responders using recently published criteria for fibromyalgia subjects [7]. Comparisons of these physiologic parameters will be made in responders versus non-responders as described in Aim 1. Since responder status is not randomized, it is expected that that the linear mixed model will also include covariates such as change in opioid status, medication intake, and TENS use. Multiple variable logistic regression (with associated odds ratio estimates and ROC curves) will also be utilized to investigate factors related to being a responder or not.

Aim #4: The primary endpoints of Aim #4 are the FIQR and SF-36 prior to randomization. PROMIS modules (also obtained prior to randomization) for depression, fatigue, pain behavior, pain interference, physical function, satisfaction with social roles, and satisfaction with discretionary social activities will be summarized and compared to validated FM instruments (FIQR and SF-36). Scores from each of the PROMIS modules will be compared to corresponding FIQR and SF-36 domains (see Table 1) by estimating Pearson correlation coefficients and testing for nonzero correlation. Multiple linear regression may also be used to investigate this relationship while controlling for potential confounding variables. Finally, FIQR, PROMIS, and SF-36 will be obtained at four different time points during this study (pre-treatment, randomized phase, and non-randomized active TENS). Summaries will include values at pre-treatment, changes from pre-treatment and percent changes. In addition to changes observed in the randomized phase, linear mixed models may also be utilized where treatment status (pre-treatment, randomized treatment, and non-randomized active TENS) is treated as a time-varying covariate to estimate the impact of changes in treatment status on these outcomes.

As an exploratory analysis, further investigation of changes in pain, responder

	status, and relationships between endpoints will be conducted for data collected during the non-randomized phase and will include those with an additional month of active TENS (originally randomized to active TENS) as well as those with a single month of active TENS (originally randomized to placebo TENS and no treatment control). Finally, exploratory examinations of the relationships between changes in pain, sensory, and quality of life measures may utilize multivariate methods (e.g. partial least squares and principal component analysis) and classification and regression trees.
Safety Measures	Physical Exam Vital Signs Clinical signs and symptoms Adverse Event analysis Increased pain with testing follow-up: Participants who experience an increase in testing will be contacted the day after testing about the status of the increase in pain (Added 12/2014) Safety analysis

Schedule of Visits and Evaluations.

The subjects will attend four visits for the FAST study. Each session will last 2-4hours for testing. Testing measures will include health history/demographics questionnaire, pain measures, multidimensional questionnaires, functional assessments and quantitative sensory testing. Home activities will include accelerometry, medication logs, TENS unit.

A general outline of measures and visits is given in Table 1, the order of testing is given in Table 2, and a list of equipment, forms, and measures is given in Table 3.

Subjects are considered enrolled after consent and meeting eligibility criteria on Visit 1. They will be randomized to treatment on Visit 2 and they will be re-reviewed for eligibility criteria.

It is expected that Visit 1 will take no more than 1h, Visit 2 will take 2-3 hours, Visit 3 will take 3-4 hours, and Visit 4 will take 2-3 hours.

Table 1: Schedule of tests and measures

Measurement	Instrument	Visit (V)	Construct and General Information	Reliability	Validity-Cronbach's-Alpha (α)	Reference
Pain and Fatigue	NRS	V1 V2 V3 V4	Self report of pain and fatigue intensity on 0-10 vertical scale;	ICC=0.71-0.99	0.71-0.78	[51, 52]

			Pain and fatigue intensity at rest and movement			
Multidimensional Questionnaires	BPI	V2 V3 V4	Pain intensity and pain interference with activities; 15 questions	r=0.57	0.85-0.88	[53]
	HH/Demo	V1	Demographic; Review of past medical history	NA	NA	NA
	FIQR	V1 V2 V3 V4	Disease specific questionnaire;21 questions	r=0.88	0.69-0.88	[54]
	GIC	V3 V4	Perception of change	r=0.87	ICC=0.9	[55]
	IPAQ	V2 V3 V4	Self report of activity level among adults; Short form	Spearman's ρ = 0.80	Spearman's ρ = 0.78	[56]
	MAF	V2 V3 V4	Fatigue questionnaire; 16 questions; 4 dimensions of fatigue	0.93	r=0.62- 0.84	[57]
	PCS	V2 V3 V4	Pain Catastrophizing scale; 13 items pain	Total Cronbach's alpha 0.95	0.42	[58]
	PSEQ	V2 V3 V4	Pain Self Efficacy; 10 items; confidence in performing activities with chronic pain	r=0.73	0.67 - 0.84	[59]
	PROMIS	V2 V3 V4	Quality of Life; NIH patient reported outcome measurement system	NA	NA	NA
	PSQI	V2 V3 V4	Pittsburgh Sleep quality index; 19 items sleep disturbance and sleep habits	0.80	R= 0.07 to 0.80	[60]
	SF-36	V2 V3 V4	General Quality of Life; 36 items	r=0.85	0.97	[61]
	TSK	V2 V3 V4	Fear of pain with movement; 17 items	r=0.64-.99	r=0.70-0.81	[62-64]
Function	6MWT	V2 V3 V4	Function; Walk test for endurance	ICC[2,1]=0.95-0.97	r=-/63-0.79	[26]
	FTSTS	V2 V3 V4	Function; Measure of leg strength	ICC 1 1>0.95	r=0.59-0.88 LBP r=0.46-0.76 Control	[65, 66]

	FR	V2 V3 V4	Function; Measure of balance	r=0.95	r=0.7	[27, 67]
	Actigraph: Actisleep+	Week Before V2 V3 V4	Function: Activity and Sleep Accelerometer worn on wrist	NA	NA	NA
Quantitative Sensory Testing	PPT	V2 V3 V4	Deep mechanical hyperalgesia; Pressure Pain Thresholds	r=0.79-0.94 ICC = 0.85-0.99 Test-retest=0.70-0.94	Significant differences between healthy and RA subjects ($p<0.05$)	[68-72]
	CPM (DNIC)	V2 V3 V4	Central Inhibition	Face validity as the same test in animals activates descending inhibitory pathways		

Table 3: List of equipment, form per test and measure

Order of Testing FAST June 2014

Key:
Blue= Assessor | Black= Subject | Red= TENS Allocator

Session 1	Session 2		Session 3		Session 4	
Pre-consent Eligibility Screen	NRS Rest - Pain,Fatigue		NRS Rest - Pain,Fatigue		NRS Rest - Pain,Fatigue	
Reimbursement Form	FIQR		FIQR		FIQR	
Consent	Medication Log		Medication Log		Medication Log	
Confirmation of Consent	Eligibility		Adverse Event Screen		Adverse Event Screen	
Adverse Event Screen	Adverse Event Screen	Download Actigraph Data	Questionnaires (4-5)	Download Actigraph Data	Questionnaires (4-5)	Download Actigraph Data
			1990 & 2010 ACR		1990 & 2010 ACR	
Medication Log	Questionnaires (4-5)		6MWT	Download/Record TENS Data	6MWT	Download/Record TENS Data
Health History	6MWT		FTSTS		FTSTS	
NRS Rest - Pain,Fatigue	FTSTS		FR		FR	
FIQR	FR		PPT		PPT	
Height, Weight	PPT		TENS Treatment 1	5 min TENS Check	TENS	5 min TENS Check
1990 FM ACR	TENS	5 min TENS Check	Questionnaires during TENS(4-5)		Questionnaires during TENS(4-5)	
2010 FM ACR	Questionnaires during TENS(4-5)		NRS Rest - Pain,Fatigue		NRS Rest - Pain,Fatigue	
EligibilityReview	NRS Rest - Pain,Fatigue		PPT		PPT	
TENS Tolerance Test	PPT		6MWT (NRS Mvmt Pain, Fatigue, BORG)		6MWT (NRS Mvmt Pain, Fatigue, BORG)	
Actigraph	6MWT (NRS Mvmt Pain, Fatigue, BORG)		FTSTS (NRS Mvmt Pain, Fatigue)		FTSTS (NRS Mvmt Pain, Fatigue)	
Adverse Event Screen	FTSTS (NRS Mvmt Pain, Fatigue)		FR		FR	
Blood Draw	FR		CPM		CPM	
	CPM		Blinding question		GIC	TENS off
	TENS Home		Turn off TENS		Survey	
	Actigaph Home		GIC		Survey/Survey	
	AES		Blinding question			
	Record and Clear Data		Debriefing (Active may be done)			
			Record/Clear Data			
			TENS Treatment 2	5 min TENS Check		
			NRS Rest - Pain,Fatigue			
			PPT			
			6MWT (NRS Mvmt Pain, Fatigue, BORG)			
			FTSTS (NRS Mvmt Pain, Fatigue)			
			FR			
			CPM			
			TENS Home			
			Actigaph Home			
			AES			
			Record and Clear Data			

Table 3: List of equipment, form per test and measure

Area	Form	Visit	Equipment: Clipboards, Pens, Computer/Form
	Screening Log	Pre Visit	Computer/Form
Surveys	Consent	1	Computer/Form
	Health History/Demographic	1	Computer/Form
	Diagnostic Confirmation	1	Computer/Form
	Eligibility Confirmation	1, 2	Computer/Form
	FIQR	1,2,3,4	Computer/Form
	MAF	2,3,4	Computer/Form
	TSK	2,3,4	Computer/Form
	Medication	1,2,3,4	Computer/Form
	SF-36	2,3,4	Computer/Form
	PROMIS	2,3,4	Computer/Form
	IPAQ	2	Computer/Form
	PSQLI	2	Computer/Form
	PSEQ	2	Computer/Form
	PCS	2	Computer/Form
	Blinding Question Researcher and Subject	3	Computer/Form
	Global Impression of Change	3, 4	Computer/Form
Pain	NRS	1,2,3,4 Previsit 2,3,4	Computer/Form
	BPI	2,3,4	Computer/Form
Fatigue	NRS, BORG CR10	1,2,3,4	Computer/Form
QST	PPT (C,L, Ant Tib)	2,3,4	Algometer, Form, Marker, Alcohol swab
	CPM	2,3,4	Bucket, thermometer, Water, Ice, Towel, Form
Function	6MWT	2,3,4	Timer, Form, Distance Measurement, Pulse Oximeter, BP Cuff, Sphygmometer
	FTSTS	2,3,4	Timer, Form, Chair with arms
	Functional Reach	2, 3,4	Yardstick, Form
	Accelerometry	1,3,4	Actigraph, home tracking, initialization & instruction sheet
TENS	TENS Trial	1	TENS, Electrodes, Batteries, Lead
	TENS Treatment at Visit	2,3,4	TENS, Lead wires, Electrodes, Batteries, Participant Handbook
Handbooks	Participant Assessor	1,2,3,4	Handbook

Data Analysis Plan

Aim	Visit (V)	Measures	Statistical Plan
General Considerations	V1 V2 V3 V4	All outcome measures: Pain NRS rest and movement, Fatigue NRS rest and movement, BPI, PPT, 6MWT, FTSTS, FR, CPM, Accelerometry FIQR, SF-36, TSK, GIC, PROMIS, MAF,	• Descriptive Statistics • n, mean, standard deviation, standard error, median, first and third quartiles, minimum, maximum • Outcomes summarized by visit • Changes from visit to baseline; shift tables may be used to investigate shifts from visit 1 to visit 3 • • If variables not normally distributed, , non-parametric tests will be used
Aim #1	V3-V2	Pain NRS with movement (6MWT and FTSTS) for the treatment groups: active TENS, placebo TENS or standard care	• Linear mixed model analysis (LMM) for repeated measures with treatment group, time (V3-V2) and treatment group*time interaction as fixed effects. • Post-hoc pair wise comparison of mean change between all three treatment groups • p-values adjusted using Bonferroni method to account for the number of tests • Potential confounders include BMI, age, race, ethnicity, educational attainment, marital status, TENS dose/intensity, change in opioid status, medication intake, rescue medications; If there are differences between potential confounders, we will include covariates
Aim #1 Intention to Treat (ITT)	V3-V2	Pain NRS with movement (6MWT and FTSTS) for the treatment groups: active TENS, placebo TENS or standard care	• Intention to treat (ITT) analyses using all available data for all randomized participants will be used • If there are missing data, missing at random (MAR) LMM will be used. Sensitivity analysis will be performed using pattern mixture models since data cannot be determined if it is MAR or missing not at random (MNAR). Multiple imputation will be used for sensitivity analysis by imputing from a non-random pattern mixture model • Modified ITT (mITT) will be conducted to account for subjects who did not achieve adequate dose (based on previous work, 5% of subjects randomized to active TENS

			are expected to not achieve adequate dose). This will be limited to those who achieved at least one adequate intensity dose [73, 74].
Aim #2	V3-V2	Primary: Fear of movement scores. Secondary: changes in function, fatigue, resting pain, use of rescue medications, accelerometry and quality of life questionnaires.	• Comparison between the randomized groups will be performed as described in Aim #1. • Additional analysis using the change in fatigue, fear of movement, function, resting pain measures and quality of life as dependent variable in linear regression models, associations between these outcomes and changes in pain values will be investigated.
Aim #3	V3-V2	Change in PPT, CPM for those who complete one month of active TENS.	• Classification of participants who complete one month of active TENS as responders or non-responders using published criteria [50] • Linear regression models will assess for factors that predict responders and non-responders to treatment using data obtained prior to the intervention.
Aim #4	V2 V3 V4	Prior to randomization: FIQR and SF-36. PROMIS modules for comparison to FIQR and SF-36.	• Pearson correlation and testing for nonzero correlation between PROMIS modules (and corresponding domains of the FIQR and SF-36. • Multiple linear regression may also be sued to investigate this relationship while controlling for potential confounding variables. • FIQR, PROMIS and SF-36 will be obtained at 3 time points and summarizes as values, changes from pre-treatment and percent changes, changes observed in the randomized phase. Time points are (1) V2: pre-treatment; (2) V3 randomized phase and (3) V4 non-randomized active TENS. • Linear models may be used where treatment status ((1) V2: pre-treatment; (2) V3: randomized phase and (3) V4: non-randomized active TENS) is treated as a time-varying covariate to estimate the impact of changes in treatment status.
Exploratory Analysis		Changes in pain Responder status Relationships between endpoints Relationships between changes in pain, sensory and quality of life measures	• Further investigation during non-randomized phase, two months of active TENS (initially randomized to active TENS and those with a single month of active TENS (initially randomized to placebo TENS or standard care) • Multivariate methods (e.g. partial least squares and principal component analysis and classification and regression trees.

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	Screening Log	Pre Visit	Computer/Form
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	Eligibility Confirmation	1, 2	Computer/Form
	FIQR	1,2,3,4	Computer/Form
	MAF	2,3,4	Computer/Form
	TSK	2,3,4	Computer/Form
	Medication	1,2,3,4	Computer/Form
	SF-36	2,3,4	Computer/Form
	PROMIS	2,3,4	Computer/Form
	IPAQ	2	Computer/Form
	PSQLI	2	Computer/Form
	PSEQ	2	Computer/Form
	PCS	2	Computer/Form
	Blinding Question Researcher and Subject	3	Computer/Form
	Global Impression of Change	3, 4	Computer/Form
Pain	NRS	1,2,3,4 Previsit 2,3,4	Computer/Form
	BPI	2,3,4	Computer/Form
Fatigue	NRS, BORG CR10	1,2,3,4	Computer/Form
QST	PPT (C,L, Ant Tib)	2,3,4	Algometer, Form, Marker, Alcohol swab
	CPM	2,3,4	Bucket, thermometer, Water, Ice, Towel, Form
Function	6MWT	2,3,4	Timer, Form, Distance Measurement, Pulse Oximeter, BP Cuff, Sphygmometer
	FTSTS	2,3,4	Timer, Form, Chair with arms
	Functional Reach	2, 3,4	Yardstick, Form
	Accelerometry	1,3,4	Actigraph, home tracking, initialization & instruction sheet
TENS	TENS Trial	1	TENS, Electrodes, Batteries, Lead
	TENS Treatment at Visit	2,3,4	TENS, Lead wires, Electrodes, Batteries, Participant Handbook
Handbooks	Participant Assessor	1,2,3,4	Handbook