Fibromyalgia TENS in Physical Therapy Study (FM-TIPS) Statistical Analysis Plan

A Cluster Randomized Study by Facility and Health Systems, Double Arm (TENS with PT versus PT only), Pragmatic Clinical Trial, and Feasibility of Implementation of TENS in PT Care in Participants with Fibromyalgia (FM)

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

AE	Adverse Event
BPI	Brief Pain Inventory
CDE	Common Data Elements
CFR	Code of Federal Regulations
cIRB	Central Institutional Review Board
CRF	Case report form
CS	Clinically Significant
DCC	Data Coordination Center
DM	Data Management
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EHR	Electronic Health Record
FDA	Food and Drug Administration
FIQR	Fibromyalgia Impact Questionnaire Revised
FM	Fibromyalgia
GAD7	Generalized Anxiety Disorder 7
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IMM	Independent Medical Monitor
ITT	Intention-to-treat
MAF	Multidimensional Assessment of Fatigue
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Movement Evoked Pain
mITT	Modified intention-to-treat
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
PCS	Pain Catastrophizing Scale
PEG	Pain, Enjoyment, General Activity Scale
PGIC	Patient Global Impression of Change
PHQ-8	Personal Health Questionnaire Depression Scale
PI	Principal Investigator
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Physical Therapy
RAPA	Rapid Assessment of Physical Activity
SAE	Serious Adverse Event
SOA	Schedule of Activities
TAPS	Tobacco, Alcohol, Prescription Medication, and Other Substance Use
TENS	Transcutaneous Electrical Nerve Stimulation
5TSTS	Five Times Sit and Stand

PREFACE

This Statistical Analysis Plan (SAP) describes the planned analyses for the FM-TIPS study, funded by the National Institutes of Health (NIH). The planned analyses identified in this SAP are intended to support the completion of a final report that will be prepared and presented to the study sponsor. All final, planned analyses identified in this SAP will be performed only after the last randomized study participant has completed the study, and all data have been cleaned and verified in accordance with applicable standard operating procedures at the FM-TIPS Data Coordinating Center (DCC). Once all data have been cleaned and verified, a "locked" version of the data will be used for reporting the final study results. Key statistics and study results will be presented verbally to the PI, DCC, Data and Safety Monitoring Board (DSMB), and Steering Committee (SC) for review and discussion following database lock and prior to completion of the final report.

The hypothesis test for the primary outcome measure to address the primary aim will be assessed at the 0.05 significance level. The same significance level will be used for all other secondary hypothesis tests on the secondary measures with no attempt to make any type of adjustment for multiplicity, unless otherwise specified.

1. STUDY DESIGN

1.1 Design

This study is a cluster-randomized pragmatic trial conducted where the initial proposed sample size was 600 across 24 physical therapy clinics. The original sample size was reduced from 600 based on a planned interim sample size recalculation following enrollment of the first ~200 participants and based on the planned interim assessment of intra-class correlation coefficient (ICC). A stratified randomization of practice sites will be employed based on healthcare system and size of the practice site (clinics) so that half of the clinics will provide transcutaneous electrical nerve stimulation (TENS) in addition to physical therapy (PT) (TENS+PT) for each enrolled participant and the other half of the clinics will provide standard of care routine individualized PT treatment (PT only). To avoid potential exposure to TENS in the clinics randomized to PT only, the clinics will be specifically instructed not to prescribe TENS to their fibromyalgia (FM) patients. Likewise, study participants in the PT only site that may be exposed to TENS through other means (relatives, friends) will also be instructed not to use TENS to prevent cross-ins. Furthermore, participants randomized to the PT only group will receive TENS unit after the primary outcome data is collected at day 60 which may also prevent cross-ins and provide equipoise. Primary analyses will be based on modified intention-to-treat which includes all participants with baseline (day 1) pre-TENS home activities.

Participants will be followed for 180 days with data collection from home at 1, 30, 60, 90, and 180 days following enrollment. Participants in the PT only group will also complete a brief assessment at day 65. The primary outcome variable will be assessed at day 60, which would be approximately at the completion of prescribed PT. Data collected at PT visits will include the types of treatments (CPT codes) and, at the clinic's usual intervals, visit type (in-person vs telemedicine), and the Patient-Specific Functional Scale (PSFS). All patient reported measures will be obtained at home via computer, tablet, or phone.

1.2 Questionnaires/Outcomes

The following questionnaires will be self-administered by participants:

- **Resting NRS for pain and fatigue:**11-point scale
- **Movement-evoked pain 5TSTS (Five times sit and stand) by NRS for pain and fatigue:** quantifies movement-evoked pain.
- **2016 FM Criteria**: diagnostic criteria for fibromyalgia.
- **PSFS (Patient Specific Functional Scale)** – quantifies activity limitation and measures functional outcomes
- **FIQR (Fibromyalgia Impact Questionnaire Revised)**: 21 items used to evaluate function, overall impact, and symptoms in patients with fibromyalgia.
- **MAF (Multidimensional Assessment of Fatigue)**:16 items measuring fatigue according to four dimensions: degree and severity, distress that it causes, timing of fatigue, and impact on various activities of daily living.
- **BPI (Brief Pain Inventory)**: 11 items measuring pain severity and interference with daily activities.
- **PROMIS-Physical function:** assesses information about physical activities.
- **PROMIS-Sleep & Sleep duration**: 8 items + a sleep duration question to assess sleep quality and quantity

• **PCS (Pain Catastrophizing Scale)**: 13 items measuring pain magnification, rumination, and helplessness.
• **PHQ-8 (Personal Health Questionnaire Depression Scale)**: 8 items measuring depressive disorders.
• **GAD-7 (Generalized Anxiety Disorder)**: 7 items measuring severity of various signs of generalized anxiety disorder.
• **RAPA (Rapid Assessment of Physical Activity)**: 9 items evaluating current level of physical activity.
• **TAPS (Tobacco, Alcohol, Prescription Medication, and other Substance use)**: 4 item screening tool for substance abuse.
• **PGIC (Patient Global Impression of Change)**: one item evaluating all aspects of patients' health and assesses if there has been an improvement or decline in clinical status.

1.3 Interventions and Duration

For the TENS+PT group, participants will be given TENS devices and electrodes following enrollment (signed consent) during their second PT visit. TENS will be applied to the upper and lower back with butterfly electrodes using the following parameters: mixed frequency (2-125Hz), strong but comfortable intensity, variable pulse duration from 100-250 microseconds. TENS will be applied for 2 hours per day at home when the patient is active and doing exercises and should be brought back to PT visits and used during PT treatment.

For the PT only group, participants will be given TENS units after the primary endpoint is collected at 60 days. The same parameters and instructions will be given to the participants as were given to the participants in the TENS+PT group. However, TENS instructions will be done virtually with a study team member rather than in person by their physical therapist.

1.4 Sample Size and Population

Initially, we proposed to enroll 600 participants from 24 physical therapy clinics: half of the clinics will be randomized to TENS+PT and the other half will be randomized to PT only. Based on a planned interim assessment of ICC for sample size recalculation, the target sample size was reduced to 450 participants (see section 9).

1.5 Inclusion Criteria

Age 18 or above

Clinician diagnosis of FM

Referred for land-based PT

Referred for treatment of FM or chronic pain (pain lasting more than 3 months)

Able to provide informed consent

Fluent in reading English

Willing to use TENS

1.6 Exclusion Criteria

Contraindications to TENS use (See Appendix 1 for Precautions and Contraindication references)

a. Pacemaker, defibrillator, implanted neurostimulator or implanted device
b. Epilepsy
c. Currently pregnant or plan to become pregnant in the next 6 months
d. Allergic reaction to patches with gel
e. Current treatment for cancer

Currently enrolled in another pain control study.

Use of TENS within the last 30 days.

Clinically unstable medical or psychiatric issues

2. PRIMARY ENDPOINT

The primary objective of the study is to determine if addition of TENS to routine PT improves movement-evoked pain in patients with fibromyalgia (FM).

A primary effectiveness outcome will involve a comparison of the reduction of movement-evoked pain during a five times sit and stand test (5TSTS) measured by 11-point NRS from baseline to 60 days between the TENS+PT and PT only groups. The severity of pain will be measured on a 0 to 10 scale at each time where 0 is no-pain and 10 is worst pain imaginable. The baseline measurement will occur at home before the first instance of the patient applying the TENS device (or at parallel time for PT only patients). The 60-day measurement of movement-evoked pain will be obtained post-TENS after 30 minutes of TENS use for the TENS+PT group or at parallel time point for the PT only group. All outcomes will be collected by the participant at home. Movement-evoked pain during 5TSTS was measured in our previous randomized clinical trial, the FAST study, and the change in this measure was used to calculate the sample size for the current study.

3. SECONDARY ENDPOINTS

The secondary objectives of the study are to:

- *Determine if addition of TENS to routine physical therapy improves disease activity and symptoms, increases adherence to physical therapy, increases the likelihood of meeting patient specific functional goals, and reduces medication use.*

Change in the resting pain score from baseline (pre-TENS) to 60 days (post-TENS session) will be used as a secondary outcome variable. The severity of pain will be measured on a 0 to 10 scale at each time where 0 is no-pain and 10 is worst pain imaginable. Other secondary outcomes include change in the following domains:

- o Pain interference (BPI)
- o FM disease activity (FIQR)
- o Resting fatigue (NRS)
- o Movement-evoked fatigue (MEF)
- o Multidimensional assessment of fatigue (MAF)
- o Rapid assessment of physical activity (RAPA)
- o Patient global impression of change (PGIC)

An exploratory outcome for patient-specific function using the patient-specific functional scale (PSFS) will be evaluated. Additional HEAL-specified measures and medications are located in the visit schedule. A brief description of the domains above can be found in section 1.2.

4. ENROLLMENT & RANDOMIZATION

Participants with fibromyalgia will be enrolled in outpatient physical therapy clinics: half of the clinics will be randomized to TENS+PT and the other half will be randomized to PT only. At each site, individualized PT treatment specified by the physical therapist alone or with TENS will be applied during each visit. Participants in the TENS+PT intervention clinics will receive TENS units and electrodes at baseline to be applied to the cervical and lumbar regions. They will take the units home and bring the units back to their PT clinic visits with instructions for use at home while active and during their exercises. The physical therapist at each clinic will complete routine documentation of treatment that will include the patient-specific functional scale (PSFS) at the intake visit and approximately monthly intervals.

This will be a cluster randomized pragmatic trial. A stratified randomization procedure by healthcare system and size of clinic will be used to randomize clinics to either TENS+PT or PT alone. Half of the clinics will be randomized to TENS+PT and the other half of the clinics will be randomized to PT only.

We hypothesize that using TENS in a PT setting is feasible and that FM patients using TENS in addition to their PT will have reduced movement-evoked pain and other symptoms and are more likely to reach their therapeutic goals and reduced medication use compared to those patients in the PT alone group.

5. TABULATIONS

All study participants who provide informed consent will be accounted for in this study. The number of randomized participants with baseline data and their study disposition will be reported overall, and by treatment group. A CONSORT diagram summarizing the final status of all study participants will be provided. The proportion of randomized study participants completing each visit will be summarized as in Table 5.1 below.

Table 5.1: Completeness of Study Data by Visit

Visit	TENS+PT (N = XX)	PT Only (N = XX)
BL (Day 1)	XX (XX%)	XX (XX%)
V01 (Day 30 ± 5)	XX (XX%)	XX (XX%)
V02 (Day 60 -5/+10) Primary Endpoint	XX (XX%)	XX (XX%)
V03 (Day 65 ± 5)	NA	XX (XX%)
V04 (Day 90 ± 5)	XX (XX%)	XX (XX%)
V05 (Day 180 ± 5)	XX (XX%)	XX (XX%)

Additional summary reports will describe:

- Number of study participants eligible, consented, and completed their day 1 home activities by site
- Reasons for exclusion
- Completeness of study visits, case report forms
- Protocol deviations
- Study Treatment (TENS) Suspensions
- Early Study Terminations
- Reportable Events
- Study Treatment Compliance
- Baseline participant data will also be summarized by treatment group (PT+TENS and PT only) with respect to important demographic characteristics. Distribution of numeric and categorical variables will be tabulated by treatment group and overall. Numeric variables will be summarized by the mean, standard deviation, minimum, and maximum. Categorical variables will be tabulated by frequency count and percentages. Variables that will be summarized include:
- Demographic Characteristics:
    - Age
    - Gender
    - Race
    - Ethnicity
    - FM Duration (Years)

- FM Characteristics
    - FM disease activity (FIQR)
    - Opioid use at baseline
    - Use of FM Medications

6. ANALYSIS POPULATIONS

6.1. Primary and Secondary Effectiveness Analyses (6 Month Treatment Period)

6.1.1. Intent-to-Treat (ITT) Population

For the primary outcome as well as all secondary outcomes during the 6 months follow-up period, all analyses will be performed consistent with the intention-to-treat (ITT) principle – per the recent JAMA Guide to Statistics and Medicine (Detry, 2014). With treatment randomization having occurred at the practice site level, the act of signing the consent automatically assigns a participant to the treatment arm the practice site was randomized to. However, it is possible that after signing consent that an enrolled participant will not show up at the PT clinic at day 1 or will not complete the home activities at day 1 where baseline measurements are obtained. Therefore, such a patient will be a "no-show" for the rest of the study duration. Thus, we will employ a modified ITT definition (mITT), such that the mITT population will include all participants assigned to a study arm that have completed baseline (day 1) home activities. All participants will be analyzed as-randomized, which means they will be analyzed based on the treatment to which they were randomized (whether the clinic is randomized to PT only or PT+ TENS), whether or not they remained compliant with respect to using their randomized TENS group assignment.

6.1.2. Per Protocol (PP) Population

To assess the sensitivity of key results and to obtain knowledge regarding the potential effects when the protocol was strictly adhered to, we will also replicate all key primary, secondary, and additional secondary effectiveness objectives using a per-protocol population. The per-protocol population includes the subset of all mITT participants who satisfy the following:

- Completed more than one PT appointment.
- And in addition, for those in the TENS group
    - Used TENS on at least 8 days within the first 30 days following day 1 homework assignment, and with an average of at least 30 minutes per day for the 30-day period (i.e. have accumulated a minimum of 15 hours of TENS use; 0.5 hr x 30=15 hours = 900 minutes),

      AND

    - Used TENS on at least 8 days during the subsequent 30 days (days 31–60), with an average of at least 30 minutes per day for the 30-day period (i.e. have accumulated a minimum of 15 hours of TENS use during days 31 to 60).

The above conditions for those in the TENS group to meet protocol assure continuous adherence of TENS use over the 60-day period.

Those in the TENS group who did not meet the definition of per protocol, 1) met criteria only for the first 30 days but not the second 30 days, or 2) provided TENS usage information but did not meet criteria for usage in both time periods, and 3) did not have any TENS usage information beyond the first day will be included in a dose response analysis of TENS.

7. PRIMARY ANALYSES

7.1 Primary Effectiveness Hypothesis: to determine if addition of TENS to routine PT improves movement-evoked pain (MEP) in patients with fibromyalgia (FM).

Primary objective: To conduct an effectiveness analysis comparing the TENS+PT and PT only groups.

The raw data for both treatment groups will be presented graphically, and summarized as in the following table:

Table 7.1: Descriptive Statistics of Movement-evoked Pain Over Time

Visit	TENS+PT (N = XX)	PT Only (N = XX)
Baseline Pre-TENS Mean (SD) (Min, Max) Missing	 XX.X (XX) (XX.X, XX.X) XX	 XX.X (XX) (XX.X, XX.X) XX
Day 30 Post-TENS (Month = 1) Mean (SD) (Min, Max) Missing	 XX.X (XX) (XX.X, XX.X) XX	 XX.X (XX) (XX.X, XX.X) XX
Day 60 Post-TENS (Month = 2) Mean (SD) (Min, Max) Missing	 XX.X (XX) (XX.X, XX.X) XX	 XX.X (XX) (XX.X, XX.X) XX
Day 65 Post-TENS (Month 2) Mean (SD) (Min, Max) Missing	 NA	 XX.X (XX) (XX.X, XX.X) XX
Day 90 Post-TENS (Month 3) Mean (SD) (Min, Max) Missing	 XX.X (XX) (XX.X, XX.X) XX	 XX.X (XX) (XX.X, XX.X) XX
Day 180 Post-TENS (Month 6) Mean (SD) (Min, Max) Missing	 XX.X (XX) (XX.X, XX.X) XX	 XX.X (XX) (XX.X, XX.X) XX

7.2 Analysis

To assess the effectiveness of TENS+PT compared to PT alone, we will compare the change in movement-evoked pain during 5TSTS from pre-TENS baseline to post-TENS at day 60. The null hypothesis can be evaluated based on an assessment of parameter estimates from a linear mixed effects model (LMM: Laird & Waire, 1982). This will be tested using LMM analysis with treatment group and movement-evoked pain level at baseline as fixed effects. Randomization will be stratified by the healthcare system and clinic size. The model will be adjusted for the fixed effect of clinic size. The proposed study involves multiple clinics under each healthcare system, which is a potential source of additional variation. Patients within a clinic tend to be correlated due to similarity of environment, e.g. because of getting PT treatment from the same set of physical therapists (Localio et al, 2001).Therefore, a random effect will be included for treatment nested within clinic, and within healthcare system.

For this analysis, the LMM can be written in the following manner:

$$Y_{ijk} = \beta_0 + \beta_1 X_{1i(jk)} + \beta_2 X_{2i(jk)} + \beta_3 T_{ijk} + a_{i(j)} + \epsilon_{\text{ijk}}$$

where:

- $\underline{Y_{ijk}}$ is the change in movement evoked pain level from baseline to day 60 for the kth participant in ith healthcare system and jth clinic.
- β_0 is the common intercept.
- $X_{1i(jk)}$ is the movement evoked pain level at baseline for the kth participant .
- $X_{2i(jk)}$ if the participant was in the large clinical size strata at baseline, 0 otherwise.
- $T_{ijk} = 1$ if kth participant in ith healthcare system and jth clinic is in the TENS+PT treatment group; = 0 otherwise.
- $a_{j(i)}$ is the random clinic effect within the ith healthcare system
- ϵ_{ijk} is a random error term for the kth participant in ith healthcare system and jth clinic.

From the fitted model, the difference in mean change on pain between the two treatment groups will be assessed by the test for treatment effect. Accordingly, the main parameter of interest is β_3, which corresponds to the estimate of the difference in mean change in MEP between the TENS+PT vs PT only groups, controlling for baseline pain. *To assess the effectiveness of TENS+PT as measured by the change in MEP between baseline and Month 2 (Day 60), we employ the* LMM described above. Assuming the linear model provides the best fit, a test for the statistical significance of the mean difference between the two groups (TENS+PT vs. PT only) will be carried out as follows:

$$H_0: \beta_3 = 0 \quad vs. \quad H_A: \beta_3 \neq 0$$

Statistical significance for efficacy of TENS+PT vs. PT alone will be based on a two-tailed test at the 0.05 significance level with treatment effect summarized as mean difference with associated 95% confidence interval. If this hypothesis is not rejected, then we will conclude that there is not sufficient evidence to conclude that the *TENS+PT* treatment group is efficacious on MEP during the first two months of the treatment period. If the null hypothesis is rejected, figures will be utilized to assess which of the treatment groups shows significant differences over time with respect to the MEP scores. Each null hypothesis can be evaluated with the corresponding likelihood ratio test. Rejecting the null hypothesis implies that there is enough evidence to conclude that the use of TENS+PT is efficacious in reducing MEP compared to PT alone.

7.3. Missing Data for mITT Analyses

In the case of subject drop-out, reasons for subject drop-out will be recorded and compared between the two treatment groups. Subject characteristics and outcome measures collected prior to drop-out for those who drop-out will be compared to those who complete the study. The modified ITT analysis will include all consented participants in their assigned treatment arm that have completed baseline (day 1) home activities for the primary outcome. This will include those with missing follow-up data. Accordingly, the modified ITT analysis for the primary outcome measure of change in movement-evoked pain at day 60 includes participants with baseline data but with missing day 60 pain values, multiple imputation of the missing pain values will be conducted. Multiple imputation analyses assuming missing at random (MAR) will be performed using SAS PROC MI and SAS PROC MIANALYZE. To avoid imputation bias, all variables in the substantive analyses and, if feasible, other variables in the study database predictive of the missing values or influencing the cause of missing data will be included.

In addition to the MI analysis under MAR, since the data under analysis cannot distinguish if data is MAR or it is missing not at random (MNAR), sensitivity analysis will also be performed. Methods for sensitivity analysis such as marginal delta adjustment, conditional delta adjustment, reference-based controlled imputation, and other pattern mixture models will be considered. If needed, variables will be transformed to satisfy approximate normality before imputation and retransformed back to original scale.

7.4 Covariate Adjustments

It is expected that stratified randomization will lessen the need for covariate-adjusted analyses. However, in the event that adjusted analyses are necessary, a secondary comparison of the primary endpoint between groups will be made by expanding the linear mixed model to include covariates. Potential covariates include age, race, ethnicity, TENS dose/intensity, opioid use, and use of FM medications (for example, anti-depressants, α2-delta ligands). In addition, opioid use at baseline as a possible effect moderator of TENS will be examined by including an opioid*treatment interaction in the model. If found to be significant, then secondary analyses to test for TENS effectiveness by opioid status will be performed with p-values adjusted using Bonferroni's method for multiple comparisons. Statistical significance for effectiveness of TENS+PT vs. PT alone will be based on a two-tailed test at the 0.05 significance level with treatment effect summarized as mean difference with 95% confidence interval.

8. SECONDARY ANALYSES

Analyses for secondary outcome measures will be performed using the analyses methods described in section 7 above. The list of the secondary outcomes is in section 3 above.

9. SAMPLE SIZE JUSTIFICATION

The required sample size was calculated to assess the effect of TENS+PT versus PT alone on the primary outcome of change from baseline to 2-month visit in pain after PT using two-independent samples t-test with inflation factor of [1+(m-1)*ICC] applied to account for average cluster size (m) and intra-cluster correlation (ICC). From the FAST study, there was a standard deviation of 2 for change in movement-evoked pain for the 5TSTS test. There was a greater decrease in pain with active- TENS compared to placebo-TENS of 1.3 (95% CI: 0.34, 2.2) for movement-evoked pain during 5TSTS. Compared to no-TENS, there was a greater decrease in pain with active-TENS of 1.8 (95% CI: 1.0, 2.8) for movement-evoked pain during 5TSTS. For this cluster randomized pragmatic trial comparing TENS+PT vs. PT alone, sample size was determined such that the statistical test at the 0.05 significance level will be able to detect a difference of at least 1.0 in mean change in pain with 80% power. Participants randomized to a treatment arm will be clustered by clinic, since PT clinics will be randomized for ease of implementation. Thus, an estimate of the intra-cluster correlation (ICC) was needed for the sample size calculation. With no prior estimate of ICC, the required sample size per treatment arm (or participants per clinic) for the desired detectable mean difference of 1.0, assuming SD=2.0, was calculated for combinations of ICC values and number of clinics per treatment arm; see Table 1 for ICC values for a sample size <300 participants per treatment arm. A pilot study examining a non-pharmacological intervention for pain by our group showed an ICC of 0.01, DeBar and colleagues used an ICC of 0.002 for sample size calculation for a chronic pain population, and Adams et al. showed widely varying ICCs between data sets, but the majority of patient-reported outcomes were below 0.095 ICC. Therefore, the study sample size was originally calculated for ICC value between 0.12 and 0.14 which resulted in a conservative sample size estimate of 456 total participants (228 per treatment arm) with complete data, for 9 to 12 clinics per arm. Table 9.1 shows the number of participants per clinic for each treatment arm, for specified ICCs and range of 9 to 12 clinics per treatment arm (C), to detect a mean difference of at least 1 (in NRS scale of 0 to 10) in pain at the 0.05 significance level with 80% power. Numbers in black are the sample size needed for combinations of ICCs and number of clinics for n≤228/arm while the tan numbers are for n>228 per treatment arm.

For example, if the ICC is 0.14, to reach 80% power with 12 clinics in each arm, complete data will be needed from 19 patients per clinic, 228 patients in each arm: 456 patients total. The dropout rate in the previous randomized clinical trial from our group, the FAST study, was 12% at 30-day follow-up. Since follow-up is 60 days in the proposed study, a higher drop-out rate is expected. The drop-out rate includes those patients who complete the informed consent form but do not complete the baseline assessment as a part of day 1 home activities, as well as those patients who start the study and dropout prior to day 60. To account for up to 24% drop-out rate, a total of 600 participants (300 per arm) will be enrolled. It should be noted that expected enrollment will average 25 patients per clinic for the scenario with 12 clinics per treatment arm, with some variability expected in the number of patients enrolled from each clinic. The number of patients enrolled from each clinic will be capped at 30 patients to allow for enrolling up to 20% more than originally planned.

An interim ICC recalculation will be conducted after the first 200 participants have been enrolled (approximately 1/3 of the sample) for the purpose of determining ICC for the primary outcome measure. This analysis to assess the primary outcome variable will be done for the purpose to only calculate the ICC value using the change in pain scores without regard to group assignment and will not require unblinding of randomization. Therefore, it does not have an impact on the type I error rate and there is no change in our planned analysis on our statistical analysis plan. This analysis will only be used to determine if the final number of subjects per site should be changed based on the ICC value. There are no stopping rules.

Table 9.1: Total study sample size with varying ICC, number of clinics per arm and subjects per clinic.

ICC	ICC values by clinics (C), per treatment arm; subjects per clinic (total subjects)			
	C=9	C=10	C=11	C=12
0.050	11 (99)	9 (90)	8 (88)	7 (84)
0.100	23 (207)	16 (160)	13 (143)	11 (132)
0.110	30 (270)	20 (200)	15 (165)	12 (144)
0.120	--	25 (250)	17 (187)	14 (168)
0.125	--	28 (280)	19 (209)	14 (168)
0.130	--	--	21 (231)	16 (192)
0.135	--	--	24 (264)	17 (204)
0.140	--	--	27 (297)	19 (228)
0.145	--	--	--	21 (252)
0.150	--	--	--	23 (276)
0.155	--	--	--	--

The original sample size calculation conservatively assumed the ICC values to change between 0.12 and 0.14, subjects to be enrolled from 12 clinics in each group, and approximately equal number of subjects to be enrolled from each clinic. During the conduct of the study, as clinics were recruited, some other clinics were deactivated. It was also observed that there was variability in the number of patients enrolled per clinic. This observed variability required the need to account for the variation in the number of enrolled participants per clinic in the sample size calculation. For this purpose, the coefficient of variation (CV), which is the ratio of standard deviation (sd) to the mean (CV = sd / mean), was used in the sample size calculation to represent variation in enrollment per clinic

The number of active clinics at the time of the ICC recalculation was 28, where 26 clinics (13 in each treatment) had at least one participant with a day 1 assessment. The observed CV was 0.6.

Plans for sample size recalculation were discussed with Drs. Liz Turner and Patrick Heagerty from the NIH Collaboratory Biostatistics Core in November 2022. This meeting resulted in two recommendations: 1) recalculating the ICC value based on the adjusted model, consistent with the final analyses. 2) Calculating the ICC and the Jackknife estimate of standard error (SE) of ICC, and calculating the sample size using both the current estimate of ICC and ICC + 1SE as a conservative estimate.

These recommendations were included in the implementation of the interim ICC estimation and sample size recalculation. With 220 enrolled subjects, the estimate of the ICC based on the adjusted model, consistent with the SAP, was 0.05 with the Jackknife estimate of the SE of ICC of 0.07. Taking into account the variability in enrollment numbers per clinic (CV = 0.6) and using 13 clinics/group, the sample size was estimated at 450 enrolled subjects to obtain a final number of 342 participants completing day 60 based on a 24% dropout rate. This sample size provides >90% power for ICC = 0.05, 81% power for ICC = 0.10, and 78% power for ICC of 0.12 (ICC + 1SE = 0.05 + 0.07). The study sample was updated to 450, assuming an ICC value of 0.10. The sample size recalculation was presented to NIAMS and the DSMB. Both NIAMS and the DSMB recommended approval of the change in sample size.

10. SAFETY MONITORING

10.1 Adverse Events

All aspects of the study will be monitored by authorized individuals in compliance with Good Clinical Practice (GCP) and applicable regulations. Refer to the Safety Management Plan for additional details.

An adverse event in this study will be defined as any unfavorable and unintended sign or symptom temporally associated with the use of the TENS units, falls while performing the Sit and Stand Test during Research Homework or physical therapy exercise, changes in health status that would impact ability to use the

intervention TENS, or hospitalizations/Emergency Department visits. Pain associated with physical therapy treatment may worsen during the study but will not be classified as an AE.

Anticipated adverse events with TENS use include:

- Skin rash or irritation from electrodes
- Anxiety, itchiness, nausea or pain with TENS

10.2 Assessment and Recording of Adverse Events

The study team may contact the participant when an adverse event has been reported to collect further information on the AE, if needed. The team will determine if the adverse event is serious, related to TENS treatment, and if any action needs to be taken, for example, discontinue TENS use, or if further reporting to regulatory authorities is necessary.

Pregnancy: Pregnancy itself is not regarded as an AE. However, TENS is not recommended for use during pregnancy and the participant will be withdrawn from treatment and the outcome of all pregnancies that occur during paternal or maternal exposure to study device (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the participant has been withdrawn from treatment.

10.3 Management of Unanticipated Problems

Unanticipated problems will be defined as unexpected adverse clinical symptoms related to TENS or electrode use. These will be reported as “other” TENS-related AE on the CRF and will be reviewed at each DSMB meeting. If unanticipated TENS-related AE are uncovered that occur in >5% of enrolled participants, the consent form will be modified, and the AE will be specifically queried on the AE CRF going forward. Participants who have completed the study will be notified of any newly recognized TENS-related AE.

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