

**Regulatory/Ethics Consultation Call:
Fibromyalgia TENS in Physical Therapy Study (FM TIPS)**

**Friday, December 20, 2019
Meeting Participants**

Joe Ali (Johns Hopkins), Emine Bayman (University of Iowa), Judith Carrithers (Advarra), Michelle Costigan (University of Iowa), Michelle Countryman (University of Iowa), Leslie Crofford (Vanderbilt), Dixie Eckland (University of Iowa), Janel Fedler (University of Iowa), John Lantos (Children’s Mercy Hospital), David Magnus (Stanford), Martha Matocha (NINR/NIH), Stephanie Morain (Baylor College of Medicine), Tina Neal-Hudson (University of Iowa), Tammy Reece (Duke), Kathleen Sluka (University of Iowa), Kayte Spector-Bagdady (University of Michigan), Jeremy Sugarman (Johns Hopkins), Wendy Weber (NCCIH), Kevin Weinfurt (Duke), Liz Wing (Duke)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS
Overview of Demonstration Project	<p>Overview: The FM TIPS study is testing the effectiveness of transcutaneous electrical nerve stimulation (TENS) nonpharmacologic treatment for pain and fatigue in patients with fibromyalgia (FM) in a real-world, physical therapy practice setting. FM is a chronic condition characterized by widespread musculoskeletal pain, tenderness, and stiffness associated with fatigue and sleep disturbance. While physical therapists are trained in TENS, it is underused in primary care. A recent study has shown that with repeated use it can be effective at reducing pain with movement and resting pain compared with placebo or no treatment. The goal of this study is to assess the feasibility of adding TENS to the treatment of patients with FM in a real-world, physical therapy setting, and to determine if the addition of TENS to physical therapy reduces pain, increases adherence to physical therapy, and allows patients with FM to reach their specific functional goals with less medication use.</p> <p>Collaborative network partners:</p> <ul style="list-style-type: none"> ○ Kepros Physical Therapy and Performance ○ Genesis Healthcare Systems ○ Vanderbilt University Physical Therapy Services ○ BenchMark Physical Therapy ○ Rock Valley Physical Therapy 	

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	<ul style="list-style-type: none"> ○ Results Physical Therapy <p>NIH Institute: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)</p> <p>Study design: FM TIPS is designed as a cluster-randomized pragmatic trial conducted with approximately 600 patients across 20-25 physical therapy clinics within 6 healthcare systems in both rural and urban settings in Iowa, Illinois, Kentucky, and Tennessee. All individuals with physician-diagnosed FM (around the trunk area, shoulder or hip) and who do not have contraindication to TENS will be eligible to participate. In the intervention clinics, TENS will be administered along with standard exercise and physical therapy in the clinic, and then patients will be sent home with TENS units to administer at home. In the non-intervention clinics, patients will receive standard exercise and physical therapy in the clinic and will be offered TENS units and electrodes after completion of the study to enhance recruitment.</p> <p>Primary and secondary outcomes: The primary outcome for the study is movement-evoked pain, a primary symptom of FM and one that interferes with adherence to physical therapy and patient-specific functional goals. Assessments will be both in-home and in-clinic. The team will provide all clinics with TENS units and electrodes as well as electronic tablets to facilitate data collection.</p> <p>Other important notes about the study:</p> <ul style="list-style-type: none"> ○ The study team expects that clinics will not already be using TENS. They will interview physical therapy clinics before initiating the study intervention to gain insight on providers' perceptions of TENS efficacy, current use of TENS and other PT interventions for FM, and perceptions about use of medications in treating FM. ○ There was discussion about discouraging crossovers for those participants not randomized to TENS, particularly because the same consent process will be used for all participants. It was suggested that the consent form should include information that, based on treatment guidelines, all patients regardless of randomization will receive physical activity as treatment and will be offered a TENS unit by the end of the study. ○ The study team believes there is equipoise in providing/withholding TENS. 	

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	<ul style="list-style-type: none"> ○ The study team expects it will be within the budget to use study funds to provide the TENS units to all participants. The study team is in discussion with TENS manufacturers to obtain the units at low cost or through manufacturer donation. Of note, TENS units are widely available over the counter. ○ Patients will use TENS equipment at home, with data collected through a patient portal. Some data will be extracted via the electronic health record (EHR) or REDCap portal. Patient-reported outcomes (PROs) will not be populated in the EHR. The team will use what is in the EHR, or create a template to unify scales across systems. <p>The study team indicated that TENS is currently approved for relief of chronic intractable pain and as adjunctive treatment of post-surgical and posttraumatic acute pain. As mentioned earlier, the primary outcome of this study is improvement of movement-evoked pain. Consequently, those on the call asked whether this was an extension of the current indication for the device, and whether an Investigational Device Exemption (IDE) would be required to use the device for this purpose in this study. The team stated they did not believe an IDE was required for the primary pain outcome; however, the study outcomes for fatigue relief may need closer assessment. The Core members asked that the study team review a paper related to FDA-regulated products and PCTs that was prompted by the need to consider similar issues in other PCTs. The team agreed to review and assess these considerations. Although the team had not planned on collecting data for a new indication, the TENS manufacturers might be interested in using the study results as grounds for an extended indication for functional improvement. The team was strongly encouraged to consult with FDA on the use of TENS in this study.</p>	<p>Tammy sent the 2015 ethics paper to those on the call on December 20:</p> <p>Anderson ML, Griffin J, Goldkind SF, et al. The Food and Drug Administration and pragmatic clinical trials of marketed medical products. Clin Trials. 2015;12:511-9. doi: 10.1177/1740774515597700.</p> <p>The Core and NIH Project Officers can provide help to the team when evaluating this issue with the FDA.</p>
Status of IRB approval	<p>The University of Iowa has agreed to serve as the single IRB of record.</p> <p>It is expected that most participating health systems will not have much experience with clinical research and will need GCP and human subjects research training. They will need to enter a reliance agreement with University of Iowa. The team is still in the process of identifying physical therapy clinics, but those who have agreed to participate understand the single IRB requirement.</p>	

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Risk classification	<p>The University of Iowa IRB does not make a formal risk determination until the full project is submitted, but through preliminary discussions, it is expected that the study will be deemed minimal risk.</p> <p>Those on the call agreed that the study appears to be minimal risk.</p>	
Consent	<p>The study team has not yet drafted a consent form.</p> <p>The study team is considering using the same consent form for both study arms. The team plans to obtain electronic consent using tablets available at each clinic. Eligible patients will self-enroll. Someone on site will be available to answer questions about the study and ensure the informed consent process is followed.</p> <p>Since everyone will get a TENS unit at some point during the study, those on the call suggested that the team include this information in the consent form.</p> <p>Although plans have not been finalized, the study team expects that information about the study will be provided via a YouTube video as part of the consent process, allowing the main PI to share information about the study in a uniform way. It was suggested that simple videos can be done and include a mock consent conversation.</p> <p>The goal is to automate consent as much as possible and have a person affiliated with study available, or have a contact number for questions, to avoid disrupting the clinical practice schedule.</p> <p>The IRB will want to evaluate both the video script and the video.</p> <p>The study team asked for a reference on e-consent, as it is an acceptable alternative under both FDA and the revised Common Rule. It was suggested that the team look at the ADAPTABLE trial (PCORnet) for information on its e-consent process.</p> <p>FDA also has a good guidance on e-consent and the team can look at that.</p>	<p>Joe Ali will provide the study team with information on video consent creation (completed 1/28/2020)</p>
Privacy/HIPAA	<p>The study team will contact stakeholders about the EHR at each health system.</p> <p>The University of Iowa is the data coordinating center and has a process for HIPAA compliance.</p> <p>The study needs to establish a patient portal. The team will be sensitive to potential issues of privacy with REDCap (e.g., inadvertent HIPAA violations). The Vanderbilt team members have experience and expertise with REDCap and can help with any issues.</p>	

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Monitoring and oversight	<ul style="list-style-type: none"> • NIAMS, which holds the grant for this study, expects to charter a DSMB and takes responsibility for this. • In the previous TENS study by this team, which was determined to be minimal risk, the DSMB did both data monitoring and advising. For example, the DSMB looked at the randomization to ensure an even distribution and hitting targets, and gave suggestions for improvements. 	2/18/2020: NIAMS confirmed it will convene the DSMB for the study
Issues beyond the study	<ul style="list-style-type: none"> • A certificate of confidentiality will be automatically provided per recent NIH policy. This certificate adds provisions for future research uses and confidentiality obligations for future data sharing. 	

Research Strategy

A. Significance

Fibromyalgia and Need for Non-Pharmacological Treatment. Fibromyalgia (FM) is a complex condition characterized by widespread pain and fatigue. A recent meta-analysis of 65 studies that included more than 3 million people worldwide showed the prevalence of FM is approximately 2% overall and 4% in women¹. Pharmacological interventions are modestly effective for FM with most individuals experiencing activity-limiting pain and fatigue despite use of multiple drugs^{2,3}. A recent population-based study reported that 22% of FM patients were using chronic opioids and 19% were using chronic benzodiazepines³. It has become increasingly recognized that non-pharmacological interventions should be considered first-line treatments for chronic pain⁴⁻⁶, and can be used as the initial treatment or added to pharmacological approaches. The recent European League Against Rheumatology Treatment Guidelines explicitly recommends that “Initial management should focus on non-pharmacologic treatment”⁵. While there is strong evidence that exercise is an effective treatment for chronic pain, including FM^{7,8}, individuals often report movement-evoked pain that limits activity-participation^{9,10}. Thus, use of non-pharmacological approaches that reduce movement-evoked pain could enhance adherence with exercise recommendations.

Transcutaneous Electrical Nerve Stimulation (TENS). TENS is a non-pharmacological intervention that delivers electrical current through the skin for pain control. Our prior work shows that TENS activates endogenous inhibitory mechanisms, including release of endogenous opioids in the central nervous system, to reduce central excitability^{11,12}, while clinical studies show TENS reduces postoperative opioid consumption¹³. Based on the mechanism of action of TENS, it may be particularly useful in individuals with FM who show reduced endogenous inhibition and enhanced central excitability^{14,15}.

Preliminary Studies. Our multi-institutional and multi-disciplinary research group recently completed an NIH/NIAMS-funded (UM1 AR063381) randomized placebo-controlled clinical trial (N=301), FAST: Fibromyalgia Activity Study with TENS (NCT01888640), that showed Active-TENS (compared to Placebo-TENS or No-TENS) reduced pain and fatigue during movement and at rest acutely (during the first application) and following 4 weeks of daily use (**Fig. 1**). After the randomized phase, all groups received Active-TENS – there was sustained improvement in the Active-TENS group and equivalent improvement in the groups originally randomized to Placebo-TENS or No-TENS. Dramatic improvement in the global rating of change occurred for the Active-TENS group when compared to placebo-TENS or no-TENS groups (**Fig. 2**). Further, TENS was well tolerated with <5% of participants reporting pain with TENS or irritation with the electrodes, which were the most common adverse events.

There are, however, **major barriers** to implementing recommended non-pharmacologic treatments. For example, our research group developed an electronic health record-based prescription for TENS and exercise for patients with a chronic musculoskeletal pain diagnosis (University of Iowa Health Care: Primary Care Chronic MSK pain SmartSet). Extensive steps were undertaken to engage primary care providers in Family Medicine and Internal Medicine before implementation including hands-on training, informational workshops, regular feedback sessions, laminated tip-sheets, provider and patient education materials (videos, handouts). Despite these efforts, there were only small increases in prescription rates for TENS at Family Medicine (4% to 10.5%) and Internal Medicine (3% to 8.5%).

Physical therapists (PTs) specialize in prescribing non-pharmacological treatments, including TENS, for pain and therefore clinical implementation barriers should be greatly reduced. Moreover, the ability of TENS to reduce pain during movement (**Fig. 1**)^{16,17} could greatly enhance patient adherence to a PT home exercise program. The availability of PT is far higher than other non-pharmacologic therapies, such as cognitive behavioral therapy, acupuncture, and meditative movement therapies, and PT is more likely to be covered by health insurance than other non-pharmacologic therapies.

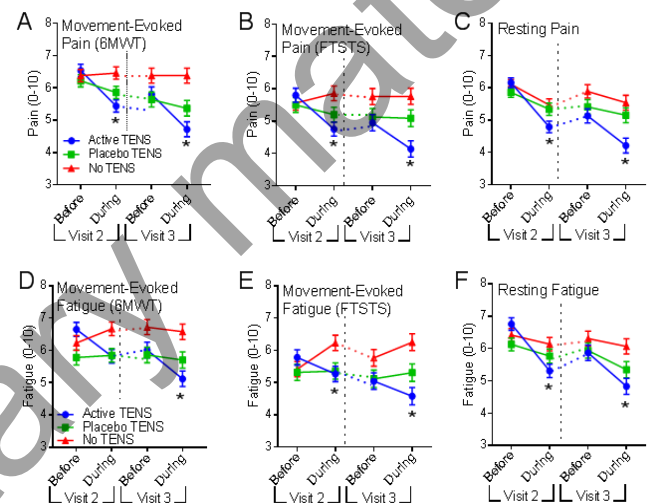


Figure 1. Active-TENS significantly decreased pain and fatigue during activity and at rest compared to placebo-TENS or no-TENS (intention-to-treat analysis). Line graphs show pain and fatigue ratings before and during treatment at Visit 2 (first TENS treatment), and before and during treatment at Visit 3 (after 1-month home use, dotted line). **A.** Movement-pain during six minute walk test (6MWT). **B.** Movement pain during five times sit to stand (5TSTS). **C.** Resting Pain. **D.** Movement-fatigue during 6MWT, **E.** Movement-fatigue during 5TSTS, **F.** Resting fatigue. Data are mean \pm SEM. *, significantly different from placebo-TENS and no-TENS.

Thus, the proposed study will enable PTs, who are trained in application and use of TENS as well as exercise prescription, to provide TENS as adjunct treatment for pain.

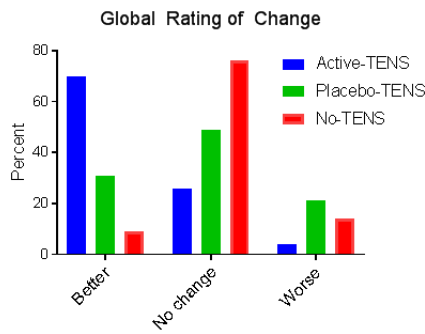


Figure 2. Active-TENS resulted in improved perception of change compared to placebo-TENS ($p < 0.0001$) or no-TENS ($p < 0.0001$). Bar graph showing the percentage of people reporting better or much better, no change, and worse or extremely worse after 4 weeks of active-TENS, placebo-TENS or no-TENS. No differences between placebo-TENS and no-TENS groups ($p = 0.175$).

Pragmatic Trial Embedded in Physical Therapy Clinics. In keeping with the intent of an embedded pragmatic clinical trial, this study is intended to determine effects of TENS as an adjunct to PT to improve outcome of patients with FM. In **Table 1**, we summarize elements of the proposed study along the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS-2)¹⁸. Increasing use of TENS as an alternative to pharmacological treatments, is far more likely if it is utilized within the context of PT where TENS is already part of clinical practice and relieves movement-evoked pain. This allows clinicians familiar with the properties and application of TENS to propose this adjunct to treatment, educate the patient on TENS, and re-enforce adherence due to frequent contact that PTs have with their patients. This proposal will (1) provide data to influence physicians, PTs, and insurers that TENS added to PT would improve tolerability of PT by reducing movement-evoked pain and would provide synergistic beneficial effects on FM symptoms and function; (2) enroll a specific population for whom the decision to employ TENS is relevant and evidence-based; and (3) streamline procedures and data collection for PT practices so that conducting this research will only minimally interfere with routine clinical practice. ***If the effectiveness of TENS is confirmed in this pragmatic trial, then our findings could ultimately***

change the practice pattern for treatment of FM by reducing prescription of drugs, including opioids, in favor of referral for non-pharmacologic interventions like TENS and exercise with far fewer adverse effects.

PRECIS-2 DOMAIN	Description
Eligibility Criteria	Who is selected to participate in the trial? All individuals with a CLINICIAN DIAGNOSIS of FM and who do not have contraindication to TENS will be eligible to participate.
Recruitment	How are participants recruited into the trial? We will recruit participants when they arrive for their regular PT referral visit at a diverse range of PT practices.
Setting	Where is the trial being done? The study will be conducted at PT practices in the Midwest and South, which are selected for diversity in terms of small and large private networks, urban and rural locations, and includes University-affiliated practices. These settings are identical to those in which the results would be applied.
Flexibility	How should the intervention be delivered and how will adherence be determined? This study uses TENS as an adjunct to usual care which will be individualized according to each therapists' usual practice. We will provide information to clinics on the optimal parameters for use of TENS for pain relief. Adherence to PT will be determined by self-report and extracted from the EHR.
Follow-up	How closely are participants followed? Each participant will be followed according to the frequency of visits prescribed by their therapist. After completing the recommended course of PT, we will contact the patient once to determine if they are still doing exercise and using TENS. We will also assess their global response to treatment.
Primary Outcome	How relevant is it to participants? The primary outcome for the study is movement-evoked pain, one of the primary symptoms of FM and one that interferes with adherence to PT and patient-specific functional goals.
Primary Analysis	To what extent are all data included? There is no allowance for non-adherence or practice variability. We will use an intention-to-treat analysis.

B. Innovation

The proposed study is highly innovative in several respects. We rely on a diverse study team incorporating experienced investigators whose clinical backgrounds are in physical therapy, medicine, and nursing, and partnering with experts in data management of large-scale clinical trials. In addition, we incorporate practicing PTs into the planning and implementation of the trial to break-down barriers of conducting research in private, free-standing PT clinics. Many clinics are operated through centralized management, which allows the research team to evaluate methods for regulatory requirements, e-consent, recruiting participants, data collection using provider and participant direct data entry, a strategy we have previously successfully employed, and data extraction from the PT electronic health record (EHR). This novel methodology for translating research into PT practice would be a major innovation for how to conduct future embedded pragmatic trials.

Central to this proposal is the hypothesis that PTs are far better positioned to utilize effective non-pharmacologic treatments than physicians. Furthermore, PTs understand the value of implementing effective treatments that facilitate adherence with an individualized exercise-based treatment plan. Our goal is to engage providers early in development of the trial to assure the research team has considered practical requirements for conducting the study AND for uptake of

the treatment if effectiveness is confirmed. The embedded pragmatic approach will allow the research team to emphasize real-world generalizability of this treatment approach. ***This study represents an unprecedented partnership between front-line PTs and a multidisciplinary research team with expertise to design and implement the intervention.***

C. Approach

C.1. UG3 Phase Overview. During the one-year planning phase for this project, we will focus on the following primary activities (1) understand current practice and goals for treatment of FM; (2) ensure practice sites have the necessary infrastructure to participate in the trial, including the ability and willingness to comply with regulatory requirements; (3) create a strategy for e-consent, finalize case-report forms that impose minimal burdens on the site, therapist, and participants, finalize EHR visit templates, and finalize a manual of operating procedures; (3) conduct a small pilot study at one site to determine readiness of study processes for implementation of the UH3 trial; (4) confirm budgets and timelines for the UH3 trial including planning for an interim analysis according to the proposed adaptive study design. We will work closely with the NIH Collaboratory and the Collaboratory Coordinating Center to complete the proposed milestones as detailed in the “Milestone Plan” according to approved policies and best practices.

C.2. Study Team. The leadership team will use a multiple PI mechanism for this application combining expertise in pain, physical therapy, FM, and trial design and coordination. Drs. Sluka and Crofford will serve as dual PIs, are well versed in pain science and have experience with multi-site clinical trials of TENS. Dr. Sluka is a physical therapist and Dr. Crofford is a rheumatologist and collaborated on the FAST multi-site clinical trial testing efficacy of TENS for FM. Our team includes Dr. Coffey and Ms. Ecklund, directors of the University of Iowa (UI) Clinical Trials Statistical and Data Management Center (CTSDMC) which has 25 years of experience providing data management and statistical support to clinical trials. Dr. Zimmerman has extensive experience with statistical analysis and design for clinical trials on pain, and regularly collaborates with the research team. Together this team has a strong working relationship and brings complimentary expertise as outlined below (see “Clinical Trial Experience” document for additional investigator experience). Partnerships between the NIH Collaboratory and the CTSDMC brings significant *scientific rigor* to the study design.

C.2.1. Leadership Team

Kathleen A. Sluka, PhD, PT, FAPTA (Project Director, PI) is a Professor in the Department of Physical Therapy & Rehabilitation Science, within the Carver College of Medicine, at the UI with expertise in basic science, mechanistic studies in human subjects, and clinical trials with a focus on non-pharmacological treatments and musculoskeletal pain. She has led initiatives as program director for multiple externally funded studies including multi-PI grants, multi-site clinical trials, and large-scale implementation studies. Her team successfully completed a large-scale multi-site clinical trial on TENS (FAST study), funded as a cooperative agreement with NIH (UM1); Dr. Sluka served as project director. Her current implementation study, dual PI with Dr. Rakel, is a large healthcare initiative to incorporate exercise prescription and TENS into primary care for chronic pain that includes multiple and diverse stakeholders and team members. Thus, Dr. Sluka brings valuable leadership and oversight to this pragmatic clinical trial.

Leslie J. Crofford, MD (PI) is a clinician and pain researcher with expertise in FM, mechanistic studies in human subjects, and clinical trial methodology. She is a Professor in the Departments of Medicine and Pathology, Microbiology & Immunology, and is Chief of the Division of Rheumatology & Immunology at Vanderbilt University Medical Center. She has published extensively including studies of the basic mechanisms underlying FM, FM guidelines/outcome measures, and clinical trials of pharmacologic and non-pharmacologic treatments of FM. She is widely regarded as an international expert on this clinical entity. She was multi-PI with Dr. Sluka on the FAST study thus has worked extensively with the research team. She brings clinical expertise and a physician perspective to the proposed trial.

Christopher S. Coffey, PhD (co-I) is a Professor in the Department of Biostatistics in the College of Public Health at the UI and Director of the CTSDMC with 20 years of experience providing data management and statistical support to clinical trials. As Director of the CTSDMC, Dr. Coffey has extensive expertise with large multi-site coordinating centers (see Investigator Experience), including the NeuroNEXT Network, Clinical Islet Transplantation Consortium and Bracing in Adolescent Idiopathic Scoliosis Trial. Dr. Coffey has published extensively in the areas of adaptive designs, missing data, model validation, and general clinical trial design, and has led numerous short courses and workshops to train others on the use of adaptive designs and clinical trial methodology. As Director of the CTSDMC, Dr. Coffey brings valuable expertise for coordinating large studies and insights into adaptive study design.

Dixie Ecklund, RN, MSN, MBA (co-I) is the Director of Operations of the CTSDMC managing day-to-day activities. She has over 30 years of experience conducting clinical trials through the CTSDMC and in her previous role as Nurse Manager of the General Clinical Research Center at the University of Iowa (GCRC). She has been involved in hundreds of clinical trials, ranging from small Phase I studies to multi-center Phase III studies. Ms. Ecklund and the CTSDMC team have

developed recruitment and retention strategies, spearheaded central IRB approvals, formed Data Safety and Monitoring Boards, and supported electronic databases and data sharing for several large consortium initiatives. Ms. Ecklund developed and uses multiple and diverse communication strategies for large multi-site consortiums. Thus, Ms. Ecklund brings considerable expertise with her years of experience managing and coordinating large clinical studies.

Miriam (Bridget) Zimmerman, PhD (co-I) is a Professor in the College of Public Health at the UI and has a long-standing relationship with Drs. Sluka and Rakel. In fact, she served as the biostatistician on FAST, and a prior study of Dr. Rakels on TENS, TENS After Total Knee Study (TANK). She routinely provides statistical support to pain studies and understands the study population and scientific questions. She has extensive expertise in large scale human subject trials including those on pain and serves as study statistician for the UI CTSA. She has published extensively using a variety of statistical techniques and patient populations. Thus, Dr. Zimmerman brings her expertise in design of clinical trials in pain and will work with Dr. Coffey and the statistical team contributing to design and data analysis.

C.2.2. Additional team members with valuable expertise:

Barbara Rakel, PhD, RN is a Professor in the College of Nursing at the UI with expertise in clinical pain populations, particularly postoperative pain and clinical trial methodology. Dr. Rakel has published over extensively manuscripts on pain in clinical populations and has particular expertise on use of TENS in a clinical setting. Dr. Rakel has a long history of collaboration with Dr. Sluka bringing expertise in study design and training and patient-reported outcome validation. She also has valuable expertise in implementation and working with EHRs. She will bring her expertise in data extraction from the EHR to this study where she will coordinate development of metrics for study design, validation of outcome measures used in EHR, and training protocols.

Carol Vance, PhD, PT is a Clinical Assistant Professor in the Department of Physical Therapy & Rehabilitation Science at the UI with 10 years clinical experience treating individuals with musculoskeletal pain. She has worked with Dr. Sluka's team for over 20 years on basic science studies, clinical translational studies, and clinical trials. She has experience in developing standardized clinical protocols, metrics for training personnel from other sites, and performing site visits to ensure consistency in protocols. She developed unique methods for training and evaluation of sites, including video training modules, monitoring procedures online, and creation of competency checklists. With Dr. Dailey (below) she developed educational materials for TENS for patients and providers.

Dana Dailey, PhD, PT is an Assistant Professor at in the Department of Physical Therapy at St. Ambrose University with a PhD in Rehabilitation Science, a master's in health care administration, and 30 years clinical experience treating patients with FM. Dr. Daily is a former employee and manager at Genesis Health Care System, one of our sites. Dr. Dailey has worked with Dr. Sluka's team for over 10 years on several translational clinical studies and served as the study coordinator for FAST. She has experience developing standardized protocols for data collection, implementation of study interventions including TENS, and data analysis working with biostatisticians and data management teams. She has developed regular communication strategies between clinical sites and diverse clinical teams that are individualized to the needs of the team and project. Her clinical expertise, multi-site trial experience, strong attention to detail, and communication skills will be valuable in helping to coordinate this trial.

Practicing Physical Therapist, Carla Franck, PT will serve as a liaison for practicing PTs during the planning phase. She is a clinical PT, with specialized training in pain management. She currently works full-time for Kepros Physical Therapy and Performance, one of our sites. She will be instrumental in developing study outcome measures, and training and implementation procedures. During the planning year, she will devote up to 2h per week to the project assisting with clinic-specific study design. Additional representatives from each participating health care system will work with the team during the planning phase to develop clinically-relevant outcomes and individualized training procedures.

C.2.3. We are partnering with the **CTSDMC** in the College of Public Health at the UI to add expertise for statistical design, data coordination and management, working with EHR, central IRB coordination, and analysis and reporting. They have extensive experience coordinating and planning large-scale clinical trials and will provide support to the project.

The Biostatistics Team (Team Leader: Jon Yankey, MS) is comprised of 8 masters-prepared individuals and 2 graduate research assistants to support all statistical aspects of CTSDMC studies. CTSDMC biostatisticians have considerable experience in traditional and adaptive study design, protocol development, generation of statistical analysis plans, report generation, and manuscript development. Mr. Yankey has 20-years of experience producing statistical analysis plans, creating reports, and generating analyses for multi-center studies; he has been the team leader for 12-years.

The Data Management Team (Team Leader: Trevis Huff, BSE) consists of 5 experienced members that develop data management plans, case report forms, user specifications, and testing plans. This team is also responsible for validating the data systems, resolving data queries, providing technical support and training to collaboration sites, data clean-

ing, and protecting the overall quality of the data. This team has extensive experience working with the NINDS Common Data Elements (CDEs) for standardization of data used extensively in NeuroNEXT. The CTSDMC has been a Gold Member of Clinical Data Interchange Standards Consortium (CDISC) since 2014, and team members attend CDISC workshops. Mr. Huff has 10-years of experience in data collection systems and clinical study methodologies.

The Information Technology Team (Team Leader: Richard Peters, BS) is responsible for development, maintenance, and security of study websites and databases. The CTSDMC online data entry systems have been designed and implemented to use Microsoft technologies and development tools. The Information Technology team includes the Team Leader and four developers. The team works closely with the Data Management team to develop, test, and validate the electronic data capture systems. Mr. Peters has 20+ years of database and web development experience.

The Protocol Coordination Team (Team Leader: Julie Qidwai, MS, CCRC) consists of eight members who perform multiple functions including development and maintenance of study documents (e.g., protocols, manuals, training documents, etc.), trial coordination, training and certification of study site personnel, monitoring site performance to ensure compliance with the protocol, safety monitoring, and facilitating communication between study personnel. This team works closely with the data management team to ensure timely and accurate data entry, and to follow up with the network sites for data cleaning. Ms. Qidwai has been a Clinical Research Specialist in the CTSDMC for over 12-years and has served as the lead Protocol Coordinator for the CIT consortium and NeuroNEXT network. Ms. Qidwai is certified by the Association of Clinical Research Professionals (ACRP) as a Clinical Research Coordinator (CCRC).

The Regulatory Team (Team Leader: Cynthia Diltz, RN, BSN, CCRC). Ms. Diltz is a Certified CCRC in the CTSDMC and has over 30-years of experience managing data collection for clinical trials, observational studies, and monitoring regulatory compliance. Ms. Diltz served as the lead regulatory coordinator for the CIT consortium and has primary responsibility for the Trial Master File, maintenance of the site regulatory files, and safety monitoring. She has assisted in the preparation of documents for a Single IRB (sIRB) and has extensive prior experience with assuring regulatory compliance. Ms. Diltz will serve as the sIRB liaison for this project.

The Administrative Team (Team Leader: Maggie Spencer, MA). Ms. Spencer is the lead administrator in the CTSDMC and has 7-years of experience support of extramurally funded projects, in particular large consortium awards. She will be responsible for directing meeting planning and administratively supporting leadership and committees by preparing and distributing meeting agendas and ensuring the accuracy of meeting minutes. Ms. Spencer will also work with University of Iowa officials and clinical sites to set up Reliance Agreements for the sIRB and ensure that any clinical trial agreements at the sites conform to both the Reliance Agreement and regulatory requirements.

C.2.4. We will work the NIH HCS Research Collaboratory Program which includes the following Core Working Groups: Biostatistics and Study Design (team contact: Coffey, Zimmerman), Electronic Health Records (team contact: Rakel, Huff), Health Care Systems Interactions (team contact: Sluka, Vance), Patient-Reported Outcomes (team contact: Crofford, Dailey), and Regulatory/Ethics (team contact: Ecklund, Diltz). Members of the leadership team and staff, listed above, will work directly with the Core Working Groups. As per the RFA, the leadership team will attend two, one and a half day workshops in the planning year, and an annual meeting in subsequent years.

C.3. Planning Year. *The 1-year planning phase will be used to address our two UG3 Specific Aims, listed below.*

UG3 Aim 1: *Recruit physical therapy practices as research sites for this embedded pragmatic clinical trial, understand usual PT practice for patients with FM to inform trial processes, and develop implementation procedures.*

UG3 Aim 2: *Ensure adequacy of infrastructure at potential study sites to complete a PT embedded pragmatic trial.*

C.3.1 Meetings. During the first quarter we will hold two **planning meetings**, one in Iowa and one in Tennessee with representatives from each healthcare system and the study team. The goals of these meetings will be to 1) determine usual PT care for patients with FM, 2) finalize outcome measures, 3) determine outcome measures that can be included in EHR, and those that will require additional data collection, 4) initiate regulatory procedures for each site, 5) determine data collection procedures for each site, and 6) determine a training protocol for each site. We will work with the Health Care Systems Interactions Working Group of the Research Collaboratory to develop strategies to engage the healthcare systems participating in our research program with an emphasis on developing low administrative and practitioner burden and effective communication. This will be necessary for Protocol Development and Study start-up and data collection procedures. **Regular study team meetings** will be held on a weekly basis during the development phase of the project. This will allow for continuous feedback to modify and refine the procedures.

C.3.2 Study Settings. PT practices are generally organized as free-standing clinical sites within larger networks that provide administrative services required to function efficiently. There may be considerable variation in the treatment? approach to patients referred for different clinical conditions. Often, the referral is merely an order to “evaluate and treat”

with the referring provider then asked to sign a proposed treatment plan and goals of treatment provided back by the therapist. Our goal is to provide only minimal guidance for the routine treatment plan, but to provide simple, clear instruction for incorporating TENS into the plan. We will plan to provide TENS units and electrodes to simplify recruitment, and electronic tablets to each clinic to facilitate data collection. We anticipate that payment for PT would be by the participants' insurance as it will proceed as usual care during the study with TENS as an adjunct.

C.3.3. Study Sites. We have contacted, discussed study design, and developed working relationships with several physical therapy healthcare systems in the Midwest and Southern United States that are willing to participate in the trial (see letters of support). Each site has agreed to participate and will have a representative available during the planning phase to develop outcomes, modify EHR as necessary, and develop training strategies. These sites are outlined below:

Kepros Physical Therapy and Performance is a group of 3 outpatient PT clinics in located in Cedar Rapids, Marion, and North Liberty Iowa that employs 11 PTs and sees 50-100 FM subjects per year. PT group uses EHR and sees patients from rural and small city environments. Kepros Physical Therapy will serve as our pilot site to test data collection procedures during the planning phase. They will also participate in data collection in years 2-4. We will work directly with their EHR to implement a templated study visit for data collection. Carla Franck, a PT with Kepros Physical Therapy will be part of the study team to help develop outcomes and training procedures for implementation of the trial.

Genesis Healthcare Systems is located in the Quad Cities serving the local Iowa/Illinois community. They have 15 outpatient PT practices which see 200-300 FM patients per year. This PT group uses EHR and sees patients from rural and city environments. They have been actively involved in clinical research within PT. They will provide a practicing PT for participation in the planning phase and will collect data from their sites on during Years 2-4.

Vanderbilt University Physical Therapy Services is located in Nashville, TN and has 2 clinics that see approximately 100 people with FM per year. This PT group uses EPIC EHR and have been involved in prior clinical research studies. They will provide a liaison to the study during the planning phase and will collect data from patients during Years 2-4.

BenchMark Physical Therapy is a large PT network with over 350 clinics serving the southern and southwestern United States. They use EHR specific PT practice. We have identified a regional network (approximately 10-15 sites) in Tennessee and Kentucky that see patients from both rural and city environments for participation in the study. Collectively, the regional network sees between 300-500 patients with FM per year. They will provide a representative for the planning phase and will collect data from patients during Years 2-4.

Rock Valley Physical Therapy is a moderate size PT network with over 50 clinics in Iowa and Illinois that regularly see people with FM. During the planning phase, we will identify those clinics with the largest population of FM subjects for implementation of the pragmatic trial. They will provide a representative for the planning phase and will collect data from patients during Years 2-4.

C.3.3. Semi-structured Interviews. To gain insight from PT providers on potential unforeseen barriers not addressed with our strategies, we will conduct semi-structured interviews, using Skype, with representative providers within the first 3 months. Data from these interviews will aid in development of provider training and adoption strategies for implementing the trial. Some of the anticipated topics for the interviews include providers' perceptions of: TENS efficacy; current use of TENS and other PT interventions for FM; perceptions about FM medication including opioids and prn medications; education and training needs; concerns related to practice (workflow, clinical efficiency, acceptance by patients); current use of clinical decision supports (problems with current system, work-arounds). Each group will be composed of representative members of the clinic staff selected to reflect provider clinical background and salient demographics (e.g., PT; PTA; gender; years of practice). Interviews will be led by Drs. Dailey and Vance, PTs with 10-20 years of clinical practice.

C.3.4 Usual Treatment of FM by Physical Therapists. There is scant understanding of usual care for patients with FM by PTs. Generally, some combination of "pain relief" and "aerobic conditioning" might be the goals of the referring physician, but generally PT referrals are "evaluate and treat" allowing PT clinicians to develop the most-effective PT plan of care based on the individual needs of the patient. It is certain, however, that there will be differences in the clinical symptoms of FM patients that will influence the treatment approaches and treatment intensity. During site selection, we aim to better understand current PT practice for FM. The information-gathering sessions during semi-structured interviews will inform the development of electronics case-report forms (eCRFs) that adequately and simply capture outcomes from the perspective of physical therapists.

C.3.5. Patient Participants. We will determine the number of potential participants at each site with the understanding that we will offer enrollment to all patients diagnosed with FM by a physician. The potential participant will not be required to be specifically referred for FM; for example, the referral may be for neck or back pain in a patient with FM. It may be that there are participants who no longer meet formal criteria for FM at the time of treatment; however, we will

remove the burden of confirming or rejecting the diagnosis from the PT in favor of being more inclusive. Our rationale for this decision is that the diagnosis of FM is imprecise with the physiology associated with FM overlapping with mechanisms involved in chronic musculoskeletal pain. Further, PTs do not routinely assess FM criteria but rather rely on diagnosis as made by a physician, and thus this reflects a more “real-world” application of the intervention.

C.3.6. Regulatory Planning. It is highly likely that many of the providers have not previously participated in research or have the necessary training to conduct human subjects research. During site selection, we will work to understand the needs of each potential site and the most efficient strategy to complete training in Good Clinical Practices (GCP). We will develop an on-site educational strategy for the responsible conduct of research allowing PTs to complete training (such as protection of human subjects training) during the session. We will also work with the IRB of record at the University of Iowa (UI) to assure that regular site visits prior to and during the study will meet their requirements for study oversight. We will work with the UI IRB to develop an e-consent that can be completed online that includes ask-back questions to assure that each participant is fully informed.

C.3.7. Single IRB (sIRB). During the planning year we will initiate and submit an sIRB application to the UI IRB - see letter of support from the UI institutional official to serve as the sIRB for this project. The sIRB liaison at the CTSDMC will work with the UI IRB to initiate reliance agreements, develop a communication plan in order to communicate and coordinate key information to relying institutions, promptly respond to questions or requests for information from relying institutions, and provide the site investigators with the IRB policies (e.g. reporting unanticipated problems, noncompliance, and subject complaints) of the UI IRB as the sIRB. Ms. Ecklund and Diltz will work directly with the Regulatory/Ethics working group of the Research Collaboratory to ensure all procedures are conducted in an ethical manner and are in compliance with federal and state regulations.

We propose the following single Institutional Review Board (sIRB) model for the FM-TIPS sIRB. During the Reliance Agreement execution process, study sites will review the document and add in site-specific information. The sIRB liaison will submit the IRB applications on behalf of all sites, including initial reviews, local amendments, personnel updates, local reportable events, and study wide information. When a protocol is initially approved, the date of approval becomes the anniversary date for all continuing reviews. However, it is possible that with the adoption of the revised Common Rule, continuing reviews may not be required for this minimal risk trial. The sIRB liaison will document receipt of the sIRB approval and all ancillary approvals. The sIRB liaison will submit each new site’s application to the sIRB as an amendment to the approved protocol. The sIRB liaison will also work directly with the sites for local context review and all ancillary approvals. All subsequent IRB-related reports will be submitted by the sIRB liaison. The sIRB liaison will communicate to the sIRB any unanticipated problems and new information reported by any of the sites that could affect IRB approval of the protocol. Sites will be provided with a “model” informed consent form that can be customized with specific site-specific language related to injury and the Federal Health Insurance Portability and Accountability Act (HIPAA), as needed. All sIRB approval letters will be provided to the sIRB liaison, who then provide them to the applicable participating sites. The UI IRB is accredited by the Association for the Accreditation of Human Research Protection (AAHRPP).

C.3.8. Data Safety and Monitoring Board (DSMB). In conjunction with the funding agency, the study team will assist in forming a DSMB. The DSMB charter will be finalized by the funding agency and meet at recommended intervals for the duration of this pragmatic trial. The DSMB will be charged to review the research protocol and ongoing study activities, including review of data quality and completeness, fidelity to the study protocol, adequacy of participant recruitment and retention, and any safety concerns. The DSMB will meet regularly in person or by teleconference to review ongoing study activities. The DSMB will monitor the studies according to guidelines specified in the study protocol and the operating procedures established at the initial meeting. Members may include pain scientists, statisticians, clinical trialists, and physical therapy researchers.

C.3.9. Development and finalization of *Study Design and Statistical Analysis* will be done in the planning year. Drs. Zimmerman and Coffey will work with the Collaboratory Biostatistics and Study Design Working Group. During the planning phase we will determine procedures for a pre-planned interim analysis using an adaptive design to refine sample size. Adaptive design allows modification to the trial or statistical procedures after its initiation without undermining validity and integrity with the goal to make trials more flexible, efficient and fast.

C.3.10. Data Management: The CTSDMC has experience providing full data management support through conception, planning, and building a study database with user-friendly, web-based data entry. Templates for the electronic case report forms have already been developed during our prior clinical trial, FAST. We will develop and validate the case-report forms in the CTSDMC online data entry system. The CTSDMC data entry systems are designed and implemented using Microsoft technologies and development tools which employs Microsoft Visual Studio.Net to create Active Server

Extended Pages (ASPX/ASP.Net). By using Microsoft products such as Internet Information Server 7 and MS SQL Server 2017 the CTSDMC can achieve a high level of integration between our web and database systems. All data entry systems at the CTSDMC are developed to follow FDA regulations (outlined in 21 CFR Part 11), and in accordance with Good Clinical Practices. Our web-based data entry system has been successfully implemented in numerous past projects, and this system will meet the needs of this project. Drs. Dailey and Crofford will work with the Patient-Reported Outcomes Working Group of the Research Collaboratory, and with Mr. Huff and Ms. Qidwai to finalize data collection forms.

C.3.11. Data Entry, Validation, & Audit Trail: The CTSDMC has developed a variety of programming tools to facilitate creation of web-based data entry, such as an enhanced Data Dictionary program that interfaces with a functionalized specifications template. Once data is entered into the database, any change to the data record is recorded in the systems' audit trail. The audit trail records which piece of data was accessed, the variable that was changed, the previous value, the new value, the data and time the change was made, and the certification number of the individual making the change. Once a change is completed, the data system re-validates all associated data. The changed form is required to pass all validity and logical consistency checks. If edit criteria fail, the system generates the appropriate queries. All changes are logged in the audit trail and are audited by CTSDMC data managers and study coordinators.

C.3.12. Integration with the Electronic Health Record: We will initiate implementation of outcomes measures into the EHR working with each individual healthcare system. We will also work with each EHR to develop data extraction procedures for individual subjects. Dr. Rakel and Mr. Huff will work with the Electronic Health Records Working Group of the Research Collaboratory to ensure that appropriate and usable data are extracted from the EHR.

C.3.13. Transfer of Data to and from External Databases: The CTSDMC also has experience with transferring data to external databases and integrating data from external databases into a study database for analysis purposes. Procedures for this are generally written out in a user interface specification document which includes an overview, definition of terms, the chain-of-possession for data that is transferred, the expected data format, the expected file name, the frequency of transfers, and follow-up procedures to reconcile missing data. The data management team will be primarily responsible for these data transfers.

C.3.14. System Security, Replication Server, & Backup: The CTSDMC has extensive procedures in place to provide system security. To maintain strict security for data entered over the internet, all data are encrypted using the Secure Sockets Layer (SSL) protocol, which allows an encrypted link to be established between the CTSDMC web server and the computer at each site. CTSDMC data entry systems have a secure firewall to protect from viral attacks or hacking via the internet. In addition, all systems are protected by antivirus software and are swept daily. Access to data entry screens is ID and password protected. All CTSDMC servers are in secured University data centers, with access restricted to authorized personnel only. The CTSDMC strives to provide 24h/7-days/week coverage by maintaining replication on mission critical and database servers. Utilizing Microsoft SQL Server "Always On" technology, the replication process allows data saved to the primary server to be simultaneously written to a secondary server. All servers are backed up regularly by performing differential backups, and weekly complete backups of all web, database, and file servers.

C.3.15. Study Materials. A major advantage of our research group is our experience doing research with TENS. We have already developed educational materials for clinicians and patients and created case-report forms templates for direct data entry by investigators AND participants. Our goal is to minimize the need for the therapist to acquire and enter data by having patient participants engage in this activity. Most of the information required for determining study eligibility and study outcomes can be collected directly from participants or extracted from the electronic health record. For example, FM criteria can be acquired exclusively by patient report. These criteria have been validated against the physician completed classification criteria developed by the American College of Rheumatology¹⁹. We have already developed a strategy to allow patients to enter data directly into the CTSDMC online data entry system using an individual log-in. We plan to extract adherence to PT visits and the Patient-Specific Functional Scale (PSFS, described below) from the EHR, thus will develop visit templates. We will also extract the primary outcome of pain during PT (movement-evoked pain), fatigue during PT, and resting pain and fatigue from the EHR using visit templates.

C.3.16. Manual of Operations (MOP) will be developed within the first year. This will include all procedures for data collection, training providers, intervention, study design and statistical analysis. A copy of the MOP will be made available electronically to all sites and will be updated regularly.

C.3.17. Pilot Study. For the pilot study, we will aim to enroll participants at one healthcare site, Kepros Physical Therapy and Performance. All participants will be offered TENS (n=3). We will use this pilot to test our research processes, determine willingness of participants to use TENS, adherence to treatment, and outcomes. These patients will do an abbreviated timeline testing all aspects of data collection (proposed within a 2-week time-period). We will test inclusion and

exclusion criteria for ease of application. Our exclusion criteria, are TENS-specific exclusions (e.g. history of spine surgery with hardware, implanted electrical devices, allergy to nickel or adhesive, see human subjects) that can be obtained by patient report. We will test the proposed outcome measures for ease of use and interference with usual practice (**Table 2**) which will allow us to determine what changes must be made to visit templates and data collection instruments.

C.4. UH3 Phase Overview. We will conduct a pragmatic clinical trial embedded in PT practices utilizing cluster randomization by facility. We anticipate requiring at least 20-22 practice sites to randomize approximately 600 patients carrying a clinician diagnosis of FM. If all sites enrolled equally, this would equate to 30 participants per site or 10 per site per each of 3 years (study years 2-4). Sites will offer participation in the study to all patients with FM using a rapid screen for eligibility during the initial PT visit. We will use video to inform patients and e-consent by electronic tablet directly into the CTSDMC online data entry system during the initial PT visit. The PT treatment plan will be developed by the therapist during the initial PT visit which will be approved by the referring physician. The treatment plan will include the Patient-Specific Functional Scale whereby the patient develops their own treatment goals. The proposed treatment plan will be sent back to the referring physician for approval including information that the patient will be participating in the trial. TENS (or no-TENS) will be applied during each visit and the PT will complete a simple visit template in the EHR. The research team will be responsible for extracting data from the visit template and EHR. We will limit the amount of data collected from patients and use direct data entry into the CTSDMC online data entry system to collect the information.

UH3 Aim 1: *Determine if addition of TENS to routine physical therapy care improves movement-evoked pain (pain with PT/Exercise) – primary outcome.*

UH3 Aim 2: *Determine if addition of TENS to routine physical therapy care improves disease activity, increases adherence to physical therapy, increases the likelihood of meeting patient-specific functional goals, and reduces medication use - secondary outcomes.*

UH3 Aim 3: *Will examine the feasibility of implementing TENS into routine PT care for fibromyalgia pain using semi-structured exit interviews of patients and PTs.*

C.4.1. Communication is critical to successful completion of this pragmatic trial. We propose to use opinion leaders, change champions and staff education as strategies to facilitate implementation. **Opinion leaders** are effective in changing behavior of health care practitioners²⁰⁻²⁴, and are from the local peer group who are enthusiastic about the change, able to provide clinical knowledge, influence peers, and alter group participation^{25,26}. Our designated liaison from each healthcare system will serve as opinion leaders for this study. **Change champions** are practitioners within the local group who are expert clinicians, passionate about the topic, committed to improving quality of care, and have a positive working relationship with other health professionals^{25,27-34}. Change champions will be identified for each clinic to assist with training and serve as a resource to other providers during the trial. A train the trainer approach³⁵ will be implemented as an education program for change champions. This educational approach will be finalized in the development phase and focus on education on use of TENS, participant enrollment and collection of templated data in the EHR. **Education of staff** is essential for implementation of the trial. Education will not only include PT providers identified as the target audience, but also clinical support staff (PT assistants). We will use a combination of group didactic and individual interactive educational sessions, combined with the use of our opinion leaders and change champions to reinforce participation and practice changes needed in this study.

C.4.2. Study Design

C.4.2.1. Clinic Randomization. A stratified randomization procedure will be used to randomize clinics to be either no-TENS or TENS added to standard of care. Clinics will be stratified on healthcare system and size so that 10-11 will be no TENS plus standard of care and 10-11 will be standard of care. In the clinics randomized to standard of care, we will have specific instructions for them not to prescribe TENS to their FM patients. We recognize that some patients may be exposed to TENS through other means (relatives, friends); however, we believe our sample is sufficiently large to account for this potential exposure of TENS in a no-TENS group. At the completion of the study, we will specifically ask each subject about their TENS use, regardless of group.

C.4.2.2. Participants. Individuals referred for PT who have been diagnosed by a physician with FM, whether that is the primary diagnosis prompting referral or not, are potential participants. Inclusion criteria are (1) Physician diagnosis of FM; (2) Referred for land-based PT; (3) Able to provide informed consent. Exclusion criteria will be intervention-specific and include (see human subjects) unwilling to use TENS, allergy to nickel or adhesives, implanted electrical devices, surgical plates or rods in the spine. Surgical plates or rods in the spine. PTs are familiar with exclusion criteria for TENS and the study will not employ study-specific exclusions in keeping with the pragmatic nature of the trial.

C.4.2.2. Descriptive Data. The demographic variables to be captured include age, sex, race/ethnicity, BMI, and reason for referral. The frequency of PT visits (sessions/week), duration of PT (in weeks), and PT interventions used will be recorded. Additional questions will record medication use and other treatment strategies used for pain. Participants will record the 2016 FM criteria into our data entry system and the Widespread Pain Index, Symptom Severity Score, and Overall Score (also called the Fibromyalgia Severity Score or Polysymptomatic Distress Scale) will be calculated. This scale will allow a categorical variable of whether patients meet criteria for FM.

C.4.2.3. Intervention. TENS will be delivered using butterfly electrodes over the cervical and lumbar spine, as done in FAST, using the AcuRelief TENS unit. We will recommend “P6” on the unit as it has TENS parameters similar to that used in FAST with a mixed frequency and mixed pulse duration at an intensity of “as strong as tolerated”. This is a wired TENS device that has the parameters necessary for the most effective pain relief. We are currently investigating potential wireless devices for ease of use with similar parameters and capabilities. Subjects will use the TENS unit during each PT session and be instructed to use TENS at home during activity including, but not limited to, home exercises. We will instruct subjects to use the unit for 2h/day with a minimum usage of 30 min for each session. In our FAST trial we found that the 89% of the Active-TENS group met per-protocol minimal TENS usage when using these instructions. Practice sites randomized to TENS will receive training on TENS application, including a recommended method for determining the strongest comfortable TENS intensity³⁶, and will be provided TENS units and electrodes along with educational materials. Educational materials, already developed, include video instruction on how TENS reduces pain and how to apply TENS, and accompanying written educational materials (free to the public; <https://uihc.org/health-topics/chronic-pain-treatments-tens>). TENS is now FDA-approved for over-the-counter (OTC) access, and PTs are trained in application of TENS for pain relief. In Iowa, Illinois, and Kentucky PTs practice independently without referral; in Tennessee they can practice with restrictions (duration of treatment, must inform physician). However, exercise, TENS, and other non-pharmacological practices are covered within the PT practice act and PTs generally develop an individualized plan of care based on patient presentation and preferences. We will capture TENS usage through self-report. We recognize the inherent issues in gathering self-report of an intervention like TENS; however, this represents the real-world tracking of intervention and cost-effective OTC TENS units do not track usage.

C.4.2.4. Schedule of Study Events. The study procedures, discussed with practicing PT Carla Franck, are shown in **Table 3**. These will be refined based on discussion with all health care systems during the planning year.

PT Initial Visit (Visit 1)	Treatment Visit 2	Treatment Visits	Final Treatment Visit	Follow up
<ul style="list-style-type: none"> • Eligibility Checklist • e-Consent/Video • Demographic data • Medications • Outcomes in EHR (Patient-Specific Functional Scale(PSFS), pain and fatigue) • Additional Outcomes (FIQR and 2016 FM criteria) • Develop a treatment plan for the patient 	<ul style="list-style-type: none"> • Instruct on use of TENS and apply during exercise treatment (TENS sites only) • Complete treatment • Outcomes in EHR (PSFS, pain, fatigue) 	<ul style="list-style-type: none"> • Apply TENS (TENS sites only) • Complete treatment • Outcomes in EHR (PSFS, pain, fatigue) 	<ul style="list-style-type: none"> • Apply TENS (TENS sites only) • Complete treatment • Outcomes in EHR (PSFS, pain, fatigue) • Additional Outcomes (FIQR, 2016 FM criteria, patient global impression of change, PGIC) • Additional outcomes (exercise frequency, TENS frequency) • Medications 	<ul style="list-style-type: none"> • Outcomes collected through study staff contact by e-mail or phone (pain, fatigue, FIQR, 2016 FM criteria, PGIC) • Additional outcomes (exercise frequency, TENS frequency) • Barriers to TENS use

C.4.2.5. Outcome Variables. In keeping with the pragmatic nature of the trial, most of the variables will be extracted from a visit template that will be embedded in each site’s EHR. Outcomes will be taken at initial visit, at discharge, and 3-month follow-up. Limited outcomes will be taken during interim visits. Additional patient-reported outcomes will be taken at initial visit, discharge and 3-month follow-up. For the follow-up visit, each participant with access to a computer will be contacted with a code for direct data entry. Participants without computer access will be called to complete questionnaires with study staff. **Pain.** PTs will record pain at rest (secondary outcome), and during exercise (movement-pain, primary outcome) using a numeric rating scale (0-10 with 0 as no-pain and 10 as worst pain imaginable)^{37,38}. During the planning year, we will determine if the pain during activity will be done during a standard activity like walking or bending, or if we let the PT or patient choose the activity. We will also utilize the **Patient-Specific Functional Scale (PSFS)** where the patient identifies 2-5 functional goals for the treatment plan, and rates their ability to do these on an 11-point scale 0 unable to perform activity and 10 able to perform at the same level as before problem³⁹. This instrument is used

in routine clinical practice and thus will be a component of the EHR with the progress towards each goal collected at the final treatment visit. This will allow us to determine the activities that are most troublesome to individuals with fibromyalgia and to examine the impact of TENS and PT on patient-reported function in an individualized manner. Validated **patient-reported outcomes** (Fibromyalgia Impact Questionnaire (FIQR), 2016 FM diagnostic criteria) will be collected at the first treatment visit, the final treatment visit, and 3 months after each participant completes PT. The FIQR is a 21-item disease specific questionnaire that is divided into 3 domains: function, overall impact, and symptoms⁴⁰. The FM 2016 diagnostic criteria is a simple assessment that the patient can self-report and allows for determination of a Widespread Pain Index, Symptom Severity Scale, and Fibromyalgia Severity Score¹⁹. The Patient Global Impression of Change/PGIC is a 7-item questionnaire used to measure perception of change for the participant³⁸ and is commonly used in fibromyalgia clinical trials and will be collected at the final treatment visit and 3 months after completion of final treatment. **Patient Adherence Indicators.** A secondary outcome of this study is how well patients adhered to PT treatments and TENS. Patient adherence to PT will be assessed through EHR queries of data recorded at follow-up visits. Data fields will be available to providers at these visits to record if the patient used TENS, attended PT, or performed their home exercise program. **Medications** will be collected through the EHR and patient report. We will ask both FM medication and doses, and prn medications and usage (opioids, NSAIDs, Tylenol). For FAST, we developed methods to record and analyze this data, and to classify subjects as chronic opioid users that will be incorporated into this study. **Additional questions for patients** at the follow-up visit will include ease of TENS use, barriers to TENS use, and general perceptions about TENS for pain control to examine the utility and feasibility of applying TENS in PT practice for pain control. At the end of the study, we will ask **exit interview questions of all PT providers** about use of TENS in PT practice for FM and chronic pain to assess likelihood of continued use. These questions will include provider perceptions on usefulness of TENS for patients, barriers to TENS use in the clinic, perceived barriers to TENS use by patients. Exit interview questions for the patients and PT providers will be developed during the beginning of Year 2 and will be collected electronically.

C.4.2.5. Monitoring and recruitment. We will regularly monitor recruitment and retention from each clinic. Feedback will be ongoing and provided to individual clinics and healthcare systems monthly. During the planning phase we will develop procedures for collection and communication of audit and feedback data. This monitoring and feedback will be conducted during data collection phase (Years 1-4). The number of enrolled subjects by each provider, each clinic, and each healthcare system will be audited from those consented and EHRs. During data collection, we will provide monthly feedback to each healthcare system by clinic and provider monthly.

ICC	Table 4: ICC values by facilities (F) per treatment arm; subjects per site (total subjects)			
	F=9	F=10	F=11	F=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	43 (387)	25 (250)	17 (187)	14 (168)
0.125	56 (504)	28 (280)	19 (209)	14 (168)
0.130	--	34 (340)	21 (231)	16 (192)
0.135	--	41 (410)	24 (264)	17 (204)
0.140	--	53 (530)	27 (297)	19 (228)
0.145	--	--	32 (352)	21 (252)
0.150	--	--	39 (429)	23 (276)
0.155	--	--	51 (561)	26 (312)

C.4.3. Sample size calculation. 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 final visit in movement evoked pain after PT. From the FAST study, there was a standard deviation of 2 for change in movement-evoked pain for two functional tasks: six minute walk task (6MWT) or five times sit to stand (5TSTS). There was a greater decrease in pain with active-TENS compared to placebo-TENS of 1.0 (95% CI: 0.2, 1.8) for 6MWT and 1.3 (95% CI: 0.34, 2.2) for 5TSTS. Compared to no-TENS, the greater decrease in pain with Active-TENS was by 1.8 (95% CI: 1.0, 2.6) for 6MWT and by 1.9 (95% CI: 1.0, 2.8) for 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 movement-evoked pain with 0.80 power. Subjects randomized to treatment arm will be clustered by facility since facilities will be randomized for ease

of implementation and thus, an estimate of the intra-cluster correlation (ICC) is needed for the sample size calculation. With no prior estimate of ICC, the required sample size per treatment arm (or subjects per facility) for the desired detectable mean difference of 1.0, assuming SD=2.0, was calculated for combinations of ICC values and number of facilities per treatment arm; see **Table 4** for ICC values for a sample size <600 subjects per treatment arm. In a pilot study examining a non-pharmacological intervention for pain by our group we show an ICC of 0.01 for movement-pain, DeBar and colleagues⁴¹ used an ICC of 0.002 for sample size calculation for a chronic pain population, and Adams et al.⁴² showed widely varying ICCs between data sets but the majority of patient-reported outcomes were below 0.95 ICC. Therefore, we are conservatively estimating sample size at 600 subjects total with 300 per treatment arm and 10 to 11 facilities per

arm, which would allow an ICC of 0.12-.14. **Table 4** shows the needed number of subjects per facility (total subjects within treatment arm), for specified ICCs throughout the range of 9 to 12 facilities per treatment arm (F), to detect a mean difference of at least 1/10 in movement-evoked pain at the 0.05 significance level with 0.80 power. Numbers in black show where we would be powered to detect a difference based on number of facilities and different ICCs for n=300/arm while the tan numbers show ICCs for >300 per treatment arm.

C.4.2.6. Analysis Plan Overview. Descriptive statistics (means, medians, percentages, standard deviations, and inter-quartile ranges) will be computed for demographic and baseline variables for each of the treatment groups. The distributions of continuous variables will be evaluated for normality. If data are non-normal, appropriate transformation will be applied or non-parametric methods used. Demographic and baseline variables will be compared between treatment groups using t-test for continuous variables, Wilcoxon-rank sum test for ordinal as well as non-normally distributed continuous variables, and Pearson Chi-square test for categorical variables. Variables that are found to significantly differ between the groups may be used as possible covariates in the comparison of outcome measures between the treatment groups. Intent-to-treat (ITT) analyses will be conducted that will include all subjects that have been randomized. The primary endpoint to assess efficacy of TENS+PT compared to PT alone is change from baseline to final visit in movement-evoked pain after PT. This will be tested using linear mixed model analysis for repeated measures with treatment group, time, and treatment*time interaction as fixed effects. Random effects include facilities (within treatment), and subjects (within facility, within treatment). In fitting the mixed model, appropriate covariance structures for longitudinal measures within subject will be considered, such as compound symmetry, or heterogeneous compound symmetry, and then selected based on Akaike Information Criteria (AIC) and Schwarz's Bayesian Information Criteria (BIC). From this fitted model, differences in mean change between treatment groups will be assessed by test for treatment*time interaction effect. It is expected that 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, medication intake, and use of FM and PRN medications. In addition, opioid use at baseline as a possible effect moderator of TENS will be examined by including an opioid*treatment*time interaction in the model. If found to be significant, then secondary analyses to test for TENS efficacy by opioid status will be performed with p-values adjusted using Bonferroni's method. 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 95% confidence interval. Similar analyses will be performed for secondary outcome measures.

While every effort will be made to follow-up with patients, it is expected that approximately 10-15% of the patients will not return for follow-up. Our FAST study had a withdrawal rate of 15% after enrollment, and after randomization 10% for Active-TENS and 4% for no-TENS groups. Since this is part of usual PT care, we expect similar or lower withdrawal rates. The ITT analysis will be performed using all available data for all randomized participants. Reasons for subject drop-out will be recorded and compared between treatment groups. Subject characteristics and outcome measures collected prior to drop-out will be compared to those that complete the study. In the presence of missing data, under the assumption of missing at random (MAR), linear mixed model analysis can handle incompletely observed subjects and uses a likelihood estimation method to provide correct likelihoods and lead to valid estimates⁴³. However, since the data under analysis cannot distinguish if data is MAR or if it is missing not at random (MNAR), sensitivity analysis will also be performed using pattern mixture models. Multiple imputation will be used for sensitivity analysis by imputing from a non-random pattern mixture model⁴⁴.

Summary, Potential Problems, Alternative Strategies. We recognize that recruitment or retention at individual facilities could be a problem. We will use prior strategies from our clinical trial on TENS in FM to enhance recruitment and retention at individual sites (see human subjects). We also recognize it may be necessary to add additional sites. Our healthcare networks are sufficiently large to be able to increase the number of sites as necessary to ensure recruitment, and we have informal commitments from several other sites. We may also have difficulty coordinating the same EHR outcomes from all 5 sites; however, we have sufficient flexibility in the data management capabilities of the CTSDMC to be able to individualize data collection to each healthcare system to ensure we collect the same outcomes between sites. We recognize that we cannot collect user-data from the TENS unit directly and will have to rely on patient self-report as cost-effective OTC TENS with adequate parameters do not have this ability. Advances in TENS technology are occurring rapidly, and we will continue to investigate TENS options to determine if a useful unit becomes available. Lastly, we have developed a milestone plane that assures the study remains on track and partnered with the CTSDMC to further ensure success of this large-scale pragmatic trial. We will continually assess study procedures using our study communication plan to adapt the study to any change in the healthcare environment.

Resource and Data Sharing Plan

The PIs of this application will follow all data deposition, quality control metrics, standardization, metadata requirements, data and software release, and public copyright license policies. The leadership team will develop, by consensus, a resource and data sharing plan.

These studies will collect data from 600 subjects with fibromyalgia over the course of the project. We will maintain online databases on a secure and protected server. The results will be made public in multiple ways. 1. Regular **presentations at national and international scientific meetings**. We will present, in abstract form, at least once per year, and the PIs will also present the data in invited talks, seminars, and workshops. 2. All data will be analyzed and **published in peer reviewed literature** and thus all resources will be readily available. Means, standard deviations, sample sizes will always be published. 3. **Publication of resources**. We will make available publically any provider and patient educational materials to facilitate widespread implementation of the intervention.

The CTSDMC has several existing policies in place in order to make datasets available to the scientific community and the public in a timely and efficient manner using a variety of approaches, and will use those policies for all data sharing activities within FM-TIPS

Sharing Data during Ongoing Protocol: Often during the course of clinical trials, situations arise where protocol-specific data needs to be transmitted to external cores involved with a particular aspect of the study protocol. Similarly, data may need to be received from these external cores for merging with data collected through the main study database. In all instances, a formal Data Transfer Agreement (DTA) will be prepared and executed through the appropriate institutional offices (e.g. Sponsored Programs). The DTA will augment the contractual agreements with clarity of the general structure of each transferred data set, the mechanism through which files will be transferred, how the data will be used, and responsibility for the conduct of any electronic checks or queries to verify the accuracy of the transferred data sets. All data files will be distributed using secure encrypted links. Information is restricted to users that have been given access through role assignments established in their personnel profile. External users accessing the disseminated study-specific information must first supply a valid user ID and password to access the link. The data files can be supplied via an agreed upon format including SAS datasets, Excel files, and/or comma-delimited files. Because the SAS statistical package is widely available, this format has proven to be an acceptable method for sharing data. To facilitate this process, datasets may be sent with a copy of supporting documentation such as the protocol, a data dictionary describing the contents of each dataset, and a user's manual that describes the process for importing data into other systems. Depending on requirements, these files can be placed in password protected read-only files to prevent direct copying or duplicating of the data.

Sharing Datasets for Public Use: At the conclusion of the study, the CTSDMC will submit datasets and associated documentation to the appropriate NIH repository for archiving and public access. The CTSDMC will provide all necessary documentation (e.g. Protocol; Manual of Procedures/Operations; Statistical Analysis Plan; Data Dictionary; Annotated Case Report Forms; CRF Mapping Spreadsheet; Read Me file; Final Publication of Study Results – when available) with each final dataset to ensure that other users can efficiently and accurately use the dataset, as well as to prevent misinterpretation or misuse.