The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

Protocol Template (for Investigator Initiated Studies)

Title: A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED STUDY OF THE LOW-LEVEL PHOENIX THERA-LASE 42 WATT LASER IN PATIENTS WITH CHRONIC FIBROMYALGIA

1. Introduction and Purpose:

Individuals who have had pain for greater than three months may exhibit widespread pain and hypersensitivity, making it challenge to resolve or manage the condition, and resulting in impaired biological, social, and psychological function. The use of various laser or light devices is an evidence based approach for treating common musculoskeletal conditions that can assist in decreasing inflammation, improving tissue metabolism, and improving pain, hypersensitivity, and physical function.

The purpose of this study is to examine the use of low level therapeutic laser (LLLT) for its effects on pain, fatigue, and physical function in individuals with fibromyalgia.

2. Background:

Fibromyalgia is a common chronic pain syndrome that is often refractory to available treatments. The syndrome is characterized by chronic fatigue, painful muscles and tender points which commonly present bilaterally in a symmetrical pattern in the posterior cervical and thoracic back areas. Recent advances in non-thermal therapeutic laser technology (termed low level laser therapy- LLLT) have introduced possible clinical advantages that would potentially impact wide-spread chronic pain conditions like fibromyalgia. These advances include greater light power outputs, allowing for therapeutic doses to be clinically applied in larger areas of symptoms as is typical in individuals with fibromyalgia. The potential of this higher power light therapy is to decrease the inflammation and irritability of the sympathetic nervous system, and improve local biochemical and metabolic support in the musculoskeletal tissues. Clinically, laser therapy has the potential to effectively relax muscle tender points and relieve pain, thereby reducing global discomfort and improving overall quality of life.

The manufacturer of the Phoenix Thera-lase elected to seek and was awarded FDA approval under "Sec. 890.5500 Infrared lamp." The election of this classification selection was based primarily on the type of photonic energy provided which is in fact infrared light and the purpose of the superficial topical application. The product codes available for this section include a wide variety of applications, including "Lamp, Infrared, Therapeutic Heating," and "Powered Laser Non-Thermal Instruments With Non-Heating Effects For Adjunctive Use In Pain Therapy." The lower powered infrared therapeutic laser is significantly different than other medical lasers which utilize much higher power and have a purpose of altering tissue anatomy through high thermal or mechanical energy conversion. Lower power therapeutic laser therapy, as with the device used in this study, works through a conversion of the photonic energy of specific wavelengths and power to provide photochemical (biochemical) changes within the diversity of tissues that absorb the light. As such, the clinical benefits of therapeutic laser therapy in the infrared range is widely used for tissue repair, pain reduction, and resolution of inflammation, and is not attributed to the excessive production of thermal energy. The perception of a warming effect is very superficial and associated with water in the superficial layers absorbing energy. This is similar to the feeling that occurs with other infrared devices.

3. Concise Summary of Project:

Fifty consenting participants with long-standing fibromyalgia (> 3 mo duration) will be randomized to one of two treatment groups (n=25 per group) according to a computer generated randomization table. Group 1 will be the 'sham' control group and Group 2 will be the 'active' laser treatment group.

The study will be conducted in a double-blind fashion using a standard 42 watt Class IV laser which has a switch at the back of the device which allows the laser to operate in the 'inactive' mode despite giving the operator and patients the appearance of being active (e.g., generates skin warmth and a red beam of light). Treatment will be administered three times/week for three weeks. Data will be collected across the 3-week intervention and at one week and one month after completion of the intervention. Data will be analyzed with appropriate statistical methods.

4. Study Procedures:
Potential participants will be identified through physician referral to the McDermott Center for Pain Management, as well as through advertisement via the UT Southwestern Campus Updates email blast. If participants meet screening criteria and are willing to participate, appropriate consent and HIPPA permissions will be obtained.

After consent, the participant will complete baseline outcome assessments and will be randomized to one of the two treatment cohorts, the experimental low level laser therapy group (LLLT), or the sham laser therapy group (Sham). The study investigator performing outcome assessments will be blinded to the treatment allocation group. The treating clinician will be aware of the treatment allocation assignment for laser application; however, the participant will remain blinded to the treatment cohort. Each treatment cohort will be completed as assigned—no crossover will be allowed. Each participant will receive a series of nine active laser or sham treatments on a M-W-F schedule over the three week treatment period.

The treatments will include multiple 60 sec applications over the bilateral sympathetic ganglion in the paraspinous region from T1-S2. To address the question of depth and localization of treatment, we propose that multiple tissues are being stimulated simultaneously with the application of the infrared light, including muscle, tendon, ligament, joint, and nerve. The reference to the treatment being applied over the sympathetic ganglion was not intended to suggest a primary focus of treating this structure, but rather, to standardize an anatomical landmark for where we could apply the laser treatment with the potential to stimulate the greatest number of tissues (paraspinal muscle and tendon, spinal zygapophyseal and costotransverse ligaments and joints, and sympathetic and peripheral nerves) within this region based on the superficial depth of penetration of infrared lasers of this power. Additionally, evidence supports the ability of infrared light to stimulate and positively affect the sympathetic ganglion in the lumbar spine, where the nerves are only 1 cm below the skin surface (Muneshige et al., Journal of Rehabilitation Research & Development, 2006).

Additionally, participants will receive treatment over any tender spots reported in the hips, knees, shoulder, or elbows. Total treatment time to the spine will range from 12-14 minutes, depending on the size of the subject. Total treatment time to extremity joints will not exceed two minutes per site, so that the total treatment time to the spine and extremities will not exceed 30 minutes. All treatment for the LLLT group will be delivered at an intensity of 42 watts. The treatment will be applied via a non-contact method, with the laser applicator held 15 inches above the participant's skin. Sham treatment will be delivered via the same protocol in terms of time, application, and areas of treatment as stated above, except the laser unit will not discharge any photonic energy. Intervention will take place in the therapy room at the Health Professions Physical Therapy Clinic, which is appropriately equipped for laser administration. Application of therapeutic laser will be completed by licensed physical therapists who have completed safety training for therapeutic laser application including appropriate use of safety eyewear, room access, laser signage for laser use, and patient monitoring.

The following outcome measures will be collected at baseline: (1)Standardized SF-36 questionnaire; (2) Symptom Impact Questionnaire; (3) Current analgesic medication usage; (4) Pressure-pain threshold testing over tender points; and (5) Spinal ROM with an inclinometer and accelerometer. Outcome measures (2) and (3) will be re-assessed during the treatment phase at the end of weeks 1, 2 and 3. At 1 week and 1 month after the last laser/sham treatment session, all baseline assessments will be repeated, in addition to a global rating of change scale (-7= very harmful, 0=

neutral, +7 = very helpful). Any patient who reports any harm from the laser/sham treatments on the helpfulness scale will be queried for specific harm details. Participants randomized to Sham will have the option of receiving LLLT treatments after they complete their study enrollment.

5. Sub-Study Procedures:
Not applicable for this study.

6. Criteria for Inclusion of Subjects:
1) 18-80 years old
2) Pre-existing medical conditions are under stable control
3) Diagnosis of fibromyalgia by standard criteria (e.g., pain in all four body quadrants for over 3 months, 11 of 18 tender points, bilaterally in the cervical and upper thoracic back areas, and chronic fatigue)
5) Able to wear laser protective eyewear during the treatment session
4) Ability to speak English and complete testing

7. Criteria for Exclusion of Subjects:
1) Presence of another pain syndrome that has anatomical overlapping with fibromyalgia pain
2) Unstable psychiatric disorders or cognitive dysfunction or serious memory impairment
3) Previous treatment with low level laser therapy
4) Contraindication to receiving laser treatments
5) Current use of photosensitive medication (has been instructed to minimize sun exposure)
6) Active metastasis
7) Active infection
8) Impaired sensation

8. Sources of Research Material:
Subject's research data will be obtained from the medical record and self-report questionnaires. Other data generated during testing (all outcome measures) will be sources of research material. All research material will be kept in a separate paper chart that will include demographic information including height, weight, age, gender, location and side of involvement, and self-report outcome measures. The paper chart will also include all objective outcome measures including the SF-36, Symptom Impact Questionnaire, global rating of change scale, and analgesic medication usage questionnaire.

9. Recruitment Methods and Consenting Process:
All participants will be recruited either from physician referrals to the multidisciplinary pain clinic or from self-referrals in response to an advertisement in Campus Updates. During the initial screening visit, one of the co-investigators will determine if the subject's condition matches the inclusion and exclusion criteria. If so, the study will be briefly described and the subject will be asked verbally if they would be interested in volunteering to participate in the study. It will be explained to subjects that participation is completely voluntary, and choosing to not participate will not impact their receipt of other medical services on campus. An affirmative verbal response will then be followed by either the PI or Co-PI obtaining written informed consent to participate and signed authorization for use and disclosure of health information gathered during the examination. They will explain the study with the written documents and answer any questions the potential subject may have. After all questions are answered, if the potential subject elects to participate, the consent forms will be signed. Subject's privacy of all private health information and study measurements will be maintained according to the UTSW standard clinical practices (within the EPIC EMR). Any electronic or paper recording of study measures will kept either on approved encrypted storage devices or locked in a secure file cabinet. Competence in the English language is an inclusion criteria for the study.

10. Potential Risks:

Primary risks or side effects of participating in this study are globally associated with the entry requirement of having a musculoskeletal condition with chronic pain. Primary risk of the study specific intervention (therapeutic Class IV laser, 42 watts) includes potential eye injury if direct contact is made without proper eye wear. All personnel involved with this study have completed safety training on proper use of all personal and environmental safety steps including use of safety eye wear for therapeutic laser application. Therefore, there is minimal risk overall with included protocols. Low level laser therapy has been used daily in our outpatient clinic for over 3 years with no adverse events or safety issues. The study intervention is standard of care in rehabilitation and could be implemented with participants regardless of study participation. All of these risks are typical with standard of rehabilitation care and manageable. There is also a potential loss of confidentially of the patient's medical information.

11. Subject Safety and Data Monitoring:
Tests and interventions used in this study represent standard procedures and care delivered by physicians and licensed physical therapists. A supervising physical therapist (blinded investigator) will be responsible for evaluating all patient complaints outside the usual presentation for medical disposition. A study physician will be informed of all patient complaints outside the usual presentation for medical disposition. The treating therapist will ensure that all participants' evaluation is consistent with standard practice.

12. Procedures to Maintain Confidentiality:
Information used in the data analysis from this research project will be transferred by the principal investigator from the patient's medical record to a written data analysis form that will be identifiable only by a subject number. Each subject's information will be labeled with a unique number identifier to avoid mixing records and to ensure confidentiality. Only the principal investigator will have access to the number key that would identify each individual subject. Subject's privacy of all private health information and study measurements will be maintained according to the UTSW standard clinical practices (within the EPIC EMR). Any electronic or paper recording of study measures will stored either on approved encrypted storage devices or locked in a secure file cabinet with the clinic department. All data derived from the investigation is only accessible by the investigative team. Medical chart information is secured by username and password access to the EPIC EMR per university policy.

13. Potential Benefits:
This clinical investigation will evaluate the use of Class IV therapeutic laser in the treatment of fibromyalgia. While the data generated by the participants will not specifically benefit them individually beyond their physical improvement, the information gathered from this study will assist the medical profession in treating chronic pain conditions in the future as well as provide a basis for future research.

14. Biostatistics:
Evaluation of the a-priori sample size was calculated utilizing a power analysis. This analysis was based on the primary outcome measure (pain) being a continuous response variable. Data from previous published research on the projects primary intervention conducted over longer periods of treatment time supports an effect size of 0.4 on the impact of Class III light therapy techniques. Power calculations for the current project were based on mean differences between two dependent groups (matched pairs), power (1-β probability) = 0.80, α error probability = 0.05, and effect size of 0.4 (GPower ver. 3.1). These parameters resulted in a total sample size calculation of 52 to reject the null hypothesis. Accounting for a dropout rate of no more than 15%, a final sample size of 60 was selected. Dependent variables will be evaluated with non-parametric analysis for reports of patient well-being, while repeated measure ANOVAs will be utilized for changes of significance over time in pain, quality of life, function, ROM, and pressure-pain threshold. Significance will be set at $p<0.05$.