COMBINED BEHAVIORAL & ANALGESIC TRIAL FOR FIBROMYALGIA (COMBAT-FM)

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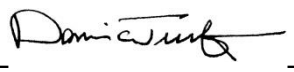
INVESTIGATOR'S AGREEMENT

Combined Behavioral & Analgesic Trial For Fibromyalgia (COMBAT-FM)

Protocol Approval Date: ___

I have carefully read the COMBAT-FM protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol and will attempt to complete the study within the time designated. I will provide copies of the protocol and all other information relating to pre-clinical and prior clinical experience to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the medication and conduct of the study. I agree to keep records on all subject information (case report forms, shipment and medication return forms and all other information collected during the study) in accordance with Good Clinical Practice and local regulations.



___ _____ 3/1/12

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Abbreviations Used in the Protocol

ACR, American College of Rheumatology
AE, Adverse Events
CBT*fm*, Cognitive-Behavior Therapy for Fibromyalgia
CHET, Center of Human Experimental Therapeutics
CGIC, Clinician Global Impression of Change
CMSU, Clinical Materials Services Unit
COMBAT-FM, Combined Behavioral & Analgesic Trial For Fibromyalgia
CS, Central Sensitization
DSMV-IV, American Psychiatric Association Diagnostic and Statisitical Manual, 4th Ed. Text Revision
DNIC, Diffuse Noxious Inhibitory Control
DSMB, Data Safety and Monitoring Board
eCRF, Electronic Case Report form
FDA, Food and Drug Administration
FIQR, Fibromyalgia Impact Questionnaire-Revised
FM, Fibromyalgia
HADS, Hospital Anxiety and Depression Scale
HE, Health Education
HIPPA, Health Information Portability and Accountability Act
IR, Immediate release
IRB, Institutional Review Board
LSC, Life Stressor Checklist
NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases
MFQ, Multidimensional Fatigue Questionnaire
MTPS, Manual Tender Point Survey
Pbo, Placebo
PCP, primary care provider
PGIC, Patient Global Impression of Change
PI, Principal Investigator
PTM, Placebo to Match
PTSD, Post Traumatic Stress Disorder
RA, Research Assistant
RC, Research Coordinator
REDCap, Research Electronic Data Capture
ROM, Range of Motion
SAE, Serious Adverse Events
SCID, Structured Clincial Interview for the Diagnosis of Mental Disorders
SE, Self-efficacy
SF-MPQ-2, Short-form McGill Pain Questionnaire version 2
SS, Sympom Severity scale
TC, Treatment Credibility
Tram, Tramadol
TS, Temporal Summation
Tx-C, Patients who completed treatment
Tx-N, Patient who did not complete treatment
UIP, University of Iowa Pharmaceuticals

UR, University of Rochester
UW, University of Washington
WPI, Widespred Pain Index

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PRÉCIS

Study Title: Combined Behavioral & Analgesic Trial For Fibromyalgia (COMBAT-FM)

Background and Statement of the Problem

Fibromyalgia (FM) is a chronic widespread pain syndrome with a number of concurrent symptoms (eg, sleep difficulties, fatigue, depression, anxiety), unknown pathogenesis, and no well-replicated biological markers, that is estimated to affect 3-6 million people in the United States. The diversity of symptoms reported by FM patients is consistent with the view that FM is a multisystem disorder, involving a complex interaction of biological, psychological, and social mechanisms. Although evaluations of numerous pharmacological treatments have shown beneficial effects, none are curative. These treatments reduce pain by approximately 35% but no more than half of patients experience clinically meaningful improvements. Similar outcomes have been reported with nonpharmacological treatments, particularly Cognitive-Behavior Therapy (CBT), which has been shown to produce equivalent benefits to medication in reducing pain and improving function. The modest outcome of these monotherapies has led to calls for combination trials of drugs and nondrug treatments. No studies have evaluated the incremental benefits of combining CBT and medication as suggested in the American Pain Society.

Objectives

We have adpated CBT especially for FM (CBT*fm*), giving greater attention to fatigue, sleep, pacing, avoidance of activity, and interpersonal communication. Tramadol (Tram) is a drug that has been shown to reduce pain and improve function in many FM patients. The primary outcome is the change in pain severity measured by the average of 5-days of daily pain dairies assessed just prior and at the end of treatment. The primary objective of the current study is to test the hypothesis that the combination of CBT*fm* + Tram will produce significantly greater reduction in pain severity or physical function compared to CBT*fm* + placebo (Pbo) drug, Health Education (HE) + Tram, and HE + Pbo drug. Specifically, that a greater proportion of patients in the CBT*fm* +Tram group will achieve at least 30% reduction in pain (on 5-day daily pain diaries) or 20% improvement in function (on the Fibromyalgia Impact Questionnaire-Revised) compared to the other 3 groups. A similar approach to using a composite outcome criterion was used in recent pivotal clinical trials submitted to the FDA for approval of milnacipran with FM.[1a-1d]

Several secondary objectives are planned. One secondary objective of the project is to test if functional improvement is greater in combination of CBT and Tram as compared to other groups. Another secondary objective is to incorporate real-time objective data collection of patients' sleep patterns and activity using actigraphic recording (actigraphy) into the assessment, treatment, and outcome evaluation of patients. Specifically, we will utilize this objective activity and sleep data to: (1) evaluate the extent to which patients demonstrate perceptual dissociation regarding their sleep quality and levels of activity; (2) reduce perceptual dissociation by providing patients with accurate feedback regarding their sleep and activity levels; and (3) measure changes in sleep quality and activity level in response to treatment.

Even when treatments provide benefits in FM, the mechanisms are largely unknown. Another secondary objective of the project is to examine psychological and physiologic mechanisms that we hypothesize mediate symptom improvement that patients demonstrate in response to Tram or CBT*fm*. Specifically, we will examine the hypothesis that reduction in pain from these treatments can be accounted for by decrease in central sensitization (CS) of noxious stimuli and improvement in mood. The final secondary objective of the proposed research is to explore processes that mediate improvements that patients demonstrate in response to treatments provided in the study. Specifically we will evaluate a mediational model of the effects of fatigue on activity level, arising

from pain level, sleep disturbance, and mood disturbance. Additionally, we will evaluate the direct effects of pain level and mood on activity levels.

The results will have important implications for developing optimal treatment programs for FM, the mechanisms underlying treatment outcome, and the associations among sleep, fatigue, activity, pain, and mood in this prevalent pain condition.

Design and Outcomes

A randomized, double-blind, placebo-controlled, 2-site clinical trial will be conducted. Systematic assessment of pain severity, physical and emotional functioning, CS, and actigraphy over the course of treatment will make it possible to accomplish the primary and secondary objectives of the study. Assessments of all primary and secondary outcomes will be conducted at 4 different in-person visits throughout the study: pre-treatment (Visits 1 & 2), mid-treatment (Visit 7-8), at the end of treatment (Visit 12), and 6-months follow-up (Visit 14) following treatment. Additionally, self-report outcomes will be collected by mail 3-months following post-treatment evaluation.

Interventions and Duration

Informed consent will be obtained on Visit 1 along with physical and baseline assessments. At Visit 2 completion of baseline assessments will occur and actigraph will be dispensed. Actigraph use will occur for a 1-week duration at several points during the study (i.e., between Visits 2-3, 7-8, 11-12). Study medication (either Pbo or Tram) will be provided on Visit 3, and subject will be titrated up over a 2-week period. On visits 4-11, which occur once per week, patients will receive behavioral health treatment intervention (either CBT*fm* or HE). Follow-up visit will occur 1 week following completion of treatment (Visit 13). Evaluation of efficacy endpoints will occur at the end of the drug maintenance/behavioral health treatment phase (Visit 13), at which point subjects will begin drug taper. Subjects will return 1 week following the start of taper (Visit 14) to facilitate taper. Subjects will be mailed a follow-up packet of self-report measures to complete and return at 3-months post-treatment. Finally, subjects will return for a follow-up visit 6-months following completion (Visit 15). (See Appendix A for complete schedule of activities).

Population and Sample Size

Men or women between the ages of 21-70 meeting the ACR criteria for FM will be enrolled for treatment. A responder is defined as a person whose pain score decreased at least 30% or a 20% improvement in physical functionigat the end of the treatment when compared to the score just prior to treatment. Our primary hypothesis may be supported by a statistically significant difference in proportion of responders among the 4 groups at the $\alpha = .05$ level, followed by a post-hoc test of difference between pairs of groups. We propose to enroll 81 individuals in each site, for a total of 162 individuals in the final intent-to-treat sample. The power for this sample size is quite high. For example, if we observe a proportion of responders of .2 for HE + Pbo, .4 for HE +Tram, .4 for CBT*fm* + Pbo, and .6 for CBT*fm* + Tram, we would have a power of .8 to find the difference between groups.

STUDY PROTOCOL

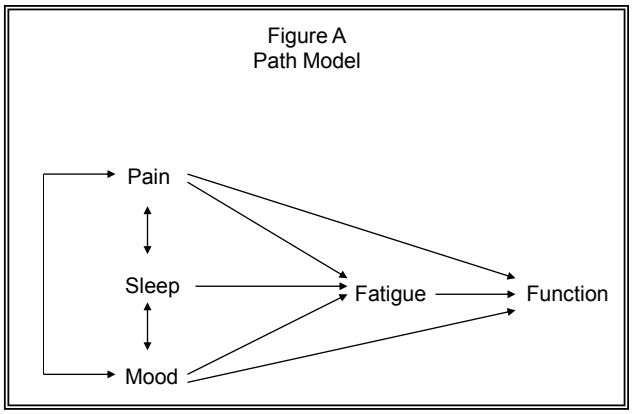
1. OBJECTIVES

1.1. Primary Objective. The primary objective of the current study is to test the hypothesis that the combination of a CBT that has been adapted for FM (CBT*fm*), a behavioral-health treatment that has been shown to improve physical functioning and pain, and Tram, a drug that has been shown to reduce pain FM patients moderately, will produce greater reduction in pain severity (as measured by the difference in the average of 5-day daily pain dairy) or physical function (FIQR) assessed just prior and immediately following treatment) than HE+Tram, CBT*fm*+Pbo, or HE+Pbo.

1.2. Secondary Objectives. Several secondary objectives are proposed. There is evidence that FM patients have inaccurate perceptions regarding their behaviors, including their physical capabilities.[1] In this protocol, we use the term "perceptual dissociation" to describe these inaccuracies. Another secondary objective of the project is to gather objective data regarding patients' sleep patterns and activity using actigraphy, and to utilize these data into the assessment, treatment, and outcome evaluation of patients, specifically: (1) to evaluate the extent to which patients demonstrate perceptual dissociation regarding their perceived and actual sleep quality and levels of activity; (2) to reduce perceptual dissociation by providing patients with accurate feedback regarding their sleep and activity levels; and (3) to measure changes in sleep quality and activity level in response to treatment.

Even when treatments provided benefits in FM, the mechanisms are largely unknown. The 3rd objective of the project is to examine psychological and physiologic mechanisms that may underlie functional improvement that patients demonstrate in response to treatment. Specifically, we will examine the hypothesis that improvement in function from these treatments will be predicted by decrease in **central sensitization (CS) of noxious stimuli and improvement in mood**. The final objective of the proposed research is to study processes that mediate improvements that patients demonstrate in response to treatments provided in the study. Specifically we will evaluate a mediational model of the effects of fatigue on activity level, arising from pain level, sleep disturbance, and mood disturbance (Figure A). Additionally, we will evaluate the direct effects of pain level and mood on activity levels.

Figure A
Path Model



The proposed project extends our research by attempting to combine promising behavioral health and pharmacological treatments, examining the dissociation of patients' beliefs and actual activity, and evaluates an important underlying mechanism that may contribute to our understanding of a biological factor associated with treatment effects and FM more generally.

2. BACKGROUND

2.1. Statement of the Problem. FM is a chronic pain syndrome with an unknown etiology and wide-ranging symptom profile including pain, fatigue, decreased activity, and depressed mood. Recently the role of perturbations in the central nervous system and the process of "central sensitization" (CS) have been implicated. Although research has demonstrated that a variety of monotherapies - including CBT and Tram – improve symptoms and functioning in FM, benefits

associated with these therapies have been modest.

2.3. Rationale and Supporting Data.

2.2.1. Combination Therapy. Since no curative therapy for FM has been discovered, treatments currently used are pragmatic and aim to maximize symptom relief and restore function. Research supports the effectiveness of various treatments, including CBT and several medications.[2, 3] However, none of these treatments is curative[2] and less than 10% of patients with FM return to premorbid levels of functioning following treatment.[4] Because of the modest benefits from monotherapies, expert panels and evidence-based guidelines[5] have recommended combinations of treatments to achieve maximal benefit. The combination of behavioral and pharmacologic treatments has been shown to have incremental benefits greater than either treatment alone for a number of problems including depression[6-9]and headaches[10], but has not been studied systematically in FM.[11]

Some research on combination therapies for FM has been reported. Typically, FM patients receiving a variety of treatments have been contrasted with controls who receive usual care.[12] This methodology does not permit analysis of the effectiveness of individual treatment elements, the addictive effects, or of the possible synergistic interactions between elements. There have only been a handful of studies that have systematically varied treatment elements, and they both provide support for combination treatment. For example, Buckelew[8] provided FM patients with either biofeedback/relaxation, exercise, both, or neither. At follow-up, patients receiving combination therapy had the best outcomes. Isomeri et al.[13] provided patients with exercise therapy, amitriptyline, or the combination of the two. Patients receiving combination treatment had lower pain scores at the end of treatment than patients receiving only a single modality. No studies have evaluated the combination of CBT and a particular pharmacologic agent.

The primary hypothesis to be tested in this application is that the combination of CBT*fm* + Tram will lead to greater decrease in pain severity or improvement in funtioning as assessed by 5-day diary and Fibromyalgia Impact Qustionnaire-Revised than CBT or Tram alone. The factorial design of the proposed study also will make it possible to examine the effectiveness of CBT*fm* and Tram as monotherapies, as well the effectiveness of the use in combination, and the possibility of interactions between the 2 types of treatment.

2.2.2. CBT*fm*. CBT has demonstrated efficacy in the treatment of FM comparable to that provided by medications.[14,15] It has been recommended in recent evidence-based clinical practice guidelines.[16-18] CBT is a generic term; there are many specific interventions that have been included (e.g., exposure, cognitive restructuring, social skills training). We propose to provide customized CBT (designated CBT*fm*) that incorporates several of the above interventions, and has been developed by our team to address issues of particular concern to patients with FM, including providing techniques to enhance sleep quality, reduce fatigue, increase physical activity, reduce fear of activity, and improve interpersonal communications.

A noteworthy feature of CBT*fm* is the use of actigraphy to address the dissociation between what FM patients' perceptions about their physical capacities and the reality of what they are actually capable of doing. An actigraph is a solid state accelerometer designed to measure ambulatory activity over extended periods of time in naturalistic settings. Actigraphic recordings have been used extensively as an indicator of activity levels while individuals are awake[19], as well as a behavioral indicator of sleep quality.[20] Actigraphic recordings have the advantage of being objective measures that are not dependent on patients' reports of activity or sleep quality. We will utilize actigraphic data during baseline assessments to evaluate the perceptual dissociation among perceived and actual sleep and functional capabilities, and actigraphy during the course of

treatment to provide patients with accurate information about their activity levels during the course of the study. Finally actigraphic recordings will be used as outcome variables to assess secondary hypotheses in the study.

2.2.2. Tramadol (Tram). The efficacy and tolerability of Tram have been demonstrated in a number of pain conditions[21] including FM[22-25] and the drug is recommended by the American Pain Society. Tram may be particularly relevant to FM due to its combination of pharmacodynamic properties.[26] Specifically, Tram has been shown to enhance analgesia by means of 3 distinct mechanisms, it: (1) binds to mu opioid receptors, and exerts a weak opioid effect; (2) inhibits the neuronal reuptake of 5-hydroxytriptamine (serotonin); and (3) inhibits the neuronal reuptake of norepinephrine. Pharmacologic studies provide evidence that all 3 mechanisms contribute to the analgesic effects of the drug. Given this pharmacodynamic profile, Tram has properties that make it particularly relevant to FM. Its effects on serotonin and norepinephrine mimic those of dual reuptake inhibiting antidepressants such as Duloxetine and Milnacipran that have been approved by the FDA for FM. Its effects as a mu-opioid agonist may also be relevant. Although the effectiveness of opioids in the treatment of FM has received little attention in research, Tram is generic and has been approved by the FDA for the treatment of chronic pain so in the proposed study it will be used "on label." Moreover, FM patients indicate that these medications are more effective than other classes of medication.[27]

2.2.3. CBT*fm* +Tram. Evidence and clinical practice guidelines[5], as well as our own experience conducting research on the treatment of FM suggest that increasing activity is a key component to reduce pain severity and improve functional outcomes. In fact research has demonstrated that one of the major benefits of CBT appears to be its impact on increasing activity.[28, 29] A key intervention in CBT is for the therapist to give patients homework assignments, including behaviors that they tend to avoid, to carry out, and monitor their responses. In order for this intervention to be effective, patients must be willing to perform the assignments. In this setting, Tram can promote behavior change by creating an initial reduction in pain, and, thereby, giving patients the confidence to try out behaviors avoided. Once they attempt these behaviors and receive real-time feedback about their actual progress, a positive (corrective) feedback loop is created in which patients may master successively more challenging tasks.

2.2.4. Mediators of Clinical Improvement in FM. Even when treatments provided benefits in FM, the biologic as well as psychological mechanisms are largely unknown. The 3rd objective of the study is to examine psychological and physiological mechanisms that may underlie functional improvement that patients demonstrate in response to Tram or CBT*fm*. Specifically, we will examine the hypothesis that improvement in function from these treatments will be predicted by decrease in **central sensitization** (CS) and improvement in **mood**.

2.2.4.1. Central Sensitization (CS) and FM*.* Although the causal mechanisms of symptoms underlying FM are not well understood, research suggests that CS of noxious sensory information is an important contributing factor. CS can be manifested by **reduced** ability to inhibit noxious stimuli (i.e., diffuse noxious inhibitory controls - DNIC), and/or by **facilitation** of noxious input (ie, temporal summation – TS). Patients with FM have been shown to have both impaired DNIC and enhanced TS of nociceptive stimuli.[30-33] We are not aware of any research demonstrating changes in these indices of CS in response to treatment. However, if, as postulated, CS is a fundamental process in FM, changes in the clinical status of FM patients should be associated with changes in CS. Because heightened sensitivity to noxious stimuli is thought to be a pathologic hallmark of FM, we hypothesize that CBT*fm*, will result in the lowering of the nociceptive responding, as evidenced by an increase in DNIC efficiency. Specifically, we hypothesize that: (1) DNIC will increase and TS decrease over the course of CBT*fm* and (2) decrease in pain severity will be associated with

decreased CS, as measured by both DNIC and TS. A recent pilot study examining a different physiological marker provides preliminary support for the feasibility of the latter hypothesis.[20]

2.3.4.2. Depressed Mood and FM. A defining feature of FM is dysphoric mood. Mood bears a synergistic relationship with symptoms whereby the presence of symptoms affects mood and negative mood influence interpretation of current state and inhibit adaptive behaviors.[34] Long-term outcomes of exercise treatment are more closely associated with **changes in** psychological variables (e.g., self-efficacy (SE)[35], self-esteem[36], coping[37], helplessness[37], fear of movement[37-39], emotional distress[34], and catastrophizing[39]) than they are to changes in physical parameters such as strength and flexibility.[28,40] Based on this research, we hypothesize that improvements in mood will predict improvement in function (Objective 3). More specifically we plan to evaluate the mediational effects of activity level on function, arising from pain level, sleep disturbance, and mood disturbance (Objective 4).

3. STUDY DESIGN

In the randomized, double-blind, placebo-controlled clinical trial described in this protocol, 162 individuals with FM will begin treatment in 1 of 4 treatment groups: (1) CBT*fm* + Tram; (2) HE + Tram; (3) CBT*fm* + Pbo; and (4) HE + Pbo. The sample size was calculated for the primary aim which is measured at post-treatment. Based on previous experience with this population, we expect that there will be about 15% attrition at the end of the 3 months follow-up and 15% more by the end of 6 months follow-up.

The primary hypothesis is that CBT*fm*+Tram will lead to greater decrease in pain or improvement in physical function than the other 3 combinations of treatments. Specifically, a significantly greater proportion of subjects in the CBT*fm*+Tram group will demonstrate at least a 30% reduction in pain severity based on the 5-day daily pain diary or 20% improvement in function on the FIQR.[1a-d] We also hypothesize that a perceptual dissociation exists between real and perceived activity levels and sleep quality, and that change in mood and CS of pain will predict improvement in function.

Systematic assessment of pain severity, physical and emotional functioning, CS, and actigraphy over the course of treatment will make it possible to accomplish the primary and secondary objectives of the study. Assessments of all primary and secondary outcomes will be conducted at 4 different in-person visits throughout the study: pre-treatment (Visit 1 and 2), mid-treatment (Visit 7-8), immediately following treatment (Visit 13), and 6 months (Visit 14) following treatment. Additionally, self-report outcomes will be collected via the mail at a 3-month follow-up visit. Based on experience working with patients with FM in clinical trials and enrollment projections by the 2 study sites, it is expected that this trial will take 4.0 years to complete enrollment.

4. SELECTION AND ENROLLMENT OF SUBJECTS

4.1. Inclusion Criteria:

1. Assess 1990 and 2010 ACR criteria for the diagnosis of FM.[41-44] If patients meet the 1990 criteria but not the 2010 criteria they will be included, but if they do not meet the 1990 crtieria they will be excluded.
2. Men or women (see 4.1.3 below) between the ages of 21-70. The prevalence of FM in children and adolescents is unclear. Furthermore, the outcome measures used to assess fear, emotional distress, and so forth were not validated for use in individuals younger than 21 years of age.
3. Women of child-bearing potential who are using a medically acceptable contraceptive regimen for at least 60 days prior to the baseline visit, and agree to continue such use until 30 days after the final dose of study medications (the first 10 weeks of the study). Reliable forms of contraception include oral, implanted, or injected contraceptives,

intrauterine devices in place for at least 3 months in conjunction with spermicide. Women must agree to and be given a urine pregnanacy test unless they are at least 2 years postmenopausal or surgically sterile.

4. Average pain intensity rating of ≥ 4 and ≤ 9 over the 5 day daily ratings (see Appendix D)
5. Must be able to provide written informed consent.

4.1.2. Exclusion Criteria.

1. Psychiatric hospitalization, suicide attempt, problems with substance abuse during the previous 12 months.
2. Cognitive, emotional, or interpersonal dysfunction which, in the judgement of the evaluating psychologist, would make the person inappropriate for participation.
3. Rheumatologic disorder or other disorder (e.g., lupus) associated with severe pain.
4. Any clinically significant medical condition or laboratory abnormality that in the investigator's judgment would interfere with the patient's suitability for participation in the study, including conditions for which treatment with Tram is contraindicated, including seizure disorder, evidence of hepatic or renal disease.
5. Presence of any other medical condition or pain condition that in the investigator's judgement could confound assessment of FM (e.g., cancer, other rheumatologic disorder, trigeminal neuralgia).
6. Any cognitive impairment that in the investigator's judgment would limit the patient's ability to provide informed consent or participate in the study.
7. Taking MAO inhibitors *
8. Other drug exclusions: amphetemines, ketamine, triptans, fenfluaramine and metaclopramide due to their possible negative interactions with Tramadol.*
9. Urine drug testing reveals evidence of illicit drug use, or use of prescription drugs that the patient did not report he/she was using.
10. Any alcohol or drug abuse history within 1 years prior to baseline.
11. Taking opioid medication and not willing and/or able to taper off for study duration.* If currently on Tram at time of initial evaluation, participant must be willing to taper off completely prior to participation in study.

*For all drug exclusions- Any medication dosage change or taper will be done under the supervision of the subjects primary care physician. Subject's must be completely off of a medication or at the allowed dose for at least 30 days prior to be enrolled into the study. Any change will be varified with their PCP.

4.2. Study Enrollment Procedures. Patients with FM will be recruited by the study sites from patients attending their clinics and from referrals from primary care providers (PCPs) and specialist physicians in their communities. The enrollement form (see Appendix B) will be used as a guide in pre-screening potential subjects in person and over the telephone before the provision of informed consent at the screening visit. This pre-screening will be conducted in accordance with all HIPAA and local IRB regulatory requirements after providing verbal HIPAA assurance and obtaining subjects' verbal consent to proceed with the interview. Records will be kept of patients who were considered ineligible for participation in the study as well as those who declined participation. All of the pre-screening source documentation will be stored with the confidential study records. The pre-screening source documentation for individuals who are not eligible for the study or who decline participation will be stripped of identifiers and stored with the confidential study records.

The study procedures and risks will be described to potential subjects in person by the project staff at the study sites. Subjects will only be allowed to sign the informed consent form when project staff are confident that they understand the procedures and risks of the study, have the capacity to

provide informed consent, and do not have evidence of cognitive impairment that in the investigator's judgment would limit ability to provide informed consent or participate in the study.

5. Study Interventions

5.1. Drug Intervention.

5.1.1. Tramadol. Tramadol hydrochloride is a centrally acting synthetic opioid analgesic.

The chemical name for Tramadol hydrochloride is (±)*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. It is FDA approved for the treatment of moderate to moderately severe pain.

5.1.1.1. Pharmacodynamics. Although Tram's mode of action is not completely understood, from animal tests, at least 2 complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to mu-opioid receptors. In animal models, M1 is up to 6 times more potent than Tram in producing analgesia and 200 times more potent in mu-opioid binding. Tram-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both Tram and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

Tram has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro,* as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of Tram. Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately 2-3 hours.

5.1.1.2. Pharmacokinetics. The analgesic activity of Tram is due to both parent drug and the M1 metabolite. Tram is administered as a racemate and both the [-] and [+] forms of both Tram and M1 are detected in the circulation. Linear pharmacokinetics have been observed following multiple doses of 50 and 100 mg to steady-state.

Absorption

The mean absolute bioavailability of a 100 mg oral dose is approximately 75%. The mean peak plasma concentration of racemic Tram and M1 occurs at 2-3 hours, respectively, after administration in healthy adults. In general, both enantiomers of tramadol and M1 follow a parallel time course in the body following single and multiple doses although small differences (<10%) exist in the absolute amount of each enantiomer present.

Steady-state plasma concentrations of both Tram and M1 are achieved within 2 days with 4 times per day dosing. There is no evidence of self-induction.

Food Effects

Oral administration of Tram with food does not significantly affect its rate or extent of absorption, therefore, Tram can be administered without regard to food.

Distribution

The volume of distribution of Tram was 2.6 and 2.9 liters/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of Tram to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 μg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Metabolism

Tram is extensively metabolized after oral administration by a number of pathways, including

CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The major metabolic pathways appear to be *N*- and *O*-demethylation and glucuronidation or sulfation in the liver. One metabolite (*O*-desmethyltramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response.

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of Tram were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine and quinidine could result in significant drug interactions. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in Tram concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of Serotonin re-uptake Inhibitors and MAO Inhibitors may enhance the risk of adverse events, including seizure and serotonin syndrome.

Elimination

Tram is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean terminal plasma elimination half-lives of racemic Tram and racemic M1 are 6.3 ± 1.4 and 7.4 ± 1.4 hours, respectively. The plasma elimination half-life of racemic Tram increased from approximately 6-7 hours upon multiple dosing.

5.1.2. Placebo (Pbo). An inert Pbo will be used in the study. Although side effects from Tram could result in unblinding of subjects and/or investigators, the possibility of unblinding from side effects will be offset by the ethical concern of using an active Pbo that will confer no benefit to subjects and possibly cause deleterious side effects (e.g., constipation).

5.1.3. Rescue Medications. Subjects will be offered acetaminophen as a rescue medication for unacceptable pain. They will be permitted to take up to 8-325 mg (i.e., 2 tablets 4x/day) of acetaminophen per day. They will be told that the rescue medication is acetaminophen, and warned not to take any other over-the-counter or prescription medications that contain acetaminophen.

Any subjects who cannot tolerate pain that has remained intractable to the blinded study medication and treatment with acetaminophen will be reminded of their right to exit the trial and be referred to a physician with expertise in pain treatment.

5.1.3.1. Acetaminophen pharmacodynamics. Acetaminophen is a centrally acting analgesic and antipyretic with minimal anti-inflammatory properties. The mechanism of action of acetaminophen in reducing pain is unknown but may be due to an inhibition of central prostaglandin synthesis (specifically cyclooxygenase (COX)-2) and an elevation of the pain threshold.

5.1.3.2. Acetaminophen pharmacokinetics.

Absorption – Rapidly absorbed via the gastrointestinal tract. Peak plasma concentrations occur in 0.5-2 hours.

Distribution – 25% protein bound; plasma concentrations do not correlate well with analgesic effect, but do correlate with toxicity.

Metabolism – 90-95% metabolized in the liver.

Excretion – Excreted in urine; elimination half-life ranges from 1-4 hours.

5.1.4. Medication Treatment Protocol.

5.1.4.1. Medication Titration. Subjects will undergo a 14-day period during which their study drug is titrated upward according to the schedule given in Table 5.1.4.1.1 They will be instructed to follow this upward titration schedule unless they experience unacceptable side effects. Subjects who cannot reach a minimum dose of 4 study pills (i.e., 200 mg) per day will be dropped from the study.

The dose achieved by each subject by Day 14 of the titration phase will be the dose given to them during the 8-week maintenance treatment phase of the study (i.e., between Days 15 and 71 of the study). However, if subjects report unacceptable side effects at some time during this 8 week period, they will be permitted to reduce their intake by 1 capsule/day. If they cannot tolerate 4 capsules per day (200mg) they will be dropped from the study. Conversely, if they are taking fewer than 8 capsuless/day as of day 14, and later report inadequate pain relief, they will be allowed to increase their intake by 1 capsule/day to the study maximum of 8 capsules (i.e., 400 mg) daily.

Subjects who are taking doses of serotonergic antidepressants that are greater than 50% of the recommended maximum dose will only titrate up to the lowest effective dose of Tramadol, 4 capsules (200mg) per day (Table 5.1.4.1.)

Table 5.1.4.1.1
Titration Schedule

Day #	Morning	Noon	Afternoon	Evening
1	0	0	0	1
2	1	0	0	1
3	1	1	0	1
4	1	1	1	1
5	1	1	1	2
6	2	1	1	2
7	2	1	1	2
8	2	2	1	2
9	2	2	1	2
10-14	2	2	2	2

Titration phase – total = 81
Treatment phase – total = 456
Taper phase – total = 34
Grand total = 571
Grand total + 10% overage = 628

Table 5.1.4.1.2
Titration Schedule for Subjects on other Serotonergic Medications

Day #	Morning	Noon	Afternoon	Evening
1	0	0	0	1
2	1	0	0	1

3	1	1	0	1
4	1	1	1	1
5	1	1	1	1
6-14	1	1	1	1

Titration phase – total = 50
Treatment phase – total = 228
Taper phase – total = 19
Grand total = 297
Grand total + 10% overage = 327

5.1.4.2. Medication taper. Starting on day 72 of the study, subjects will go through a 10 day taper of their study drug, as shown in Table 5.5.4.2.1 and Table 5.5.4.2.2. During the taper phase of the protocol (Days 72 to 81), the open-label rescue medication can be used to control pain. To prevent the possibility of the subject developing withdrawal symptoms, this taper medication protocol must be followed whenever subjects discontinue participation in the protocol at any time for any reason. If subjects are not taking the maximum dosage of the blinded study medication at the point they begin the taper schedule, they are to begin their taper at whatever point in the schedule corresponds to their current dosage of study medication; the taper schedule will therefore not always be 10 days in length for every subject.

Subjects will be told that if they develop characteristic opioid withdrawal symptoms (e.g., diarrhea, diaphoresis, insomnia, agitation, piloerection, rhinorrhea) during the 10 day taper of their study medication, they should contact the research team. The study clinician will evaluate them. If he or she feels that a participant cannot complete the taper of the study drug within 10 days, the study clinician will modify the taper schedule to allow a longer period for the patient to be tapered entirely off the drug.

The study physician will re-evaluate subjects on day 85. He or she will discuss the subject's responses during the treatment phase of the study, and during the taper phase. Subjects who have experienced significant symptom relief during the treatment phase will be advised that although the study clinician remains blinded to the study medication, the participant might benefit from a trial of Tram supervised by his/her primary care provider.

Table 5.5.4.2.1
Taper Schedule

Day #	Morning	Noon	Afternoon	Evening
1	2	2	1	2
2	2	1	1	2
3	1	1	1	2
4	1	1	1	1
5	1	1	0	1
6	1	1	0	1
7	1	0	0	1
8	1	0	0	1
9	0	0	0	1
10	0	0	0	1
11	0	0	0	0

Table 5.5.4.2.2
Taper Schedule for Subjects on other Serotonergic Medications

Day #	Morning	Noon	Afternoon	Evening
1	1	1	0	1
2	1	1	0	1
3	1	1	0	1
4	1	0	0	1
5	1	0	0	1
6	1	0	0	1
7	0	0	0	1
8	0	0	0	1
9	0	0	0	1
10	0	0	0	1
11	0	0	0	0

5.1.5. Medication Distribution, Storage, and Accountability.

5.1.5.1. Packaging. Study drug [50 mg tramadol IR tablets] will be purchased from the manufacturer. To maintain the blind study drug will be over encapsulated and Pbo to Match (PTM) capsules will be manufactured and packaged into its primary container closure system by the University of Iowa Pharmaceuticals (UIP). A total of 100 capsules of 50mg active Tram IR or PTM (0mg Tram IR) will be packaged in each bottle by UIP.

UIP will then create identically matching 13-week kit boxes containing 6, 100 capsule count bottles per kit box and distribute these kits to the study sites. Each subject is expected to receive 1, 13-week kit box for this 13-week study. In order to prepare subject study drug kits, UIP will receive a list of randomization codes and attendant study drug assignment and behavioral health treatment assignment from the study Biostatistician at the University of Washington (M. Ciol, PhD). The behavioral treatment assignment (CBT*fm* or HE) will be on the pill bottles, within the sealed drug kit, so that research staff are blind to next assignment.

5.1.5.2. Labeling. At a minimum the following information will be included on each thirteen (13) week kit box and each bottle:

- Name of Sponsor
- Name and address of distribution center
- Study number/Acronym
- Drug treatment (Generically listed as either tramadol *or* placebo capsule)
- Behavioral Health Treatment (Behavioral Health 1, or Behavioral Health 2)
- Pharmaceutical dosage form
- Route of administration
- Quantity of dosage unit
- Directions for use
- Storage conditions
- Space for information to be completed by Investigator/designee:
  - Name and telephone number of Investigator
  - Dispensing date
  - Subject number
- Statement “Caution: New Drug – Limited by federal law to investigational use”

- Statement: “Keep out of reach of children”

5.1.5.3. Storage. All drug supplies should be stored at controlled room temperature, 15°-30°C (59°-86°F). The study drug must also be stored in a secure location with limited access. At the University of Washington, the study drug will be stored at the Investigational Drug Services Pharmacy at the University of Washington Medical Center. Designated study personnel will pick up prescriptions from the pharmacy and deliver the study medication to the participants.

5.1.5.3.1. Accountability of Study Drug Supplies. Study drug will be shipped from UIP in batches of 12 kits to each participating site. Sites will be required to acknowledge receipt of study drug within 48 hours of receiving a shipment. The site Investigator, Study Coordinator, or Pharmacist must maintain accurate records (including dates) of all supplies received. All study drug supplies issued to, used by, and returned by each subject must be recorded on a Drug Log (see Appendix J) completed by the Investigator, Study Coordinator, or Pharmacist. Current dispensing records will be maintained, including the date and amount of medication delivered per subject. Subjects will receive sufficient study medication to use until their next scheduled visit. A detailed dispensing schedule will be given to subjects with their study medication. The sites will log in kit numbers on the dispensing log in the subjects’ electronic case report forms (eCRFs). Subjects will be instructed to return all unused medications. All unused and returned study medication not required by applicable federal and state regulations to be held by the clinical facility must be destroyed in accordance with applicable federal and state regulations or be returned as directed immediately after the study is completed.

5.1.6. Blinding and Unblinding of Study Medication. Subjects will be unblinded to their study medication if required for their safety or if the subject needs emergency surgery and information about all treatment interventions is requested; this is expected to occur very rarely, if ever. Only in the event of an emergency that the investigator feels cannot be adequately treated without knowing the identity of the study medication can the medication blind be broken for a particular subject. Individual drug assignment will be included in a sealed document within each drug kit. In the event an emergency situation arises that would require possible disclosure of the study assignment, study physician will be paged, and then if decided to release this information, study staff will break this seal to identify patient assignment. In the event that an emergency disclosure of treatment assignment is required, a call from study staff will be made to inform the the PD, of such disclosure, and appropriate protocol deviation form completed and faxed. All remaining sealed and unsealed code envelopes/labels must be returned to the University of Washington Biostatistician, Dr. Ciol, at the conclusion of the study.

5.2. Behavioral Intervention.

Both CBT and HE treatment sessions should be scheduled at weekly intervals at identified times +/- 2 days window timeframe. If subject or provider needs to reschedule the behavioral sessions due to unforeseen circumstances the behavioral provider may schedule two sessions or elect to do a phone session to review content material necessary for that timeframe.

5.2.1. CBT*fm*. CBT has demonstrated efficacy in the treatment of FM comparable to that provided by medications.[14,15] It has been recommended in recent evidence-based clinical practice guidelines.[16-18] CBT is a generic term; there are many specific interventions that have been included (e.g., exposure, cognitive restructuring, social skills training). We propose to provide customized CBT (designated CBT*fm*) that incorporates several of the above interventions, and has been developed by our team to address issues of particular concern to patients with FM, including providing techniques to enhance sleep quality, reduce fear of acivity, increase physical activity, and improve interpersonal communication (see Table 5.2.1.).

A noteworthy feature of CBT*fm* is the use of actigraphy to address the dissociation between what FM patients' perceptions about their physical capacities and the reality of what they are actually capable of doing. We will utilize actigraphic data during baseline assessments to evaluate the perceptual dissociation among perceived and actual sleep and functional capabilities, and actigraphy during the course of treatment to provide patients with accurate information about their activity levels during the course of the study.

CBT*fm* is adapted from our previous NIH funded projects (AR47298, AR 44724) that were originally based on the treatment described by Turk et al[45] and used in Turk et al[46] and Swanson et al.[47] The program has 3 primary modules that will be integrated in the 8 CBT*fm* sessions: general CBT, Physical Activity related to FM, and Sleep Management (Table 5.2.1.). The general CBT module will focus on maladaptive thought processes and behaviors specifically related to pain, mood, sleep, fatigue, and activity. All of the sessions will be designed to help subjects understand that this is no cure and thus they have to view themselves as important in their own rehabilitation. Sessions will emphasize coping and managing stress symptoms and fear, and fostering SE through information, practice, and mastery. Subjects will be given information, taught a set of skills that they can use on their own, and will be encouraged to practice these at home (See Appendix VIII for details).

The Physical Activity Module will include teaching subjects behavioral strategies for increasing physical activity that have been developed by Fordyce for treating chronic pain.[48] Subjects will address perceptual dissociations by comparing their subjective perceptions regarding physical activity with objective data. They will be given assignments designed to help them monitor their physical activity and gradually increase it (See Appendix VIII for details).

The Sleep Management Module will focus on problems that subjects report regarding their sleep, and on perceptual dissociations that they may have regarding the quality and quantity of their sleep (See Appendix VIII for details).

Table 5.2.1.

CBT*fm* General Outline

Session 1: Rationale: Information about FM, behavior and physiology, sense of control. Relaxation

Session 2: Stress Management, Physiology of stress, Relaxation techniques, Pacing, Actigraphy homework

Session 3: Fatigue and activity pacing, Attentional focus, Homework

Sessions 4: Role of thoughts in generating emotions and their impact on behavior: negative thinking importance of fear in avoiding activities and the impact of reduced activity on physical conditioning and sleep. Homework

Session 5: Role of expectations on fatigue and activity, use actigraphy data to illustrate the perceptual disconnect between anticipation and actuality, effective communication, Homework

Session 6*: Sleep hygiene: sleep/wake pattern, caffeine, relaxation techniques, Homewok

Sessions 7: Relapse prevention, Managing Flare-ups, Homework

Session 8: Review, summary, and preparation of maintenance

Each session will include:

- Review of previously material, home practice, and difficulties encountered
- Presentation of new material with opportunities for discussion
- Practice of how and when to apply acquired skills

- ❖ Behavioral experiments to address catastrophic expectations and misinterpretations ("if…then…" statements test; If I engage in a specific activity, I will be exhausted tomorrow, thus I should avoid the activity).
- ❖ Review of new material covered and assignment for home practice

5.2.2. Health Education (HE). HE, will involve didactic presentations on health themes with discussions.[49] HE will serve as an attention control for CBT*fm* as information alone is not sufficient to produce a significant effect on health-related behavior.[50]

The HE will be comparable in length of the CBT*fm* and will include homework assignments (supplementry reading). The HE will provide information on a range of topics related to FM, including the role of exercise in the management of FM (see Appendix VIV for details).[49,51] During the meetings the patients will be allowed to discuss their symptoms with *no emphasis or guidance given to performance of exercise*. The HE treatment is outlined in Table 5.2.2.

Table 5.2.2.

Health Education (HE)
Treatment Outline

Session 1

- History of FM
- Explanation: What is Fibromyalgia (FM)
- Similarities to other illnesses
- Overlapping syndromes
- Who gets FM-genetics, triggers
- FM in children
- You are not alone
- What FM is not
- How is FM diagnosed
- Common symptoms of FM
- Memory and concentration problems
- Tender points

Session 2

- Acute and chronic pain
- Costs of chronic pain
- Acceptance
- Building relationships with health care providers
- Common treatments for FM
- Complementary and alternative therapies
- Beware of quackery – evidence for treatments
- Trial-and-error
- Employment issues
- Steps involved in disability
- Communication with employer and co-workers

Session 3

- What causes FM?

- Role of physical or emotional trauma
- Effects of the weather
- Effects of FM on mood
- Depression and FM
- Feeling of frustration
- Spiritual strength
- Distorted pain perception
- Biochemical basis of FM
- Gate control theory of pain

Session 4

- Role of stress
- Physiological response to stress
- Understanding the stress response
- Good days, bad days

Session 5

- Problem arising in response to presence of pain
- Importance of sleep and rest
- Stages of sleep
- Sleep disturbance (e.g., insomnia, sleep apnea, snoring, grinding teeth)
- Importance of nutrition
- Importance of physical fitness
- Keeping a health journal

Session 6

- Making lifestyle adjustments
- Type A personality
- Perfectionism
- Importance of family and significant others
- Impact of FM on significant others
- FM and sexuality
- New normal – life with chronic illness
- Stages of adjustment

Session 7

- FM research – biochemistry
- FM research – neurophysiology
- Role of hormones

Session 8

- Treatments on the horizon
- Understanding Clinical trials
- Using the internet wisely
- Closing thoughts

The HE will be conducted by experienced health professionals. Study subjects will be provided information about FM and encouragement. HEs will provide non-directive support as the subjects discuss physical problems and psychological distress in general and related to FM, but no information or training to help subjects improve coping skills will be provided. Although the skills education content will be similar to that provided CBT*fm*, there will be: (1) no specific emphasis on patients' observation of their own behavior and SE and (2) no discussion of the importance of patient observation of their own behavior or SE in adaptation to FM.

Homework. Study subjects in both the CBT*fm* and the HE groups will be given material to read each week summarizing and supplementing the information that is covered during the sessions. Also, subjects in the CBT*fm* group will be given behavioral assignments as described in Appendix VIII.

6. STUDY EVALUATIONS AND ASSESSMENTS

6.1. Schedule and Timing of Assessments.

Phone Screening

1. RA Completes phone screening form
2. If subject meets preliminary criteria, schedule visit
3. Mail/email a copy of the informed consent to review and the HIPPA/ release of information (ROI) for their treating physicians (e.g., PCP, Pain Specialist, Rheumatologist, Psychiatrist) to release relevant medical records for review by the study medical provider.
4. Mail/email the concomitant medications form to fill out before initial visit.
5. Provide postage paid return envelope for forms.
6. 5-6 business days prior to initial screening, if medical records have not been received, study staff will call the subject and any relevant providers to get records. If they are not received prior to the visit, the subject will be rescheduled.

Visit 1: Initial Screening

1. Informed consent by subjects
2. Patient contact form (see Appendix O)
3. Physical Examination
    - Vital Signs (initial vitals form)
    - Medical evaluation
    - ACR 1990 criteria for a classification of FM
        - Duration of symptoms
        - Figure drawing
        - Manual Tender Point Survey
    - ACR 2010 provisional criteria for classification of FM
        - WPI
        - SS
    - Physical tests
        - Range of Motion (ROM)
        - Strength
        - Sit-stand
4. **Laboratory Testing**
    - Urine toxicology screen

- Urine dipstick pregnancy test for female subjects
- Additional blood/screening tests at the discretion of the study MD/ARNP to confirm eligibility.

5. **Questionnaires** completed by patients (see Appendices for the questionnaires)
    - Pain Diagram (see Appendix P)
    - STOP-bang sleep apnea questionnaire (see Appendix X)
    - Background and history form (electronic) (see Appendix II)
    - Symptom Checklist
6. **Health Care Provider Contact** *(ONLY patients who will need to reduce dosage of or titrate off any current medications for eligibility)*
    - Examining clinicians will contact provider who is prescribing patient's antidepressant to confer about eligibility.
    - If the subject's response to the STOP-bang assessment indicates a substantial risk for sleep apnea the examining clinician will confer with a sleep specialist regarding the appropriateness of enrolling the subject.

Visit 2: Screening visit:

1. Urine toxicology report review (see Appendix Q)
2. Treatment Credibility (TC – pre-treatment form)
3. **Baseline Questionnaires** completed by patients electronically (see Appendix III)
    - Fibromyalgia Impact Questionnaire-Revised (FIQR)
    - Short-form McGill Pain Questionnaire-2 (SF-MPQ-2)
    - Hospital Anxiety and Depression Scale (HADS)
    - Multidimensional Assessment of Fatigue (MAF)
    - Life Events Checklist (LEC)
    - PTSD Checklist (PCL)
    - Pain Catastrophizing Scale (PCS)
    - PROMIS
4. **Assessment of Central Sensitization**
    - Temporal Summation (TS) (see Appendix R)
    - Diffuse Noxious Inhibitory Controls (DNIC) (see Appendix S)
5. 6-minute walk test
6. **Daily Diary Packet dispensed**
    - Pain Severity
    - Fatigue
    - Sleep Quality
7. **Actigraphy**
    - Patients will be provided the actiwatch and given verbal and written instructions on how to use it correctly.

Visit 3: Treatment visit Week 1- titration (Drug Day 1)

1. Daily diary and actiwatch returned
2. Final determination of eligibility based on diary completion and a pain score ≥4 and ≤ 9. If subject has not completed 4 out of 5 daily diaries, they will be informed that study

participation is contingent on them completing this diary and participating in all aspects of the protocol, including completing diaries, questionnaires, behavioral-treatment homework and medication adherence. They will be sent home and given 1 more week to complete the diary. If they return and did not complete the diary, they will not be eligible for the study.

3. Pain rating/AE sheet completed by subject (BPI/AE form)
4. Vital signs
5. Conference with subject to discuss final determination of eligibility.
6. Concomitant medications reviewed
7. Complete enrollment form
8. Randomization
9. Clinician visit for titration
10. Give handouts for study medication information and titration schedule.
11. Study drug (i.e., Tram, Pbo) + rescue med (acetaminophen) delivered
12. HE or CBT therapist review patient history form prior to first treatment and sign off

Phone call: Titration check

3 to 4 days after starting study medication, study staff will call the subject to see how they are adapting to the study medication. If the subject reports any adverse events (AEs) the staff will confer with the medical provider to determine the appropriate course of action.

Optional in person Treatment visit- Week 2 (Day 7 +/-2) (ONLY AS NEEDED BASIS FOR TITRATION MED ISSUES)

1. Pain rating/AE sheet completed by subject
2. Evaluation with medical provider

Visit 4: Treatment visit – Week 3 (Day 14 +/- 2)

Titration Complete/First Behavioral Health Treatment

1. Pill count performed by RC/RA to document medication adherence, concomitant medications reviewed
2. Pain rating/AE sheet completed by subject (BPI/AE form)
3. Serotonin syndrome checklist
4. Vital Signs
5. Clinician visit-titration complete, decision of exclusion made if subject is unable to tolerate study dose.
6. CBT*fm* of HE Session 1
7. Therapist rating of treatment progress, attendance, task completion
8. Study drug delivered (Tram/Pbo) as needed

Visit 5: Treatment visit- Week 4 (Day 21 +/- 2)

1. Pill count performed by RC/RA to document medication adherence, concomitant medications reviewed
2. Pain rating/AE sheet completed by subjectVital Signs
3. Hospital Anxiety and Depression Scale (HADS)
4. CBT*fm* or HE Session 2
5. Therapist ratings of treatment progress, attendance, and task completion
6. Study drug

Visit 6: Treatment visit- Week 5 (Day 28 +/- 2)

1. Pill count performed by RC/RA to document medication adherence, concomitant medications reviewed
2. Pain rating/AE sheet completed by subject
3. Serotonin syndrome checklist
4. Vital Signs
5. CBT*fm* or HE Session 3
6. Therapist ratings of treatment progress, attendance, and task completion
7. Study drug (Tram/Pbo) delivered

Visit 7: Treatment visit- Week 6 (Day 35 +/- 2)

1. Pill count performed by RC/RA to document medication adherence, concomitant medications reviewed
2. Pain rating/AE sheet completed by subject
3. HADS
4. Vital signs
5. CBT*fm* or HE Session 4
6. Therapist ratings of treatment progress, attendance, and task completion
7. Study drug (Tram/Pbo) delivered
8. Actiwatch and daily diary provided

Visit 8: Treatment visit Week 7 (Day 42 +/- 2)

1. Daily diary and actiwatch returned
2. Pill Count performed by RC/ RA to document medication adherence, concomitant medications reviewed
3. Pain rating/AE sheet completed by subject
4. Serotonin syndrome checklist
5. Vital signs
9. Mid-treatment Questionnaires (see Appendix IV): performed prior to CBT/HE
    - FIQR
    - SF-MPQ-2
    - HADS
    - MAF
    - PCS
6. Central Sensitization evaluation (DNIC/TS) performed prior to CBT/HE
7. 6-minute walk test
8. Urine toxicology screen
9. CBT*fm* or HE session 5
10. Therapist ratings of treatment progress, attendance, and task completion
11. Study drug (Tram/Pbo) delivered

Visit 9: Treatment visit Week 8 (Day 49 +/- 2)

1. Pill count performed by RC/RA to document medication adherence, concomitant medications reviewed

2. Pain rating/AE sheet completed by subject
3. HADS
4. Vital Signs
5. CBT*fm* or HE Session 6
6. Therapist ratings of treatment progress, attendance, and task completion
7. Study drug (Tram/Pbo) delivered

Visit 10: Treatment visit Week 9 (Day 56 +/-2)

1. Pill count performed by RC/RA to document medication adherence, concomitant medications reviewed
2. Pain rating/AE sheet completed by subject
3. Serotonin Syndrome Checklist
4. Vital Signs
5. CBT*fm* or HE Session 7
6. Therapist ratings of treatment progress, attendance, and task completion
7. Study drug (Tram/Pbo) delivered

Visit 11: Treatment visit Week 10 (Day 63 +/- 2) Last Behavioral Health visit

1. Pill count performed by RC/RA to document medication adherence, concomitant medications reviewed
2. Pain rating/AE sheet completed by subject
3. HADS
4. Vital Signs
5. CBT*fm* or HE session 8
6. Treatment credibility (TC – post-tx form) – completed by patient after CBT*fm*/HE
7. Therapist ratings of treatment progress, attendance, and task completion
8. Study Drug (Tram/Pbo) delivered
9. Daily diary and actiwatch provided

Visit 12: Post-Treatment Evaluation Week 11 (Day 70 +/-2): Post-Treatment Evaluation

1. Actigraphy and daily diary returned
2. Pill count performed by RC/RA to document medication adherence, concomitant medications reviewed
3. Pain rating/AE sheet completed by subject
4. Serotonin syndrome checklist
5. Vital Signs
6. Physical Examination
    - Manual Tender Point Survey
    - Physical tests
        - 6-minute walk
        - Range of Motion (ROM)
        - Strength
        - Sit-stand
7. Clinician visit-drug taper

8. 6-minute walk test (must be done before removal of actiwatch)
12. Central Sensitization evaluation (DNIC/TS)
9. Post-Treatment Questionnaires (see Appendix V) completed by patient:
    - FIQR
    - SF-MPQ-2
    - HADS
    - MAF
    - PCL
    - PCS
    - Patient Global Impression of change (PGIC)
    - PROMIS
10. Clinician Global Impression of change (CGIC) completed by clinician
11. Study Drug (Tram/Pbo) delivered for taper
12. Drug taper information provided to subject

Phone Call- Drug Taper check in (Day 77 +/-2)

Study staff will call the subject to check on adherence and any issues related to study drug taper; any AE to be reported.
Study staff will review AEs or any other pertinent issue with the study medical provider to determine if an interim visit should be scheduled.

Drug Taper visit (ONLY AS NEEDED BASIS DEPENDING ON HOW PATIENT IS RESPONDING TO THE DRUG TAPER)

1. Adverse events reviewd and reported
2. Evaluation by medical provider

Visit 13: Final Treatment Visit (Day 84 +/- 2)

1. Medication turned in, final pill count performed, concomitant medications reviewed
2. Evaluation by medical provider
3. Vital signs
4. Pain rating/AE sheet completed by subject
5. HADS

3 Month Follow-up and monthly phone contact:

3 months from the post-treatment date a 3 month follow-up electronic questionnaire (see Appendix VI) will be emailed to subjects to be completed from their home on their computer. The RA will call subjects to inform them of the email, and if they request to fill out a paper-and-pencil form then that will be mailed to them with a postage paid return envelope. The RA will also call each subject once/month from the completion of treatment until the 6-month follow-up. There will be no forms completed during these calls, with the exception of the 3 month follow-up described above. The RA will only be calling to check in with the subject.

Visit 14 (6-month follow-up)

1. Concomitant medications reviewed
2. Vital signs
3. 6-minute walk test
4. Central Sensitization evaluation (DNIC/TS)

5. Medical evaluation
    - Manual Tender Point Survey
    - Physical tests
        - 6-minute walk
        - Range of Motion (ROM)
        - Strength
        - Sit-stand
6. **6-Month Follow-Up Questionnaires** (see Appendix VII) completed by subject:
    - FIQR
    - SF-MPQ-2
    - HADS
    - MAF
    - PCL
    - PCS
    - PGIC
    - Brief pain inventory (BPI)
7. CGIC completed by clinician
8. Adherence assessed
9. Daily diary and actiwatch provided

Patients will wear the Actiwatch for 7 days after the 6-month post-treatment assessment. They will be asked to mail this, along with their daily diary packet, to the research center with provided postage paid envelopes. Research staff will follow-up with a phone call if paperwork and Actiwatch have not been returned within 2 weeks.

6.2. **Description of all procedures, evaluations, and outcome measures.**

Patient Self-reported Outcome Measures

6.2.1.1. Demographic variables and medical history. Basic demographic data—date of birth, sex, ethnicity, race, marital status, living arrangements, and years of education—will be assessed during the baseline visit in an electronic CRF. The subject's will complete a medical history, including information regarding past and current medical disorders, treatments, and medications as well as past and current painful conditions.

6.2.1.2. Self-report outcome measurse. *5-day daily pain diary.* As recommended in recent guidelines for assessing treatment outcomes in chronic pain clinical trials[52,53], pain will be assessed by asking subjects to rate their average pain on an 11-point rating scale ranging from 0 ("No pain") to 10 ("Pain as bad as you can imagine"). Such pain intensity ratings have been extensively used as primary outcomes in the assessment of a wide variety of acute and chronic pain syndromes. Subjects will also be asked to rate their sleep quality and fatigue in this 5-day daily pain diary (see Appendix D). Subjects will be asked to complete a 5-day daily diary at baseline, mid-way through treatment, post-treatment, and at 6-month follow-up.

Fibromyalgia Impact Questionnaire – Revised (FIQR) will be used to assess pain quality, physical and emotional functioning.

Short-form McGill Pain Questionnaire-2 (SF-MPQ-2)[54] is a revised version of the Short-form McGill Pain Questionnaire[55] that includes the original descriptors assessing sensory and affective dimensions of pain supplemented by neuropathic pain descriptors. The reliability and validity are

well-documented, and studies of the reliability and validity of the SF-MPQ-2 in a large sample of chronic pain patients have recently been completed.[54]

Hospital Anxiety and Depression Scale (HADS)[56] will be used to assess the extent to which pain interferes with emotional functioning.

Multidimensional Assessment of Fatigue (MAF)[57] will be used to assess self-reported fatigue. This scale measures five different elements of fatigue; degree, severity, distress, impact on activities of daily living, and timing of the fatigue over the past week.

PTSD Checklist (PCL) will be used to measure the 17 DSMV-IV-TR symptoms of PTSD.

Pain Catastrophizing Scale (PCS) will be used to assess catastrophic thinking relating to pain.

The *FIQR*, *SF-MPQ-2*, *HADS*, *MAF*, *PCL* and *PCS* will be administered at baseline (Visit 2), mid-treatment (Visit 8), post-treatment (Visit 12), 3 months after treatment (electronically), and at the 6-month follow-up (Visit 14).

Life Events Checklist (LEC) will be used at Visit 2 to assess any traumatic or stressful life events, including how upsetting these events were at the time and how much they have affected the participant's life in the past year.

Patient Reported Outcomes Measurement Information System (PROMIS) will be used at visits 2 and 12 to measure how patients perceive their physical and mental health status.

Stop-Bang Questionnaire will be used at visit 1 to assess for significant risk of sleep *apnea.*

Serotnin Syndrome Checklist will be used to monitor symptoms that may be related to serotonin syndrome.

Post-treatment evaluation of treatment.

Patient Global Impression of Change (PGIC).[58] Subjects will provide a global rating of their improvement by answering the single question rated on a 7-point scale: "Since the start of treatment (last rating), how much would you rate your overall improvement?"

Evaluation of the double-blind. To evaluate the integrity of the double-blind, at the final visit all subjects and their physicians will be asked whether they believe the subject was assigned to Tram or to Pbo, CBT*fm* or HE and to indicate the basis of this judgement.

Treatment Credibility Ratings. Subjects will rate how believable (credible) they perceive the treatment they receive to be on a set of 4 items, 9-point Likert-type scale developed by Borkovec and Nau (see Appendix E).[59] These ratings will be made both at pre-treatment (Visit 2) and at the end of the final treatment session (Visit 11). This method has been shown to have good internal consistency (α .91) and was used in a previous project (AR44724).

6.2.2. Clinician Assessments and Evaluations.

6.2.2.1. Clinician exam of eligibility.

Diagnosis. The diagnosis of FM will be made clinically on the basis of the subject's history, tender point exam, and symptom severity ratings by physician investigators following the ACR 1990[44] classification criteria and the ACR 2010 provisional diagnostics procedures[44] FM will be defined as meeting the 1990 (widespread pain of at least 3-months duration and at least 11/18 specific tender points upon administration of the Manual Tender Point Survey,[60] The 2010 criteria will also be assessed (Widespread Pain Index, WPI [0-19] based on self-reported number of painful body sites and Symptom Severity Score, SS [0-12]: Fatigue [0-3], Waking unrefreshed [0-3], Cognitive symptoms [0-3], Somatic symptoms [0-3]. FM is diagnosed if any of the following are met: WWPI ≥7 and SS score ≥5 or 3 < WPI < 6 and SS score ≥9. Symptoms have been present at a

similar level ≥3 months and Absence of another disorder that would otherwise explain the pain.

Review of medical systems and targeted physical examination. The physician will review the subjects complete a medical history, including information regarding past and current medical disorders, treatments, and medications as well as past and current painful conditions. A targeted physical examination will be conducted, with particular attention paid to symptoms and signs relevant to this protocol.

Physical examination. Physician will also assess participants' physical capacity using 6-minute walk test, neck and lumbar range of motion, knee extension, grip strength, and the sit-stand test (see Appendix F).

6.3. Titration visits. Subjects will undergo a 14-day period during which their study drug is titrated upward according to the schedule given in Table 5.5.4.1. They will be instructed to follow this upward titration schedule unless they experience unacceptable side effects. Subjects who cannot reach a dose of 4 study pills per day will be dropped from the study.

The dose achieved by each subject by Day 14 of the titration phase will be the dose given to them during the 8-week treatment phase of the study (i.e., between Days 15 and 71 of the study). However, if subjects report unacceptable side effects at some time during this 8-week period, they will be permitted to reduce their intake by 1 tablet/day. Conversely, if they are taking fewer than 8 tablets/day as of day 14, and later report of inadequate pain relief, they will be allowed to increase their intake by 1 tablet/day.

6.4. Clinician post-treatment evaluation. *Clinician Global Impression of Improvement in Treatment*. Clinical Global Impression of Change (CGIC) for each subject (7-point scale similar to what patient will complete).

Evaluation of the double-blind. To evaluate the integrity of the double-blind, at the final visit physicians and nurse practitioners will be asked whether they believe the subject was assigned to Tram or to Pbo, CBT*fm* or HE and to indicate the basis of this judgement.

6.5. Psychologist Assessments and Evaluations.

6.5.1. Eligibility Evaluation.

6.5.1.1. Therapist Ratings. The psychologists and health educators will complete ratings of subjects' mood, pain behaviors, comprehension, participation, proficiency of coping techniques, and receptivity following each session (see Appendix H). These will be combined to create session-by-session progress ratings. This procedure was originally used in Turk et al.[46] and in an ongoing project (AR44724). The process measures will be used as independent variables to predict treatment response.

6.6. Actigraphy. After the screening evaluation and provision of consent, subjects will wear an actigraph (Actiwatch, Philips Respironics, Bend OR) on their wrists for 5 days in order to provide 2 types of data: (1) objective sleep data and (2) a global index of physical activity level during waking hours. They will wear the watch also at mid-point of treatment (between Visit 7-8), upon completion of treatment (between Visit 11-12), and for 5 days following 6-month follow-up visit.

6.6.1. Sleep parameters. Sleep-wake patterns will be calculated from body movement data using the Actiware Sleep version 3.4, which bases its algorithm on the amplitude and frequency of detected movements scored in 30 sec epochs.[61-63] Total sleep time, sleep efficiency, and number of awakenings are measured.[64, 65]

6.6.2. Physical activity level when a subject is awake. A global index of physical activity level during waking hours will be derived from the actigraphic data summed over waking hours.

At the end of the 5-day home recordings, the activity data will be downloaded to a computer and subsequently processed. The mean of daytime activity levels, nighttime activity levels, and percentage time spent asleep during the daytime and nighttime, respectively will be calculated. This protocol is currently being used in a study being conducted by the project team (Turk et al., in progress).

6.7. Central Sensitization.

6.7.1. Central Sensitization (CS) and FM*.* Although the causal mechanisms of symptoms underlying FM are not well understood, research suggests that CS of noxious sensory information is an important contributing factor. CS can be manifested by **reduced** ability to inhibit noxious stimuli (i.e., diffuse noxious inhibitory controls - DNIC), and/or by **facilitation** of noxious input (i.e., temporal summation – TS). Patients with FM have been shown to have both impaired DNIC and enhanced TS of nociceptive stimuli.[30-33] If, as postulated, CS is a fundamental process in FM, changes in the clinical status of FM patients should be associated with changes in CS. Because heighted sensitivity to noxious stimuli is thought to be a pathologic hallmark of FM, we hypothesize that CBT*fm*, will result in the lowering of the nociceptive responding, as evidenced by an increase in DNIC efficiency. Specifically, we hypothesize that (1) DNIC will increase and TS decrease over the course of CBT*fm* and (2) decrease in pain severity will be associated with decreased CS, as measured by both DNIC and TS. A recent pilot study examining a different physiological marker provides preliminary support for the feasibility of the latter hypothesis. [20]

6.7.1.1. Assessment of CS. Potential subjects who are found to be eligible for the study will undergo CS assessments. The protocol described is currently being used in a pilot project by the project team.[66]

6.7.1.2. Temporal Summation To assess temporal summation (TS), an indicator of the ascending excitatory mechanisms of pain processing, we will follow methods described by Granot et al[67]. Briefly, we will administer sequences of brief, repetitive mechanical stimuli using a 6.45 g von Frey monafilmament to the ventral side of the non-dominant forearm, and patients will be asked to rate the level of pain intensity on a scale from 0 to 10 after each application. Prior to testing patients will first be given brief training in order to familiarize them with the von Frey monofilament, the sensations, and the task. They will be told that we will ask them to rate the pain on the 1st and 10th prick, and we will apply the prick twice on the lower half of the volar aspect of the non-dominant forearm. Immediately following this training, 10 pricks will be applied with the monofilament, all within a dime sized area of skin on the upper half of the volar aspect of the non-dominant forearm, with 1 sec interval between pricks. Subjects will be asked to rate the first time of the application, and then 10th time. Temporal summation will be calculated by subtracting the first pain rating from the last rating in each 10-pulse sequence.

6.7.1.3. Descending Noxious Inhibitory Controls (DNIC) assesses the degree to which exposure to an ongoing painful “conditioning” stimulus inhibits the pain caused by a brief, repeated painful “test” stimulus. DNIC assessment will be conducted following a published procedure (Appendix I).[68] The assessment involves test stimulation (conditioning stimulus), and then a second test stimulation concurrently with the conditioning stimulus. Patients will be asked to avoid any medications (eg, acetaminophen) for at least 6 hours prior to testing. For test stimulation, we will use contact heat pain produced by the TSA-II stimulator. For conditioning stimulus, we will use a 46.5°C hot water bath.

Training phase: Subjects will be exposed to 2 short heat stimuli (43^{o} & 44°C), applied to their dominant forearm using a heat probe, each lasting 7sec from the time the stimulus intensity reaches the target temperature. Subjects will be asked to rate the level of pain on a scale from 0 to 10.

Determination of test stimulus intensity (*pain-60*): After completing the training phase, the RA/RC will determine the "*pain-60*" value for each patient (ie, the temperature rated by the subject as a 6 on a 0-10 point scale). To determine *pain-60* subjects will be exposed to a series of heat stimuli, each 0.5 s in duration. The first series will consist of 43, 44, and 45^{o} C stimulations with a 1-min interstimulus interval. After each stimulus, subjects will be asked to rate the level of pain on a 0-10 numerical rating scale. If one of these stimuli is rated as 6, that temperature will be chosen as the stimulus for the TS assessment; if not, additional steps for determining *pain-6* will be applied. If the pain rating is > 6, additional stimuli of 46 and 47^{o}C will be applied, and so on until *pain-6* is reached. The maximum temperature will be 49^{o}C. In order to reconfirm the pain-6 temperature, an additional stimulus at the same intensity will be given and rated by the subject.

Administration of test stimulus: The thermode will be strapped in place on the forearm and the test stimulus will be applied for 30s at the *pain-6* temperature. In each test stimulus period, subjects will rate the level of pain intensity 4 times: at 0, 10, 20, and 30s after the onset of the *pain-6* temperature. The mean score of the 4 pain ratings will be calculated.

Conditioning stimulus: Five minutes after delivering the first test stimulus, subjects will be asked to place their non-dominant hand in the hot water bath in a still position with their fingers wide apart for 60s. Patients will be asked to rate the level of pain intensity 4 times: at 0, 10, 20, and 30s after immersion of the hand into the water.

The mean score of the 4 pain ratings will be calculated as the conditioning pain score. Subsequent to the 4th pain rating for the conditioning stimulus (after 30s of the hand being immersed in the hot water), Patients will be asked to shift their focus to the contact heat pain and the test stimulus will be applied again for 30s at the *pain-6* temperature. Subects will rate the level of contact heat pain intensity 4 times: at 0, 40, 50, and 60s after immersion of their hand in the hot water bath, while their non-dominant hand remains in the hot water bath. The mean score of the 4 pain ratings will be calculated.

DNIC will be calculated as follows: The mean of the 4 pain ratings made during the first test stimulus administration will be subtracted from the mean of the 4 pain ratings made during the second test stimulus administration (at the end of the conditioning stimulus condition). Negative scores indicate pain inhibition, positive scores pain facilitation and scores of 0, for example, would indicate no DNIC (no pain inhibition).

TS and DNIC will be assessed prior to initiation of treatment, following treatment session 5, and post-treatment.

6.8. Research Staff Procedures.

6.8.1. Recruitment. Records will be kept of all contacts that occur between potential subjects and the sites, including eligibility based on inclusion and exclusion criteria and reasons for non-participation. All HIPAA, IRB, and local regulations regarding the recording and retention of these records will be followed.

6.8.2. Prescreening. During this telephone contact, the RA will explain study requirements. All potential subjects who contact the project office will be screened over the telephone to determine if they (1) meet minimal inclusion and exclusion critieria and (2) are willing to commit to the requirements of the study (e.g., obtain consent of a healthcare provider, attend regular sesssion, taper any medication currently taking). During this telephone contact, the RA will provide an overview of the study and will explain study participant requirements (See Appendix C).

6.8.3. Medication Log and Pharmacological Adherence. At all visits following the baseline visit, all returned medication will be recorded in a medication log (see Appendix J) for each subject. Pharmacological adherence wil be assessed through these weekly pill counts. All use of

concomitant medications and any other treatments that may have an effect on FM pain will be evaluated during all of the in-person and telephone interviews (and from the daily diaries during the first month) and recorded in logs provided for that purpose. These data will make it possible to examine the relationship between analgesic equivalence levels[e.g.,69] and pain. Adverse events will be evaluated during all of the in-person and telephone interviews (and from the daily diaries during the first month) and recorded in logs provided for that purpose (see section 10.3). At all of the follow-up visits and telephone contacts throughout the trial, any new medical conditions and treatments will be documented (see Appendix K). Particular attention will be paid to documenting any office visits, procedures, inpatient admissions, treatments, and any other use of health care resources associated with the subject's FM since the previous visit or telephone contact.

7. **Compensation.** Subjects will be compensated $25 for completion of each of the 2 pre-treatment, an additional $100.00 for the completion of treatment, and $150 for return at the 6-month follow-up asssessment (Total possible = $300.00). They will not be reimbursed for any travel expenses that they incur for scheduled or unscheduled visits.

8. ADVERSE EVENTS ASSOCIATED WITH STUDY MEDICATIONS

The most common adverse effects and side effects associated with the medications being administered in this protocol are listed below. Common side effects associated with the medications being administered in this study will be managed, when necessary, by halting titration of blinded study medication by 1 pill/day. If subjects report unacceptable side effects that they attribute to the rescue medication (acetaminophen), they will work with the study clinician to modify the dose of their acetaminophen. Dose reductions of 1, 2, 3, 4, 5, 6, 7, or 8 tablets/day might be instituted, and if unacceptable side effects continue, permitting reduction of blinded study medication and rescue medication as described above.

Tramadol (Tram): light-headedness, dizziness, tiredness, constipation, excessively high spirits, irritability, nausea, vomiting, sweating, redness of face, decreased ability to cough, slowed breathing, itching, physical tolerance and dependence if taken for sustained periods of time.

There is some indication that Tramadol may also be associated with a new onet or worsening of Restless Legs Syndrome (RLS), a disorder in which there is an urge or need to move the legs to stop unpleasant sensations.

Acetaminophen: headache, liver damage and failure, jaundice, skin rash, shortness of breath, chest pain, problems with blood.

9. CRITERIA FOR INTERVENTION DISCONTINUATION

The participation of subjects in this study may be terminated by the site investigators or the PI without the subject's consent for the following reasons: if it appears to be medically harmful to the subject, if the subject fails to follow directions for participating in the study, if it is discovered that the subject does not meet study requirements, or if the study is ended.

10. STATISTICAL CONSIDERATIONS

10.1. General Design Issues and Outcomes. The study biostatistician (Dr. Ciol) will be responsible for creating an analysis data set and making any data transformations that are necessary, as well as for conducting all statistical analyses and reviewing the results of the analyses with the PD, PIs, and the investigators. The biostatistician will also be responsible for preparing drafts of the results of the analyses for conference presentations and manuscript preparation.

10.1.1. Primary outcome measure. The primary outcome will be mean pain severity derived from 5-day daily diaries (see Appendix D) and and physical functioning derived from the Fibromyalgia Impact Questionnaire-Revised (FIQR).[70]

10.1.2. Secondary outcome measures. The secondary and exploratory outcome measures include: The Short-form McGill Pain Questionnaire-II (SF-MPQ-2)[54] total and subscale scores, Hospital Anxiety and Depression Scale (HADS[56]), Multidimensional Assessment of Fatigue (MAF), PTSD Checklist (PCL), the Pain Catastrophizing Scale (PCS), Patient Reported Outcomes Measurement Information System (PROMIS), the Patient Global Index of Change (PGIC), and the Clinician Global Index fo Change (CGIC). In addition, adverse events (AEs), serious adverse events (SAEs), study withdrawals, and medication compliance will be examined to evaluate the tolerability and safety of treatment of FM subjects with Tram.

10.2. Sample Size. In this clinical trial, 162 subjects will be randomly assigned to receive one of 4 treatments: CBT*fm* + Tram, HE +Tram, CBT*fm* +Pbo, HE + Pbo (50/group). This sample size should be sufficient for detecting a clinically meaningful effect of CBT*fm* +Tram, allowing for a maximum 15% discontinuatiton rate. The primary outcome variable will be a reduction of at least 30% on the pain score (5-day daily pain diary) or 20% improvement in physical function (FIQR) from baseline (pre-treatment) to post-treatment. Subjects who achieve such decrease in pain or improvement in function will be labeled “responders.” A similar approach to using a composite outcome criterion was used in recent pivotal clinical trials submitted to the FDA for approval of Milnacipran with FM patients.[1a-d] Our primary hypothesis may be supported by a statistically significant difference in proportion of responders among the 4 groups at the $\alpha = .05$ level using a chi-square test, followed by a post-hoc test of difference between pairs of groups. We propose to enroll 81 individuals in each site, for a total of 162 individuals in the final intent-to-treat sample. The power for this sample size is quite high. For example, if we observe a proportion of responders of .2 for HE + Pbo, .4 for HE +Tram, .4 for CBT*fm* + Pbo, and .6 for CBT*fm* + Tram, we would have a power of .8 to find the difference between groups.

10.3. Data Analyses.

10.3.1. Premature termination. In order to assure that the patients who did not complete the protocol (“tx-N”) are not different from those who completed (“tx-C”), the tx-Ns will be compared with the tx-Cs on demographics, medical history, and symptoms, and assignment group. A similar strategy will be used to compare those who refuse to participate following the initial evaluation. The assessment of treatment efficacy will be performed using the intention-to-treat method. Intention-to-treat is a method of data analysis in which the primary tabulations and companion summaries of outcome data are by assigned treatment, regardless of treatment completion or cross-over to a different treatment. This approach safeguards against making an erroneous claim of efficacy because of biases resulting from exclusion of those who fail to complete treatment as prescribed.

10.3.2. Therapist Effects. Since 2 psychologists and 2 HEs are involved in each of the treatment conditions, it is important to assure that treatment efficacy is not biased due to therapist effects. In order to minimize the potential therapist effects, several steps will be taken: (1) use of detailed treatment protocol, (2) review of audiotaped therapy sessions that are randomly selected by the PIs for review, and (3) weekly meetings between therapists and PIs to discuss process and progress.

10.3.3. Analytical Software. Data will be analyzed using IBM SPSS (Statistical Software Package for Social Sciences) for Windows or Mac (version 18 or higher), and SAS version 9.1.3. or higher.

10.3.4. Analytical Approach

10.3.4.1 Assumptions for Statistical Procedures. Prior to conducting any statistical analyses to test hypotheses, exploratory analyses will be performed as needed in order to check the underlying assumptions for each statistical procedure (e.g., normal curve plots, testing for the homogeneity of variance).

10.3.4.2 Analytic Approach for the Primary Aim.

The primary outcome will be a reduction of at least 30% on the pain score (mean for 5-day daily pain diary) or improvement of 20% physical function (FIQR) from baseline (pre-treatment) to post-treatment. Individuals who achieve such decrease in pain will be labeled "responders."

Hypothesis 1A: The group of FM patients receiving combination therapy (CBT*fm*+Tram) will have a larger proportion of responders as compared to the other 3 treatment groups. Hypothesis 1B: The differences in proportion of responders will be maintained at the 6-month follow-up.

1. The primary analytic approach is a Chi-square test of homogeneity among the 4 treatment groups, using the classification "responder" or "non-responder" for each person. The test will use a signifcance level of 0.05. If the test is not statistically significant, we will conclude that the 4 treatment groups yield the same proportion of responders. If the test is statistically signifcant, we will proceed with a post-hoc test to identify which groups are different from each other. In addition, we will calcuate confidence intervals for proportion of responders in each group.
2. To determine if combined treatment results in better maintenance as compared to the other 3 groups, the same type of analysis will be conducted with post-6 months outcomes (responder versus non-responder).
3. Individuals will be analyzed in the group assigned to them through randomization regardless of their adherence to the treatment (intent-to-treat approach). Missing values for outcome variables will be treated as described below in 10.3.6.

Hypotheses 2-5 are secondary hypothesis and will be interpreted as exploratory.

Hypothesis 2: Decrease in CS, as assessed via TS and DNIC, and decrease in affective distress will predict improvement in function.

We will conduct a sequential regression analysis, with percent change in FIQR as the dependent variable, and baseline pain severity entered in Step 1, and TS, DNIC, and HADS scores entered in step 2. Hypothesis 2 will be supported by a statistically significant beta weight for TS, DNIC, and HADS.

Objective #3: Test of the Perceptual Dissociation between perceived and actual sleep quality and activity.

Hypothesis 3: Modest to weak relationships among objective measures of sleep and activity and self-report measures of sleep and functioning.

Correlations will be $\leq$ 0.30 among objective measures of sleep and activity and self-report measures of sleep and functioning.

1. Bivariate correlations among self-report and objective measures of sleep and activity will be evaluated.
2. Multiple regression analyses will be conducted to investigate the relative importance of perceived and actual sleep quality, as predictors of activity levels.

Objective #4:

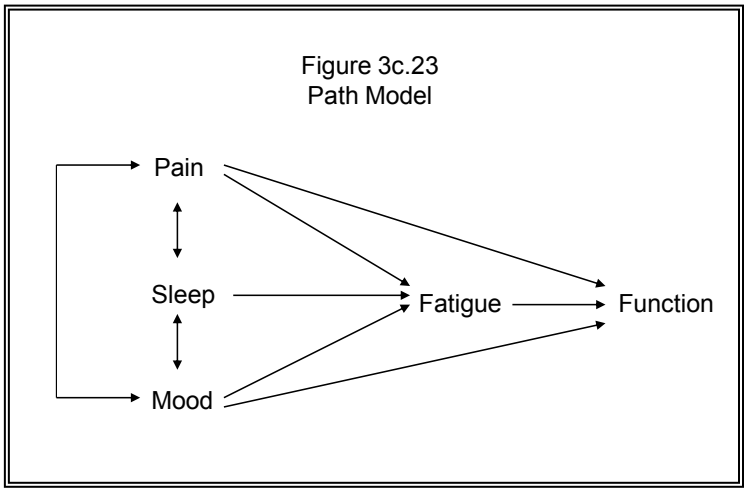
Test mediational model of activity.

Hypothesis 4-5: 4. Pain and Mood will predict increase in activity (as assessed via actigraphy).

5. The path analysis will indicate a mediational effect of fatigue level on physical function (FIQR), driven by measures of pain level, sleep quality, and mood.

Path analysis will be conducted to test the model presented in Figure D6.5 for all patients at baseline (implemented using PROC CALIS in SAS version 9.1.3). Specifically, the model posits a meditational effect of fatigue on activity level, arising from pain level, sleep disturbance, and mood disturbance. Additionally, direct effects are indicated for pain level and mood on activity levels. Two main analyses will be included as part of the path analysis.

Figure 3c.23
Path Model



First, the proposed model will be tested for adequate fit, given the data, and will be described in terms of the Comparative Fit Index (CFI). The CFI ranges from 0 (poor fit) to 1 (perfect fit), and is a widely-accepted fit index used in structural equation modeling approaches to data analysis.[72]

Second, parameter estimates for each path described will be evaluated for relative importance using the Wald test. Path coefficients not significantly differing from the null can be concluded to play no role or effect on activity level [72], and the model will be subsequently modified and re-tested for adequacy of fit.

10.3.5. Adverse Events. The number and percentage of patients in each group who experience a treatment-emergent adverse events (AEs) will be summarized. Associated adverse events will also be summarized, and include those events the investigators consider to be possibly, probably, or definitely related to treatment, and those for which the relationship is unknown (See Appendix M).

10.3.6. Treatment of missing data. Every effort will be made to retain subjects in this study and to collect all data at every visit. If a subject cannot tolerate or refuses to continue taking study medication, follow up and evaluation will continue if the subject is willing. If a subject drops out, attempts will be made to bring the subject in for a final evaluation. Adherence with trial procedures, dropouts/dropins, and reasons for subject withdrawal will be carefully tracked throughout the study. If a subject is missing a response at a particular visit, missing data will be imputed using a multiple imputation algorithm based on linear or logistic regression (depending on the whether the outcome is a numeric or binary variable). For subjects with complete data up to a particular visit, a regression model will be fit that includes the outcome at that visit as the response variable and outcomes at previous visits, treatment group, center, age, sex, pain intensity, as explanatory variables. Separate models will be similarly constructed for each visit. Using these regression models, a missing value for a subject at a particular visit will be imputed as a draw from the predictive distribution given the outcomes at previous visits (some possibly imputed), treatment group, center, age, sex, acute pain intensity. This will be done sequentially starting with the Day 4 visit. This process will be repeated 10 times, resulting in 10 complete analysis data sets. The analyses will be performed separately for each of the 10 complete analysis data sets, and the results will be combined into one multiple imputation inference (estimated treatment effect and associated confidence interval and p-value). This strategy is appropriate for data sets that have a monotone missing pattern. If the data set does not precisely have this pattern, the monotone data augmentation method using Markov-Chain

Monte-Carlo will be used to impute the small amount of missing data that is required to make the missing data pattern monotone before applying the multiple imputation algorithm described above.

This approach to imputation is considered superior to other strategies such as carrying forward the last available observation, which often yields unrealistic imputed values. Also, the use of multiple imputation avoids the problem of artificially increasing power through data imputation associated with single-imputation methods because it accounts for the uncertainty associated with the imputation. It is hoped that the overall conclusions regarding the effects of the interventions will not depend greatly on the analysis or imputation strategy used, particularly if the occurrence of missing data is minimized.

10.4. Data Monitoring. A data and safety monitoring board (DSMB) established by NIAMS (KAI contract). Information on all AEs, SAEs, recruitment and retention, data completeness, and data quality will be available for review by the DSMB. It is not anticipated that there will be any major safety concerns with the medications administered in this trial, all of which are FDA approved and have well-characterized safety and tolerability profiles. Tram has been studied in FM, there is no reason to believe that its safety and tolerability will be a significant problem. Interim analyses of all AEs and SAEs will be performed periodically throughout the trial for the DSMB. The safety of subjects will be a primary concern of the DSMB and project team, and AEs and particularly SAEs will need to be carefully considered by the DSMB. If anything appears problematic in the combined data or at the specific request of the DSMB, we will provide analyses of AEs and SAEs broken down by the 4 groups separately, and we will provide completely unblinded analyses if the DSMB believes this is necessary. Since Tram and the behavioral-health interventions used in this project have been shown to have modest benefits as monotherapies, we do not anticipate that efficacy will be sufficiently disparate across groups to warrant terminating the trial.
In addition, the DSMB will periodically review data regarding the rate of subject accrual over time. If the NIAMS, in consultation with the DSMB, determines that the accrual rate falls substantially below that which is necessary for timely completion of the trial, the trial may be halted for futility. The trial may also be halted for futility if other indicators of trial performance (e.g., subject retention, data quality) suggest that this is appropriate.

11. DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

11.1. Data Collection and Retention. The investigators and staff at the study sites, the PD, PIs, Project Reseach Coordinator, and all personnel involved in subject assessment, monitoring, analysis, and data management will be blinded to the subject assignment. In order to ensure that information that could potentially bias handling of data is not disclosed, the following precautions will be practiced: randomization code envelopes will be maintained in fire-proof safes; no access to these codes will be permitted to those involved in subject data handling; maintenance of the code sealed envelopes by the investigator in a locked cabinet at each study site will be carefully monitored; and medications will be packaged in a way that maintains the double blind.

Study data will be collected and managed in the Research Electronic Data Capture (REDCap) tool hosted at the University of Washington.[73] REDCap is a secure, web-based application designed to support data capture for research studies, providing: (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources. REDCap allows users to build and manage online surveys and databases quickly and securely. User rights may be customized, and access to specific data fields restricted. A separate contact worksheet will be maintained within REDCap that will contain subject names, address, phone numbers, and study id for the purpose of contacting subjects throughout the study period. This worksheet will be password protected, and access will be limited

to only research assistant and coordinator who are responsible for contacting participants throughout the course of the study. All other research data will be maintained in a separate worksheet, and access to each field limited to only study staff that will be utilizing that specific field (e.g. treating psychologists will only have access to treatment progress notes fields). UR and UW data will be collected within the same project, however all rights to data access to each individual site will be limited to only staff within each site.

11.2. Site Monitoring.

11.3. Adverse Experience Reporting (See Appendix M for reporting forms).

11.3.1. Definition of an adverse event. An adverse event (AE) is any untoward medical occurrence in a subject that occurs during the conduct of a clinical study of a pharmaceutical product that does not necessarily have a causal relationship to the study medication. This can, therefore, be any unfavorable and unintended physical sign, symptom, laboratory parameter, or disease entity that develops or worsens in severity during the course of the study, whether or not considered related to the study medication.
Accordingly, an adverse event could include any of the following:

- Inter-current illnesses
- physical injuries
- events possibly related to concomitant medications
- significant worsening (change in nature, severity, or frequency) of the disease under study or other preexisting conditions
- events occurring during diagnostic procedures
- a laboratory or diagnostic test abnormality occurring after the start of the study (once confirmed by repeat testing) that results in the withdrawal of the subject from the study, requires medical treatment or further diagnostic work-up, or is considered by the study investigator to be clinically significant. Note: abnormal laboratory determinations at the screening visit that preclude a subject from entering the study or receiving study medication are not considered adverse events, but will be captured in order to monitor data from screen failures.

11.4. Recording and reporting adverse events. For the purpose of AE recording, the study period is defined as that time period beginning when the subject signs consent to completion of medical drug taper. All AEs that occur during the study period must be recorded on the AE form, regardless of the severity of the event or judged relationship to the study medication. For SAEs, the site director, Drs. Dworkin for UR and Turk at the UW, will be notified by the site staff within 24 hours of the site's notification of the event. Within 24 hours of notification of the AE, the site will be required to submit the AE information on the AE transmittal form, to overall program director, Dr. Turk. If an AE occurs after the study period and is considered by the investigator to be possibly related to the study medication or study participation, it must be recorded on the AE Transmittal Form and reported immediately.

At each weekly visit following commencement of treatment subjects will be provided an AE-form which asks "Since your last visit, have you experienced any new or worsening symtpoms or medical problems? If yes, please specify." Addtionally, subjects are asked in an identical format if they have experienced any new or worsening emotional changes or changes in their ability to concentate or remember things. All reported or observed signs and symptoms should be recorded individually, except when considered manifestations of a medical condition or disease state.

The clinical course of each AE that is active at the final visit should be monitored at suitable

intervals until resolution or stabilization, a determination of a cause unrelated to the study is made, or the subject is referred to the care of a local physician.

The onset date, stop date, action taken with the study medication, and outcome of each AE will be recorded on the AE form. The relationship to study medication, severity, and seriousness of each AE as judged by the investigator will be recorded as described below.

11.4.1. Relationship of an adverse event to study medication. For each AE, the relationship to the study medication must be recorded as one of the choices on the following scale:

DEFINITE	*Causal relationship is certain* (i.e., the temporal relationship between medication exposure and the AE onset/course is reasonable, there is a clinically compatible response to dechallenge, other causes have been eliminated, and the event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary).
PROBABLY	*High degree of certainty for causal relationship* (i.e., the temporal relationship between medication exposure and the AE onset/course is reasonable, there is a clinically compatible response to dechallenge [rechallenge is not required], and other causes have been eliminated or are unlikely).
POSSIBLY	*Causal relationship is uncertain* (i.e., the temporal relationship between medication exposure and the AE onset/course is reasonable or unknown, dechallenge/rechallenge information is either unknown or equivocal, and while other potential causes may or may not exist, a causal relationship to the study medication does not appear probable).
UNLIKELY	*Not reasonably related, although a causal relationship cannot be ruled out* (i.e., while the temporal relationship between medication exposure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the AE than the study medication).
UNRELATED	*No possible relationship* (i.e., the temporal relationship between medication exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study medication is implausible).

11.4.2. Severity of an adverse event. The severity of each AE will be recorded as 1 of the choices on the following scale:

MILD	No limitation of usual activities
MODERATE	Some limitation of usual activities
SEVERE	Inability to carry out usual activities

11.4.3. Serious Adverse Events (SAE).

Definition of an SAE. AEs are classified as either serious or non-serious.
An SAE is any adverse event occurring at any dose, which results in any of the following outcomes or actions:

- death
- a life-threatening AE (i.e., the subject was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- in-patient hospitalization or prolongation of existing hospitalization (Hospitalizations

scheduled before enrollment for an elective procedure or treatment of a pre-existing condition, which has not worsened during participation in the study will not be considered an SAE.)

- a persistent or significant disability/incapacity (i.e., a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition; any new diagnosis of cancer (made after study enrollment) will be considered an important medical event

An AE that does not meet any of the criteria for seriousness listed above should be regarded as a non-serious adverse event.

Reporting SAEs. All SAEs that occur either during the study period, regardless of relationship to the study medication, or after the study period, if considered possibly related to study medication or participation, must be immediately reported within 24 hours of the investigator's knowledge of the event or, when this occurs on a weekend or federal holiday, at the latest on the following working day. The initial report must be made by telephone to one of the following individuals, with contact attempted in this order:

- Laurie Al-Nasr (telephone: 206-221-6851)
- PD: D. Turk, PhD (telephone: 206 616-2626)
- PIs: J P. Robinson, MD, PhD (telephone: 206 998-0125); R. Dworkin, PhD (telephone: 585-275-8214)

The site investigator should continue calling until he/she speaks to an individual personally. Do not leave a voicemail message, as it is always possible that the person you called is not in the office. Within 48 hours of this initial report, the investigator must report to KAI by facsimile with a signed Serious AE Transmittal Form completed to the greatest extent possible and a copy of all relevant source documents. The site must also ensure that all data has been entered appropriately into the Adverse Events form on REDCap for reconciliation. The timely provision of the SAE Transmittal Form should not be delayed in the event that information is partial or incomplete. Follow-up information received on all SAEs will follow the same procedure and timelines as indicated above for the initial report. Address facsimile to:

The PD or PIs will review the submitted information and SAEs determined to be unexpected will be forwarded to the data safety and monitorin board and the FDA as set forth in 21 CFR Part 312. The investigator must also ensure that the IEC/IRB is informed of the event in accordance with local IRB reporting requirements.

11.5. Premature withdrawal from the study. Any subject who experiences an AE may be withdrawn from the study at any time at the discretion of the investigator. If a subject is withdrawn wholly or in part because of an AE, both the AE page and Study Completion/Withdrawal form will be completed at that time. The subject will be monitored until the event has resolved or stabilized, determination of a cause unrelated to the study is made, or the subject is referred to the care of a local physician. The investigator will report a subject's premature withdrawal from the study (for any reason) to the PD within 24 hours (or the next working day) of its occurrence. Additional reports must be provided when requested.

11.6. Medical emergencies. Medical emergencies will be reported to Dr. Robinson (After hours calling the paging operator at 206-598-6190 and ask to have Dr. Robinson paged). Equipment,

supplies, and properly skilled medical personnel will be accessible for use in an emergency in the event of an unexpected AE. Subjects to be included in the study will be carefully selected and the study will be conducted in an appropriate manner. Any intentional or unintentional dose of study medication taken in excess of that prescribed will be immediately reported to PD.

11.7. Protocol deviations because of an adverse event. In the event of an AE or medical emergency, allowing departures from the protocol will be determined on a case-by-case basis. The investigator or other physician in attendance in such an emergency will contact the PD/PI as soon as possible to discuss the circumstances of the emergency. The investigator, in consultation with the PI, will decide whether the subject should continue in the study. All protocol deviations and the reasons for such deviations will be recorded in the study deviations form (See Appendix T).

12. HUMAN SUBJECTS

12.1. Institutional Review Board (IRB) Review and Informed Consent. The study will be approved by the IRB of the PI's institution (UW, UR). The rationale, inclusion and exclusion criteria, and procedures will be described in lay terms to potential subjects after they have been referred to the study or identified by other means. If the potential subject remains interested in participating, written informed consent will be obtained by the investigator or other key study personnel qualified to obtain consent.

12.2. Risks to the Subjects. The study described in this protocol presents greater than minimal risk to subjects. This risk involves the potential for side effects and other adverse events from the study medications that will be administered to subjects. These medications include generic tramadol-IR and acetaminophen, which will be administered to any subjects with unacceptable pain.

It can be anticipated that some subjects will have unrelieved pain, either because they are in the placebo group, because they do not respond to treatment with generic tramadol-IR or the rescue analgesic, or because these medications are not efficacious in FM.

12.3. Subject Confidentiality. The investigator will ensure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. US sites are reminded that, effective April 14, 2003 they may have additional privacy obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA). On the eCRFs and other documents participant records, subjects will not be identified by their names, but by a subject identification number.

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRF. This may be done by the study monitor, properly authorized persons on behalf of the, or regulatory authorities. Personal medical information will always be treated as confidential. All records will be kept in a locked file cabinet, or in a password protected electronic data capture software, REDCAP. All computer entry and networking programs will be done using subject identification numbers only. Identifiable clinical information will not be released without written permission of the subject, except as required for monitoring by the IRB, the FDA, and the OHRP.

12.4. Adequacy of Protection Against Risks. Subjects will be routinely and carefully evaluated for the presence of side effects and other AEs. It can be anticipated that some subjects will have unrelieved pain, but the structured approach to providing rescue analgesia will reduce the likelihood that subjects will experience unacceptable acute pain during the placebo-controlled phase of the trial. Any subjects who cannot tolerate severe pain that has remained intractable to the blinded study medication and treatment with rescue medication will be reminded of their right to exit the trial and be referred to a physician with expertise in pain treatment.

Subjects will be unblinded if required for their safety or if the subject needs emergency surgery and

information about all treatment interventions is requested; this is expected to occur only very rarely. Only in the event of an emergency that the investigator feels cannot be adequately treated without knowing the identity of the study medication can the medication blind be broken for a particular subject. With each shipment of drug kits, sealed codes will also be provided to the site investigators, and these codes must remain sealed under the responsibility of the investigator. In the event that an emergency disclosure of treatment assignment is required, a call will be made to inform the the PD, PIs, of such disclosure; the actual treatment assignment, however, will not be disclosed to the staff during this phone call.

12.5. Potential Benefits to Subjects. There are several potential benefits to subjects of participating in this study:

1. Subjects will be evaluated and treated without charge for their FM by healthcare providers who have expertise in FM.
2. All subjects will be treated for unacceptable pain using rescue analgesia, and their pain will be carefully monitored and treated throughout the study.

12.6. Alternatives to Participation. The alternatives to participation in this study are for subjects to be treated by their primary care doctor or from a physician with expertise in FM or pain treatment. Treatment might also include the use of various medications with analgesic effects, including the generic tramadol IR used in this study, for control of the subject's pain.

12.7. Inclusion of Women, Minorities, and Children. We propose to include both females and males with FM in this project. Since women are substantially more likely to seek treatment for FM (8 to 1) we expect that a similar female/male ratio will be represented in the current study.

12.8. Inclusion of Minorities. People with FM of all ethnic and racial groups represented in the population of King and surrounding counties, Washington and Monroe and surrounding counties, New York. Ethnic and racial composition of King County, Washington is approximately 87% White, 13% racial and ethnic minorities including 7% Asian, 2% Black, 2% American Indian, and 2% Hispanic. The ethnic and racial composition of Monroe County, New York is approximately 80% White, 15% Black, and the remainder American and Alaskan Indian, Asian, and Native Hawaiian and Other Pacific Islanders, with approximately 6% persons of Hispanic or Latino origin.

Investigative staff at both sites (UW, UR) will make every effort to enroll all patients who meet eligibility criteria in the proposed trial, irrespective of race or ethnicity, and the databases have been designed to collect all information regarding race and ethnicity according to the NIH guidelines. We will monitor the racial and ethnic composition of our sample. If the distribution of subjects recruited is substantially different from the general distribution in King County, WA, Monroe County, NY and surrounding counties, we will actively recruit an increased number of members of the under-represented minorities by increasing efforts to recruit in parts of the country with higher percentages of minority populations. Special efforts will be devoted to enrolling Black and Latino subjects, and the goal will be to have 15% minority participation. Efforts to ensure adequate recruitment of minority subjects will include: (1) the PIs and their staffs will closely monitor recruitment of minority subjects, develop plans to actively recruit minority subjects through community lay groups and via direct contacts with minority organizations in the local areas, and also ensure that efforts to increase enrollment emphasize recruitment of minorities; (2) local minority recruitment initiatives will include targeted advertising in minority publications and in support of efforts to actively recruit minority subjects through community organizations; (3) speaking engagements will be scheduled by the PIs and other study staff at minority physician and health care provider groups in which FM and the clinical trial will be discussed; (4) materials will be developed and advertising undertaken to publicize the trial in local and regional newsletters and newspapers with predominantly minority readership; and (5) the resources of the NIH-funded centers on minority recruitment will be used to

augment local efforts and the trial will be publicized on the NIH clinicaltrials.gov website. In addition, to ensure that minorities are adequately represented in the study at the UW site, investigative staff will recruit patients receiving care at Harborview Medical Center, a facility where ethnic minorities make up a substantial proportion of patients.

Our previous research and current project (AR44724) has demonstrated that we are able to recruit targeted populations. We will aggressively attempt to recruit racial-ethnic monitories by (1) creating an advisory board of racial and ethnic minorities from the community to provide advice on recruitment, (2) advertise the project in media that target minorities, and (3) place information about the study in venues that are likely to be seen by minorities (churches, community centers, health clinics locate in areas of high concentration of minorities.

12.9. Study Modification/Discontinuation. The study may be modified or discontinued at any time by the IRB, the NIAMS, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

13. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the three PIs. Any presentation, abstract, or manuscript will be made available for review by the NIAMS prior to submission.

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