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Randomized Clinical Trial of Fibromyalgia Integrative Training (FIT Teens) for adolescents with Juvenile Fibromyalgia – FIT Teens Study (Umbrella)

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ABSTRACT

Juvenile-onset fibromyalgia (JFM) is a chronic, debilitating pain condition that typically persists into adulthood for the majority of patients. Whereas medications offer limited and short-term symptom relief for JFM, our research group has demonstrated that cognitive-behavioral therapy (CBT) is safe, effective and durable in reducing functional disability and depressive symptoms in adolescents with this condition. However, 60% of patients receiving CBT did not show *clinically significant* improvement in functional disability, and pain levels remained in the moderate range despite being reduced overall. Objectively measured sedentary activity also did not significantly improve with CBT. Incorporation of a physical exercise component emerged as a logical next step to enhance CBT, yet regular participation in any physical activity has been shown to be difficult to initiate and maintain in FM patients. In our prior research, we have documented poor movement competence, deficits in movement confidence and fear of physical activity as variables that likely underlie deficiencies in daily physical activity for teens with JFM. Our multidisciplinary team of experts in Behavioral Medicine, Rheumatology and Exercise Science has developed and tested the feasibility of a new Fibromyalgia Integrative Training program for Teens (FIT Teens), which enhances the established CBT intervention with a novel neuromuscular exercise training program derived from evidence-based pediatric injury prevention research. Innovative features include - 1) neuromuscular training specifically designed to limit muscle soreness; and 2) seamless integration with CBT to enhance psychological coping skills, decrease fear of movement and increase physical activity participation. Pilot testing showed excellent patient engagement, no adverse effects and very promising early results indicating this treatment to have even stronger effects on disability and pain outcomes than CBT alone. This rigorous 3-arm randomized clinical trial (RCT) will test whether the FIT Teens intervention is more effective than CBT alone or graded aerobic exercise (GAE) alone and whether treatment effects are sustained over 1 year follow-up. We will also evaluate treatment mechanisms – of how changes in coping, fear of movement, adherence, biomechanical changes and physical fitness predict changes in disability and pain outcomes. Results are expected to have a significant impact on the clinical management of JFM.

ABBREVIATIONS

FIT Teens: Fibromyalgia Integrative Training for Teens
CBT: Cognitive Behavioral Therapy
GAE: Graded Aerobic Exercise
PROMIS: Patient Reported Outcomes Management Information System

1. PURPOSE OF STUDY

A. Primary Objectives

Aim 1a: To test whether the combined FIT Teens intervention is more effective in reducing functional disability (primary outcome) than CBT alone or GAE alone.
H1a. The FIT Teens group will show significantly greater reduction in functional disability at 3-month follow-up compared to CBT and GAE, respectively.

Aim 1b: To test whether disability levels in the FIT Teens group are maintained at lower levels than CBT alone or GAE alone over time.
H1b. Functional disability in the FIT Teens group will remain significantly lower than CBT and GAE at 6-, 9- and 12-month follow-up.

Aim 1c: To test whether more patients who receive FIT Teens achieve clinically meaningful improvement in functional disability compared to those who receive CBT and GAE.
H1c. A significantly greater proportion of the FIT Teens group will achieve clinically meaningful reduction in functional disability (defined as a $\geq$ 7.8 point reduction in FDI score) at 3-month follow-up than CBT and GAE.

Aim 2: To test whether the combined FIT Teens intervention is more effective in reducing pain intensity (secondary outcome).
H2. We hypothesize that the FIT Teens group will show significantly greater reduction in pain intensity at 3-month follow-up compared to CBT and GAE and that pain intensity in the FIT Teens group will remain significantly lower than CBT and GAE over time (6-, 9- and 12-month follow-up).

B. Secondary Objectives

Exploratory Aim: To examine a mechanistic model of how treatment-related improvements in psychological (coping, fear of movement, adherence) and physical factors (objectively measured physical activity, biomechanical changes and fitness) explain changes in disability and pain outcomes.

2. BACKGROUND

A. Supporting Information

JFM is a chronic and disabling condition for which there is no cure. Pharmacotherapy has modest benefits and tends to be poorly tolerated by many fibromyalgia patients. Our research group conducted a rigorous RCT of Cognitive Behavioral Therapy (R01AR050028) in which CBT was found to be efficacious in reducing disability and alleviating mood difficulties in JFM. Despite the very promising results of CBT, with findings showing statistically significant improvement, when a

higher bar of *clinical significance* was used, approximately 60% of patients who received CBT did not have sufficiently large gains in functioning to be considered treatment responders. Also, while pain was significantly improved (average pain rating decreased from 5.7 to 4.9 on a 0-10 scale), it remained in the moderately high range. Moreover, patients did not show any increases in physical activity/exercise. Patients with JFM find it extremely challenging to incorporate regular exercise into their routines due to physical factors (e.g., deconditioning) and psychological factors (e.g., fear of pain with movement). The newly designed FIT Teens program provides both the psychological coping skills and specialized neuromuscular training to lay the foundation for safe exercise.

There is empirical evidence that physical exercise leads to pain reduction in fibromyalgia. However, the benefits of exercise diminish because of poor adherence to regular exercise. In collaboration with experts Fin Exercise Science, we have discovered that specialized neuromuscular exercise training can be combined with CBT to offer a highly engaging way to improve adolescents' ability and confidence in exercise by teaching them proper body biomechanics and fundamental movement skills. The greatest benefits of neuromuscular training are that it is designed to reduce muscle soreness and to improve strength, gait, posture and balance for teens to exercise safely. In a NIAMS funded study (R21AR063412), we have completed Phase 1 feasibility, acceptability and safety testing of the new FIT Teens intervention which combines our established CBT program with neuromuscular exercise training (N =16 JFM patients). Not only is the treatment safe and highly engaging for patients, but initial efficacy results on disability and pain are also very promising. In Phase 2 testing, we are completed a single-site randomized pilot trial of FIT Teens (N=40) comparing FIT Teens with CBT (N=20 in each group) at Cincinnati Children's Hospital. Thirty-six patients completed treatment (90% retention) and 3-month follow-up. Results showed superiority of the FIT Teens intervention to CBT, with greater improvement in both disability andpain in the FIT Teens group. In the proposed trial we plan to test if the combined effects of the FIT intervention are more powerful than CBT alone or a traditional exercise-only program (Graded Aerobic Exercise).

B. Preliminary Work

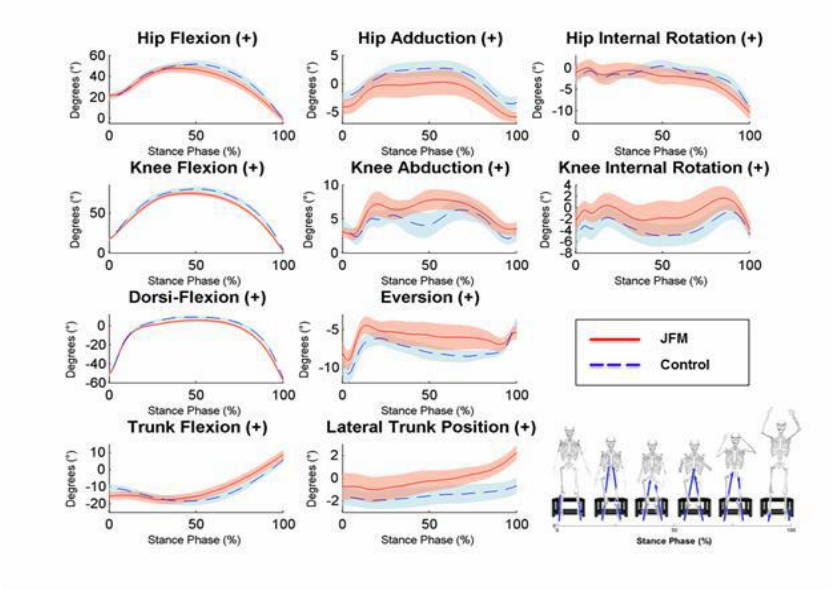
Randomized clinical trial of CBT in adolescents with JFM. The main objective of this completed 4-site single-blind randomized clinical trial (R01AR050028, PI: Kashikar-Zuck) was to test whether (CBT) was superior to fibromyalgia education (FE) in reducing functional disability in JFM. Participants were 114 adolescents (ages 12-17) with JFM. After being stabilized on usual medical care for 8 weeks, patients were randomized to either CBT or FE and received 8 weekly individual sessions with a therapist and 2 post-treatment booster sessions (at 2- and 4-months). Assessments were conducted at baseline, immediately following the 8-week treatment and at 6-months follow up. Retention was excellent (87.7% completing the trial per protocol) and there were no study-related adverse events. The results of this rigorously controlled RCT were that CBT was significantly superior to FE in reducing functional disability (95% CI 1.57-9.22; p = 0.007) with a large effect size for CBT (d = .85). CBT also resulted in a significant, but small reduction in pain (Mean reduction from 5.7 on a 0-10 scale to 4.9 at the end of treatment; d = .22)[1]. This study demonstrated that CBT is a highly promising intervention for reducing disability in adolescents with JFM. However, although the effect size for functional disability improvement was large, a secondary analysis using the Reliable Change Index as a cut-off for clinical significance (reduction in FDI score by ≥ 7.8 points) showed that 60% of patients did not achieve *clinically meaningful* changes in disability. Pain reduction was also not sufficient to be considered clinically significant using a criterion of ≥ 30% improvement [2]. These findings highlighted ***the need for more powerful interventions to achieve***

clinically meaningful improvements in disability and pain in JFM.

Physical activity in adolescents with JFM. Using objective physical activity monitoring in 104 patients with JFM enrolled in the RCT described above, we found that adolescents with JFM are very sedentary – mean of ~9 hours of sedentary/inactive time during daytime hours [3]. Results also suggested that higher levels of physical activity were associated with lower pain levels and that older adolescents were more sedentary than younger teens. In the trial reported above, we found that CBT intervention did not lead to any increase in objectively monitored moderate-vigorous physical activity, despite patients' self-reported improvements in overall functioning [4]. The high levels of inactivity found in JFM patients, even after treatment, is concerning. Despite training in coping skills and efforts made by physicians and health care providers in usual medical care to educate JFM patients about the importance of exercise, these recommendations were clearly not being followed.

Potential reasons for lack of activity engagement in JFM patients. In a recent study, we compared movement competence including gait, strength and balance in 17 JFM patients and 14 healthy controls (matched for age and gender) using highly sensitive biomechanical assessments including 3-D gait analysis. Participants completed tests of lower extremity strength (isokinetic knee extension/flexion, hip abduction) and functional performance (walking at self-selected and prescribed speed, Drop Vertical Jump task) along with self-report measures of disability, pain intensity, depressive symptoms, and fear of movement. Patients with JFM demonstrated mild deficiencies in walking gait and significantly lower bilateral knee extension and flexion strength (19-26% deficit), bilateral hip abduction strength (33-37% deficit), and functional performance (Drop Vertical Jump: see Figure 1 for differences between JFM patients and healthy controls). Patients with JFM also reported significantly higher functional disability, pain intensity, depressive symptoms, and fear of movement relative to controls. These observations led us to conclude that the levels of inactivity we previously reported were accompanied by objective signs of movement deficits (possibly due to more guarded movements and loss of strength/deconditioning) that may place patients at risk for pain during exercise. Their high levels of fear related to movement may also fuel further activity avoidance [5].

Figure 1. Differences in DVJ Stance Phase kinematics between JFM and healthy adolescents.



Pilot work on the FIT Teens intervention. Over several months in 2012, we designed the new FIT Teens intervention, incorporating a neuromuscular training component specifically tailored to the needs of JFM patients with our established CBT protocol. In 2013, we enrolled 16 adolescents with JFM in a pilot study of the feasibility, safety and acceptability of the FIT Teens intervention. Inclusion criteria were ages 12-17, diagnosed with JFM and moderate or higher pain (≥ 4 on a 0-10 VAS). Patients were excluded if they had any other rheumatic disease, documented developmental delay or any medical contraindication for exercise. We recruited ~50% of eligible patients approached for the study (Of the 17 refusals, 7 were due to distance, 8 due to time commitment/school conflicts and 2 to pursue other treatments). Treatment was conducted in groups of 3-5 patients and used an 8-week, 16 session protocol (60 minutes per session). Adverse events (particularly any flares in JFM pain or other symptoms) were carefully monitored, attendance recorded at each session, adherence with the treatment in session and at home monitored via daily diaries, and difficulties with any particular exercise noted along with resulting modifications. At the end of treatment, patients completed a detailed individual semi-structured interview in which they gave feedback about the session content, format, perceived helpfulness and acceptability of the FIT Teens protocol. Interviews were coded for thematic content and this patient-oriented feedback was combined with staff and therapist feedback to modify the program to improve uptake and acceptability[6]. Briefly, the patients' comments about the program were extremely positive, with patients reporting much better energy levels, feeling stronger and having greater confidence in physical activity, as well as improved mood and coping. Only one reported having a JFM flare which was reported as not being related to the treatment. A number of patients noted temporary soreness in specific muscles which they could easily distinguish from JFM pain and which resolved without intervention. Patients uniformly enjoyed the group format as well as the extensive support from the therapist/trainer as they progressed to new levels of challenge.

Through an iterative process in Phase I testing, several changes were made to the FIT Teens protocol, namely, 1) later timing of sessions, i.e., after 4 pm to create less conflict with school times, 2) increasing the session length from 60 to 90 minutes to allow ample time for CBT and exercise components, more education and review of home practice 3) several modifications to exercises to allow a range of fitness abilities 4) adding illustrated handouts about how each of the exercises related to daily functional abilities 5) addition of a sleep hygiene component 6) providing written instructions to help them remember homework exercises and 7) specific instructions for gradually increasing engagement in moderate -vigorous activity of their choice outside of sessions to eventually build-up to 30 minutes of exercise at least 2 times per week by the end of treatment. Patients and parents also requested periodic booster sessions to help with maintenance and to extend group support for continued coping and engagement with the program. Of the 16 patients enrolled, 12 patients completed disability and pain measures before and after treatment. Mean FDI reduction after the 8-week intervention was over 10 points (24.75 to 14.25) which was equivalent to effects seen in our published CBT trial at the *6-month time point* showing that these changes can be achieved much faster with the combined FIT Teens intervention. Moreover, 50% of the patients achieved a clinically significant reduction in disability (based on the Reliable Change Index defined ≥ 7.8 point reduction) at post-treatment. Based on our knowledge of CBT effects from our completed trial, we expect that the reduction in disability will become even larger over follow-up (with periodic booster sessions). Pain reduction after treatment was small as expected (Mean VAS 6.63 to 6.05), due to ongoing adaptation to the new exercise regime, but continued to decline over time as patients adapted to higher (self-reported) activity levels (based on phone-call follow-up 3-5

months after treatment ended, the last FIT Teens group of 4 adolescents reported and average pain VAS of 4.75, a >30% reduction).

This pilot work was extended to an additional site (Connecticut Children's). The research team from the Connecticut site visited Cincinnati in December 2013 for a 2-day intensive training program in which they were trained in the FIT Teens protocol and biomechanical assessment methods. They successfully completed feasibility testing of FIT Teens (N=12) in June 2015 with zero drop-out and no adverse effects. Preliminary results are consistent with the improvements noted above for the Cincinnati site and a paper presenting the combined results from both sites has been published[7].

We recently completed a small-scale randomized trial comparing FIT Teens with group-based CBT (based on our standardized CBT protocol modified for group format). Enrollment of 40 JFM patients using identical inclusion/exclusion criteria as prosposed for this trial is complete and 36 patients (N=20 randomized to each treatment arm) have completed the 8-week treatment and 3 month follow up (90% retention). There were no study related adverse events. Initial results at post-treatment assessment suggest that the FIT group showed stronger reductions in functional disability and pain than the CBT group (post-treatment FDI score = 18.7 in the FIT group and 23.9 in the CBT group [p = .07]; and post-treatment pain 0-10 VAS score = 4.69 in the FIT group and 6.38 in the CBT group [p = .03]. Results have been submitted for publication. Objective biomechanics measures of hip strength and balance also show stronger gains in the FIT group.

Aerobic exercise for adolescents with JFM. This small-scale RCT was conducted by our collaborators at the Hospital for Sick Kids – Toronto [8] and informed the development of the (exercise-only) GAE intervention arm for the planned U01. The study compared a 12-week (3 times weekly, 1-in person and 2 at-home sessions) program for adolescents (8-18 years old), where patients were randomized to an aerobic exercise (AE) or a qigong intervention. The AE program consisted of a range of graded low-impact aerobic movements (e.g., cardio-boxing) with a goal of building up to 30 minutes of exercise at or above 70% of their baseline heart rate, followed by 10 minutes of gentle stretching. The qigong program consisted of gentle flowing motions combined with isometric holds and heart rate maintained at <70% of their baseline. The primary aim was to test the feasibility and safety of exercise interventions in JFM. In addition, assessments included fitness measures and self-report of pain, fatigue, functioning and quality of life. The aerobic program was found to be safe and well tolerated. AE was superior to qigong with respect to improving physical function, pain and fatigue but did not result in overall cardiorespiratory fitness or engagement in physical activity. This study demonstrated the *feasibility of a graded AE program* for adolescents with JFM, initial evidence of efficacy with respect to improvement in function and pain. However, similar to our CBT trial, daily activity levels did not improve even after aerobic exercise training and it is unknown whether patients continued to exercise after the treatment. The results of this study strongly suggest that *an exercise-only program may be insufficient to achieve powerful and sustained improvements*, likely because the psychological coping deficits, fear of movement and poor body mechanics were not directly addressed.

3. STUDY DESIGN

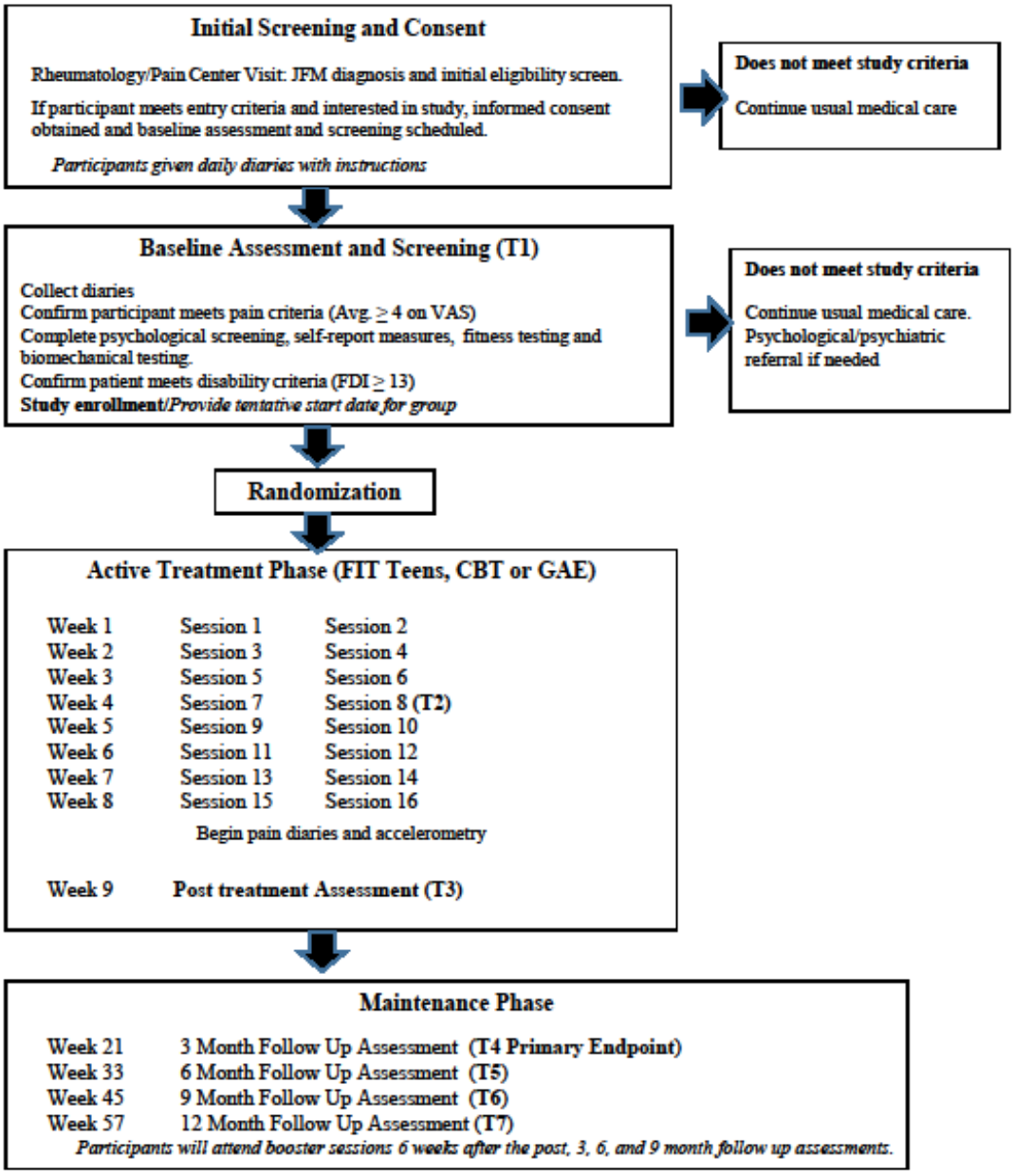
A. Overview

The project is a 3-arm multi-site randomized clinical trial which will examine the efficacy of the new FIT Teens intervention in reducing disability in adolescents with JFM compared to CBT only or GAE only. A longitudinal design will be employed with assessments at baseline, mid-treatment, post-treatment, 3-, 6-, 9- and 12-months follow-up. We will enroll up to 420 JFM patients ages 12-17 into this trial (with at least N=105 randomized to each condition). Each treatment arm will consist of 16 in-person group-based sessions (or remote group-based sessions administered via video-platform during pandemic restrictions) held twice per week over 8 weeks. Sessions last 90 minutes and will be led jointly by a psychologist/therapist and exercise trainer using manualized protocols. Group size will vary from 4-6 JFM patients per group which has been found to be the ideal group size in our pilot work based on feedback from both trainers and patients. Parents will be included in 6 of the 16 sessions and they will receive education about the treatment and instructed in how to support the teen in their behavior change efforts outside of sessions to enhance generalizability to the home environment. After the 8-week active treatment phase, participants will return for a total of 4 group-based "booster/ maintenance" sessions (according their group assignment), or attend booster sessions via remote video sessions, at 3 month intervals through the follow-up phase in order to review their use of skills/maintenance of exercise and encourage continued practice.

The primary study endpoint is the 3-month follow-up assessment. Additional follow-ups will be conducted at 6-, 9- and 12-months post-treatment. Participants randomized after 11/22/22 will not complete the 9- or 12- month follow up or the last 2 "booster/maintenance" sessions due to a reduction in the scope of work in this project to complete the project expeditiously within the remaining timeframe and funding support.

(Protocol continued on next page)

B. Study Visit Flowchart



Participants randomized after 11/22/22 will not complete the 9- or 12-month follow up assessment (T6 and T7) or the last 2 booster sessions due to a reduction in the scope of work in this project.

C. Participants

Inclusion Criteria

1. JFM diagnosed by a pediatric rheumatologist or pain physician using 2010 American College of Rheumatology (ACR) criteria based upon the Widespread Pain Index (WPI) and Symptom Severity (SS) checklist modified for pediatric use.[9]
2. 12-17 years of age
3. Functional Disability Score ≥13 indicating at least moderate disability
4. Average pain intensity in the past week ≥ 4 on a 0-10 cm Visual Analog Scale and
5. Stable medications prior to enrollment (See table below for a list of commonly used medications for JFM and stabilization period)

Medication Stabilization Period Prior to Baseline Visit (T1)[1,2]

Medications requiring a minimum 2 week stabilization period	Medications requiring a minimum 4 week stabilization period)
Ambien (Zolpidem)	Cymbalta (Duloxetine HCl)
Antiepileptic agents	Effexor (Venlafaxine)
Benzodiazepines	Low-Dose Naltrexone (LDN)
Celexa (Citalopram)	Lyrica (Pregabalin)Prozac (Fluoxetine)
Desyrel (Trazadone)	Remeron (Mirtazapine)
Flexeril (Cyclobenzaprine)	Symbyax (Olanzapine/Fluoxetine)
Lexapro (Escitalopram)	Tegretol (Carbamazepine)
Lunesta (Eszopiclone)	Tricyclics/Antidepressants
Luvox (Fluvoxamine)	
Neurontin (Gabapentin)	
Provigil (Modafinil)	
Paxil (Paroxetine)	
Savella (Milnacipran)	
Skeletal muscle relaxants	
Soma (Carisoprodol)	
Topamax (Topiramate)	
Welbutrin (Bupropion)	
Zoloft (Sertraline)	

[1]This is not considered to be a comprehensive list but includes commonly prescribed medications for juvenile fibromyalgia. Medications are listed by brand name and generic drug name.
[2]For this trial, the stabilization period for the initiation of new medications and the washout of discontinued medications are based on a combination of the clinical effects of medications and the biological effect time frame as noted in Micromedex® and the Lexicomp® Pediatric Dosage Handbook.

Exclusion Criteria

1. Comorbid rheumatic disease (e.g., juvenile arthritis, systemic lupus erythematous)
2. Untreated major psychiatric diagnoses (e.g., bipolar disorder, psychoses, symptoms of major depression) or documented developmental delay
3. Any medical condition determined by their physician to be a contraindication for physical exercise
4. Taking opioid pain medication

Informed Consent and Enrollment: Eligible patients will be identified for the study from new or existing JFM patients being seen at the pediatric rheumatology or pain clinics by physicians at each of the clinics. Patients will be introduced to the study by their physician and if they are interested, a trained research assistant will explain the study to the patient and the parent or primary caregiver in greater detail. They will be assured that their usual medical care

will not be affected based upon whether or not they choose to participate. If the patient and their parent/caregiver agree to participate, written informed consent will be obtained from the parent/caregiver and written assent will be obtained from the adolescent (consent may be obtained electronically to reduce need for in-person visits during pandemic restrictions). If the adolescent turns 18 in the course of the trial, they will be re-consented as an adult. A screening/baseline visit will be scheduled. Participants will be given a smartphone based daily pain diary application (or paper diary if they do not have a smartphone) for daily pain ratings for one week prior to their screening/baseline assessment. If the patients meet all eligibility criteria at the end of the screening visit (T1), they will be eligible for randomization in the trial. Each participant's parent will be asked to voluntarily complete a brief survey about the family history of pain. A waiver of documentation of consent is included at the top of the survey form.

The participant and their parent/legal guardian may be contacted remotely (typically by phone) to intiate the screening process for study. This remote communication will occur using a phone script which will explain and document that verbal permission is being obtained to collect the patient or parent/caregivers's email address and set up an online account for collecting daily pain information used to determine study eligibility. This online account will be used to collect daily pain diaries for 7 days leading up to the baseline assessment appointment. In these instances, informed consent will be obtained at the subsequent baseline assessment visit (or electronically during pandemic restrictions) before initiation of randomization or commencement of any study interventions. This process will increase study flow and reduce burden on the participant/participant's family while determining study eligibility by eliminated the need for a separate visit to obtain informed consent.

D. Study Interventions

Common Treatment Format: To ensure equivalence of session frequency, session format and contact with the intervention team, each treatment arm will consist of 16 in-person (or remote) group-based sessions held twice per week over 8 weeks. Sessions last 90 minutes and will be led jointly by a psychologist/therapist and exercise trainer using manualized protocols. Group size will vary from 4-6 JFM patients per group. Parents will be included in 6 of the 16 sessions and they will receive education about the treatment and instructed in how to support the teen in their behavior change efforts outside of sessions to enhance generalizability to the home environment. In instances where it is deemed necessary (e.g. COVID-19 pandemic restricting in-person group-based contact), the treatment sessions will be conducted via a remote visit using a secure video platform (e.g. Skype, Zoom, MS Teams) with appropriate safeguards to ensure participant safety. Treatment manuals have been specifically modified so that participants can receive the same components of treatment but attend the group-based sessions in a home/private setting. For remote sessions, psychology and exercise trainers from the local study site will conduct the sessions. Back-up trainers from the primary Cincinnati site will be able to provide coverage for remote session/s if a local trainer is not available. We will ensure that a parent or other adult caregiver is physically present at the location in case any safety issues arise. If sessions are being conducted via remote format, participants will be provided with handouts and basic supplies (Bosu balance trainer or portable heart rate monitor as needed) following randomization.

CBT: The CBT intervention will consist of training in psychological coping skills training based on our established treatment protocol. Topics include education about the gate control theory of pain, behavioral strategies such as muscle relaxation and activity-pacing, and cognitive strategies including distraction, problem-solving and using calming self-statements. This group-based CBT protocol was used in the completed R21 pilot trial at CCHMC.

FIT Teens*:* Sessions will include training in pain coping skills training based on our established CBT intervention and enhanced with specific use of these skills to increase engagement in the neuromuscular training component. Participants learn to apply the CBT skills (e.g., breathing relaxation, activity pacing, distraction, calming statements) in-vivo as they learn new exercises and progress through increasing levels of challenge in the neuromuscular training program. The neuromuscular training begins with an introduction to the specific exercises with education about proper form and technique, the benefits of each of the exercises and relationship of each exercise with improved ability for performing daily activities – e.g., climbing stairs, walking briskly, sitting in class, waiting in line, bending to pick up an object. Exercises follow a specialized progressive resistive protocol that employs phasic progression based on the different muscle actions and their associated propensity for induced muscle pain and soreness during and after exercise. The four phase protocol is systematically progressed from Level 1: Holding Movement Exercises, Level 2: Creating Movement Exercises, Level 3: Resisting Movement Exercises to Level 4: Functional Movement Exercises. The prescribed exercises, sets and repetitions will be individualized so that they are attainable for each patient, and also modified as needed. Beginning Session 4, all adolescents are given instructions to gradually increase moderate-vigorous physical activity of their choice – walking, playing a sport, outdoor play, swimming etc. beginning with 10 minutes 1 X per week and working up to the recommended JFM guidelines of 30 minutes 2 X per week by the end of treatment.

GAE: This protocol was modified from a published study[7] on the efficacy of aerobic exercise for JFM. We will utilize a circuit-training approach (using an elliptical machine, stationary bicycle, treadmill and cardio/dance movements in rotation) with short intervals of exercise interspersed with brief (~60 second) rest breaks. If delivered remotely, participants will be trained using a variety of floor-based aerobic exercises that do not require gym equipment. Participants will be given a continuous heart rate monitoring device during training sessions and taught how to calculate their own "cardio-zone" for training. We will set the target heart rate to 50%-70% above baseline heart rate. These modifications were made based on feedback from authors of the original study that JFM patients had difficulty keeping up with a sustained 30 minute aerobic program and tended to self-pace and lose interest/motivation. The circuit approach with built-in rest breaks and slowly increasing the level of challenge is more suitable for this population because it has a more gradual and varied approach that is better adapted to their needs.

Make-Up Sessions: If a participant misses a session, he/she will be asked to attend a make-up session immediately preceding the next regularly scheduled session (e.g., if the participant misses the first session of the week, they will be asked to come early to the second session of the week). Make-up sessions will last for approximately 15 minutes; during which study therapists will review content and/or demonstrate exercises (when applicable) that were taught during the missed session and share the handouts for the missed session. Attendance at make-up sessions will count towards attendance at a regularly scheduled session.

Maintenance Phase: After the 8-week active treatment phase, participants will attend a total of 4 group-based "booster/ maintenance" sessions (according their group assignment) at 3 month intervals through the follow-up phase in order to review their use of skills/maintenance of exercise and encourage continued practice. In instances where it is deemed necessary (e.g. COVID-19 pandemic), the group based "booster/maintenance" session may be replaced with a remote visit (e.g. Skype, Zoom, MS Teams) where the trainers will contact participants and review the use of skills/maintenance of exercise and encourage continued practice. Participants randomized after 11/22/22 will complete only 2 group-based "booster/maintenance sessions due to a reduction in the scope of work in this project.

E. Treatment Integrity

Sessions will be video-recorded and an independent evaluator will review 20% of randomly selected treatment sessions from each condition and complete a treatment integrity checklist to ensure there is no "therapist drift" or contamination of treatments. Regular reviews of therapist treatment delivery will be conducted to ensure consistent implementation of the treatments across sites and monthly booster training sessions (held via conference-call format) will be held to prevent therapist drift. We have experience with this method of treatment integrity checking in our completed trials with resulting high levels of treatment fidelity.

F. Concomitant Interventions

Patients will be asked not to begin any new treatments for JFM during the active treatment phase of the study and up to the 3-month primary study end point. Medication changes during this time will be allowed *if medically necessary* and will be documented.

At baseline, patients will provide self-report data on any JFM treatments (e.g. CBT, physical therapy, acupuncture, or aquatic therapy) and the dose received in the year prior to enrollment in the study. The same information will be documented at each visit during the maintenance phase.

Changes in prescription medication will be coded as a binary indicator of whether or not a medication change occurred. Non-pharmacologic treatments will be coded as a count variable computed as the product of frequency and duration. For example, if a participant reports receiving massage therapy twice a week (frequency) for a period of one month (duration), that participant would receive a non-pharmacologic treatment variable value of 8. For the statistical analyses that test for maintenance of treatment gains following the 3-month study intervention period, both the binary medication change variable and the non-pharmacologic treatment count variable will be entered into the longitudinal analysis model as time-varying control covariates.

G. Adherence Assessment

a. Atttendance at treatment sessions, including make up sessions, will be recorded.
b. Attendance to 12 out of 16 regularly scheduled sessions (i.e. 75%) will be considered receipt of full treatment per protocol.
c. Home practice of coping skills and/or exercise will be recorded by the patients during the active treatment phase on a smart phone based application which will be modified to include these items or a paper diary, in the unlikely even that they do not have a smartphone.

4. STUDY EVALUATIONS

A. Study Assessments

The following validated and developmentally appropriate measures will be used to assess physical and psychological functioning at baseline (T1), mid-treatment (T2) immediately post-treatment (T3), primary study endpoint (3-month follow-up, T4) and 6-, 9- and 12-month follow-up (T5, T6 and T7). Participants randomized after 11/22/22 will not complete the 9- and 12-month follow up (T6 and T7). Specific time table for assessments is as below with X marks indicating when the measures will be administered.

Self-report questionnaires (with the exception of the CDI-2 which will be administered in-person or via video-platform) will be collected via REDCap data capture to minimize need for in-person contact during pandemic restrictions. Fitness, biomechanics and actigraphy assessments will be completed only when it is deemed safe – based on each participating institution's guidelines.

Background, Primary and Secondary Outcome Measures					
I. Background Information and Clinical Characteristics	**T1**	**T2**	**T3**	**T4**	**T5 -7**
1. *Demographic/Background Info:* Includes adolescent age, race/ethnicity, family socioeconomic status, medical or psychiatric diagnoses, current medications and family chronic pain history.	X				
2. *Clinician Global Assessment Rating:* 0-10 VAS scale anchored with descriptors of patient "doing very poorly" and "doing very well"	X	X	X	X	X
3. *Fibromyalgia Symptom Severity Questionnaire, Widespread Pain Index*	X		X	X	X
II. Primary Outcome Measure					
1. *Functional Disability Inventory (FDI)*: 15-item self-report measure, developed to assess perceived difficulty in the performance of daily activities in home, school, recreational, and social domains due to pain. Well validated, with published cut-points for minimal, moderate and severe disability as well as published Reliable Change Index in JFM	X	X	X	X	X
III. Secondary Outcome Measure					
1. *Pain Intensity (VAS): Visual Analog Scale* of average pain intensity levels (0-10 cm scale) based on daily pain ratings for one week using a smartphone application or paper diaries.	X	X	X	X	X
IV. Biomechanical Assessments*					
1. *Gait and Balance*: standard gait analysis for walking gait at both self-selected and prescribed speed. (1.2 m/s) using a 10 camera, real-time, high speed, 3-D motion analysis system (Eagle, Motion Analysis Corp., Santa Rosa, CA). Lower extremity dynamic stability will be assessed using the star excursion balance test (SEBT).	X		X	X	
2. *Strength:* Bilateral strength assessments will be performed with an isokinetic dynamometer (Biodex Medical Systems, Shirley, NY) for knee strength and isometric dyanomometry for hip abduction strength[10]	X		X	X	
V. Fitness Assessments					
1. *Harvard Step Test:* is a test of aerobic fitness in which the participant steps up and down on the platform at a rate of 30 steps per minute (every two seconds) for 5 minutes or until exhaustion.	X		X	X	X
2. *6-minute Walk Test:* the distance an individual is able to walk over a total of six minutes on a hard, flat surface. Has been frequently used as a measure of fitness in fibromyalgia research.	X		X	X	X
Secondary Measures					

1. *Daily Diary Report:* Patients will record daily diaries of pain, fatigue, sleep quality, mood, stress, muscle soreness and physical activity level ratings. All of these are measured on a 0-10 VAS scale. They will be instructed to complete these diaries electronically using a link sent to their smart-phone (or paper-pencil diaries if they do not have access to a mobile device or computer).	During active treatment			X	X
2. *Adherence:* Adolescents with JFM will also complete daily diaries of home practice of coping skills and physical exercises to measure self-reported adherence using items which will be built into the smartphone application or paper diary. During *follow-up*, a retrospective self-report checklist of continued practice of coping skills/exercise will be completed.	During active treatment			X	X
3. *Pain Catastrophizing Questionnaire: 13*-item measure used to assess extent of catastrophic thinking about pain in children and adolescents	X		X	X	X
4. *Pain Coping Efficacy:* Three item subscale from the Pain Coping Questionnaire (PCQ) that assesses perceived ability to manage and cope with pain [111111]	X		X	X	X
5. *Tampa Scale of Kinesiophobia:* 11-item self-report measure developed to assess fear of movement related to fear of pain and consisting of two subscales, activity avoidance and somatic focus.	X		X	X	X
6. *Child Depression Inventory (CDI-2):* 27-item well validated instrument assessing self-reported symptoms of depression in adolescents for the past two weeks.	X	X	X	X	X
7. *Physical Activity Levels:* objectively assessed using a hip-mounted omnidirectional accelerometer **(Actigraph) for one week which yields information on daily activity counts, peak activity and time spent in sedentary, mild, moderate and vigorous activity each day.	X		X	X	
8. *NIH PROMIS Measures:* 8-item short form of the PROMIS Pediatric Pain Interference Scale, 10-item Fatigue Scale, and 8-item Pain Behavior Scale.	X		X	X	X
9. *Adverse Events (AE):* Will be documented using an AE symptom checklist arranged by body system, rating of severity and relationship to treatment as in our previous trial.	X	X	X	X	X
10. *Therapeutic Factors Inventory (TFI-A) -Participants and Therapists:* The participant measure is a short 10 item self-report measure to assess participant's experiences in the group sessions using a 5 point scale. The therapist version is a 1-item measure evaluating the overall group cohesiveness on a 5-point scale.			X		
11. *COVID Impact.* A 12-item subscale from the COVID-19 Adolescent Symptom & Psychological Experience Questionnaire (CASPE)[12] will be used to assess the impact of COVID-19 restrictions in social, school and family domains. Participants rate the concerns they have in each of these areas on a 5-point Likert scale.	X		X	X	X

[1] If active treatment is delayed, and the baseline assessment is 6 or more weeks from Session 1, re-administer the FDI and VAS rating on FDI form prior to randomization.
[2] Accelerometry data collection was temporarily ceased in March 2020 due to restrictions regarding the COVID 19 pandemic; it was piloted again in Cincinnati for cohort 11. Accelerometry was removed from the study procedures permanently in October 2021.
[3] Participants randomized after 11/22/22 will not complete the 9- and 12-month follow up (T6 and T7).

Biomechanical assessments will take place at four of seven sites (Cincinnati, Columbus, Connecticut and Boston) that have fully equipped and compatible motion/gait labs.

Gait and Balance: Quantitative assessments of functional movements will be performed using a standard gait analysis for walking at both a self-selected and prescribed speed (1.2 m/s) using a 10 camera, real-time, high speed, 3-D motion analysis system (Eagle, Motion Analysis Corp.,

Santa Rosa, CA). Assessment of landing techniques will be performed with the same 3-D motion analysis system. The subjects will land from a 31 cm box with both feet contacting separate force platforms. We have successfully used similar methodology to objectively report patient outcomes following rehabilitation, surgery, and neuromuscular training (and these tests have posed no safety concerns in these samples).

Balance/stability will be assessed using the Star Excursion Balance Test which is a functional screening tool to assess lower extremity dynamic stability, motor rehabilitation progress, assess deficits following injury and identify those at risk for lower extremity injury.

Strength: Bilateral strength assessments will be performed with an isokinetic dynamometer (Biodex Medical Systems, Shirley, NY). Peak quadriceps and hamstrings force output will be recorded during ten knee flexion/extension repetitions for each leg at 300°/second. Peak hip abduction force output will be recorded during hip abduction.[13] The tests used for assessment of gait, balance and fitness have been validated for use in healthy adolescent populations.

****Accelerometry**

Participants will be given a hip mounted accelerometer (Actigraph) for activity monitoring at 3 timepoints during the study (T1, T3, and T4). Prior to each assessment, participants will be asked to wear the device for 24-hours a day for 7 consecutive days - except when bathing, swimming or showering. For T1 the Actigraph will be given to participants at the first treatment session. For T3, the Actigraph will be given to paticipants at the last weekly treatment session, and for T4, the Actigraph will be mailed to participants then collected at T4. The Actigraph is a small, non-obtrusive, objective and sensitive measure of physical activity. We successfully used the identical procedures for activity monitoring in our completed clinical trial of CBT for juvenile fibromyalgia.

5. STATISTICAL CONSIDERATIONS

A. Data Entry and Management

The main study database will be housed at the Data Coordinating Center (DCC) at the Cincinnati Children's Hospital and use a centralized electronic database into which site coordinators will directly enter data from Case Report Forms (collected either in paper-pencil format or via REDCap). Medidata Rave® is a robust electronic data capture (EDC) platform for capturing, managing and reporting clinical research data that has been customized and built for this trial. As a single platform, Medidata Rave® combines easy-to-use EDC and advanced clinical data management capabilities. Medidata Rave's® extensive capabilities including wide support of industry data standards, flexibility to implement any data management workflow and a rich set of on-demand data extraction and ad hoc reporting tools provide a robust platform to manage site-, patient- and lab-reported data from EDC and other third party systems.

Databases for accelerometry and biomechanical assessments, which are both extremely data intensive and involve specialized software associated with the equipment will be stored in separate databases in a centralized location at Cincinnati Children's Hospital. Once the data is cleaned, and pre-processed for analysis, the relevant variables will be merged with the final database for analysis at the close of the trial.

B. Handling of Missing Data

We have many procedures in place to guard against missing data including proper staff training and monitoring, as well as automated query resolution procedures for missing/inappropriate values in Medi-Data Rave® which will minimize missing data. However, we understand the importance of being responsive to missing data issues, and realize that the handling of missing data, including missing data due to differential drop-out raises some special considerations. We will try to obtain as much information as possible to account for missingness including reasons for drop-out. Depending on the nature of missing data, we will use strategies consistent with best statistical practice, including but not limited to multiple imputation and maximum likelihood estimation methods with auxiliary correlate variables included to make a missing at random (MAR) assumption more plausible. For example, we will use a multiple-group comparison approach with an updated estimation algorithm (i.e., MLR or WLSMV) in the most current version of MPlus that enables the proper handling of missing variable data prior to analysis. The primary analysis will be intent-to-treat analysis. However, in the case of differential attrition, if missing data not at random are suspected, sensitivity analyses under varying assumptions will also be conducted to reduce the potential for bias.

C. Analytic Plan

Analyses will be carried out on the full intent-to-treat sample as the primary analysis. Data analysis will begin with a review of all relevant variables in the dataset. For continuous variables, parametric as well as nonparametric measures of central tendency, variability, and association, will be computed. Distributional properties of potential outcomes will be evaluated and tested for normality where appropriate. Those differing markedly from normality will be considered candidates for transformation or alternative modeling techniques. Unless otherwise noted, $\alpha = 0.05$ (two-sided) will serve as the criterion for statistical significance for all analyses.

D. Rationale for analytic approach

The design of this study is a multi-site RCT with 3 treatment arms (FIT, CBT and GAE). The main scientific focus of this trial is the efficacy of the treatments and maintenance of treatment effects over time. The treatments are designed to be group-based and patients will be randomized to receive treatment in small groups (clusters of 4-6 patients per group). We will recruit at multiple sites to ensure feasibility of achieving the necessary sample size. There will be equal numbers of patients in each of the treatment arms across sites (60 patients per site, 20 in each arm). Although site effects and effects of being assigned in particular "clusters" are not the primary focus of this study, we recognize the statistical issues that arise due to the nested nature of the design. The particular concern is of non-independence in outcomes among patients within the same group (cluster) and within the same sites regardless of treatment assignment. To handle the longitudinal design while also addressing potential bias that may influence results due to clustering, we considered 2 approaches for analyzing the continuous outcome of functional disability – multi-level modeling using a hierarchical linear model (HLM) approach and latent growth curve structural equation modeling (SEM). Both approaches can address the issue of clustering but an SEM approach was selected for several reasons -1) Longitudinal SEM & HLM have been shown to be equivalent analysis models, 2) a 'group * time' effect in HLM can be equated to 'slope on group' effect in SEM, and 3) although equivalent analysis models, research has shown SEM to have the greater statistical power.

E. Aim 1a

To test whether the combined FIT Teens intervention is more effective in reducing functional disability than CBT alone or GAE alone. **H1a.** The FIT Teens group will show significantly greater reduction in functional disability at 3-month follow-up compared to CBT and GAE, respectively.

Significant changes in continuous FDI scores from baseline to 3-month follow-up between the FIT, CBT, and GAE groups will be tested via a longitudinal SEM approach using the current version of MPlus software. Groups will be dummy-coded with FIT as the reference class; we hypothesize significant and positive 'slope on group' coefficients for CBT and GAE indicating a significantly lower FDI for FIT vs. CBT & GAE. Non-independence of FDI scores within participant clusters and within sites will be addressed in three steps: 1.) declaring site as the complex clustering variable, and 2.) estimating a saturated patient cluster-level model (i.e., estimating all possible covariances among FDI repeated measures variances at Level 2 so that, 3.) unbiased parameter estimates and significance tests can be obtained from the longitudinal SEM growth model specified at Level 1. The primary analysis will be intent-to-treat analysis. Sensitivity analyses may also be conducted to explore the impact of the COVID-19 pandemic (those who completed treatment prior to when enrollment was suspended on March 12, 2020 and those who completed treatment after enrollment was re-initiated in Fall, 2020 with treatment delivered via remote format).

F. Aim 1b

To test whether disability levels in the FIT Teens group are maintained at lower levels than CBT alone or GAE alone over time. **H1b.** Functional disability in the FIT Teens group will remain significantly lower than CBT and GAE at 6-, 9- and 12-month follow-up.

To test whether group differences on FDI scores are maintained over time, a longitudinal SEM approach will again be used. Groups will be dummy-coded with FIT as the reference class. Significant and positive 'intercept on CBT' & 'intercept on GAE' coefficients will indicate significantly lower FDI scores for FIT vs. CBT & FIT vs GAE at 6-, 9-, & 12-month assessments. Significant and positive 'slope on CBT' & 'slope on GAE' coefficients would indicate worsening FDI scores for CBT & GAE over time relative to FIT scores that have stayed the same or further improved. Any new treatments (medications or non-pharmacologic treatments) initiated during the follow-up phase will be entered into the longitudinal analysis model as time-varying control covariates. Nesting of clustered participants within sites will be again handled with the SEM model in Mplus described above.

G. Aim 1c

To test whether more patients who receive FIT Teens achieve clinically meaningful improvement in functional disability compared to those who receive CBT and GAE. **H3.** A significantly greater proportion of the FIT Teens group will achieve clinically meaningful reduction in functional disability at 3-month follow-up than CBT and GAE.

Clinically meaningful reduction in disability is defined as a 7.8 point or more reduction in FDI score based on a Reliable Change Index. To test changes in the dichotomous (improved vs not improved) endpoints of functional disability from baseline to 3-month follow-up, baseline FDI scores will be subtracted from the 3-month follow-up FDI to identify those who did and did not achieve a clinically significant FDI change score. Results will be analyzed via separate difference between two

independent proportions analyses for FIT vs. CBT & FIT vs. GAE testing H_0: 50% of participants in the three study arms will achieve a reliable FDI decrease versus H_A: 55% of participants in the FIT arm, and 35%-40% of participants in each of the CBT and GAE arms, will achieve a clinically significant FDI decrease.

H. Aim 2

To test whether the combined FIT Teens intervention is more effective in reducing pain intensity (secondary outcome). **H2a.** The FIT Teens group will show significantly greater reduction in pain intensity at 3-month follow-up compared to CBT and GAE; and **H2b**. pain intensity in the FIT Teens group will remain significantly lower than CBT and GAE over time (6-, 9- and 12-month follow-up).

A similar longitudinal SEM approach as described in Aims 1a and 1b will be used to examine changes in 1) the continuous pain intensity VAS scores at the 3-month primary endpoint and 2) VAS scores at 6-, 9- and 12-month follow-up to assess maintenance.

I. Exploratory Aim

To examine a mechanistic model of how treatment-related improvements in psychological (coping, fear of movement, adherence) and physical factors (objectively measured physical activity, biomechanical changes and fitness) explain changes in disability and pain outcomes.

Tests of the mechanisms that influence functional disability and pain intensity outcomes will be conducted using a multiple path mediation analyses. 1) All possible indirect pathways between psychological mechanisms (coping skills, decreased fear of activity, adherence) and physical assessments (biomechanics, physical activity and physical fitness) with the outcomes of functional disability and pain intensity will be tested for statistical significance within each of the three (FIT, CBT & GAE) groups via bias-corrected bootstrap testing of all indirect pathways, and 2) The magnitudes of the indirect effects will be tested for statistically significant differences between the three treatment groups via a multiple-group analysis. The False Discovery Rate will be used to maintain the nominal Type-1 error rate for all indirect effect tests.

J. Sample size and rationale (Power calculation)

The primary outcome for this RCT is reduction in functional disability. As such, the power calculations provided below are for the ability to detect whether FIT Teens results in significantly greater reduction in disability for Aims 1a, 1b and 1c.

Aim 1a. Differences between groups at the 3-month primary endpoint.
Power was calculated via the external Monte Carlo simulation capabilities in Mplus in two steps. First, 5000 dataset replications of hypothetical FDI scores were generated in a multiple group SEM format assuming: 1.) standardization of FDI scores, 2.) no differences in the three groups at baseline due to randomization ($d = 0$), 3.) group differences in FDI scores at 3 months, consistent with effect sizes from prior studies as follows: GAE ($d = 0.40$), CBT ($d = 0.52$), & FIT ($d = 0.90$), and 4.) $N = 420$ minus 20% attrition makes $N = 336$ ($n = 112$ per group) available for analysis assuming proper missing data handling. Second, the 5000 Monte Carlo replications were then analyzed using a longitudinal SEM assuming linear trend (i.e., slope loadings coded 0, 2, & 3) with dummy-coded CBT & GAE groups (FIT = reference). Results showed power > 0.80 if the standardized 'slope on group' coefficient for either CBT or GAE is $\beta > 0.12$ assuming proper handling of cluster by site nesting as described above. With a revised sample size of N=315 (n=105 per group), our re-

calculated power analysis estimates power of >.80 for the GAE arm (versus reference group) and .79 for the CBT arm.

Aim 1b. Maintenance of treatment gains over follow-up.
Power was again calculated via the external Monte Carlo simulation capabilities in Mplus in two steps. First, 5000 dataset replications of hypothetical FDI scores were generated in a multiple group SEM format assuming: 1.) standardization of FDI scores, 2.) maintained differences between the three groups at 6-, 9-, & 12-months as follows: GAE (d = 0.40), CBT (d = 0.52), & FIT (d = 0.90), and 3.) N = 315 randomized(n = 105 per group) available for analysis assuming proper missing data handling. Second, the 5000 Monte Carlo replications were then analyzed using a longitudinal SEM assuming an intercept-only model (i.e., slope fixed and random effects both = 0) with dummy-coded CBT & GAE groups (FIT = reference). Results showed power ≥ 0.80 if the standardized 'intercept on group' coefficient for either CBT or GAE is β > 0.38 assuming proper handling of cluster by site nesting as described above.

Aim 1c. Proportion of patients achieving clinically meaningful change.
We anticipate that the FIT Teens intervention will result in a greater proportion of patients achieving the binary outcome of clinically meaningful reduction in FDI compared to CBT and GAE. This difference is expected to be between 15%-20% based on pilot studies showing ~55% of FIT and 35-40% of CBT groups achieving clinically meaningful change. The proportion of GAE patients achieving this binary outcome is expected to be similar to CBT. Power was calculated via G*Power3 assuming 20% attrition and proper handling of missing data making n = 105 within the three arms available for analysis. Results showed power will be ≥ 0.80 for either the FIT vs. CBT or FIT vs. GAE comparison if difference between two independent proportions is at least 17% or greater (False Discovery Rate Type-1 error control will be used to evaluate results from both tests). A difference in proportion of ≥17% between FIT Teens and CBT or GAE will provide useful information for patients and providers about the relative efficacy of the interventions.

K. Data and Safety Monitoring Plan

This project is a Phase III multi-site randomized clinical trial and a comprehensive data and safety monitoring plan is required. This project will be monitored by an independent Data and Safety Monitoring Board (DSMB) set up by a third party (Navitas Clinical Research, "NCR") appointed by the study sponsor (NIAMS). The DSMB includes a panel of national experts completely independent of the Clinical Coordinating Center (CCHMC) and collaborating sites and includes a physician, a psychologist, a biostatistician, and a safety officer. The DSMB Chair was appointed by DSMB members.

The DSMB Charter serving as a written agreement to guide roles and responsibilities of the DSMB members and the study team, includes plans for 1) a DSMB meeting at study initiation to approve the Manual of Operating Procedures, Study Protocol, Case Report Forms, and monitoring of study progress (recruitment, randomization, drop-outs etc.) and safety and adverse event/serious adverse event (AE/SAE) reporting and stopping rules. The DSMB will meet at least once every 6 months by teleconference or more often as determined to be necessary by the Chair. CCHMC Data Coordinating Center will assist with the development of standard reporting tools for study progress and regulatory requirements based on the standard NIAMS templates.

Monitoring of Adverse Events (AEs): During treatment, adverse events, whether or not they are thought to be treatment-related will be monitored and documented in several ways.

1. For the FIT Teens and GAE group, trainers will make note of any reports of increases in pain that persists for more than the expected temporary soreness with neuromuscular or aerobic training. These training logs will be reviewed by trainers. In instances of any reports of pain lasting >48 hours deemed to be beyond the expected temporary soreness or discomfort associated with initiating a new exercise, the study coordinator will be contacted and the informationwill be recorded as an adverse event. If deemed necessary, the site PI and/or primary site rheumatologist will be informed of the event.
2. For patients in all groups, the study coordinator in consultation with the study physician will conduct a patient safety assessment at the mid-point of treatment (T2), the end of treatment (T3) and at the follow-up assessments, to document global assessment of symptoms and any adverse events.
3. The therapists (Exercise Physiologist and Psychology Therapist/Fellow) will be trained to note signs of increased pain behavior and/or psychological distress. In addition, any adverse events spontaneously reported by the participants during the sessions or noted during review of daily diaries at each session. The site coordinator will be made aware of the AE and will document the occurrence as an adverse event. If deemed necessary, the site PI and/or primary site psychologist will be informed of the event.

Safety Reporting: Case report forms for AEs and SAEs have already been developed. An AE documentation form will be completed by a clinician at every assessment time point, whether or not an adverse event has occurred and throughout the trial if any AEs/SAEs are spontaneously reported by participants. AEs include new events not present during the pre-intervention period or events that were present during the pre-intervention period but have increased in severity. AEs will be recorded by body system, preferred term, severity and relationship to the study. The primary study team will meet weekly to monitor the progress of the study and safety of participants in blinded fashion.

Resolving Adverse Events
Coordinators (CRCs) will complete Form V. Adverse Event Query Form prior to and during each assessment visit. Prior to the visit, the CRCs will document the ongoing AEs on Form V. During the visit, the CRCs will prompt the participant/family on any updates, including inquiring if the event is resolved.

The lead coordinator at the CCC will review all AEs on a bi-annual basis in preparation for DSMB meetings. Events which are ongoing will be reviewed with the site staff to review status for accuracy. Events which are considered “likely” or “definitely” related to the study and are ongoing at study exit will be reviewed by the PI and plans for additional follow-up will be made on a case-by-case basis.

Serious Adverse Events (SAEs): If an AE is deemed as a Serious Adverse Event, additional details will be completed on the Adverse Event Detail CRF. The site investigator must notify the CCC PI within 24 hours of the SAE occurrence or as soon as the SAE is discovered. The CCC PI will notify the Medical or Mental Health Safety Officer (as appropriate) to review the SAE. The DSMB Safety Officer and NIAMS will be notified of all SAEs through the Executive Secretary, Navitas Clinical Research Group (NCR) within 48 hours of the PI becoming aware of the event regardless of relatedness or severity.

6. HUMAN SUBJECTS PROTECTION

A. Potential Risks and Discomforts

Injury, Pain, or Fatigue: During neuromuscular testing, the primary risks are related to potential injury from the measurement of isokinetic leg strength. Participants may also be at risk of injury from a fall or improper landing during the drop vertical jump task (DVJ). Although the risk of injury during testing is real, ongoing studies utilizing these testing procedures in our laboratory have occurred over the past 7 years resulting in over 2000 subjects being tested. During this time, no injuries have occurred as a result of these procedures. Maximal effort will be requested during these measurements but participants will be instructed that they are free to stop if they experience too much discomfort. Rest breaks between measures will be allowed. We have completed neuromuscular assessment of over 40 adolescents with JFM as part of our preliminary work. Of these, 2 patients declined the drop vertical jump at initial testing, but were able to successfully complete the task after treatment. There were no injuries or adverse effects of the testing. Neuromuscular and aerobic training. Our pilot studies have shown that participants commonly report temporary increases in muscle soreness or fatigue when they initiate new exercise and this is to be expected. The PI, study physicians as well as our clinical physical therapists in the Rheumatology and Pain Clinics, all of whom have extensive experience treating adolescents with JFM, have reviewed and approved the neuromuscular and aerobic training protocol and provided their input to ensure that it is safe for use in this population.

Emotional Distress: Asking the adolescent participants to complete self-report measures about their symptoms, physical and psychological functioning typically does not result in distress. However, given the risk of elevated depressive symptoms in some JFM subjects, some responses on the depression measure may reveal depressive affect and/or suicidal thoughts. The CBT intervention used in this study has been well-tested in past studies and has not been associated with any adverse effects.

Confidentiality: There is a minimal risk that the data collected for each subject may be viewed by individuals outside the research team. The group-based treatment also presents a small risk to confidentiality if participants share personal information outside of the group sessions. Remote delivery via video-format also may pose some concerns about confidentiality if participants are not in a private location.

Note: Due to the COVID-19 pandemic and ongoing risk for virus transmission, we are cognizant that special safety precautions will be necessary for any in-person components of the study assessments and remote delivery of interventions.

B. Adequacy of Protection Against Risks

Injury, Pain, or Fatigue: The minimal risk of injury involved in neuromuscular testing will be further reduced by utilizing trained exercise physiologists supervised by site co-I's who are experts in exercise science research and an active warm-up and stretching period prior to the tests. In the unlikely event of an injury during the testing, a physician will be on site to supervise and take appropriate action. Designated lab space and exam rooms will be used to protect each subject's individual privacy throughout the testing procedures. Exercise difficulty for both the FIT

and GAE treatment protocols can be modified to the participants' abilities to minimize soreness and fatigue. Participants will also be allowed to take rest breaks during sessions. A study physician will be available at each site throughout the study to respond to any reports of JFM symptom flares or adverse events requiring medical attention, e.g., reports of severe pain beyond the expected muscle soreness related to initiating a new neuromuscular or graded aerobic exercise.

Emotional Distress/Suicidal Ideation: In the event that a participant reveals severe depressive symptoms or suicidal ideation (e.g. on the Children's Depression Inventory), a licensed psychologist co-I at the site will be immediately notified. A risk assessment, including detailed information about suicidal ideation, intent and/or plans, access to means to hurt themselves, major stresses, availability of social supports, access to treatment, and plans for safety will be discussed in detail with the patient and their parent. The assessment will be conducted by a PhD level psychologist. If the CDI is administered remotely (via video platform) due to pandemic restrictions, the site psychologist or institutional safety hotline mental health worker will be available to join the video call for further assessment. A referral to the ER (if necessary), and/or a referral to the Psychiatry Division or outpatient Psychology clinic, as appropriate, will be made. All actions taken will be documented in the participant's confidential folder and documented on an AE form. The cognitive-behavioral component of FIT Teens will be delivered by a trained licensed psychologist or postdoctoral fellow. Our extensive experience using CBT for JFM over the past 12 years indicates that participants have no difficulty with coping skills training, and no adverse effects related to CBT have occurred.

Confidentiality: All study staff are trained and certified in human subjects' protections including protection of confidentiality. Confidentiality will be maintained through the use of subject identification numbers on all case report forms. All consent forms, contact information and identifying data will be stored in a secure location within the PI's research lab on a password-protected computer. The primary study database will use the Medi-data Rave® platform which is the industry standard clinical trials software and will be customized to this study. This platform follows all the most updated good clinical practice guidelines for protecting subject information. All study data in the trial database will be entered with a Subject ID number only. The subject codebook and randomization schedule will be held confidentially by the study biostatistician (Dr. Peugh) and the Regulatory Manager and will not be released until the data is locked down for analysis. Site coordinators will upload the video recordings on a restricted access server managed by the Clinical Coordinating Center. Site investigators will not have access to these videos nor will videos be linked to study data or a participant's PHI. Videorecordings of the sessions will be destroyed every six months, once they have been reviewed and rated. Before they begin the group-based sessions, adolescents and parents will be informed about the importance of confidentiality and will sign a confidentiality contract which affirms that they will not share any personal or health information about other study participants outside of the study group (including on any social networking sites).

Note: for the duration of the COVID-19 pandemic, group-based in-person sessions will be replaced by remote sessions as described. Assessments will be minimized to brief in-person study visits (with most outcome measures collected electronically via REDCap surveys) and only include procedures allowable by each participating site's institutional policies. At the beginning of each treatment session, a "safety check" will be performed which will include ensuring that participants

are in a private location.

C. Informed Consent

The parent/legal guardian of each patient will provide written informed consent and the adolescent will provide written assent with the option of obtaining consent on an IRB approved paper consent, or via REDCap e-Consent using a computer, electronic tablet, or smart phone. When e-Consent is used, consent and/or assent will be collected by a typed signature or by obtaining the participant and parent's electronic signature using your finger, a mouse, or a stylus, depending on the resources available to the family. Once the e-Consent form is signed, the parent or legal guardian will be able to download a PDF version and/or receive an e-mail with a PDF attachment of the signed consent form. This will all be conducted before any study measures and interventions are undertaken. If the adolescent turns 18 in the course of the trial, they will be re-consented using an adult Consent Form. The parent of each participant will be asked to voluntarily complete a brief survey about the child's family history of pain. A waiver of documentation of consent is included at the top of the survey form.

In instances where it is necessary to consent a parent/legal guardian and child remotely using a paper form, the child and parent/legal guardian will be provided with copies of the IRB approved consent and assent (if applicable) to review prior to the call. Both the child and parent must be present remotely to participate in the remote consenting process. Study staff will review the consent (and assent, if applicable) documents with the family and provide time for the parent and child to ask questions and receive answers. The parent and child will sign and date the consent document(s) during the call. A copy of the entire consent (and assent if applicable) documents must be returned to study staff (either electronically, digitally, or via postal mail). The consentee will sign and date the documents using the same date of the call. Documentation that the consent was obtained remotely will occur on the informed consent/assent and the informed consent process note.

D. Participant Compensation

Participants will be reimbursed $15 for transportation/mileage/effort for each study visit (participants residing greater than 25 miles from the treatment location will receive $25 if they need to travel to the site for an in-person visit) and $40 for each assessment. Those in the FIT group will receive a BOSU Balance Training Ball to facilitate exercise training at home. The CBT group will receive a gift basket of relaxation CDs/software, squishy stress balls etc. to facilitate use of relaxation and distraction strategies at home. The GAE group will receive a user-friendly activity monitor and heart-rate monitor to facilitateparticipation in aerobic activity.

E. Potential Benefits of the Proposed Research to Subjects and Others

Based upon our prior work with CBT and exercise interventions, we expect that all adolescents (CBT, FIT, and GAE) will experience direct benefit including better ability to cope with their pain, as well as improved mood and functioning. We have published a rigorous randomized clinical trial showing the benefits of CBT in reducing disability and mood difficulties in JFM. The enhanced protocol of CBT integrated with neuromuscular exercise training (FIT Teens) has been piloted by our team and shown to be a safe and highly engaging way to improve adolescents' ability and confidence in exercise by teaching them proper body biomechanics and fundamental movement skills. FIT Teens provides both the psychological coping skills and the foundation for safe exercise. Graded aerobic exercise has also been found to be feasible, safe and beneficial for

adolescents with JFM. If successful, this line of research has the potential to significantly impact clinical care for all adolescents suffering from JFM and improve their physical and emotional health outcomes.

F. Importance of Knowledge to be Gained

JFM is a chronic condition with no cure, and for which pharmacologic options show limited benefit. The knowledge gained in this study has a very high potential to improve the physical and emotional health of adolescents with juvenile fibromyalgia by integrating a self-management intervention into usual medical care. The new FIT Teens intervention goes beyond CBT techniques alone by combining CBT with neuromuscular training to improve fitness and physical function and reduce pain in adolescents with JFM. In this RCT, we will test if the combined effects of the FIT intervention are more powerful than CBT alone or a traditional exercise-only program (GAE).

G. Risk Benefit Analysis

There is minimal risk associated with participation in this study. The benefits to research participants include receiving an established evidence-based CBT intervention (in 2 of 3 groups) which is known to reduce disability and improve mood. Exercise interventions (neuromuscular training and aerobic exercise) have also shown early evidence of increasing strength, providing greater confidence in movement and improving daily functioning. Meeting and receiving support from other adolescent patients with JFM and obtaining more information about their pain condition have been uniformly reported as being highly beneficial by both participants and their parents. Potential risks for injury during exercise testing are very small. Although there is some risk for exercise induced/delayed onset muscle soreness which may be temporarily uncomfortable for some of the participants, the benefits of increased fitness, strength and longer-term pain reduction outweigh this risk. Information obtained from this relatively low-risk study will be extremely valuable to establishing the evidence for behavioral and exercise-based interventions for the treatment of adolescent JFM patients and potentially impact the clinical care for adolescents with this chronically painful condition.

7. STUDY TIMELINE

The revised timeline was approved by the Sponsor and DSMB due to delays caused by the pandemic.

	Year 1				**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**
	Q1	Q2	Q3	Q4						
Screening patients										
Enrollment and Treatment					N = 105	N = 210			N=315	
Follow-up assessments										
Data analysis and Manuscript Preparation										

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