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Randomized clinical trial of Fibromyalgia Integrative Training (FIT teens) for adolescents with juvenile fibromyalgia – Study design and protocol

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ABSTRACT

Objective: Juvenile-onset fibromyalgia (JFM) is a chronic debilitating pain condition that negatively impacts physical, social and academic functioning. Cognitive-behavioral therapy (CBT) is beneficial in reducing functional disability among adolescents with JFM but has only a modest impact on pain reduction and does not improve physical exercise participation. This randomized controlled trial (RCT) aims to test whether a novel intervention that combines CBT with specialized neuromuscular exercise training (the Fibromyalgia Integrative Training program for Teens "FIT Teens") is superior to CBT alone or a graded aerobic exercise (GAE) program. *Design/Methods:* This 3-arm multi-site RCT will examine the efficacy of the FIT Teens intervention in reducing functional disability (primary outcome) and pain intensity (secondary outcome), relative to CBT or GAE. All interventions are 8-weeks (16 sessions) in duration and are delivered in small groups of 4–6 adolescents with JFM. A total of 420 participants are anticipated to be enrolled across seven sites with approximately equal allocation to each treatment arm. Functional disability and average pain intensity in the past week will be assessed at baseline, post-treatment and at 3-, 6-, 9- and 12-month follow-up. The 3-month follow-up is the primary endpoint to evaluate treatment efficacy; longitudinal assessments will determine maintenance of treatment gains. Changes in coping, fear of movement, biomechanical changes and physical fitness will also be evaluated.

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Conclusions: This multi-site RCT is designed to evaluate whether the combined FIT Teens intervention will have significantly greater effects on disability and pain reduction than CBT or GAE alone for youth with JFM. Clinical trials.gov registration: NCT 03268421.

1. Introduction

Juvenile-onset Fibromyalgia (JFM) is a chronic, disabling condition affecting 2–6% of children, primarily adolescent girls [1–5]. Youth with JFM suffer from persistent pain and significant physical, social and emotional impairment [6–11]. In a long-term prospective study, the majority of adolescents with JFM (~85%) continued to experience pain and/or associated symptoms of fibromyalgia into adulthood [12]. The known public health burden of adult chronic pain [13,14] underscores the importance of optimizing early interventions for *youth* with chronic pain before pain and disability become more entrenched and refractory to treatment.

There are currently no approved medications for the treatment of JFM and evidence indicates limited effectiveness and tolerability of available drug therapies [15,16]. Certain non-pharmacologic treatments have emerging evidence of promising beneficial effects but also have their limitations. In particular, research has shown that cognitive-behavioral therapy (CBT) improves functional disability in JFM but is not reliably effective for reducing pain or promoting regular physical exercise [17,18]. Exercise interventions have some evidence of efficacy in pediatric chronic pain [19], but youth with JFM often find exercise recommendations challenging to implement and sustain due to physical (e.g., deconditioning) and/or psychological factors (e.g., fear of pain with movement). They also demonstrate deficits in gait, postural stabilization and strength [20,21]. This combination of biomechanical deficits and the fear of movement that often accompanies them are not addressed in traditional CBT or physical exercise programs and may constrain the effectiveness of these individual treatments.

In an effort to improve both disability and pain outcomes in JFM, our research group has piloted a novel intervention that enhances CBT with a specialized neuromuscular exercise training program. The objective of the Fibromyalgia Integrated Training program for Teens (FIT Teens) is to teach active, adaptive pain coping skills while promoting fundamental movement skills and confidence in engaging in physical activity [22,23]. The treatment is an intensive 16-session treatment program (twice weekly for 8 weeks) held in a small group format with 4–6 JFM patients in each group. Phase 1 and Phase 2 testing of the FIT Teens intervention has been completed. Phase 1 included feasibility testing, qualitative feedback and iterative development of the manualized treatment with patient input [22,24]. This early phase testing found the treatment to be well-tolerated by adolescents with JFM. In Phase 2, we conducted a pilot randomized trial (N = 40; NCT # 01981096) [25] comparing FIT Teens to CBT only (without an exercise component). Results of this trial revealed significantly greater benefit of the FIT Teens intervention compared to CBT including greater pain reduction. FIT Teens has not yet been directly compared with aerobic exercise which has also shown some promise in reducing pain in adolescents with JFM[19]. The current Phase 3 randomized controlled trial (RCT) is a comparative effectiveness study designed to determine whether the combined FIT Teens intervention is superior to CBT only or graded aerobic exercise (GAE) only; and whether treatment gains are maintained over time.

2. Methods

2.1. Design overview and aims

This 3-arm, multi-site, randomized control trial (RCT) will examine the efficacy of the FIT Teens intervention in reducing disability (primary outcome) and pain intensity (secondary outcome) in adolescents with JFM compared to CBT only or GAE only. A total of 7 participating sites are planned including six children's hospitals in the United States and 1 children's hospital in Canada. Sites were selected based on having: (a) established clinical programs in pediatric pain and/or rheumatology with a substantial referral base of youth with widespread chronic pain; (b) availability of research collaborators including physicians, behavioral and exercise treatment experts; and (c) adequate space, facilities and equipment suitable to implement the group-based therapy arms.

Each site is anticipated to enroll approximately the same number of patients allocated to all 3 treatment arms. A longitudinal design will be employed with assessments at baseline, post-treatment, 3-, 6-, 9- and 12-months follow-up. The 3-month follow-up is the primary endpoint of the trial. Selection of the 3-month follow-up as the primary endpoint was based on the goal of assessing whether reductions in disability and pain are durable beyond the 8-week active treatment phase. Participants in all three treatment arms will likely experience some immediate benefit from treatment - but the 3-month endpoint will allow for a more definitive test of which treatment had the strongest and more durable effect. Longitudinal assessments over a 12-month period are designed to measure maintenance of treatment gains over time. Functional disability (primary outcome), pain intensity (secondary outcome), and additional outcomes of fear of movement, depressive symptoms, pain catastrophizing, strength and fitness will be assessed at each time point. Objective measurement of physical activity (via actigraphy) will be conducted at baseline, post-treatment and 3-month follow-up. Further, 4 participating sites will also collect biomechanical (3D motion capture) measures at baseline, post-treatment and 3-month follow-up.

2.2. Study aims and hypotheses

Aim 1a: To determine whether the combined FIT Teens intervention is more effective in reducing functional disability (primary outcome) than CBT alone or GAE alone. It is hypothesized that participants in the FIT Teens arm will show significantly greater reduction in functional disability at the primary end point (3-month follow-up) compared to those who receive CBT or GAE.

Aim 1b: To examine whether reductions in disability in the FIT Teens group are maintained at lower levels than CBT alone or GAE alone over time. It is hypothesized that participants in the FIT Teens arm will maintain significantly lower levels of functional disability than those who receive CBT or GAE at 6-, 9- and 12-months follow-up.

Aim 1c: To test whether a greater proportion of those who receive FIT Teens achieve clinically meaningful improvement in functional disability compared to those who receive CBT and GAE. It is hypothesized that a significantly greater proportion of participants in the FIT Teens arm will achieve clinically meaningful reduction in functional disability ($\geq$ 7.8 reduction in FDI score) at the 3-month follow-up than CBT or GAE arms.

Aim 2: To determine whether the combined FIT Teens intervention is more effective in (a) reducing the secondary outcome of pain intensity than CBT or GAE at the 3-month follow-up and (b) maintaining these reductions over time. It is hypothesized that pain intensity scores at the 3–6-, 9- and 12-month follow-up will be significantly lower for participants in the FIT Teens arm compared to CBT and GAE.

Exploratory aims include evaluating changes in physical activity, fear of movement, depressive symptoms, pain catastrophizing, strength, fitness and measures of biomechanics.

2.3. Sample characteristics

2.3.1. Eligibility criteria

Four hundred twenty adolescents with JFM ages 12–18 will be enrolled across 7 sites (N = ~ 60 per site). ***Inclusion criteria*** include: 1) primary JFM syndrome diagnosed by a pediatric rheumatologist or pain physician using 2010 American College of Rheumatology (ACR) criteria [26] modified for pediatric populations [27] based upon the Widespread Pain Index (WPI) and Symptom Severity (SS) checklist; 2) moderate levels of functional disability as indicated by a Functional Disability Score (FDI) ≥13 [28]; 3) average pain intensity in the past week ≥4 on a 0–10 cm Visual Analog Scale; and 4) stable medications for 2–4 weeks (depending on the medication's half-life and time to clinical effect) prior to enrollment. Use of medications to manage JFM symptoms as part of usual medical care is allowable during the trial but participants must be on a stable dose prior to enrollment to minimize any confounding effects of starting new medications while initiating study treatments. ***Exclusion criteria*** include: 1) comorbid rheumatic disease (e.g., juvenile arthritis, systemic lupus erythematous) or other underlying medical diagnosis (e.g., sickle cell disease); 2) untreated major psychiatric conditions (e.g., major depression, bipolar disorder, psychoses) or documented developmental delay; 3) any medical condition determined by their physician

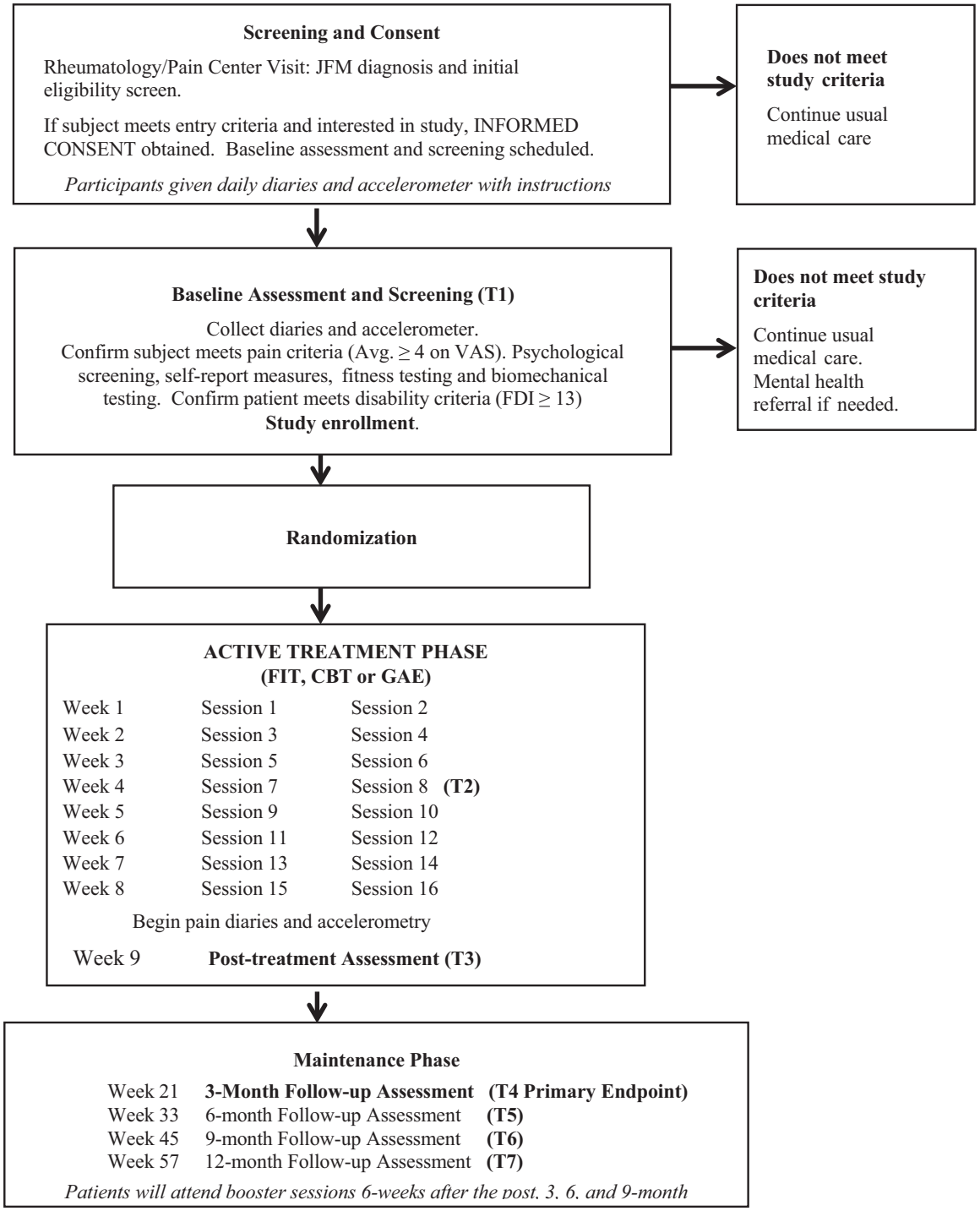

Fig. 1. Study visit flowchart.

to be a contraindication for participation; and 4) currently in pain-focused CBT or in a structured physical therapy program. Past CBT or physical therapy participation or the presence of common comorbid conditions including current mood/anxiety disorder and benign joint hypermobility (e.g., Beighton score [29]) will not be exclusionary. Both sexes are eligible to participate but based on the female predominance in prevalence of JFM and the demographics of patients in JFM studies over the past 15 years, it is anticipated that ~85% of the sample will be females. See Fig. 1 for Study Visit Flow Chart.

2.4. Recruitment process, consent and screening for eligibility

Eligible patients will be identified from new or existing patients with JFM being seen at the pediatric rheumatology or pain clinics by physicians and study staff. Patients will be introduced to the study by their physician or other clinical provider and if interested, a trained research coordinator will explain the study to the patient and the parent or primary caregiver in greater detail. If the patient and their parent/caregiver agree to participate, written informed consent will be obtained. The study will be implemented under the centralized approval of an Umbrella Institutional Review Board protocol based at the primary study site with reliance agreements from all other participating sites in the US. The Canadian site will perform the study under the approval of the Research Ethics Board (REB) at their institution. Written consent from the parent/caregiver and written assent will be obtained from the adolescent for all US sites. If the adolescent turns 18 in the course of the trial, they will be re-consented as an adult. (Note: the Canadian REB requires signed written informed consent from the adolescent only).

After consent is obtained, a screening/baseline visit will be scheduled. As part of the assessment, participants will be given access to a web application to complete one week of daily pain diaries on their smartphone or computer (or paper diaries if they do not have a smartphone or have technical difficulties) 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.

2.5. Randomization and blinding

Participants will be randomized into one of the three treatment arms (FIT Teens, CBT or GAE) based upon a randomization schedule maintained by the biostatistician. Due to the relatively slow rate of anticipated recruitment at each site (2–3 patients per month) only one group at a time will be conducted at each site (in other words, FIT, CBT and GAE groups will not be running concurrently at a single site). This allows us to begin treatment as soon as we have a group of 4–6 eligible patients and avoids the problem of a lengthy wait for patients, which we learned in our pilot work was the most seamless process for study flow. As we have done in the past, randomization-by-group will be used for this trial. Once sufficient participants have been screened and found to meet all eligibility criteria to form a group (~ 4–6 participants), the biostatistician or study regulatory manager (who will jointly maintain the randomization schedule) will directly inform the interventionists of the next group assignment for that cohort, while the investigators and assessment staff will remain blinded. Randomization will be stratified by site in order to ensure approximately equal proportions of patients from each site in each of the 3 arms. Stratification by sex and race/ethnicity is not planned due to the very small numbers of males and minorities presenting with JFM and the practical challenge of having potentially long delays in initiation of study treatment while patients wait for an "opening" for a suitable group randomization.

A single-blind design will be used where investigators, physicians and assessment staff will be blinded to treatment assignment. Only the biostatistician, primary site coordinator, regulatory manager and interventionists will be aware of patients' group assignment. Because this is a behavioral intervention study, participants cannot be blinded to their treatment assignment.

2.6. Assessments

Study assessments will occur at baseline (T1, before randomization), mid-treatment (T2 – abbreviated assessment of disability and pain only), immediate post-treatment (T3), 3-month follow-up (T4, the primary study endpoint) and 6-, 9- and 12-month follow-up (T5-7). Assessments will be conducted by trained research coordinators blinded to treatment assignment.

2.6.1. Outcome measures

The following validated and developmentally appropriate measures will be used to assess the primary physical and psychological functioning outcomes. The selected outcome measures have been successfully used in past trials in JFM or other pediatric pain conditions [30,31]. Unless otherwise noted, all measures will be completed at baseline, post-treatment and each follow-up assessment.

2.6.1.1. Primary outcome. The Functional Disability Inventory (FDI) is a 15-item self-report inventory developed to assess perceived difficulty in the performance of daily activities in home, school, recreational, and social domains due to pain. Given that the primary goal of both CBT and exercise approaches is to facilitate participants' return to usual daily activities, the FDI was selected as the primary outcome for the trial. The FDI is a well-established measure [30,32,33] and was recommended by the Pediatric Initiative of Methods, Measurement and Pain Assessment in Clinical Trials (PedIMMPACT) guidelines [31]. Clinical cut-off scores for the FDI are: 0–12 Minimal/Mild disability,13–29 Moderate Disability and 30+ Severe Disability [28]. Furthermore, using the Reliable Change Index, a $>$ 7.8-point reduction on the FDI has been characterized as a clinically significant change in disability in youth with JFM undergoing CBT [34].

2.6.1.2. Secondary outcome. The pain intensity Visual Analog Scale (VAS), one of the most widely used scales for pain assessment and validated for use with children over the age of 5 years [31,35] will be used to assess pain levels. Changes in pain intensity following treatment is another important treatment outcome for pain trials and was included as the secondary outcome for this study. Participants will be asked to mark their average pain intensity level at the end of each day on an electronic daily pain diary on a 0–10 VAS scale anchored by "no pain" and "pain as bad as it can be." To encourage completion of diaries, an electronic reminder system has been developed so that participants receive a text message reminder on their phone each day to complete the diary and a second reminder if they have not completed the diary within 2 h. Average pain ratings for one week at each of the assessments will be calculated. In addition, participants complete a single 0–10 cm VAS pain rating of their average pain for the preceding week during each in-person assessment in case of missing or inadequate days of e-diary completion.

2.6.1.3. Additional outcomes. Additional study outcomes for exploratory aims will include measures assessing fear of movement [36,37], depressive symptoms [38], JFM symptom severity [26,39], pain catastrophizing [40], pain coping [41], physical activity (via actigraphy) [42], fitness (Harvard Step Test and 6-min walk test [43,44]) and physician global assessment. The NIH PROMIS-Short Form Measures were used to assess pediatric pain interference, fatigue, and pain behavior [45,46]. To gather more in-depth quantification of biomechanical changes in strength, gait and movement mechanics, four of seven sites will also conduct knee and hip abduction strength assessments and 3-D motion capture during standardized tasks (walking gait, Drop Vertical Jump and STAR balance test) [47–50]. See Fig. 1 for Study Visit Flow Chart and Table 1 for a description of these measures and a specific timetable of assessments.

Table 1
List of measures.

Assessment time point	T1	T2 T3	T4	T5 T6 & T7
Background information and clinical characteristics				
Demographic/Background Information: Includes age, race/ethnicity, family socioeconomic status, comorbid diagnoses, current medications.	X	Medication changes monitored		
Clinician Global Assessment Rating: 0–10 VAS scale anchored with "patient doing very poorly" and "doing very well."	X	T3	X	X
Pain Symptom Assessment Tool including Fibromyalgia Symptom Severity index, Widespread Pain index: measure assessing number of pain locations, severity of symptoms (i.e. fatigue, waking still feeling tired, concentration/memory problems), and number of associated symptoms.	X	T3	X	X
Outcomes				
Primary outcome: Functional Disability Inventory (FDI): 15-item self-report measure. 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
Secondary outcome: Pain Intensity (VAS): Visual Analog Scale of average pain intensity levels (0–100 mm scale) based on electronic daily pain ratings for one week using a smartphone application.	X	X	X	X
Biomechanical assessments*				
Gait and Balance: standard gait analysis for walking gait and the Drop Vertical Jump task using a 10 camera, high speed 3-D motion analysis system (Eagle, Motion Analysis Corp., Santa Rosa, CA or Vicon Systems). Dynamic stability will be assessed using the Star Excursion Balance Test.	X	T3	X	–
Strength: Bilateral strength assessments will be performed with an isokinetic dynamometer (Biodex Medical Systems, Shirley, NY or Humac System) for hip and knee strength.	X	T3	X	–
Fitness assessments				
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 min or until exhaustion.	X	T3	X	X
6-min 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	T3	X	X
Other measures				
Pain Catastrophizing Questionnaire: 13-item measure used to assess catastrophic thinking about pain in children and adolescents.	X	T3	X	X
Pain Coping Efficacy: Three item subscale from the Pain Coping Questionnaire (PCQ) that assesses perceived ability to manage and cope with pain.	X	T3	X	X
Tampa Scale of Kinesiophobia: 11-item self-report measure to assess fear of movement related to fear of pain.	X	T3	X	X
Child Depression Inventory (CDI-2): 27-item instrument assessing self-reported symptoms of depression in adolescents for the past two weeks.	X	T3	X	X
Physical Activity Levels: hip-mounted omnidirectional accelerometer (Actigraph) for one-week which yields information on daily activity, peak activity and time spent in sedentary, mild, moderate and vigorous activity each day.	X	T3	X	X
NIH PROMIS Short-Form Measures: 8-item PROMIS Pediatric Pain Interference, 10-item Fatigue and 8-item Pain Behavior Scales.	X	T3	X	X
Adverse Events (AE): Will be documented using an AE symptom checklist arranged by body system, rating of severity and relationship to treatment.	X	X	X	X
Daily diaries. The smartphone application will include self-reported adherence to home practice, and 0–10 VAS ratings of pain intensity, pain unpleasantness, muscle soreness, fatigue, physical activity and sleep quality	During active treatment	X	X	

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

2.7. Interventions

All treatment arms will be delivered over 16 sessions (twice weekly for 8 weeks) of 75–90 min duration per session in group format of 4–6 participants per group. Each session will be led by 2 trained therapists - a doctoral-level psychology interventionist and an exercise trainer based on manualized protocols for each treatment arm. The psychology trainers will take the lead on the CBT components and the exercise trainer will take the lead on the exercise components. Parents will be included in 6 of the 16 sessions to receive education about the treatment and will be instruction in how to support the adolescent in their behavior change efforts. Participants in all groups will receive activity trackers (e.g., Garmin) and an electronic daily diary application to monitor physical activity, pain symptoms and adherence to home practice. Completed diaries will be reviewed by the trainers at the beginning of each session to monitor progress of participants and discuss barriers to extending treatment goals to the home setting.

2.7.1. Cognitive behavioral therapy (CBT)

The CBT intervention arm will consist of training in psychological pain coping skills and is based on established protocols that have been modified for a 16-session group-based format. This group-based CBT protocol was successfully used in our Phase 2 pilot trial [25]. Topics include education about the gate control theory of pain, training in behavioral pain management strategies such as relaxation, and activity-pacing, and training in cognitive coping strategies such as distraction, problem-solving and calming self-statements. See Table 2.

2.7.2. Fibromyalgia integrated training for teens (FIT teens)

The FIT Teens intervention protocol has undergone extensive feasibility and initial efficacy testing in our prior studies. It will include a combination of training in pain-focused CBT skills as described above, enhanced with specific application of these skills to increase engagement in the neuromuscular exercise training component. Participants will learn to apply the CBT skills (e.g., 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 specific neuromuscular training program has been tailored for adolescents with JFM and has been published in detail elsewhere [51]. The program 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 to improve

Table 2
Cognitive Behavioral Therapy (CBT) manual – session outline.

Week 1	**Session 1** (Parents and teens)	Introductions, rapport building, ground rules Introduction to the CBT Program and diaries Introduction to Coping Skills training
	Session 2 (Parents and teens)	Effects of pain on activities, thoughts and feelings Rationale for behavioral pain management Gate Control Theory of Pain
Week 2	**Session 3** (Parents and teens)	Parental guidelines
	Session 4 (Teens only)	Progressive muscle relaxation
Week 3	**Session 5** (Teens only)	Mini-relaxation and diaphragmatic breathing
	Session 6 (Teens only)	Pleasant imagery
Week 4	**Session 7** (Teens only)	Pleasant activities and a doing a pleasant activity
	Session 8 (Parents and teens)	Open session: review progress with skills, CBT Trainer meets with parents alone to review parent guidelines
Week 5	**Session 9** (Teens only)	Activity pacing
	Session 10 (Teens only)	Impact of thoughts and beliefs on pain perception Identifying negative thoughts example Introduce calming statements
Week 6	**Session 11** (Teens only)	Cognitive strategies, using calming statements
	Session 12 (Teens only)	Thinking errors, more calming statements
Week 7	**Session 13** (Teens only)	Problem solving
	Session 14 (Teens only)	Plan for maintenance
Week 8	**Session 15** (Parents and teens)	Review of coping skills CBT Trainer meets with parents alone to review progress and concerns.
	Session 16 (Parents and teens)	Review plan for maintenance and problem solving Elicit feedback and answer questions

Note. CBT is structured so that education is presented in the first three sessions, then behavioral strategies (sessions 4–9), followed by cognitive focused interventions (sessions 10–16). Parents are included in 6 sessions.

Table 3
Fibromyalgia Integrative Training for Teens (FIT Teens) session outline.

Week 1	**Session 1** (Parents and teens)	Introductions, rapport building, ground rules Introduction to the FIT Teens Program and diaries Introduce training equipment and Level 1 exercises
	Session 2 (Parents and teens)	**CBT**: Effects of pain on activities, thoughts and feelings, Rationale for behavioral pain management, Gate control theory of pain **Neuromuscular Training**: Education about muscle strength, fatigue, and pain; Begin Level 1 neuromuscular training exercises
Week 2	**Session 3** (Parents and teens)	**CBT:** Parental Guidelines, In vivo practice for parents on how to support their teen during exercises **Neuromuscular Training**: Level 1 neuromuscular exercises
	Session 4 (Teens only)	**CBT:** Progressive muscle relaxation **Neuromuscular Training:** Level 1 neuromuscular exercises
Week 3	**Session 5** (Teens only)	**CBT:** Mini-relaxation, graduated physical activity **Neuromuscular Training:** Begin Level 2 neuromuscular exercises
	Session 6 (Teens only)	**CBT:** Pleasant imagery **Neuromuscular Training:** Level 2 neuromuscular exercises
Week 4	**Session 7** (Teens only)	**CBT:** Pleasant activities and how to incorporate more vigorous activity that is also fun **Neuromuscular Training:** Level 2 neuromuscular exercises
	Session 8 (Parents and teens)	**CBT:** Open session: review progress with skills, adherence to training exercises; CBT Trainer meets with parents alone to review parent guidelines **Neuromuscular Training:** Level 2 neuromuscular exercises
Week 5	**Session 9** (Teens only)	**CBT:** Activity pacing **Neuromuscular Training:** Begin Level 3 neuromuscular exercises
	Session 10 (Teens only)	**CBT:** Impact of thoughts and beliefs on pain perception **Neuromuscular Training:** Level 3 neuromuscular exercises
Week 6	**Session 11** (Teens only)	**CBT:** Cognitive Strategies, using calming statements **Neuromuscular Training:** Level 3 neuromuscular exercises
	Session 12 (Teens only)	**CBT:** Thinking errors, more calming statements **Neuromuscular Training:** Level 3 neuromuscular exercises
Week 7	**Session 13** (Teens only)	**CBT:** Problem solving **Neuromuscular Training:** Begin Level 4 neuromuscular exercises
	Session 14 (Teens only)	**CBT:** Plan for maintenance **Neuromuscular Training:** Level 4 neuromuscular exercises
Week 8	**Session 15** (Parents and teens)	**CBT:** Review of coping skills; CBT Trainer meets with parents alone to review progress and concerns. **Neuromuscular Training:** Level 4 neuromuscular exercises
	Session 16 (Parents and teens)	**CBT:** Review plan for maintenance and problem solving, Elicit feedback and answer questions **Neuromuscular Training:** Level 4 neuromuscular exercises/introduction to home exercises with BOSU

Note. CBT is structured so that education is presented in the first three sessions, then behavioral strategies (sessions 4–9), followed by cognitive focused interventions (sessions 10–16). Neuromuscular training proceeds from Level 1 (isometric), to Level 2 (concentric), to Level 3 (eccentric) to Level 4 (full functional movement). Parents are included in 6 sessions.

ability for performing daily activities – e.g., climbing stairs, walking briskly, sitting in class, waiting in line. Led by an exercise trainer, the 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 designed to progress in the following sequence: Level 1: Holding Movement Exercises (isometric-focused exercises); Level 2: Creating Movement Exercises (concentric focused exercises); Level 3: Resisting Movement Exercises (eccentric focused exercises); and Level 4: Functional Movement Exercises (combining all previous levels of movement). The prescribed exercises will be individualized in intensity and modified based on participants' abilities. Beginning at Session 5, adolescents are given instructions to gradually increase moderate-vigorous physical activity of their choice outside of the sessions – e.g., brisk walking, playing a sport, outdoor play, etc. beginning with 10 min one time per week and working up to the recommended FM guidelines of 30 min two times per week by the end of treatment [52]. See Table 3.

2.7.3. Graded aerobic exercise (GAE)

The GAE protocol used in this trial was modified from a published study on the efficacy of aerobic exercise for JFM [19]. The previously published study used graded low-impact aerobic movements (e.g., cardio-boxing) with a goal of gradually building up to 30 min of exercise ≥70% of patients' baseline heart rate, followed by 10 min of gentle stretching. In consultation with the authors of that study (collaborators in this trial), the GAE protocol has been modified to include a circuit-training approach (using an elliptical machine, stationary bicycle, treadmill and cardio/dance movements in rotation) with short intervals of exercise (e.g., 2 to 5 min) interspersed with brief (~60 s) rest breaks. The inclusion of a variety of aerobic movements with brief rest breaks was designed to improve tolerability and adherence to sustained movement and reducing participants' tendency to self-pace during the session. Participants will also be given a continuous heart rate monitoring device and taught how to calculate their "cardio-zone" for training based upon age-appropriate pediatric guidelines [53,54]. The target heart rate for the group ranges from 97 to 136 beats per minute.

See Table 4.

2.7.4. Maintenance/follow up phase

After the 8-week active treatment phase, participants will return for a total of 4 group-based "booster" sessions (according their group assignment) timed to occur at the mid-point between 3-, 6–9- and 12-month assessment visits in the follow-up phase. During these sessions, interventionists will review participants' use of skills/exercise and encourage maintenance of skills/activities and continued home practice.

2.8. Interventionist training

The primary study site will host trainings for all site interventionists. Psychology and exercise interventionists from all sites will attend a two-day training in-person workshop led by the PI and experienced lead interventionists at the primary site. Once the trial is underway, continued training and feedback/monitoring will occur over monthly interventionist teleconferences. Periodic refresher training or training for new interventionists over the course of the study will be overseen by the primary study site staff to ensure high levels of competence in the delivery of the treatment components. Interventionists will also receive feedback and re-training in cases of non-adherence to the protocol or therapist "drift" is identified during fidelity checks (described below).

Table 4
Graded Aerobic Exercise (GAE) session outline.

Week 1	**Session 1** (Parents and teens)	Introductions, rapport building, ground rules Introduction to Aerobic Training Program and diaries Education about heart rate calculation, aerobic exercise, instructions for heart rate monitors Introduce training space, Activity Trackers, & equipment Begin Aerobic Training (pending remaining time): 2:00 min work/1:00 min rest, 5 active stations* Cardio Zone time (97–136 bpm) = **10 min**
	Session 2 (Parents and teens)	2:00 work/1:00 rest, 5 active stations Cardio Zone time (97–136 bpm) = **10 min**
Week 2	**Session 3** (Parents and teens)	2:00 work/1:00 rest, 6 active stations Cardio Zone time (97–136 bpm) = **12 min**
	Session 4 (Teens only)	2:00 work/1:00 rest, 6 active stations Cardio Zone time (97–136 bpm) = **12 min**
Week 3	**Session 5** (Teens only)	3:00 work/1:00 rest, 5 active stations Cardio Zone time (97–136 bpm) = **15 min**
	Session 6 (Teens only)	3:00 work/1:00 rest, 5 active stations Cardio Zone time (97–136 bpm) = **15 min**
Week 4	**Session 7** (Teens only)	3:00 work/1:00 rest, 6 active stations Cardio Zone time (97–136 bpm) = **18 min**
	Session 8 (Parents and teens)	3:00 work/1:00 rest, 6 active stations Cardio Zone time (97–136 bpm) = **18 min**
Week 5	**Session 9** (Teens only)	4:00 work/1:00 rest, 5 active stations Cardio Zone time (97–136 bpm) = **20 min**
	Session 10 (Teens only)	4:00 work/1:00 rest, 5 active stations Cardio Zone time (97–136 bpm) = **20 min**
Week 6	**Session 11** (Teens only)	4:00 work/1:00 rest, 6 active stations Cardio Zone time (97–136 bpm) = **24 min**
	Session 12 (Teens only)	4:00 work/1:00 rest, 6 active stations Cardio Zone time (97–136 bpm) = **24 min**
Week 7	**Session 13** (Teens only)	5:00 work/1:00 rest, 5 active stations Cardio Zone time (97–136 bpm) = **25 min**
	Session 14 (Teens only)	5:00 work/1:00 rest, 5 active stations Cardio Zone time (97–136 bpm) = **25 min**
Week 8	**Session 15** (Parents and teens)	5:00 work/1:00 rest, 6 active stations Cardio Zone time (97–136 bpm) = **30 min**
	Session 16 (Parents and teens)	5:00 work/1:00 rest, 6 active stations Cardio Zone time (97–136 bpm) = **30 min**

Note. GAE uses a circuit training approach and is structured so that cardio intervals are increased by either time or number of stations every 2 sessions, starting with 10 min of total cardio activity and working up to 30. Parents are included in 6 sessions.

* A station refers to each different type of exercise – treadmill, elliptical, stationary bike, floor exercise etc.

2.9. Treatment fidelity

All treatment sessions will be video-recorded. An independent evaluator will review 20% of randomly selected recorded 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 interventionist training sessions (held via teleconference) will be held to prevent therapist drift.

2.10. Adherence assessment

Participants' adherence to treatment will be assessed in two ways – 1) attendance at treatment sessions and 2) self-report of home practice of skills/exercises. Attendance at treatment sessions and make-up sessions (if a session is missed) will be documented. Attendance at 12 out of 16 sessions (i.e. 75%) will be considered receipt of full treatment per protocol. Home practice of coping skills and/or exercise will be recorded by the patients during the active treatment phase on their electronic daily diaries using a smart phone (or a paper diary, in the unlikely event that they do not have a smartphone). For each day, participants will be asked to report whether they practiced all, some or none of their assigned skills/exercises.

2.11. Adverse event monitoring

Adverse events (AEs) for the trial will include new symptoms or diagnoses (physical or psychological) not present at the baseline assessment, or symptoms or diagnoses that were present at baseline but have increased in severity. All AEs will be regularly monitored and documented for all participants for the duration of their enrollment in the trial - whether or not the AEs are thought to be study or treatment-related. Adverse events will be recorded by body system, severity and relationship to the study using standard reporting forms. A patient safety assessment will be routinely performed by a study coordinator (with consultation from the study physician/ psychologist if appropriate) at the mid-point of treatment (T2), the end of treatment (T3) and at each follow-up assessment.

In addition, the psychology and exercise therapists will be trained to monitor AEs reported during the course of treatment. Temporary increases in muscle soreness with introduction of new physical exercises are to be expected for the FIT and GAE interventions and are not considered AEs unless they do not resolve within 2–3 days or need medical intervention. Any AEs spontaneously reported by the participants during the sessions will be reported. The site coordinator will be made aware of the situation and will document the occurrence as an AE. If deemed necessary, the site PI and/or primary site psychologist will be informed of the event and an action plan will be developed if necessary. AEs will be reviewed by study staff at the primary site to ensure consistency of reporting and ongoing monitoring of participant safety. AEs will be reported to the Data and Safety Monitoring Board (DSMB; described below) and study sponsor at regular intervals throughout the trial.

A serious adverse event (SAE) is defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, or is an expression of active suicidal ideation or action. The primary site will immediately (within 24 h) inform the appointed Safety Officer of the DSMB and study sponsor about the SAE and any actions taken. If the SAE meets criteria for reporting to the institutional IRBs they will be informed as well.

2.12. Data and safety monitoring

This study will be monitored by an independent DSMB appointed by the study sponsor. The DSMB will be composed of a panel of experts completely independent of the main study and collaborating sites and is expected to include a physician, a psychologist, a biostatistician, and an ethicist. The DSMB will elect a Chair and a Safety Officer from its members. The DSMB will monitor the study by receiving regular reports of study enrollment, performance and safety and is expected to meet at least once every 6 months by teleconference or more often as needed.

2.13. Data management and quality control

The main study database will be housed at the main study site and will use a centralized electronic database (Medidata Rave®) into which site coordinators will directly enter data. Medidata Rave® is a robust electronic data capture (EDC) platform for capturing, managing and reporting clinical research data that has been customized to build a database specifically for this trial. All patient-reported outcomes will be entered into this database. Data for measures of physical activity (e.g., accelerometry and biomechanical assessments) use their own specialized software (e.g. Cortex and REDCap) and will be stored in separate databases in a centralized location at the main study site. Alternatively, the isokinetic strength, star balance measures, laxity outcomes, and patient demographics (height, weight, preferred foot) will be entered via an online database (e.g. REDCap). 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.

2.14. Analytic plan

A Statistical Analysis Plan (SAP) document has been developed for the trial. Analyses will be carried out on the full intent-to-treat (ITT) 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.

Non-independence in outcomes among patients within the same group (cluster) and within the same sites regardless of treatment assignment will be addressed through using a latent growth curve structural equation modeling (SEM).

2.14.1. Aim 1a

To test whether the combined FIT Teens intervention is more effective in reducing functional disability than CBT alone or GAE alone, 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. Groups will be dummy-coded with FIT as the reference class; significant and positive 'slope on group' coefficients for CBT and GAE indicating a significantly lower FDI for FIT vs. CBT and GAE are hypothesized. To address non-independence of FDI scores within participant clusters and within sites, we will declare site as the complex clustering variable and estimate a saturated patient cluster-level model (i.e., estimate all possible covariances among FDI repeated measures variances at Level 2) so that unbiased parameter estimates and significance tests can be obtained from the longitudinal SEM growth model specified at Level 1.

2.14.2. 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, 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' and '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. Nesting of clustered participants within sites will be handled with the SEM model in Mplus software that enables the proper handling of missing variable data prior to analysis.

2.14.3. Aim 1c

The following analyses will test whether more patients who receive FIT Teens achieve clinically meaningful improvement in functional disability (defined as a > 7.8 point reduction in FDI score based on a Reliable Change Index) compared to those who receive CBT and GAE. To test changes in the dichotomous (meaningfully 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 differences between two independent proportions analyses for FIT vs. CBT and FIT vs. GAE testing to assess whether a greater proportion of FIT participants achieved meaningful improvement compared to CBT and GAE.

2.14.4. Aim 2

The analysis for Aim 2 will test whether the combined FIT Teens intervention is more effective in reducing pain intensity (secondary outcome) than CBT alone or GAE alone. A similar longitudinal SEM approach as described in Aims 1a and 1b will be used to examine changes in 2a) the continuous average pain intensity VAS scores at the 3-month primary endpoint, and 2b) VAS scores at 6-, 9- and 12-month follow-up to assess maintenance of pain reduction.

In addition to the primary ITT analysis, supplemental analyses will examine the impact of adherence on outcomes. Specifically, we will examine whether low versus high adherence to treatment (using a 75% cut-point for adherence to session attendance and home practice) impacts functional disability and pain intensity outcomes using a complier average causal effect (CACE) analysis [55].

2.15. Power calculation and sample size

We plan to enroll a sample size of $N = 420$ JFM participants in this trial. Given an estimated attrition rate of up to 20%, we anticipate a final sample of $N = 336$ ($n = 112$ per group) available for ITT analysis. When assessing differences between groups at the 3-month primary endpoint on the primary outcome variable, power was calculated via the external Monte Carlo simulation in two steps. First, 5000 dataset replications of hypothetical FDI scores were generated in a multiple group SEM format using the following assumptions: (a) standardization of FDI scores; (b) no differences in the three groups on FDI scores at baseline due to randomization ($d = 0$); and (c) group differences in FDI scores at 3 months being consistent with effect sizes from prior studies as follows: GAE ($d = 0.40$), CBT ($d = 0.52$), & FIT ($d = 0.90$). 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 group). 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 in the analytic plan.

In order to assess maintenance of treatment gains over follow-up, power was calculated via Monte Carlo simulation in two steps. First, 5000 dataset replications of hypothetical FDI scores were generated in a multiple group SEM format using the following assumptions: (a) standardization of FDI scores; (b) 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 (c) N = 336 (n = 112 per group) available for analysis (N = 420 minus 20% attrition) 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 and GAE groups (FIT = reference). Results showed power > 0.94 if the standardized 'intercept on group' coefficient for either CBT or GAE is $\beta >$ 0.38 assuming proper handling of cluster by site nesting as previously described.

It is anticipated 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 [25]. The proportion of GAE patients achieving this binary outcome is expected to be similar to CBT. Power for this study aim was calculated via G*Power3 assuming 20% attrition (n = 112 within each of the three study arms) and proper handling of missing data. Results showed power will be >0.80 for either the FIT vs. CBT or FIT vs. GAE comparison if a 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.

2.16. Handling of missing data

Procedures such as proper staff training and monitoring will be in place to minimize missing data as much as possible. Automated query resolution procedures for missing/inappropriate values in Medi-Data Rave® will also be used to minimize missing data. Standardized routine review of data completeness will be regularly implemented, and coordinators will attempt to rectify missing data with original source data. Should a participant drop out, as much information as possible will be obtained to account for missingness, including reasons for drop-out. Depending on the nature of missing data, strategies consistent with best statistical practice will be used, 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, a multiple-group comparison approach will be used 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.

3. Discussion

JFM is a complex and disabling chronic pain condition for which effective and long-term treatments are urgently needed. Medications used in usual clinical care tend to be of limited and short-term benefit and have problems with long-term side-effects/tolerability. Non-pharmacologic treatments on the other hand, which include cognitive-behavioral [17,56–60] and physical exercise approaches, show strong promise in treating JFM. So far, the emerging literature has shown that CBT and exercise programs can be safe, effective and well-tolerated by patients - but there are no randomized clinical trials directly evaluating the efficacy of these approaches when used individually versus combined for maximal impact.

Rigorous testing of a nonpharmacologic approach is timely given the societal concern about misuse of medications for pain management and risk for addiction. In addition, the importance of early and safe interventions for the long-term management of pain and disability in youth with JFM cannot be overstated with the knowledge that symptoms are likely to persist into adulthood [61] and the burden of chronic pain to the individual and to society is enormous [14,62,63]. This study will serve as one of the largest trials to date of nonpharmacologic treatments in adolescents with JFM. It is a randomized, single-blind study testing three evidence-based interventions. The longitudinal design with long-term follow-up will provide important new information about whether treatment effects can be sustained beyond the 8-week active treatment phase. The trial will be conducted with a large sample of youth with chronic JFM pain at multiple sites, thereby enhancing the generalizability of results. Trained interventionists will use manualized protocols that will make the treatment/s amenable to dissemination if found to be effective.

The new FIT Teens intervention goes beyond CBT techniques alone by combining CBT with specialized neuromuscular training to improve fitness and physical function and reduce pain in adolescents with JFM. Based upon prior work with CBT [17] and exercise interventions [19], it is expected that adolescents in each of the treatment arms (CBT, FIT, and GAE) will experience direct benefit including better ability to cope with their pain, and/or improved mood and physical functioning. However, the FIT Teens intervention is expected to further enhance these outcomes and result in clinically meaningful change.

The FIT Teens protocol has been extensively piloted by our study team. It has been 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 in a group-based setting with other teens with JFM. FIT Teens is anticipated to provide both the psychological coping skills and the foundation for safe exercise.

In addition to the primary study findings, this trial will collect comprehensive data on adherence, coping efficacy, fear of movement and objective measures of biomechanics, fitness and physical activity which will be utilized to interrogate potential mechanisms (psychological and physical) for how each of the 3 treatments exerts it effects. Such work will lay the foundation for future, more mechanistically informed refinements of interventions for JFM.

We anticipate minimal risk associated with participation in this study and very few study-related adverse effects. Participants in all treatment arms could receive potential benefit from receiving an established evidence-based CBT intervention (in 2 of 3 groups) which is known to reduce disability and improve mood, and/or an exercise intervention (neuromuscular training or aerobic exercise), each of which also have shown early evidence of benefit. Both participants and parents involved in pilot testing have uniformly reported that meeting and receiving support from other adolescents with JFM and obtaining more information about their pain condition is highly beneficial. Although there is a potential for temporary exercise induced delayed onset muscle soreness from the initiation of new exercises during treatment, the benefits of increased fitness, strength and longer-term pain reduction outweigh this temporary discomfort. 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 youth with JFM and potentially impact the clinical care for adolescents with this chronically painful condition. If the aims of this RCT are achieved, 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. Once efficacy has been determined, the intervention protocols can be further refined if needed and larger efforts at dissemination can be deployed.

The current trial is focused only on youth with primary JFM so results will be limited in generalizability to this pain disorder at this time. The reason why other pain conditions were excluded is because there is very little research evidence for effective treatments specifically in JFM. Also, because JFM is so poorly understood, our study team plans ancillary investigations to this trial that will examine underlying

mechanisms of JFM (such as neuroimaging and experimental sensory testing studies) that require a well-defined patient population. Although this will limit the generalizability of findings only to JFM patients at the end of this trial, combined CBT and specialized neuromuscular training approaches could be tested for other pain conditions in the future. This line of research may eventually have implications for the treatment of children and adolescents with other chronic musculoskeletal pain and rheumatic diseases beyond JFM (e.g., back pain, juvenile arthritis etc.) that may also be associated with functional limitations.

As with the design of any trial, several methodologic decisions were made based on prior research and our pilot studies, ethical considerations, and practical limitations of clinical research with adolescents. The choice of comparison groups (CBT and GAE) for this trial was based on several considerations: 1) a placebo arm would be unethical and unacceptable to patients given that CBT and/or physical therapy are often offered as part of clinical care, 2) CBT and graded aerobic exercise are the most commonly recommended treatments for JFM but rarely delivered together in a combined approach 3) both have been tested in prior research with promising results when used as individually-delivered treatments and finally 4) the combined effects of CBT and GAE have never been formally tested which would make it challenging to use as a comparator from a trial design perspective.

In pediatric populations, it is possible that youth with JFM may have reductions in pain during the summer vacation months when they have less stress and more flexibility in their schedules. The entry criteria for the study (at least moderate pain and disability) will ensure that only those who are still experiencing significant symptoms will be enrolled. Dates of active treatment (summer months versus school year) will also be documented so that at the conclusion of the study, it will be possible to explore whether the timing of treatment impacted study findings in any way.

In our pilot studies, we learned that there may be some selection bias in enrollment because patients who enroll are likely to be the most motivated due to the commitment required to attend twice weekly sessions and study assessments. This is expected for the current trial phase. Nevertheless, results will need to be interpreted in this context and future work will need to address wider dissemination and accessibility. Another potential pitfall is the possibility of differential drop-out in one of the three treatment arms. Drop-out rates will be carefully monitored during the trial - but our experience so far suggests that the appeal of a group-based intervention format for adolescents seems to outweigh their concerns about the particular treatments involved. Teens enrolled in our pilot studies felt very positively about being in a group with others who suffer from the same condition.

Seminal work on CBT for adolescents with JFM from our research group has already changed medical practice in several pediatric rheumatology/pain clinics nationwide and internationally. If the new FIT Teens program proves to be more effective than CBT or GAE, the intervention manual can be made widely available to pediatric rheumatology and pain clinics who often have access to physical therapists and psychologists/counselors that have the necessary expertise to implement the manualized program. The treatment itself requires minimal and inexpensive equipment and does not require use of state-of-the-art biomechanics testing labs; the biomechanics labs used in the trial allow for assessment and better understanding of the mechanisms of change. Once the program is well-tested and the mechanisms better understood, it will become possible to modify the treatment protocol and test alternate delivery strategies (e.g., fewer in-person clinic sessions supported by video/virtual reality or online training) for wider access to reach patients who do not live within easy driving distance of a medical center.

In summary, this is the first rigorous large-scale trial of non-pharmacologic treatment for adolescents with JFM, and if successful, could dramatically impact clinical care for this complex and disabling pain condition. Extensive planning efforts and pilot work have informed the design of this study. The current trial and ancillary studies that will be conducted using the infrastructure for this trial are expected to contribute substantially to the field of JFM research and treatment.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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