FIT Teens RCT for juvenile fibromyalgia: Protocol adaptations in response to the COVID 19 pandemic

Susmita Kashikar-Zuck, Kimberly A. Barnett, Sara E. Williams, Megan Pfeiffer, Staci Thomas, Katie Beasley, Leigh Ann Chamberlin, Katiliya Mundo, Richard F. Ittenbach, James Peugh, Robert C. Gibler, Anne Lynch-Jordan, Tracy V. Ting, Brooke Gadd, Janalee Taylor, Alana Goldstein-Leever, Mark Connelly, Deirdre E. Logan, Amy Williams, Emily O. Wakefield, Gregory D. Myer, for the FIT Teens Clinical Trial Study Group and the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Pain Workgroup Investigators

Objective: To describe protocol adaptations to the Fibromyalgia Integrative Training for Teens (FIT Teens) randomized controlled trial in response to the COVID-19 pandemic. The overarching aims of the FIT Teens multi-site 3-arm comparative effectiveness trial are to assess whether a specialized neuromuscular exercise training intervention combined with cognitive-behavioral therapy (CBT) is superior to CBT alone or graded aerobic exercise alone.

Design/methods: The trial was originally designed as an in-person, group-based treatment with assessments at baseline, mid- and post-treatment, and four follow-up time points. The original study design and methodology was maintained with specific modifications to screening, consenting, assessments, and group-based treatments to baseline, mid- and post-treatment, and four follow-up time points. The original study design and methodology has been successfully implemented in remote format since July 2020. Trial metrics thus far demonstrate a consistent feasibility and allowed for sustained enrollment, retention, and treatment fidelity comparable to the in-person treatment sessions for accuracy and fidelity, complete programming of REDCap assent/consent and assessment materials, train study staff for new procedures and obtain regulatory approvals. The trial was relaunched and has been successfully implemented in remote format since July 2020. Preliminary findings indicate that FIT Teens protocol adaptations from in-person to remote are feasible and allowed for sustained enrollment, retention, and treatment fidelity comparable to the in-person.
1. Introduction

Juvenile fibromyalgia (JFM) is a chronic and disabling musculoskeletal pain condition for which there are limited therapeutic options [1–5]. The Fibromyalgia Integrative Training (FIT Teens) trial is an ongoing multi-site, 3-arm randomized controlled trial (RCT) to evaluate whether the FIT Teens intervention, which combines cognitive-behavioral therapy (CBT) with specialized neuromuscular exercise training, is superior to CBT alone or graded aerobic exercise (GAE) alone [6]. A description of the FIT Teens study protocol has been previously published [7].

Trial enrollment began in January 2018. With the declaration of the COVID-19 pandemic in March 2020, restrictions on in-person research activities presented challenges for trial implementation. New enrollment was temporarily halted to focus on modifying study processes and treatments for use in a remote (telehealth) format and obtaining sponsor and regulatory approval for these changes. Active recruitment resumed in August 2020 as lockdown measures relaxed, but in-person research visits remained restricted.

The purpose of the current report is to describe the modifications made to the FIT Teens study protocol in response to the COVID-19 pandemic, along with the scientific principles and practical multi-site study implementation issues that guided our decision-making. We first describe all relevant adaptations to the trial which focused on maintaining scientific integrity of the study. Next, trial metrics (i.e., enrollment, randomization, retention, session attendance rates and safety) are provided for the 22-month period following protocol changes. Finally, the implications of trial modifications that will inform the interpretation of study findings at trial completion are discussed.

Fig. 1. Study Visit Flow Chart with Adaptations (*in italics)

*Note: As in T1, all self-report measures are completed remotely via REDCap, while fitness assessments are conducted in-person.
2. Design/methods

2.1. Overview of original trial design

The FIT Teens trial aims to enroll 420 adolescents (ages 12–17) with JFM who are randomly assigned to one of the three active interventions. Each intervention arm involves group-based treatment sessions held twice per week over eight weeks, originally designed to be completed in-person. The primary outcome is functional disability, with pain intensity being the secondary outcome. Additional measures include patient report of fatigue, coping efficacy, and mood, as well as objective measures of physical fitness, strength, and functional biomechanics. We hypothesized that those who receive the FIT Teens intervention will demonstrate significantly greater reduction in functional disability and pain at the 3-month assessment following treatment compared to the CBT and GAE interventions. Follow-up assessments at 6-, 9- and 12-months will assess maintenance of treatment gains (see Fig. 1).

2.2. Participants/sample characteristics

Inclusion and exclusion criteria for study eligibility remain unchanged. Adolescents (ages 12–17 years) diagnosed with primary JFM are eligible if they do not have comorbid rheumatic disease, untreated psychiatric condition (e.g., major depression, bipolar disorder, psychoses, and substance abuse/ misuse) or developmental delay that may interfere with treatment. Psychiatric screening is performed using subscales of the validated Adolescent Symptom Inventory (ASI- Parent Report; [8]) and the Children’s Depression Inventory – 2 (CDI- II; 9). If the participant/parent endorses symptoms indicating a psychiatric condition, additional assessment is performed, in consultation with the site psychologist to determine if treatment is ongoing and symptoms are well-controlled. If not, referrals for appropriate mental health care are provided. Anxiety disorders are common comorbidities in JFM and as long as they are not disabling enough to interfere with study participation, are not exclusionary.

Adolescents have to meet American College of Rheumatology (ACR 2010) criteria for fibromyalgia [10], have at least moderate disability (Functional Disability Inventory Score ≥13), and pain intensity rating (in the past week) of ≥4/10 on a visual analog scale [7].

Potential impact on sample characteristics. Most study visits are now conducted remotely, which may provide flexibility to some families who were not otherwise able to participate due to distance and travel. Therefore, it will be important to consider whether the change to remote delivery resulted in systematic differences in demographic characteristics of participants enrolled pre-versus post-pandemic (e.g., geographic location, distance from medical center).

2.3. Recruitment process, consent, and screening for eligibility

Participants are identified from new or existing patients with JFM who present to pediatric rheumatology or pain clinics. Prior to the pandemic, recruitment involved primarily face-to-face interactions between research coordinators and patients/families in medical clinics. Based on adapted recruitment processes, clinicians and/or other clinical providers introduce the study to participants. Interested families can also view a 3-min study overview video. With verbal permission, research coordinators use remote means (i.e., overview video, phone contact, and email) to provide study details and pre-screen for eligibility. Families who remain interested in participation are scheduled to confirm eligibility and complete the formal assent/consent process. The informed consent process was adapted to be conducted via video/phone call using an electronic consent form programmed into REDCap [11,12] and signed electronically, in accordance with institutional policies. After consent (and child assent) are obtained, parent/caregiver and participants receive email links to self-report assessment measures (REDCap).

In addition, they complete a 7-day electronic pain diary on a smartphone app in the original e-diary format.

Since resuming the trial in remote format, we have maintained a consistent rate of enrollment - on average 6.5 participants per month pre-pandemic versus 6.6 participants per month since August 2020. Thus far, 724 total patients have been referred to the study, with 316 participants enrolled as of March 1, 2022 [of which 169 (58%) were enrolled pre-pandemic], and 257 randomized to receive treatment (of which 136 were randomized prior to March 2020) (Fig. 2).

2.4. Assessments

2.4.1. Patient-reported outcome measures

All measures were initially completed in-person via pencil and paper. Following protocol adaptations, the majority of the study measures were modified to be administered remotely via REDCap [11,12]. Measures include the primary outcome measure, Functional Disability Inventory (FDI; [9, 13]), secondary outcome measure Visual Analog Scale of Pain Intensity (VAS; [14]), as well as four additional outcome measures (e.g., Tampa Scale of Kinesiophobia [15], Pain Catastrophizing Scale [16], NIH PROMIS Short Form Measures [17,18], and Pain Coping Efficacy [19]). Given the potential for safety concerns (e.g., suicidal ideation) on the CDI-II [5], it was decided that participants must complete this measure with trained research coordinators during synchronous video or telephone appointments to facilitate immediate risk assessment and implementation of safety protocols as needed.

To assess the pandemic’s impact on study participants, we added a measure to assess perceived effects of the COVID-19 pandemic and related restrictions on social, academic, and family functioning. This measure is a 16-item subscale from the COVID-19 Adolescent Symptom & Psychological Experience Questionnaire (CASPE). Response options are on a 5-point rating scale, representing degrees of concern (“very little or not at all” to “a great deal”) [20].

School format (e.g., regular school, online, homebound etc.) was assessed as a supplementary indicator of daily functioning in the original protocol. As online schooling became almost universal during the COVID era, this variable had to be revised to record additional modes of instruction and clarify the reason for any homebound/online instruction (i.e., COVID-19 worries, pain-related problems, and personal preference). Subsequent analyses will likely need to account for this factor, because academic functioning is a component of functional disability and the pandemic impacted all students’ academic functioning.

Potential impact of mode of assessment. All questionnaires utilizing REDCap were publicly available, such that adapting the self-report questionnaires to electronic data capture was relatively straightforward. The only copyrighted study measure is the CDI-II, which is individually administered by a trained research coordinator via telehealth. To facilitate future investigation of the impact of mode of administration on psychometric properties of outcome measures, we created a new binary indicator variable in the database (i.e., 0 = paper-pencil, 1 = online administration).

2.4.2. Physical assessments

Physical assessments included functional biomechanics, fitness, strength, and daily physical activity. During initial pandemic lockdowns, all physical assessments were suspended. As restrictions on in-person visits were relaxed by institutions, fitness assessments that could be conducted following social distancing requirements were resumed (i.e., 6-min walk test and Harvard step test). Physical assessments requiring proximity between assessors and participants for marker placements and equipment adjustments, such as strength and biomechanic assessments, were gradually reintroduced following approval of safety protocols at each institution. Actigraphy measures of daily physical activity were discontinued due to COVID-19 surface transmission considerations and logistical challenges with device management (shipping etc.). The majority of the sites resumed in-person fitness assessments within 2 months of initiating the remote protocol.
Motion capture assessments requiring more stringent safety and sanitation procedures resumed approximately 4 months later. Regional variation in COVID restrictions did not systematically affect ability to perform assessments. However, staffing difficulties common during the pandemic, did affect one site’s ability to resume fitness and motion capture assessments.

Potential impact on trial aims. Because collection of physical assessments was more severely affected by pandemic restrictions, we expect more missing data for these analyses. These missing data will not affect the primary outcomes of the trial but may limit our proposed exploratory analyses looking at the mediating role of fitness and biomechanical improvements in treatment outcomes. Therefore, we retain data collection on these measures whenever possible due to their innovative nature and the potential to inform future studies.

2.4.3. Interventions

Modifications to the CBT and exercise treatment arms (i.e., FIT Teens, GAE) from an in-person group-based protocol to remote format were necessary to balance treatment fidelity with participant safety during the pandemic. Treatment manuals were adapted so that all study visits and intervention components could be conducted via secure, synchronous video communication (i.e., Zoom or Microsoft® Teams based on site preference) (for session-by-session treatment content [7]. To help participants randomized to the FIT Teens groups learn the neuromuscular exercises in session, study exercise staff created a library of videos to ensure treatment fidelity and consistency of delivery across sites. The videos were designed to be easily integrated into the virtual platforms and played as needed during remote sessions [21]. The CBT components of the FIT Teens treatment and CBT alone protocols were also adapted for remote delivery. Treatment educational materials and handouts were digitized and/or made into editable documents for easy screen sharing during virtual sessions.

Lastly, adapting the GAE treatment to remote delivery required us to modify the circuit training approach. Instead of using gym equipment (i.e., treadmill, elliptical, or stationary bike), the GAE protocol was adapted to rely on floor-based aerobic exercises and heart rate monitors to set the difficulty level.

Because of privacy and safety concerns when conducting sessions in a home-based setting, additional precautions are implemented to ensure safety and confidentiality. To encourage compliance with safety measures, participants are reminded at the start of group sessions that they must be in a private space, with a parent or caregiver present for the entire session, and their video turned on. If any of these requirements are not met, the participant is asked to leave the remote session and join only when these criteria are met. Feedback from trainers indicates there have been few instances of participant noncompliance with safety measures.

The remote treatment protocols require that all materials be delivered to participants prior to the first session. A single, contactless pick-up visit is coordinated to deliver equipment and handouts to participants. Specifically, the CBT treatment group receives a basket of relaxation materials (i.e., CDs/software, squishy balls) to facilitate the use of relaxation and distraction strategies at home. The FIT Teens treatment group receives a BOSU® (Both Sides Up) Balance Trainer Ball to facilitate neuromuscular exercise training at home, while the GAE treatment group receives an activity monitor and heart rate monitor to facilitate implementation of the aerobic training program. Each participant also receives a packet of printed treatment handouts specific to their group assignment, including worksheets for coping skills practice and/or exercise logs and pictures.

Thus far, feedback from participants and their families indicates high levels of satisfaction with the convenience and accessibility of the remote treatment sessions. Attendance rates for the remote format average 14.87/16 sessions attended, which is comparable to 14.67/16 for in-person attendance prior to the pandemic. Of 41 families asked about their preferences for treatment format, 100% of parents/caregivers expressed preference for a remote format going forward due to lower cost and time of transportation and ease of family schedules. Feedback from adolescents was mixed, with 16 indicating a preference for the in-person format (to meet the other teens in person and get to know them better) and 25 for the remote format. Based on overall family preferences for remote sessions and due to continuing concerns about virus transmission, we decided to continue treatment delivery in remote format for the remainder of the trial.

Potential impact on intervention delivery. Prior research indicates that in-person versus remote (telehealth) psychological interventions can produce equivalent results [22–26]. Similarly, exercise-based approaches can also be effectively delivered in telemedicine format comparable to in-person delivery [27–29]. Nevertheless, changing mid-trial from in-person to remote treatment delivery will allow us to assess whether mode of delivery had a differential impact on outcomes and, if so, we will control this in the final intent-to-treat analysis. We created two additional indicator variables to track whether each session took place pre- or post-pandemic, and the mode of treatment delivery for each group.

2.4.4. Interventionist training

At the beginning of the trial (in 2018), all study interventionists participated in a 2-day training at the primary site facilitated by the lead FIT-Teens psychology and exercise trainers. Given restricted travel
during the pandemic, trainers had to complete retraining on the adapted study protocols remotely. To accommodate this, all revised manuals and study materials (e.g., handouts, presentation materials) were uploaded to a file sharing program to allow trainers to review the adapted protocols. Next, the lead site’s trainers completed a 2-h virtual training session during which key adaptations to the manuals and remote study protocols were reviewed. Specialized instruction for exercise and psychology trainers was delivered separately in smaller sub-groups for trainers to further discuss how to deliver the CBT and exercise training portions. Lead trainers reviewed safety considerations, new virtual materials such as the trainer presentation guide and exercise videos, and tips for clinical implementation in a remote delivery setting. The training session was also recorded for future educational purposes related to staffing changes.

Each site was provided with additional site-specific virtual trainings on the revised treatment manuals with more detailed discussion focused on patient safety. This included managing safety if a participant did not have a parent/caregiver in the home during a session, facilitating one-on-one communication during groups, etc. Ongoing remote trainings continue to be provided to help train new study staff on standard operating procedures and treatment protocols. Monthly virtual trainer meetings provide a forum for study updates and problem-solving; these meetings were held both pre- and post-pandemic.

2.4.5. Treatment fidelity

Independent review of sessions to ensure fidelity of treatment delivery has been part of the trial since it began. For in-person groups, sites recorded sessions with tablets and uploaded video files to a protected server. The same general process was followed with the transition to remote groups, leveraging the recording features of each virtual platform and using existing fidelity rating forms. A preliminary assessment suggests that high treatment fidelity has been maintained between the in-person delivery of the treatment protocol (98.4%) and the remote format (99.7%). Treatment fidelity data continue to be reported to the Data Safety Monitoring Board (DSMB) at regular intervals.

2.4.6. Adverse event monitoring

Adverse events are regularly assessed during the treatment sessions and assessment visits, documented, and reported to the DSMB and study sponsors as appropriate, with no changes to pre-pandemic procedures. A review of adverse events after the pandemic onset did not show any remarkable changes in the frequency or nature of events, by body system, except for non-study related respiratory adverse events which increased slightly due to the COVID-19 pandemic. Since the start of the pandemic, we have had twenty-one adverse events due to a positive COVID-19 diagnosis among participants. One participant had a severe adverse event related to COVID-19 complications which required brief hospitalization. Adverse events deemed to be “definitely” or ‘possibly’ study-related in the remote protocol remained similar to the in-person format and included mild and temporary musculoskeletal symptoms, which is expected given that 2 of the 3 interventions involve physical exercise training.

2.4.7. Data and safety monitoring

Due to the protocol modifications, the DSMB convened quarterly rather than every six months to monitor the integrity of the trial and participant safety during the transition to remote delivery. Since the trial was successfully relaunched, the meetings have resumed a biannual meeting schedule with monthly enrollment reports.

2.4.8. Data management and quality control

The main study database is housed within the data coordinating center at the primary site and utilizes Medidata Rave® as the centralized electronic database. As noted, all patient-reported outcome measures were adapted to be completed via REDCap. A notable limitation arising from this modification is that REDCap data exports are unable to be merged with the Medidata Rave® data. As a result, all research coordinators manually transfer information from the electronic case report forms (CRFs) from the REDCap system into Medidata Rave®. Quality control checks remain unchanged. The data-coordinating center conducts audits of electronic CRFs and Medidata Rave® data entry to prevent missingness and ensure accuracy of the data entered. For the primary and secondary outcome variables, data entry has been maintained at 99% accuracy.

2.4.9. Analytic plan

Our primary data analysis plan remains as originally proposed, with slight modifications to account for changes in format of treatment delivery. We will begin with an initial review of all relevant variables, including those added after onset of the pandemic (e.g., COVID-19 impact questionnaire). Baseline group comparisons will be compared for equivalence on functional disability and pain intensity across the three intervention groups. In addition, we will explore any potential shifts in demographic characteristics of the sample before and after the onset of the pandemic and between group differences on the COVID-19 impact questionnaire for those enrolled after the onset of the pandemic.

Primary analyses will utilize a longitudinal Structural Equation Modeling (SEM) approach as planned, where repeated longitudinal assessments (level 1) are nested within participants (level 2) who are tested in cohorts of participants (level 3) within each of the six study sites (level 4). The longitudinal SEM approach will determine if the FIT Teens treatment is superior to GAE and CBT at reducing functional disability, and whether group differences in functional disability scores are maintained over time (6-, 9-, and 12-month follow-up). To assess the impact that modifications to the treatment delivery have on study outcomes, we will test whether in-person versus remote mode of delivery has a differential effect on functional disability and pain. Further, as an exploratory analysis, the mode of treatment delivery indicator variable will be used to create an independent group interaction term (e.g., format x GAE, format x CBT) to evaluate any differential impact of mode of treatment on treatment allocation (CBT, FIT or GAE).

3. Discussion

The FIT Teens trial is a multi-site comparative effectiveness RCT that aims to establish whether a multi-component intervention (CBT + neuromuscular exercise training) is superior to CBT or GAE in the treatment of JFM. In the context of the ongoing opioid crisis that continues to surge during the pandemic [30], the evaluation of safe and effective non-addictive and non-pharmacologic approaches for chronic pain disorders is even more critical to disrupt the often unremitting course of pain and disability from adolescence to adulthood.

The FIT Teens trial was adapted in its third year as a result of the COVID-19 pandemic and has been implemented with minimal interruption. Implementing the adapted, remotely delivered treatment protocols have been feasible as evidenced by sustained participant enrollment, retention, and fidelity of treatment in a manner comparable to in-person delivery. Notably, remote delivery of the adapted treatment protocols has maintained participant safety and produced no untoward effects on adverse events. With appropriate precautions we have found that remote treatment can be administered safely in a comparable manner to in-person treatment. Moreover, although some families expressed a reluctance to participate in remote treatment due to “Zoom fatigue,” enrollment and retention was comparable to when treatment was in-person. Parents/caregivers expressed a preference for remote treatment due to convenience. Feedback from the teens was more mixed, with many favoring the in-person format for more direct socialization with their peers. Preferences for in-person versus remote format did not appear to be site/region specific and seemed to be more related to teen’s personal preferences.

Even with considerable efforts to preserve the integrity of the trial after the onset of the pandemic, we need to consider new factors
introduced midway through the trial in the final interpretation of study outcomes.1) the unprecedented scale and duration of the pandemic has unknown psychosocial, health, and economic effects on research broadly and our study population [31], specifically. This raises important questions about whether these environmental factors will influence study outcomes. Fortunately, we are ameliorating validated measures of psychological distress and coping that will allow us to examine these effects in a post-hoc fashion (including newly added measures of COVID impact and disrupted schooling). Given reports of the mental health impact of the pandemic on teens, we examined whether there was a significant increase in baseline depressive symptoms in the FIT Teens cohort from pre-pandemic to after the onset of the pandemic. Contrary to what we expected, we found that depressive symptoms actually reduced slightly after the onset of the pandemic [32] which may have resulted from reduction in school and social expectations. This somewhat attenuates our concern about marked changes in baseline emotional functioning of the sample. A second factor for consideration would be the differential impact of in-person versus remote treatment delivery on study outcomes. Therefore, the mode of treatment delivery will need to be examined separately or controlled for in the final intent to treat analysis. Third, measurement invariance across modes of administration (paper-pencil versus electronic) of patient-reported outcomes is uncertain and will need to be evaluated.

From a process standpoint, successful implementation of the adapted treatment protocol and study relaunch relied heavily on the coordinated effort and investment of the study staff, including research coordinators, interventionists, and investigators across all sites. A critical ingredient to successful implementation was high quality communication, which was accomplished through regularly scheduled virtual meetings to keep sites and research staff at all levels engaged and allowed the trial to be relaunched synchronously across all study sites. Real-time problem-solving and maintaining team morale was critical in the context of furloughs/absences due to illness or quarantine, remote work, training/retraining staff remotely, and rapidly changing institutional (and state-level) regulations for research activities.

Although the realities of the pandemic resulted in more complexity than initially planned, unexpected innovations have emerged that may inform future work. Specifically, remotely delivered group-based treatment can provide pilot data on whether intervention efficacy is equivalent between treatment modalities. These data may be used to inform future trials aimed at optimizing dissemination. For instance, if the FIT Teens treatment protocol is determined to be superior to CBT and GAE, adapting the treatment protocol to increase ease of access will be a useful next step. In response to parents’ preferences for a fully remote intervention and some adolescents’ desire for more in-person contact, it may be beneficial to offer either in-person or remote treatment and potentially a hybrid option, mixing in-person and remote sessions to maximize social engagement.

Social distancing requirements during the pandemic necessitated considerable reliance on technology by treatment providers that quickly outpaced the literature and majority of evidence-based treatment modalities for chronic pain. This rapid push to integrate technology to outpace previous overreliance on traditional treatment modalities for solving and maintaining team morale was critical in the context of the FIT Teens trial, no one declined or discontinued trial participation due to lack of internet; however, on occasion internet speed or bandwidth issues have hindered audio connectivity for participants. Based on feedback from trainers, audio issues were frequently circumvented using the chat function and/or dialing into the virtual session using a separate device. In addition, the ability to deliver the treatment protocols in a remote format allowed us to capitalize on expertise irrespective of geographical location. For instance, with the remote format, psychology and exercise trainers from the primary site were able to help provide coverage to ongoing groups at study sites across the country.

4. Conclusion

This paper described modifications to the implementation of the FIT Teens RCT that allowed the trial to resume enrollment, maintain retention, and ensure participant safety in a manner consistent with trial implementation prior to the pandemic. At the completion of the trial, it is hoped that this transparency in reporting will allow clarity in the interpretation of trial results and establish the foundation for dissemination efforts if the study hypotheses are supported.

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