Graded exposure treatment for adolescents with chronic pain (GET Living): Protocol for a randomized controlled trial enhanced with single case experimental design

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**Abstract**

Chronic musculoskeletal pain in adolescence is a significant public health concern with 3–5% of adolescents suffering from significant pain-related disability. Pain-related fear and avoidance of activities has been found to have a significant influence on pain outcomes in children and adolescents and is a risk factor for less favorable response to treatment. To address this need, we developed graded exposure treatment for youth with chronic pain (GET Living). We describe the rationale, design, and implementation of a two-group randomized controlled trial (RCT) enhanced with single-case experimental design (SCED) methodology with a sample of 74 adolescents with chronic musculoskeletal pain and their parent caregivers. GET Living includes education, behavioral exposures, and parent intervention jointly delivered by pain psychology and physical therapy providers. The multidisciplinary pain management control group includes pain psychology delivered education and pain self-management skills training (e.g., relaxation, cognitive skills) and separate physical therapy. Assessments include brief daily diaries (baseline to discharge, 7-days at 3-month and 6-month follow-up), comprehensive in-person evaluations at baseline and discharge, and questionnaire across all time points (baseline, discharge, 3-month and 6-month follow-up). Primary outcome is pain-related fear avoidance. Secondary outcome is functional disability. We also outline all additional outcomes, exploratory outcomes, covariates, and implementation measures. The objective is to offer a mechanism-based, targeted intervention to youth with musculoskeletal pain to enhance likelihood of return to function.

**1. Introduction**

Chronic musculoskeletal pain in adolescence is a significant public health concern with 3–5% of adolescents suffering from significant pain-related disability [1]. Pain-related fear and avoidance of activities has been found to have a significant influence on pain outcomes in children and adolescents [2–4] and is a risk factor for less favorable response to treatment [3]. In addition to the child’s fear of pain, parental fears and avoidance behaviors in the context of their child’s pain also contribute to the child’s fear and disability levels [5,6]. When parents interpret an adolescent’s pain expression through the lens of their own catastrophic appraisals and pain-related fears, they are more likely to engage in maladaptive parenting behaviors (i.e., protective behaviors) [7]. This, in turn, is known to negatively influence adolescent pain-related function [8]. Conversely, when adolescents actively confront negative beliefs and emotional distress associated with activities that are associated with pain (i.e. exposure) and parents encourage adaptive functioning in the presence of pain, dysfunctional pain-related...
beliefs are challenged and a gradual return to function occurs [6].

Most current psychological and physiotherapeutic treatments for adolescents with chronic pain involve promoting pain coping strategies via psychological interventions, with separate physical therapy prescribed [9]. The debilitating influence of pain-related fear avoidance can interfere with progress in pain coping efforts and engagement in physical therapy, resulting in continued high healthcare utilization without symptomatic improvement [10–12]. Graded in-vivo exposure treatment (GET) targets functional improvement by exposing patients to avoided activities with demonstrated success among adults [13–16]. There is one ongoing randomized controlled trial of multimodal pain rehabilitation for adolescents with chronic musculoskeletal pain in the Netherlands that combines GET and physical therapy [17], but does not specifically target patients with elevated fear avoidance.

For the last decade our group has focused on pain-related fear and avoidance in children, with efforts centered on effective assessment [4,6] and intervention [3,18]. Our first evaluation of GET for youth with chronic pain (GET Living: NCT01974791) was designed as a sequential replicated and randomized baseline single-case experimental design (SCED) with multiple measures and no comparison arm. Using multilevel modeling of daily diary reports, we observed significant decreases in pain-related avoidance and pain intensity with increased pain acceptance at the end of treatment when compared to baseline that maintained at 3- and 6-month follow-up. Moreover, decreases in pain-related fear and catastrophizing were observed at 3-month follow-up compared to baseline, with improvements maintained 6 months after treatment (Simons et al., in revision). Examining questionnaires administered at baseline, discharge and follow-up, functioning was significantly improved at discharge and persisted at 3- and 6-month follow-up (Functional Disability Inventory partial eta² = 0.534; PedsQL School partial eta² = 0.456; Simons et al., in revision). However, GET Living has not been compared to multidisciplinary pain management (MPM) in youth with chronic pain.

Here we present a two-group randomized controlled trial (RCT) enhanced with SCED methodology. The primary aim is to measure changes in pain-related fear avoidance (primary outcome), and functional disability (secondary outcome) for adolescents with chronic musculoskeletal pain when comparing GET Living to MPM.

2. Methods

2.1. Participants and setting

Adolescents and a primary caregiver (N = 74) will be recruited from the outpatient Pediatric Pain Management Clinic (PPMC) at Stanford Children's Health (SCH). Adolescents will be eligible to participate if they have 1) musculoskeletal pain (e.g., localized [back, limb] or diffuse), inclusive of complex regional pain syndrome [19], not due to an acute trauma (active sprain or fracture); 2) are between 8 and 17 years old; 3) have moderate to high pain-related fear (Fear of Pain Questionnaire- FOPQ-C ≥ 35); 4) have moderate to high functional disability (Functional Disability Inventory ≥ 13) [20]; and 5) are proficient in the English language. Adolescents will be ineligible to participate if they have 1) significant cognitive impairment (e.g., brain injury) or 2) significant medical or psychiatric problem that would interfere with treatment (e.g., active psychosis, seizures, suicidality). This study is approved by the Institutional Review Board at Stanford University (Protocol # 39514) and registered at clinicaltrials.gov (NCT03699007).

2.2. Recruitment

Providers (physician, psychologist, physical therapist, nurse practitioner) at Stanford Children’s Health will refer patients to GET Living during initial or follow-up clinic visits. Patient families will receive a brochure that describes the program and includes contact information for the study team. Providers will send a completed eligibility checklist for each patient referred to GET Living via secure email to the research team. Additionally, a study flyer and additional brochures will be available in the patient waiting room for patients to self-refer to the study. For each patient, self- or provider-referred to the trial, eligibility for enrollment will be verified by the research team via a brief screening phone call and online screening measures (FOPQ-C and FDI).

2.3. Study design

This is a two-arm randomized control trial that is enhanced with a single-case experimental design (SCED) with multiple measures. In single case experiments, a subject is observed repeatedly at different levels of at least one independent variable (e.g., baseline vs. treatment). To accomplish this, patients will be randomly assigned to a pre-treatment/baseline phase of 10–21 days in duration and will complete daily diary measures from Day 0 to end of treatment (Day 0 + N) and for 7-days at 3- and 6-month follow-up. Upon arrival at the first treatment session, patients will be informed if they are assigned to GET Living (i.e., combined PT and Psychology) or MPM (i.e., separate PT and Psychology). The two arms are considered equal treatments, differing only in method of delivery (i.e., combined or separate). The treatment phase consists of 12 sessions (1-h in duration twice a week or 2-h in duration once a week) scheduled over 6–8 weeks. In total, the study will be conducted over the course of 32 months. Twenty-four months will be dedicated to study enrollment, randomization, and completion of the

**Fig. 1. Study Flowchart.** Eligibility Screening: Once a potential adolescent is referred to the GET Living trial, the research coordinator confirms eligibility and schedules the baseline assessment. Baseline: At the baseline assessment the adolescent and parent begin daily diaries, adolescents begin wearing the Actigraph watch, and biomechanical assessment is completed. At the baseline visit the adolescent and parent receive a treatment start date and schedule for sessions (arm allocation is not revealed). Active Treatment: Adolescent and one caregiver/parent present (as developmentally appropriate) for 12 sessions of treatment scheduled over the course of 6–8 weeks, taking into account holidays and vacations. Discharge assessment occurs at the conclusion of treatment. Actigraph is returned to the research team and daily diaries end. Follow-up: Adolescents and parents are sent a battery of questionnaires and daily diaries via REDCap for a 7-day period at 3-month and 6-month follow-up.
intervention. An additional 8 months will be dedicated to completing 3- and 6-month follow-up assessments (See Fig. 1 for Study Flow).

2.4. Rationale for study design

RCTs provide estimates of the between-subject treatment response (the average difference between the two groups) but does not provide sufficient data on how a specific individual responds to a given treatment i.e. due to heterogeneity in treatment effects [21]. An individual patient in an RCT could show no improvement, have an adverse reaction to treatment, or benefit from the control (even if the control is shown to be statistically inferior) [22]. Although subgroup analyses are now encouraged in an effort to better elucidate differences in treatment response between individuals, it requires large cohorts of patients for sufficiently powered analyses [23]. For specialized patient groups such as youth suffering from chronic pain, obtaining sufficiently large cohorts for mediation and moderation analyses within the confines of multidisciplinary RCTs is often not feasible. SCED allows the collection of statistically rigorous data at the level of the individual patient. Moreover, such data can be used in meta-analyses of individual effect sizes and multilevel modeling to provide group level results from small and distinctive cohorts.

2.5. Randomization

Randomization schemes are developed and maintained by the study Statistician (DB).

2.5.1. Pre-treatment/baseline randomization

Patients will be randomized to a baseline period of 10–21 days using block randomization with blocks of size twelve in which each baseline period length will be randomly assigned to one patient.

2.5.2. Treatment arm randomization

Following the pre-treatment/baseline phase, patients will be randomized to one of two treatment conditions: GET Living or Multidisciplinary Pain Management (MPM) and will be stratified by pain-related fear (moderate/high; FOPQ-C: moderate [35–49], high [50–96]; derived from validation sample [4]) and functional disability (moderate/severe; FDI: moderate [13–29], severe [30–60] [20]); to minimize the probability of imbalance between the two treatment arms. To allow the use of small blocks while minimizing the probability of a blinded staff member predicting the next group allocation, we will use blocks sizes of two and four, which will be randomly chosen. The study biostatistician will create separate randomization lists for each of the four strata prior to the start of patient recruitment with each list long enough to include the total planned study size. A series of block sizes (either two or four, with equal probability weights) will be randomly created and within each block half of the sample will be randomly assigned to GET Living and the other half to MPM. Copies of the randomization lists will be kept by the biostatistician and research coordinator and will not be shared with other members of the team.

2.6. Intervention procedures

Both interventions are provided by a multidisciplinary treatment team which includes a physical therapist (PT) and a pain psychologist. Patient families will be instructed to not initiate other pain treatments from baseline assessment to end of active treatment. Both treatments consist of 12 1-h patient sessions (1-h in duration twice a week or 2-h in duration once a week) across 6–8 weeks, and 3 parent-only sessions. The primary aim of both treatment arms is to support the patient in returning to valued activities of daily life and restoring daily functioning.

2.7. GET Living (see Table 1 for detailed treatment description)

The GET Living program was based on the following books and protocols: “Pain-related fear: exposure-based treatment for chronic pain” [24], “Multimodal CBT treatment for childhood OCD: a combined individual child and family treatment manual” [25], and “The ACT for teens program” [26].

2.7.1. Education and goal setting

The psychologist and physical therapist jointly deliver content to the patient and parent. Session 1–5 goals are to educate the patient and parent about the interpersonal fear avoidance model of pain (individual and interpersonal), present the treatment rationale and formulation, present ‘pain dilemma’ (the conceptualization of the dysfunctional behavioral strategies) [27], create values-based treatment goals to enhance motivation toward increased function vs. pain reduction, and create a pain-related fear activity list (‘activity ladder’) using the Photographs of Daily Activities-Youth in English (PHODA-YE) [28] to facilitate selection of individually tailored exposure targets and activities.

2.7.2. Graded exposure

As detailed in Table 1, physical therapists lead the exposures (sessions 6–11) that consist of engaging in activities perceived as potentially ‘harmful’ or ‘worrisome.’ Patients collaboratively select with the PT the exposure activity. Prior to beginning the activity, the patient completes the WILD scale assessing four relevant aspects of each task: 1) Willingness –patient’s willingness to complete the task, 2) Importance – importance of the activity to the patient, 3) Likelihood of success – patient’s assessment of likelihood of success in completing the activity, and 4) Difficulty – patient’s assessment of the activity’s level of difficulty. After completing the WILD scale, the patient generates an Exposure Action Plan (EAP) to potentially implement during the exposure activity if needed to maintain activity engagement when pain and distress may increase. EAP activities include strategies such as breathing, stretches, movement breaks, helpful thoughts (e.g., just get into it), and facilitators. Importantly, facilitators are not meant to be distractions. The patient attends to the activity at least in part to observe that the feared outcome either did not happen or was manageable (prediction error). Facilitators are activities that can coincide with the exposure activity to facilitate its completion – e.g., listening to music while working out. After each exposure activity, patients re-complete the WILD scale, discussing discrepancies between expectancies and experiences. Patients repeat, continue, and extend exposure activities outside of session (home-based exposures; HBEs) until competence in performing the activity increases across settings. HBEs can also be used to address activities that cannot be completed in session (e.g., riding public transportation, prolonged activities) and to address values-based goals as appropriate.

2.7.3. Parent component

Parents are integrally involved throughout treatment. In addition to attending and participating in sessions 1–5, parents observe some graded exposure sessions and provide encouragement in the execution of HBEs. During the other exposure sessions, parents meet individually with the psychologist. These sessions focus on education and parent behavior change. Module 1 focuses on parent distress in the context of their child’s pain, expectations for treatment, and strategies to promote activity engagement. Module 2 emphasizes reacting vs. responding to child pain. Module 3 centers on child self-responsibility in treatment, the concept of rescuing vs. riding it out when the child is in distress, and addresses what messages are being sent with behavioral responses toward the child.

2.7.4. Wrap-up

Relapse prevention, long-term goal setting, and termination focuses on the maintenance and generalization of earlier treatment gains.
through problem solving. The patient and parent generate a 'Top Lessons Learned' during the final treatment session.

### 2.8. Multidisciplinary Pain Management [29,30] (see Table 2 for detailed treatment description)

#### 2.8.1. Cognitive behavioral therapy (CBT) for pain management

CBT consists of six patient sessions and three parent-only sessions delivered by the psychologist. The initial CBT session is delivered jointly with the child and parent and focuses on psychoeducation on pain management. The next four child-only sessions focus on education about the biopsychosocial model and the gate control theory of pain, as well as goal setting, relaxation, coping skills training (including diaphragmatic breathing, progressive muscle relaxation, and guided imagery), and cognitive restructuring. The parent-only CBT sessions address setting goals, parent responses to the child’s pain (identifying maladaptive responses and shifting to appropriate and adaptive responses), coping skills, and cognitive restructuring. The final CBT session is delivered jointly to the child and parent and focuses on relapse prevention, long term goals, and reviewing accomplishments made during treatment.

#### 2.8.2. Physical therapy (PT) for pain management

PT consists of six sessions delivered by a licensed physical therapist. The initial PT session focuses on history-taking, conducting a standardized systems review, and using tests and measures to establish baselines for strength, range of motion, balance and proprioception, sensation, coordination, endurance, movement patterns, postural impairments, and pain. The remaining treatment sessions are based on the Guide to Physical Therapy Practice 3.0 and focus on establishing and monitoring a home therapeutic exercise program, progressing activities and exercises as tolerated, the use of modalities (e.g., heat/ice) as appropriate, and providing patient and caregiver education. The final PT session focuses on maintenance and generalization of earlier treatment gains to prevent future complications, a review of accomplishments made during treatment, and recommendations for ongoing treatment.

### Table 1

<table>
<thead>
<tr>
<th>Session</th>
<th>Topic</th>
<th>Adolescent Content</th>
<th>Parent Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rapport Building, Education, &amp; the Pain Dilemma</td>
<td>Build rapport; obtain patient history; discuss referral impressions and treatment expectations (e.g., increase in functioning vs. pain reduction); using Pain Dilemma, discuss possible life directions toward pain reduction vs. valued activities; discuss negative impact of the Cycle of Avoidance; introduce GET Living paradigm; graded exposure as means to return to valued activities</td>
<td>Joint session: same content</td>
</tr>
<tr>
<td>2</td>
<td>Pain-Worry Cycle &amp; Individualized Formulation</td>
<td>Build rapport; increase program engagement through motivational interviewing strategies; discuss the Fear Avoidance Model (FAM) and Interpersonal FAM (IFAM) to identify unproductive patterns of activity avoidance; resume discussion of GET Living paradigm, introducing pain willingness (attitude) and activity engagement (action) as tenets</td>
<td>Joint session: same content; present parent with Interpersonal FAM to be discussed in future session.</td>
</tr>
<tr>
<td>3</td>
<td>Setting Values-based Treatment Goals</td>
<td>Review FAM and GET Living homework; discuss values and contrasts with goals; assist in identification of adolescent's values across various life domains; discuss appropriate goal-setting; assist adolescent in completing values-based goals.</td>
<td>Joint session: same content; assist in identification of parents' own values across various life domains; assist parent in completing values-based goals that support adolescent's values-based goals</td>
</tr>
<tr>
<td>4</td>
<td>Establishing a Fear Hierarchy</td>
<td>Review values-based goals; discuss rationale for exposures using metaphor and exposure graph; review PHODA results to select activities for upcoming exposure sessions; place valued activities from each life domain upon hierarchy, from least to most worrisome.</td>
<td>Joint session: same content; encourage parent to share any valued activities that are not listed on PHODA for inclusion as needed.</td>
</tr>
<tr>
<td>5</td>
<td>Introduction of WILD scale &amp; Exposure Action Plan</td>
<td>Review completed hierarchy and rationale for exposures, as needed; discuss use of WILD scale; conduct mini-exposure with a mildly worrisome activity; modify activities and offer support as needed; plan Home Based Exposures (HBEs)</td>
<td>Joint Session: Same Content Parent observes adolescent exposure session, participating as appropriate. Psychology offers further explanation and rationale, as well as support to parent.</td>
</tr>
<tr>
<td>6</td>
<td>Graded Exposure with Behavioral Experiments-1</td>
<td>Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan HBEs</td>
<td>Parent meets separately with psychologist; review IFAM to discuss and normalize cognitive and emotional responses to adolescent in pain; review values-based goals; discuss strategies for increasing distress tolerance, promoting activity engagement and independence, and conveying confidence in adolescent Parent observes adolescent exposure session, participating as appropriate. Psychology offers further explanation and rationale, as well as support to parent.</td>
</tr>
<tr>
<td>7</td>
<td>Graded Exposure with Behavioral Experiments-2</td>
<td>Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan HBEs</td>
<td>Parent meets separately with psychologist; discuss strategies for increasing distress tolerance, promoting activity engagement and independence, and conveying confidence in adolescent Parent observes adolescent exposure session, participating as appropriate.</td>
</tr>
<tr>
<td>8</td>
<td>Graded Exposure with Behavioral Experiments-3</td>
<td>Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan HBEs</td>
<td>Parent meets separately with psychologist; discuss strategies for increasing distress tolerance, promoting activity engagement and independence, and conveying confidence in adolescent</td>
</tr>
<tr>
<td>9</td>
<td>Graded Exposure with Behavioral Experiments-4</td>
<td>Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan HBEs</td>
<td>Parent observes adolescent exposure session, participating as appropriate.</td>
</tr>
<tr>
<td>10</td>
<td>Graded Exposure with Behavioral Experiments-5</td>
<td>Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan HBEs</td>
<td>Parent meets separately with psychologist; discuss strategies for increasing distress tolerance, promoting activity engagement and independence, and conveying confidence in adolescent</td>
</tr>
<tr>
<td>11</td>
<td>Graded Exposure with Behavioral Experiments-6</td>
<td>Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan HBEs</td>
<td>Parent observes adolescent exposure session, participating as appropriate.</td>
</tr>
<tr>
<td>12</td>
<td>Relapse Prevention, Termination &amp; Future Goals</td>
<td>Review HBEs; review general progress and accomplishments; discuss potential obstacles with Hot Seat cognitive-restructuring and problem-solving activity; assist adolescent in developing long-term goals; identify &quot;lessons learned&quot; throughout treatment; present graduation certificate.</td>
<td>Joint session: same content.</td>
</tr>
</tbody>
</table>
2.9. Assessment of outcomes

All patient and parent surveys and daily diaries will be completed online through the secure, web-based application REDCap (Research Electronic Data Capture). Patients and parents attend in-person baseline and discharge assessment visits, with 3- and 6-month follow-up completed online. Table 3 lists outcomes (primary, secondary, additional, SCED, exploratory, implementation) and covariates.

2.9.1. Baseline assessment

Once eligibility is confirmed, patients and parent will be asked to attend an initial baseline study visit, which will occur at the Motion and Sports Performance Laboratory at Stanford Children's Health. Following consent and assent, patients and parent will complete baseline assessments, including a baseline biomechanical assessment, measuring gait at varying speeds, as well as self-report questionnaires. During this visit, patients will be given an Actigraph, which will monitor sleep and activity level throughout treatment. Patient and parent will also be introduced to the electronic Daily Diaries, which they will complete each day while enrolled in treatment. Following this baseline study visit, patients will undergo a pre-treatment data collection period (ranging from 10 to 21 days). The study biostatistician will create a randomization scheme to determine the number of days for the pre-treatment baseline period for each individual adolescent. During this time, patients will wear the Actigraph, and patients and parents will be asked to complete Daily Diaries.

2.9.2. Discharge assessment

Discharge assessment occurs after all treatment sessions are complete at the Motion and Sports Performance Laboratory at Stanford Children's Health. Assessment will consist of biomechanical motion analysis, self-report questionnaires, and an exit interview. Electronic daily diaries will conclude and patients will return the Actigraph watch at the discharge assessment.

2.9.3. Follow-up assessment

Follow-up assessment occurs at 3 and 6-months post-discharge. During the follow-up period, patients and parents will complete 7-days of daily diaries and the battery of self-report questionnaires online, no in-person visit is scheduled.

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Rapport Building, History</td>
<td>Build rapport; obtain patient history. Discuss goals for treatment.</td>
<td>Joint Session: Same content</td>
</tr>
<tr>
<td>2</td>
<td>PT Session 1</td>
<td>Child in Physical Therapy</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>Biopsychosocial Model</td>
<td>Biopsychosocial model of pain; gate control theory of pain; stress-pain connection</td>
<td>Joint Session: Same content</td>
</tr>
<tr>
<td>4</td>
<td>PT Session 2</td>
<td>Child in Physical Therapy</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>Setting Treatment Goals</td>
<td>Discuss SMART goals; assist adolescent in completing goals.</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>PT Session 3</td>
<td>Child in Physical Therapy</td>
<td>Parent meets separately with psychologist; Discuss SMART goals with the parent that focus on enhancing adolescent coping; assist parent in completing goals.</td>
</tr>
<tr>
<td>7</td>
<td>Coping Skills training</td>
<td>Learn and rehearse relaxation techniques (e.g., breathing, progressive muscle relaxation, imagery)</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>PT Session 4</td>
<td>Child in Physical Therapy</td>
<td>Parent learns relaxation techniques (e.g., breathing, progressive muscle relaxation, imagery) being taught to the patient and how to encourage the patient to use these skills at home.</td>
</tr>
<tr>
<td>9</td>
<td>Cognitive Restructuring</td>
<td>Introduction to fundamental cognitive-behavioral strategies including active coping, distraction, and cognitive restructuring</td>
<td>N/A</td>
</tr>
<tr>
<td>10</td>
<td>PT Session 5</td>
<td>Child in Physical Therapy</td>
<td>Parent introduction to fundamental cognitive-behavioral strategies taught in the adolescent session including active coping, distraction, and cognitive restructuring</td>
</tr>
<tr>
<td>11</td>
<td>Relapse Prevention, Termination &amp; Future Goals</td>
<td>Review accomplishments; assist adolescent in developing long-term goals; identify “lessons learned” throughout treatment; present graduation certificate.</td>
<td>Joint Session: Same content</td>
</tr>
<tr>
<td>12</td>
<td>PT Session 6</td>
<td>Child in Physical Therapy</td>
<td>N/A</td>
</tr>
</tbody>
</table>

2.10. Primary outcome

2.10.1. Pain-related fear avoidance

Pain-related fear avoidance is the primary outcome for the GET Living trial. It will be measured by the Fear of Pain Questionnaire (FOPQ-C [4] and Photograph Series of Daily Activities-Youth English (PHODA-YE [28]). The FOPQ-C consists of 24 items, with each item rated on a 5-point Likert scale (0 = “strongly disagree” to 4 = “strongly agree”). The FOPQ-C contains two subscales: Fear of Pain (11 items) and Avoidance of Activities (13 items). Total score is derived by summing items, with higher scores indicating greater pain related fear and avoidance of activities. The PHODA-YE is a 50-item electronic measure assessing worry associated with activities of daily living (13 items), exercise/sports activities (15 items), social/school activities (15 items), and upper extremity activities (9 items). To complete each item the patient is exposed to a photograph and label of the activity and asked to rate their worry “that this activity would be harmful to your pain” by dragging each photograph along a ‘worry thermometer’ ranging from 0 to 10. Each photograph is given a rating according to its position on the thermometer. Patients then rate their anticipated pain if they engaged in the activity. Mean perceived harm and anticipated pain scores (ranging from 0 to 10) is calculated as the sum of each rating divided by the total number of pictures.

2.11. Secondary outcome

2.11.1. Functional disability

Functional disability will be assessed using the Functional Disability Inventory (FDI [31]), a 15-item self-report measure of perceived difficulty in performing activities in school, home, physical, and social contexts. Items are rated on a 5-point Likert scale ranging from 0 (no trouble) to 4 (impossible). Items are summed to create a total score, with higher scores indicating greater disability. The FDI is widely used in pediatric pain research and is recommended as the gold-standard measure of physical functioning for school age children and adolescents for clinical trials in pediatric chronic pain.

2.12. Additional outcomes: child

2.12.1. Pain

Patients will provide their pain rating on a standard Visual Analog

Table 2

Description of multidisciplinary pain management.

<table>
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<td>PT Session 1</td>
<td>Child in Physical Therapy</td>
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<td>Joint Session: Same content</td>
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<tr>
<td>4</td>
<td>PT Session 2</td>
<td>Child in Physical Therapy</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>Setting Treatment Goals</td>
<td>Discuss SMART goals; assist adolescent in completing goals.</td>
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<td>6</td>
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<td>Relapse Prevention, Termination &amp; Future Goals</td>
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</tr>
<tr>
<td>Domain/Outcomes</td>
<td>Measure</td>
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| Readiness to Change | Pain Stages of Change Questionnaire (PSOCQ-A; PSOCQ-P) | 13-item measures assessing adolescent readiness to adopt a self-management approach to chronic pain and parent readiness to support this approach.
| Depression | Children's Depression Inventory (CDI-2) | 28-item measure assessing depressive symptoms.
| Anxiety | Multidimensional Anxiety Scale for Children (MASC) | 33-item measure assessing anxiety.
| Cognitive Functioning | | |
| Medical History | | |
Scale (VAS) equating to a range from 0 ("no pain") to 10.0 ("most pain possible") on a daily basis from baseline to end of treatment [32,33]. Average pain intensity ratings will be calculated for 7 days prior to the first treatment session (baseline average pain) and 7 days prior to the discharge assessment (discharge average pain).

2.12.2. Pain catastrophizing
The Pain Catastrophizing Scale -Child Version (PCS-C [34]) assesses negative cognitions associated with pain. The PCS-C is comprised of 13-items rated on a 5-point Likert scale (0 = "not at all true" to 4 "very true"). A total score is obtained by summing all items. Higher scores indicate higher levels of catastrophic thinking.

2.12.3. Pain acceptance
Patient report on the Chronic Pain Acceptance Questionnaire for Adolescents-short form (CPAQ-A8 [35]) will be used to assess pain acceptance in the child. The CPAQ-A8 is an 8-item measure consisting of two subscales: activity engagement (4 items) and pain willingness (4 items). Items are rated on a 5-point Likert scale ranging from 0 (Never True) to 4 (Always True).

2.12.4. School functioning
The Pediatric Quality of Life School Functioning subscale (PedsQL [36]) consists of 5 items rated on a 5-point Likert scale (0 = "never" to 4 = "almost always"). Completed by the parent, higher scores equate with better school functioning.

2.13. Additional outcomes: parent

2.13.1. Parent psychological flexibility
The Parent Psychological Flexibility Questionnaire [37,38] (PPFQ-10 [39]) is a parent self-report questionnaire assessing a parent’s ability to accept their own distress and respond adaptively and flexibly to their child's pain. Items are rated on a 7-point Likert scale (0 = "never true" to 6 = "always true"). Higher scores indicate greater parent psychological flexibility.

2.13.2. Parent pain acceptance
The Parent Pain Acceptance Questionnaire (PPAQ [40]) is used to assess parents’ acceptance of their child’s pain. The PPAQ contains 15-items rated on a 5-point Likert scale (0 = "never true" to 4 = "always true") with two subscales: activity engagement and acceptance of pain-related thoughts and feelings. Higher scores indicate greater parent acceptance of child pain.

2.13.3. Parent pain-related fear and avoidance
The Parent Fear of Pain Questionnaire (PFOPQ [6]) assesses parent’s fear associated with their child’s pain experiences. The PFOPQ contains 23 items assessed on a 5-point Likert scale (0 = "strongly disagree" to 4 "strongly agree"). Items are summed to create a total score, with higher scores indicating greater parent fear of their child’s pain.

2.13.4. Parent pain catastrophizing
Pain Catastrophizing Scale-Parent Version (PCS-P [41]) assesses parents’ negative cognitions associated with their child’s pain. It is comprised of 13 items rated on a 5-point Likert scale (0 = "not true at all" to 4 = "very true"). A total score is derived by summing items, with higher scores indicating higher levels of catastrophic thinking.

2.13.5. Parent protective responses
Adult Responses to Children’s Symptoms (ARCS [42]) assesses parents’ behavioral responses to children’s pain behaviors. The protect scale (13 items) will be utilized in this study. The Protect scale refers to protective parental behavior, such as giving the child special attention and limiting the child’s normal activities and responsibilities. All items are rated on a 5-point Likert scale (0 = “never” to 4 “always”), with

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Note. Each word in bold is a separate construct assessed on the daily diary. BL = baseline; End = Discharge; D = Daily; W = Weekly; S = session.
higher scores indicating greater use of a particular type of response to their child’s pain.

2.13.6. Parent miscarried helping

The Helping for Health Inventory (HHI [43]) is a 15-item questionnaire assessing miscarried helping (i.e., parental behaviors intended to be helpful, but inadvertently reinforce pain behaviors and functional decline) in parents of children with chronic pain. Items are rated on a 5-point Likert scale (1 = "rarely" to 5 = "always"). Items are summed to create a total score, with higher scores indicating greater miscarried helping.

2.14. SCED outcomes


The child daily survey consists of 16 items assessing pain and functioning in the last 24 h (see Table 4 for child diary items). Based on validated questionnaires administered in this study, 11 of the diary items were selected to assess the following constructs: worry/fear (2 items), avoidance (2 items), function (3 items), activity engagement/acceptance (2 items), and pain reactivity (2 items). These 11 items are rated on a visual analog scale ranging from 0 (no pain) to 10 (worst possible pain), tell us how much pain you are feeling right now.

\[ \text{Pain} = \frac{\text{VAS score}}{10} \]

\[ \text{Activity Engagement/Acceptance} = \frac{\text{items rated 5-8}}{9} \]

\[ \text{Worry/Fear} = \frac{\text{items rated 8-10}}{2} \]

\[ \text{Avoidance} = \frac{\text{items rated 2-4}}{2} \]

\[ \text{Functioning} = \frac{\text{items rated 5-7}}{3} \]

\[ \text{Stress} = \frac{\text{items rated 4-6}}{2} \]

\[ \text{Sleep} = \frac{\text{items rated 5-7}}{2} \]

\[ \text{Protective Parent Behavior} = \frac{\text{items rated 5-7}}{2} \]

\[ \text{Family Impact} = \frac{\text{items rated 4-6}}{2} \]

\[ \text{Activity Engagement/Acceptance} = \frac{\text{items rated 5-8}}{9} \]

\[ \text{Worry/Fear} = \frac{\text{items rated 8-10}}{2} \]

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\[ \text{Sleep} = \frac{\text{items rated 5-7}}{2} \]
Anxiety Scale for Children-2 (MASC-2 [55]) is a 50-item self-report scale assessing anxiety in children and adolescents. Higher scores indicate greater anxiety symptoms.

2.16. Covariates

2.16.1. Medical history

Variables related to chronic pain including pain onset, duration, and intensity of pain symptoms, as well as course, and medications, will be collected.

2.16.2. Demographics

Demographic variables, including age, sex, educational level, family composition, parental labor force status, hours of work, income, job loss, and ethnic background, will be assessed via patient and parent report at baseline.

2.16.3. Readiness to change

Pain Stages of Change Questionnaire, Adolescent and Parent report (PSOCQ-A; PSOCQ-P [53]) short forms are 13-item versions that assess adolescent self-report of readiness to adopt a self-management approach to chronic pain and parent reports of their mindset regarding motivation to change with respect to their adolescents current behavior. Both the adolescent self-report and the parent-are rated on a 5-point Likert scale (1 = “strongly disagree” to 5 = “strongly agree”).

2.16.4. Depression

Symptoms of depression will be assessed using the Children's Depression Inventory-2 (CDI-2 [54]). The CDI-2 is a 28-item self-report measure of youth depressive symptoms. Higher scores indicate greater depressive symptoms.

2.16.5. Anxiety

Anxiety symptoms will be assessed using the Multidimensional Anxiety Scale for Children-2 (MASC-2 [55]) a 50-item self-report scale assessing anxiety in children and adolescents. Higher scores indicate greater anxiety symptoms.

2.17. Implementation outcomes

2.17.1. Treatment satisfaction

Treatment satisfaction at the end of treatment will be evaluated by examining mean satisfaction scores on an adapted version of the Pain Service Satisfaction Test (PSST [56]). The PSST consists of 22 items and assesses the patient and parent’s experience of pain clinic services. The items were tailored to the intervention.

2.17.2. Treatment expectancy

Treatment acceptability will be measured by the Treatment Expectancy and Creditability measure (TEC-C, TEC-P [57]). The TEC is comprised of 6 items assessing expectations related to the effectiveness of the current treatment. The TEC is completed by the patient (TEC-C) and the parent (TEC-P) at the end of the first treatment session in both arms.

2.17.3. Treatment adherence

Adherence and retention will be assessed by examining parent and patient adherence to daily diary completion, percent of patients who drop out prior to treatment completion, and percentage of sessions completed on schedule.

2.17.4. Treatment fidelity

Treatment elements for each arm have been labeled into one of five categories (essential and unique, essential but not unique, unique but not essential, compatible, prohibited) [58]. A trained research assistant will listen to audio/video recordings of treatment sessions and complete treatment fidelity checklists for presence/absence of treatment elements and treatment process, for both parents and child sessions across treatment arms.

2.18. Data analysis

The study biostatistician will conduct all analyses. Covariates (age, pain variables, gender, diagnosis, readiness to change, anxiety, depression) will be examined for the primary, secondary, additional, and exploratory outcomes.

2.18.1. Primary, secondary, and additional outcomes

Linear mixed effects models will be used to compare GET Living to MPM across all non-SCED outcomes. We will model our outcomes at four time points using a mixed effects linear model with fixed effects for treatment assignment, time period, the interaction between treatment and time period, and baseline covariates and a random effect for individual. The random effect will allow us to account for the correlation in the outcome within individual over time.

2.18.2. Exploratory outcomes

To examine biomechanical data, biomechanical variables will be extracted using Polygon 4.3.3 (Vicon) for error free data reduction. Variables extracted include speed, step length, step width, peak hip and knee extensor moments, peak ankle plantar-flexor moment, and peak sagittal and frontal plane kinematics of the hip and knee joints. We will model biomechanical variables using mixed 2 (time) x 2 (group) ANOVAs. If biomechanical variables differ by pain site (upper, trunk, lower, diffuse) this will be included as a covariate. To examine Actigraphy data, Actilife software will be used to extract data and calculate mean and peak daily activity. Published data reduction methods will be used [49]. We will model physical activity (mean, peak) at two time points using mixed 2 (time) x 2 (group) ANOVAs. Rate of change in physical activity from baseline to discharge will also be examined using the randomization tests used for SCED outcomes, described below. To examine healthcare cost data, we will model healthcare cost variables using t-tests and linear and mixed regression models.

2.18.3. Implementation outcomes

Mean satisfaction scores will be examined. Additionally, mean parent and adolescent adherence to daily diary completion, percent of patient dropout prior to treatment completion, and percent of sessions completed on-schedule will also be examined.

2.18.4. SCED outcomes

The data obtained from the randomized single-case experimental phase design used in this study have a hierarchical two-level structure with observations (level 1) nested within patients (level 2). This nested structure induces dependency within the data: observations vary not only due to random sampling within a patient, but also between different patients. For analysis of the data, we will use a hierarchical linear model, allowing us to combine all patients’ data into one single multilevel model while also taking account both within- and between-patient dependencies [59,60]. The within- and between-patient variability will be modeled, as well as the overall effects of the treatment across patients. For conducting the multilevel analysis and for obtaining inference results in R [61], MultiSCED will be used (http://52.14.164.253/MultiSCED/) [62]. This daily individual data also allows for use of randomizations tests (https://tumikd.shinyapps.io/scda/) [63] to assess the difference between baseline to discharge and baseline to 3 and 6-month follow-up on Daily Dairies [16,64].

2.19. Sample size and power analysis

The largest feasible sample size was chosen to obtain as precise estimates as possible of improvement in adolescent disability while also ensuring adequate power for the treatment difference in the
improvement in adolescent pain-related fear avoidance. In our primary power calculation, we assumed that the improvement in adolescent pain-related fear avoidance at 3-months would be 21.5 in Get Living and 5 in MPM, a difference of 16.5, with a standard deviation for change of 18.8 derived from our prior work [65]. Under this scenario we will have power of 91% with 58 (29 in each arm) at end of study. Under more conservative assumptions, we still have power of 87% with this treatment difference but only 52 at the end of study, and power of 81% with a smaller treatment difference of 15.5 and 50 at end of study. This resulted in a total sample size of 74 (n = 37 for each treatment arm). A recent retrospective exposure treatment for youth with chronic pain observed a medium effect size (cohen’s d = 0.73) improvement in pain-related fear, suggesting a sample size of 31 per group to achieve 80% power, suitably within range of these estimates [66]. Based on pilot data (Get Living: NCT01974791; in revision), roughly 19% attrition is expected during treatment, resulting in a total of 60 adolescents at discharge. Further attrition to N = 58 is expected at the end of follow-up (6-months post discharge from the study). Power calculations were first performed using paired t-tests to assess the change from baseline to 3 and 6-months. Means and standard deviations of observed changes in pilot data were also examined. Data was then simulated from the analytic model using the standard deviations at each time point and standard deviations of change to calculate correlation, and the random effect and error variance. The mixed model simulation allowed the use of more data and yielded slightly higher power estimates.

2.20. Monitoring

The GET Living RCT will be monitored by KAI, the executive secretary of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). A Safety Monitoring Committee (SMC) of three experts, approved by the NIAMS, will meet quarterly to review overall subject enrollment status, accrual, adherence, protocol deviations and adverse events.

2.21. Trial status

GET Living was prospectively registered on ClinicalTrials.gov with the U.S. National Library of Medicine on 10/8/2018 (NCT03699007). Participant recruitment began in January 2019 and is expected to complete in December 2020, with data collection ceasing approximately 9 months later.

2.22. Discussion

Effective treatment for chronic pain likely requires focusing on mechanisms that perpetuate the persistent pain state, rather than treating all patients with chronic pain as ‘the same’ [67]. Based on an empirically validated theoretical model with rigorous experimental evidence [68,69], graded in-vivo exposure has emerged as a promising treatment for patients struggling with chronic pain and fear avoidance. This RCT represents the first study to directly compare multidisciplinary pain management to graded in-vivo exposure in adolescents with chronic musculoskeletal pain. Moreover, this RCT is enhanced with a single case experimental design (SCED) framework in order to answer clinically relevant questions regarding what works better for whom and when these changes occur over the course of treatment.

Providing a framework where multidisciplinary RCTs can be rigorously combined with SCEDs represents a critical step forward in the field and will enable an investigation of group differences in terms of efficacy and individual response patterns. The results of this trial are expected to provide a model for future studies to adopt this research and statistical design and well as provide substantive findings regarding the effectiveness of graded in-vivo exposure for youth with chronic musculoskeletal pain.

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References


