GET Living: Graded Exposure Treatment for Children and Adolescents with Chronic Musculoskeletal Pain

Clinical Protocol

Principal Investigator:

Dr. Laura Simons, PhD

Associate Professor
Department of Anesthesiology, Perioperative, and Pain Medicine
Stanford University School of Medicine

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
9.4 Interim Analyses and Stopping Rules	Addition of interim analysis plan	To provide procedures for stopping the trial if overwhelming futility or efficacy is proven.

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STUDY TEAM ROSTER

Principal Investigator - **Laura Simons, PhD**
Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University School of Medicine; 1070 Arastradero Rd. Suite 300, Palo Alto, CA, 94304, phone (650) 736-0838, fax (650) 724-8692, lesimons@stanford.edu

Co-Investigator - **Korey Hood, PhD**
Department of Pediatrics, Department of Psychiatry and Behavioral Sciences, Lucile Packard Children's Hospital; 780 Welch Rd., CJ320G, Palo Alto, CA, 94304, kkhood@stanford.edu

Co-Investigator - **Michael Orendurff, PhD**
Motion & Sports Performance Laboratory, Stanford Children's Health; 1195 W. Fremont Ave., Sunnyvale, CA 94087, phone (408) 426-8128, fax (408) 426-8124, morendurff@stanfordchildrens.org

Biostatistician- **Derek Boothroyd, PhD**
Department of Medicine and Quantitative Sciences Unit, Stanford University School of Medicine; 1070 Arastradero Rd. 3C3101, Palo Alto, CA, 94304, phone (650) 498-9243, derekb@stanford.edu

Consultant - **Johan Vlaeyen, PhD**
Department of Health Psychology, University of Leuven; Tiensestraat 102, 3000 Leuven, Belgium, phone +32 1632 5915, fax +32 1632 6144, johannes.vlaeyen@kuleuven.be

Consultant – **Rikard Wicksell, PhD**
Department of Behavioral Medicine Pain Treatment Service, Karolinska University Hospital; Karolinska vägen, 171 76 Solna, Sweden, phone +46 (0) 8 – 524 823 08. rikard.wicksell@ki.se

Clinical Research Coordinator
Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University School of Medicine; 1070 Arastradero Rd. Suite 300, Palo Alto, CA, 94304, phone (650) 497-9562, pedspainlab@stanford.edu

Treatment Provider (Psychologist)
Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University School of Medicine; 1070 Arastradero Rd. Suite 300, Palo Alto, CA, 94304

Treatment Provider (Physical Therapist)
Center for Rehabilitation Services, Stanford Children's Health, Lucile Packard Children's Hospital; 725 Welch Road, Suite 350, Palo Alto, CA, 94304, phone (650) 206-0190, fax (650) 479-8491

Safety Monitoring Committee (Medical Expertise) – **Lonnie Zeltzer, MD**
Pediatric Pain and Palliative Care Program, David Geffen School of Medicine at UCLA; 5041 Valjean Ave, Encino, CA 91436. lzeltzer@mednet.ucla.edu

Safety Monitoring Committee (Clinical Psychology Expertise) – **Soumitri Sil, PhD**
Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University School of Medicine; 2015 Uppergate Drive, Rm 426H Atlanta, GA 30322. soumitri.sil@emory.edu

Safety Monitoring Committee (Physical Therapy Expertise) –**Tarcisio De Campos, PT**
Department of Health Professions, Macquarie University; Ground Floor, 75 Talavera Rd
Macquarie University, NSW 2109, Australia. tarcisio.decampos@mq.edu.au

Study Abbreviations

Acronym	Expanded Term	Section(s)
ACT	Acceptance and Commitment Therapy	10.3.1
AE	Adverse Event	7.3, 7.4
ANOVA	Analysis of Variance	9.1
BAS	Baseline study visit	3, 6.2.2, 9.1, 9.5.5
CBT	Cognitive Behavioral Therapy	2.1, 5.1, 10.3.1
CHOIR	Collaborative Health Outcomes Information Registry	3
CITI	Collaborative Institutional Training Initiative	10.3.1
DD	Daily Diary	3, 9.1
DSMP	Data Safety Monitoring Plan	7.6
EAP	Exposure Action Plan	2.2, 5.1
eCRF	Electronic Case Report Form	6.2.2, 7.4, 10.3.4
FAM	Fear Avoidance Model	5.1
FDA	Food and Drug Administration	11.3, 11.4
FDI	Functional Disability Inventory	3, 6.2.2, 9.1, 9.5.2, 9.5.5
FOPQ-SF	Fear of Pain Questionnaire – Short Form	4.1
GCP	Good Clinical Practice	10.3.1
GET Living	Graded in-vivo Exposure Treatment	1.1, 2.1, 2.2, 3, 4.3, 5.1, 5.2, 5.4, 6.2.1, 6.2.2, 6.2.5, 9.1, 9.2, 9.6, 10.3.1
HBE	Home-Based Exposure	5.1
IFAM	Interpersonal Fear Avoidance Model	2.1, 5.1
ICH	International Conference on Harmonisation	10.3.1
IRB	Institutional Review Board	7.4, 7.5, 7.6, 10.3.4, 11.1, 11.3, 11.4
JFM	Juvenile Fibromyalgia	2.1
MSPL	Motion and Sports Performance Laboratory	10.2
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases	7.4, 10.3.4, 11.3, 11.4
NIH	National Institutes of Health	10.3.1, 13
OHRP	Office for Human Research Protections	11.3, 11.4
PA	Physical Activity	2.1
PD	Protocol Deviation	10.3.4
PHODA-YE	Photographs of Daily Activities – Youth English	2.2, 5.1, 9.5.1, 9.5.5
PI	Principal Investigator	7.4, 8, 10.3.2, 10.3.4, 12
PID	Participant Identification Number	11.3
PPMC	Pediatric Pain Management Clinic	3, 5.1, 6.2.1
PROMIS	Patient-Reported Outcomes Measurement Information System	4.1
PSY	Psychology/Psychologist	5.1, 10.3.1
PT	Physical Therapy/Therapist	3, 5.1
RC	Research Coordinator	6.2.1, 6.2.2
REDCap	Research Electronic Data Capture	6.2.2, 7.4, 10.1, 10.2
SAE	Serious Adverse Event	7.3, 7.4
SCH	Stanford Children's Health	3, 5.1, 6.2.1, 10.2
S.M.A.R.T.	Specific, Measurable, Achievable, Relevant, Time-Bound	5.1
SMC	Safety Monitoring Committee	7.4, 7.6, 10.3.4
TPM	Typical Pain Management	1.1, 2.1, 3, 4.3, 5.1, 6.2.2, 6.2.5, 9.1, 9.2, 9.6
SR	Self-Report	3
UP	Unanticipated Problem	7.3, 7.4
WILD	Willingness, Importance, Likelihood of Success, Degree of Difficulty	2.2, 5.1

PARTICIPATING STUDY SITES

The study will be conducted at Stanford Children's Health Facilities.

PRÉCIS

Study Title

GET Living: Graded Exposure Treatment for Adolescents with Chronic Musculoskeletal Pain

Objectives

Reducing elevated pain-related fear promotes participation in daily activities[1-4]. When patients experience how disengagement from safety behaviors does not lead to catastrophic consequences, their misinterpretations are challenged and disconfirmed, enabling them to correct their fear expectancies[5-7]. **GET Living** is the first program to explicitly targeted pain-related fear and associated disability in adolescents. Currently, most rehabilitative treatments for adolescents with chronic pain involve promoting pain coping strategies via psychology with separate physical therapy prescribed. Unfortunately, the debilitating influence of pain-related fear can stymy progress in both domains resulting in continued high healthcare utilization without symptomatic improvement.

Design and Outcomes

This study will be a randomized control trial (RCT) including approximately 74 children, ages 8-18, with musculoskeletal pain who present for treatment at Stanford Children's Health (SCH).

A "*participant*" in this study is defined as a child and at least one parent. The term "*patient*" is used to describe the child participant only. Participants will attend an initial baseline assessment (BAS) to perform consent/asset, undergo a biomechanical assessment by the Motion and Sports Performance Laboratory of SCH, and complete self-report questionnaires. Child participants will also be given an Actigraph and will be introduced to the daily diaries. Following BAS, participants will undergo a pre-treatment baseline period where daily diaries will be collected and Actigraphy monitoring will occur. After the baseline period, participants will be randomly assigned to a treatment group, Graded Exposure Therapy (GET Living) or Typical Pain Management (TPM) stratified on their fear and disability scores. Participants in the GET Living intervention group (n=37) will engage in 1-hour sessions of GET Living for 12 sessions jointly facilitated by a pain psychology therapist and physical therapist. Participants randomized into the TPM treatment group (n = 37) will engage in 6 sessions of cognitive behavioral therapy and 6 sessions of physical therapy following BAS. Parents enrolled into the TPM arm will engage in 3 parent-only sessions with the child's cognitive-behavioral therapist. All participants complete a Daily Diary during treatment.

At treatment discharge for the GET Living intervention group and TPM treatment, participants will undergo a second biomechanical assessment and complete self-report questionnaires. After completion of the second assessment evaluation, participants are contacted for follow-up evaluation, which includes completion of the Daily Diary for a 7-day window and self-report questionnaires at each follow-up time point (3 and 6 months post-second assessment).

Interventions and Duration

The GET Living intervention will be compared to Typical Pain Management (TPM) provided at Stanford Children's Health. Each participant will be enrolled in the study for up to 40 weeks – Starting with the BAS visit, 2 weeks (on average) of a pre-treatment baseline period, approximately 6 weeks of active treatment, Discharge Assessment, and 3 and 6-month post-discharge follow-up. (See Figure 3 for a break-down of the study milestones and expected timeline.)

Sample Size and Population

An ideal recruitment site, Stanford houses a tertiary care pediatric pain management treating approximately 300 unique patients in the clinic each year. Patients who meet eligibility criteria will be informed of the study by their pain clinicians at clinic appointments and provided a study brochure. We aim to recruit a total of 74 participants into the study.

1.1 Primary Objective

1a. To evaluate pain-related fear outcomes between GET Living and TPM. Hypotheses: Compared to TPM, the GET Living group will (1) have significantly less pain-related fear avoidance (adolescent, parent) at discharge, with continued gains at 3 and 6-month follow-up; Exploratory: (2) have fewer number of days to pain-related fear avoidance improvement via daily diaries.

1b. To evaluate disability and parent responses to pain outcomes between GET Living and TPM. Hypotheses: Compared to TPM, adolescents receiving GET Living will have (1) significantly less functional disability and protective parent responses at discharge, with continued gains at 3 and 6-month follow-up; Exploratory: (2) fewer number of days to achieve decreased functional disability and protective parent responses, assessed via daily diaries; (3) significantly better adolescent joint kinetics at discharge, assessed via motion analysis; and (4) demonstrate significantly greater increases in daily physical activity levels at discharge via Actigraphy. We will also examine treatment response correlates: age, pain, gender, diagnosis, and readiness to change.

2. To characterize feasibility and acceptability of GET Living compared to TPM to inform implementation of a large multi-site RCT. Hypotheses: GET Living participants will have (1) high treatment satisfaction ratings (mean score $\geq$ 40 of 60; reflective of satisfied or very satisfied); Secondary: (2) $\geq$ 80% sessions completed on-schedule, $\leq$ 20% attrition rate, $\geq$ 80% adolescent and parent daily diary adherence; Exploratory: (3) fewer health care costs at 3 and 6-month follow-up compared to TPM.

2. BACKGROUND AND RATIONALE

2.1 Background and Significance

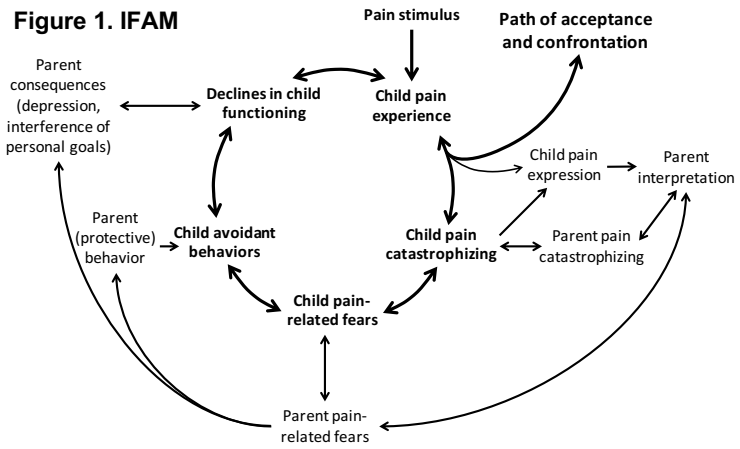
Overall Scientific Premise. Chronic musculoskeletal pain in adolescence is a significant public health concern with median prevalence rates of 11 to 38%[8,9], with 3 to 5% of adolescents suffering from significant pain-related disability[10,11], costing society $19.5 billion annually in the US alone[12]. Notwithstanding the personal suffering and persistent physical and economic consequences for families, chronic pain in adolescence can predispose the development of adult chronic pain[13]. Fear avoidance is a particularly salient influence on pain outcomes[14-17] and is a risk factor for less treatment responsiveness[18]. Typical Pain Management (TPM) yields only modest improvements in functional disability and no change in pain-related fear avoidance[19]. These findings underscore the need to specifically target pain-related fear avoidance in adolescents to potentially avert sustained pain-related disability. *Thus, the current exploratory randomized controlled trial (RCT) tests graded in-vivo exposure treatment (GET) for adolescents with chronic musculoskeletal pain (GET Living).* While TPM focuses on pain control via pain management psychology and impairment-based physical therapy, GET Living is jointly delivered by a pain psychologist and physical therapist targeting functional improvement through exposing participants to activities previously avoided due to fear avoidance of pain or re-injury. Implementing GET Living will represent a significant treatment paradigm shift by focusing on a key mechanism (pain-related fear avoidance) rather than on pain itself. Knowing that RCTs of GET are successful in adults with chronic musculoskeletal pain[2,3,20-24] and with compelling preliminary results from our pilot work of GET Living, this exploratory RCT will provide the necessary findings to support or refute a large multi-site RCT serving as the basis for potential large-scale implementation of GET Living nationwide and ultimately expand effective, tailored treatment options for adolescents struggling with persistent musculoskeletal pain, fear, and disability.

Scientific premise for GET Living. Reducing elevated pain-related fear promotes participation in daily activities[1-4]. When patients experience how disengagement from safety behaviors does not lead to catastrophic consequences, their misinterpretations are challenged and disconfirmed, enabling them to correct their fear expectancies[5-7]. GET Living is the first program in the United States to explicitly targeted pain-related fear and associated disability in adolescents. Currently, most rehabilitative treatments for adolescents with chronic pain involve promoting pain coping strategies via psychology with separate physical

therapy prescribed. Unfortunately, the debilitating influence of pain-related fear can stymy progress in both domains resulting in continued high healthcare utilization without symptomatic improvement.

Scientific premise for addressing pain-related fear in adolescents and parents. Adolescent pain-related fear is associated with disability, depressive symptoms, and school impairment[24,25]. Recent work has identified that it is equally important to assess and address parental fears. Parent emotional responses serve as key guides to a child's learning of safety and danger, in turn influencing subsequent behavior[26,27]. Growing evidence supports parent pain catastrophizing and protective behavior in prioritizing pain control[28], higher functional disability[29,30] and school dysfunction[31] in youth with pain. Building from the Fear Avoidance Model of Pain[32-34], we developed and validated the Interpersonal Fear Avoidance Model of Pain (IFAM) (**Figure 1**)[35]. Within the IFAM, parents interpret an adolescent's pain expression through the lens of their own catastrophic appraisals and pain-related fears, and are more likely to engage in maladaptive parenting behaviors (i.e., protective responses), in turn negatively influencing adolescent pain-related function.

Figure 1. IFAM



Scientific premise for biomechanical assessment and physical activity monitoring. A cycle of fear of movement, activity avoidance, and abnormal movement patterns (kinesics) in adolescents with chronic pain can lead to decreased tolerance to physical activity that persists into adulthood[37]. Abnormal kinesics, such as asymmetry in range of motion, or timing of muscle activation or joint motions, commonly exist as a compensatory mechanism in (adult) chronic pain[38,39] and potentially amplified by pain-related fear[40]. Adolescents with juvenile fibromyalgia (JFM) have higher fear of movement and greater variability in lower extremity mechanics during gait assessment and drop landing compared to healthy controls[37]. Moreover, in a small pilot trial (n=11) of CBT and neuromuscular training in JFM, improvements were observed in walking gait (stride length) and functional performance (drop vertical jump)[41]. Building from work in JFM, examining biomechanics of gait and functional movements among a diverse group of chronic pain patients in this RCT allows us to precisely define the joint motions and forces that are altered by chronic pain, and the changes that occur with TPM compared to GET Living.

In order to understand the impact of altered biomechanics observed in the laboratory, this trial includes real world objective physical activity (PA) monitoring via a wrist-worn actigraph. Actigraphy is particularly useful as self-report measures can be prone to response shift and reporter bias[42,43]. Unlike laboratory-based objective measures of physical activity, such as timed walks and peak oxygen consumption during exercise, actigraphy provides high ecological validity with unobtrusive measurement of activity levels during daily life[44]. Adolescents with chronic pain have lower mean and peak activity levels compared to healthy peers[43]. Although changes in physical activity via actigraphy have not been demonstrated for adolescent fibromyalgia patients using cognitive-behavioral therapy alone[45], it is hypothesized that the integrated GET Living approach will increase mean and peak physical activity levels.

Significance of the expected research contribution*: (1) targeting pain-related fear, a key mechanism associated with pain-related dysfunction, (2) addressing parent distress and behavior to enhance adolescent*

fear eradication, and (3) providing proof-of-principle of innovative daily tracking and biomechanical measures to define clinical endpoints and assess treatment progress within this clinical trial.

2.2 Study Rationale

Preliminary Studies/Progress Report

Over the past 10 years we have executed a line of research focused on pain-related fear avoidance in children spanning assessment and treatment intervention development.

We have implemented the first US pilot of graded in-vivo exposure for youth with chronic pain (**GET Living**; NCT:01974791). GET Living was designed in close consultation with **Johan Vlaeyen, PhD**, developer of GET and consultant on this application. The pilot was designed as a sequential replicated and randomized single-case experimental design with multiple measures with no comparator arm.

Preliminary Clinical Endpoints without Controls. As displayed in **Table 1**, patients reported significant improvements in disability, fear, avoidance (large effects). Moreover, parent fear, avoidance, and protective behavior were also impacted (large effects). These results suggest that 1) GET Living treatment results in significant improvements in primary (disability) and secondary/mechanistic (fear, avoidance) endpoints, 2) gains continue at 3 and 6-months follow-up, and 3) this approach is particularly effective for parents on fear, avoidance, and protective behavior.

Table 1. GET Living Outcomes

Outcome	Admit	Discharge	3-mos	□2
Adolescent (n=26)				
Pain-related Fear (0-96)	52.2	36.3	30.7	0.36**
Disability (0-60)	24.8	15.8	11.3	0.51**
Pain (0-10)	5.9	4.5	3.7	0.26*
Parent (n=23)[a]				
Pain-related Fear (0-52)	37.9	24.5	21.4	0.71**
Protect (0-4)	1.5	1.0	0.8	0.62**

In addition to standard questionnaires, patients complete the **Photographs of Daily Activities-Youth English (PHODA-YE)**[46], a diagnostic tool we validated to determine perceived harmfulness of activities and movements. The PHODA-YE is administered electronically with a photograph for each activity. Treatment providers receive a detailed PHODA-YE report that is shared with the patient to develop an exposure hierarchy prior to the start of exposures. Examining PHODA-YE outcomes (**Figure 2**), patients report significant decreases in activity-engagement worries (large effect sizes across domains), with largest sports activity engagement improvements. *These results suggest that specifically targeting worrisome activities in GET Living treatment results in appreciable improvements at end of treatment that are maintained.*

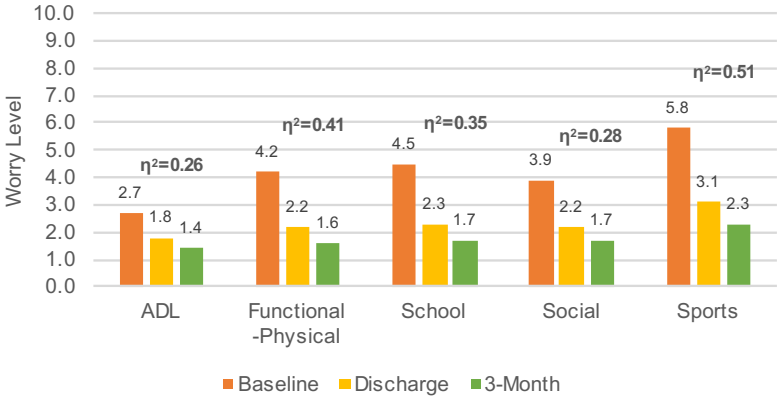


Figure 2. PHODA-YE Outcomes (n=26)

Note. [a]One young adult participated without a parent. Two parents did not complete follow up self-reports; **p<0.001; *p=0.001

The proposed study focuses on evaluating an innovative treatment adolescents with pain-related disability and fear. GET is successful and empirically supported for reducing disability in adults with substantial pain-related fear. However, the efficacy of exposure-based treatment for children with chronic pain has not been tested.

Feasibility and Acceptability Data. A total of 37 patients (Mean age=13.7; 82% female) enrolled. Of the **34** patients who began treatment (3 dropped out during baseline), 28 completed (**18**% attrition rate) and 27 have reached 3-months with one lost to follow-up (**96**% follow-up retention rate). Average duration of treatment for completers was 64 days with an **86%** patient daily diary completion rate and **82**% for parents. Families also provided feedback at discharge interviews: *"My son gained confidence, and I was taught how to support him"* (mom), *"I can break activities down- it doesn't have*

to be all or nothing" (patient). *Developmentally sensitive modifications. "The word "worry" was used too often."* (mom and dad). Patients also struggled distinguishing between numerical ratings of worry and pain. In response, we developed a rating scale for exposure activities based on **W**: Willingness, **I**: Importance, **L**: Likelihood of Success, and **D**: Degree of Difficulty (**WILD** scale). "Diaries became repetitive" (patient). In response, we created multiple versions of the diaries with items in varying order. Families requested 'coping tools'. In response, we devised exposure action plans (EAP) to increase task persistence (e.g., movement break, music during task).

3. STUDY DESIGN

This study employs a two-group randomized, controlled design to test GET Living, for adolescents with chronic musculoskeletal pain and elevated pain-related fear (**Figure 3**). ***Primary outcome*** *is pain-related fear avoidance (adolescent, parent).* ***Secondary outcome*** *is disability. Additional outcomes are parent responses to pain and pain acceptance. Exploratory: adolescent biomechanics and physical activity.*

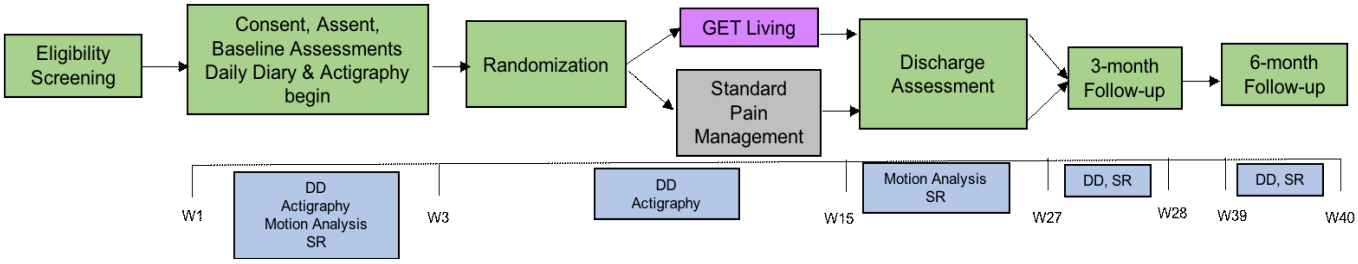


Figure 3. Study Design. a) Eligibility Screening: musculoskeletal pain patients (ages 8-18; pain > 3 months) at Stanford Children's Health (SCH); b) Baseline Visit (BAS): Consent/Assent, Baseline Assessment: SR, motion analysis; Baseline Daily Diary: DD and actigraphy; c) Randomization: randomization to treatment group; d) GET Living and TPM begin: DD and actigraphy ongoing; e) Discharge Assessment: SR, motion analysis; f) 3-month Follow-Up: SR, 7-day DD, g) 6-month Follow-Up: SR, 7-day DD. *Note.* **DD**=daily diary; **SR**=self-report; **W**=week.

Recruitment. An ideal recruitment site, Stanford houses a tertiary care pediatric pain management treating approximately 300 unique patients in the clinic each year. We will recruit adolescent patients and a primary parent (N = 74) from the outpatient pediatric pain management clinic (PPMC) at Stanford Children's Health (SCH). We will also recruit patients from Kaiser Permanente Bay Area satellite clinics, contingent upon referrals from pain rehabilitation clinicians. ***For inclusion,*** the patients: 1) are 8-18 years old; 2) have musculoskeletal or neuropathic pain (e.g., localized [back, limb], diffuse)[47] not due to an acute trauma (active sprain or fracture); 3) have pain-related fear (FOPQ ≥ 35), 4) functional limitations (FDI ≥ 13), and 5) be English language proficient. ***Patient exclusion criteria are:*** 1) significant cognitive impairment (e.g., brain injury) and 2) significant medical or psychiatric problem that would interfere with treatment (e.g., seizures, psychosis, suicidality). **Identification of Eligibility:** Patients and their parents who meet eligibility criteria will be informed of the study by their pain clinicians at clinic appointments and provided a study brochure. Additionally, a study flyer will be posted on our bulletin board of all active clinical studies in the patient waiting room. **Screening:** For each patient referred to the trial, eligibility for enrollment will be determined by the GET Living research team via chart review, along with the Clinician Referral Checklist (MOOP Supplemental Materials I) and a screening phone call. **Study Entry and Randomization:** Individuals passing the first two stages will enter the study by attending the Baseline Assessment visit (BAS). Once enrolled, adolescents will be randomized to either GET Living or TPM and stratified on fear (moderate/high; FOPQ-C: low [0-34] moderate [35-49] high [50-96]) and disability (moderate/severe; mild [0-12] moderate [13-29] severe [30-60][48]), to minimize the possibility 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 assignment, we will use blocks of size two and four and randomly choose block sizes. The study biostatistician (**Derek Boothroyd, PhD**) 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 probability weights two thirds and one third respectively) will be randomly created and within each block half will be randomly assigned to GET Living and the other half to TPM. Copies of the randomization lists will be kept by the biostatistician and Research Coordinator and not shared with other members of the team. The

biostatistician will also create a randomization scheme to determine the number of days for the pre-treatment baseline period for each individual participant (2 weeks on average).

Study Procedures. At the BAS visit participants will complete informed assent/consent, complete baseline questionnaires, begin daily diaries, and begin wearing an Actigraph. Child participants will undergo biomechanical assessment (**Michael Orendurff,** Director of the Motion and Sports Performance Laboratory at SCH) during this visit. Notification of treatment arm allocation will occur at the end of the pre-treatment baseline period, and treatment will begin according to randomized group allocation: GET Living or TPM. Discharge testing occurs at the end of GET Living or TPM and includes participant questionnaires, child biomechanical assessment, and an exit interview. Daily diary and actigraphy ends at discharge. At 3 and 6 months follow-up, participants complete daily diaries for 7-days and self-report questionnaires.

Treatment Conditions. Participants will be randomized into: **GET Living** or **Typical Pain Management** (**TPM**). During the study, participants will be instructed to not seek new treatments for pain. **GET Living.** An outpatient team consisting of a pain psychologist and physical therapist (PT) provide GET Living, both trained in this modality of treatment by Laura Simons, PhD with ongoing consultation from Johan Vlaeyen, PhD (lead innovator of GET in adults) and exposed to treatment session videos from participants in the pilot. GET Living is focused and individually tailored. The primary aim of GET Living is returning to valued activities of daily life and restoring daily functioning, including return to school. The treatment manual, entitled **GET Living: Graded Exposure Treatment for children and adolescents with chronic pain** was adapted from the adult treatment manual[49] (see **Section 5.1** detailed description). The protocol consists of 12 50-minute sessions delivered twice a week for up to 12 weeks. Sessions 1-5 (education, formulation, goals) are conducted with the psychologist, PT, adolescent, and parent. Graded exposure begins in session 6. The psychologist and PT co-lead a portion of the exposure sessions. During the remaining exposure sessions, the PT leads the exposures while the pain psychologist meets individually with the parent. The final two sessions focus on relapse prevention and future goal setting. **Typical Pain Management.** After randomization, participants allocated to the TPM group will initiate treatment, as indicated by the TPM treatment manual. To ensure dose equivalency, we increased this to 6-Psychology/6-PT with 3 parent-only sessions. In pain management psychology[50] child and parent sessions focus on biopsychosocial model education, goal setting, pain coping skills training, and cognitive restructuring. PT sessions are based on Guide to Physical Therapy Practice 3.0[51]consisting of 1) therapeutic exercise, 2) balance and proprioception, 3) strength training, and 4) use of modalities (e.g., heat/cold pack).

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Child participants must meet all the following inclusion criteria to participate in this study:

- 8-18 years old; Male or Female
- Musculoskeletal or neuropathic pain (e.g., localized [back, limb], diffuse)[45] **not** due to acute trauma (e.g., active sprain or fracture).
- Moderate to High pain-related fear (≥ 35 on the Fear of Pain Questionnaire, FOPQ), or clinician-indicated referral if scores below 35.
- Moderate to High functional disability (≥ 13 on Functional Disability Inventory, FDI), or clinician-indicated referral if scores below 13.
- Be English Language Proficient

4.2 Exclusion Criteria

Child participants meeting any of the following exclusion criteria at baseline will be excluded from study participation:

- Significant cognitive impairment (e.g., brain injury)
- Significant medical or psychiatric problems that would interfere with study (e.g. seizures, psychosis, suicidality)

4.3 Study Enrollment Procedures

Patients who meet eligibility criteria will be informed of the study by their pain clinicians at clinic appointments and provided a study brochure. Additionally, a study flyer will be posted on our bulletin board of all active clinical studies in the patient waiting room. For each patient referred to the trial, preliminary eligibility for enrollment will be determined by the clinical team at the PPMC or Kaiser via chart review and a brief conversation with the patient family. If interested in participating, a member of the research team will conduct a brief screening phone call to confirm general eligibility requirements. At this point, the research team will conduct a secondary screening assessment to determine if the patient's scores on the FOPQ and FDI meet cut-offs for the clinical trial. If eligible, patients and parent will be asked to come into the clinic for an initial baseline study visit (BAS) where consent and assent will be obtained. During this visit, following consent, participants will complete baseline assessments, including a baseline biomechanical assessment and self-report questionnaires. Child participants will also be set up with an Actigraph (activity monitoring device), and all participants (child & parent) will be introduced to the Daily Diaries. Following BAS, participants will undergo a pre-treatment data collection period (2 weeks on average). During this time, participants will be asked to complete Daily Diaries and child participants will wear the Actigraph. Following the pre-treatment baseline period, participants will be randomized into one of two treatment conditions: GET Living or Typical Pain Management (TPM).

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

GET Living: *Participants randomized into the* ***GET Living*** *intervention group, will participate in 12 sessions, 1-hour each, delivered twice a week over for up to 6 weeks.*

Phase I-III. The goals of Phase I-III are to educate the participants about the fear avoidance model of pain (individual and interpersonal), present the treatment rationale and formulation, create values-based treatment goals to enhance motivation, and create a pain-related fear hierarchy from the PHODA-YE results to design specific exposures. The pain psychology therapist (PSY) and PT are both present for these sessions to ensure that the treatment message is consistent from both providers to the family. Most of these activities are conducted jointly with the adolescent and parent present, although this varies with the developmental level of the adolescent. For example, while younger adolescents require parental input when developing fear hierarchies, most older adolescents do not want or need parent involvement to complete this task. In addition, depending on parent awareness of their own distress and behavior that may be impacting their adolescent's functioning, the interpersonal fear avoidance model formulation may initially be presented separately. The decision on whom to include for the different treatment exercises in these initial sessions will be jointly negotiated by the therapists, patient, and parents.

Phase IV. Graded Exposure consists of engaging in activities perceived as potentially 'harmful' or 'worrisome' in a controlled and continuous manner in order to elicit anxiety and to foster habituation and the subsequent

reduction of the fearful response (extinction). Exposures can be either in-vivo or imaginal, depending on the ability to execute the activity in session. Exposures are presented in a graded fashion according to a fear hierarchy. Milder feared activities are presented first to allow patients to more easily practice the treatment techniques and to maximize the chance of successful habituation and initial treatment success. Each activity or movement is first modeled by the therapist, conveying to the patient that it is a safe thing to do. After completing exposure activities and having anxiety diminish within the safety of the clinician-supervised treatment session, patients are asked to complete exposure activities outside of session until distress diminishes across settings. *Parent presence during exposures is at the discretion of the therapist team and patient comfort level. An adolescent may not want a parent present for any exposure sessions.*

Behavioral Experiments, or methods used to empirically test the validity of a belief, are conducted during exposure sessions. In essence when an adolescent performs an activity that challenges the validity of their catastrophic assumption or belief, they are empirically testing the belief. Progress can be monitored by asking patients to predict the occurrence of harm before the experiment and repeating the same question after exposure to that activity, "How would you rate the probability (0-100%) that you will be unable to move after doing this activity?" When the rating has decreased substantially, the therapist can move on. You can also ask the patient to predict their performance level, "How far do you think you will be able to go? One foot? 10 feet? 50 feet?" Often patients will under estimate their ability and this can serve as salient feedback on their performance.

WILD Scale: Clinical experience from the pilot study indicated that patients with chronic pain tend to have difficulty differentiating their numeric rating of pain from a numeric rating of distress/worry about anticipated pain. This renders the SUDs rating scale (Subjective Units of Distress) typically used in exposure-based interventions somewhat difficult to use in a meaningful way (as a measurement of distress) in this population. Therefore, in order to assess distress as required (as well as extend our assessment of each particular activity on the ladder), we generated a rating scale to assess four relevant aspects of each task. These are:

- **Willingness:** patient's willingness to complete the task
- **Importance:** important of the activity to the patient
- **Likelihood of Success:** patient's assessment of their likelihood of successfully completing the activity
- **Difficulty:** patient's assessment of the activity's level of difficulty

Exposure Action Plan (EAP): Once again, clinical experience from the pilot study indicated that participants were coming to the program with limited, if any, exposure to pain coping skills, or active pain management strategies. The Exposure Action Plan is intended to provide the patient with a basic foundation in active pain management strategies, so that should pain increase (as is very possible) during an activity, the patient is able to persist with that activity. This plan is not intended as an all-encompassing pain coping psychoeducation module; rather, it is intended to offer the patient a number of basic pain management strategies so that they may feel more empowered and in control while completing challenging tasks. Such strategies included in the EAP are breathing, stretches, movement breaks, helpful thoughts, "getting into it," and facilitators. (Note: Facilitators should not be confused with distractions. The patient needs to attend to the activity at least in part to observe that the feared outcome either did not happen or was manageable. Facilitators are activities that can coincide with the exposure activity to facilitate its completion – e.g., listening to music while working out).

Home-based exposures (HBEs): are "homework" activities implemented at home or in the community, which typically entail the repetition, continuation, or extension of exposure activities already completed in session. However, on occasion, 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.

HBE Worksheets describing the specific instructions for the exposure activities, the pre-activity WILD scale, and the EAP are completed in session and sent home with patient to be brought back in the following session.

The Parent Component is integrally linked to individual treatment and is primarily delivered by the PSY. In addition to parent participation in Phases I-III, observation of selected graded exposure activities and providing support in the execution of home-based exposures, there is a unique parent-only intervention that consists of education and behavior change. **Education** is designed to discuss the etiology and treatment of pain-related fear to normalize the problem and promote increased treatment compliance. The interpersonal fear avoidance model will be revisited. **Parent behavior change** will focus on alternative responses to distress and avoidance behavior that both the adolescent and parent experience. The change in how parents respond to distress and avoidance behaviors in themselves and their adolescent is an essential treatment component aimed at fostering adolescent independence and treatment success.

Phase V. Relapse prevention, long-term goal setting, and termination is designed to foster the maintenance and generalization of earlier treatment gains through problem solving.

Discharge will consist of a second biomechanical motion analysis, an exit interview, and self-report questionnaires.

Follow-ups will occur 3 and 6-months post-discharge assessment. During the follow-up periods, patients will be asked to complete 7-days of daily diaries and complete self-report questionnaires.

Table 2. GET Living Intervention Sessions

Session	Topic	Adolescent Content	Parent Content
1	Rapport Building, Education, & the Pain Dilemma	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	Joint session: same content
2	Pain-Worry Cycle & Individualized Formulation	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	Joint session: same content; present parent with Interpersonal FAM to be discussed in future session.
3	Setting Values-based Treatment Goals	Review FAM and GET Living homework; discuss values and contrast with goals; assist in identification of adolescent's values across various life domains; discuss appropriate goal-setting; assist adolescent in completing values-based goals.	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
4	Establishing a Fear Hierarchy	Review values-based goals to ensure appropriateness; discuss rationale for exposures using metaphors and exposure graphs; review PHODA results to identify themes and select activities for upcoming exposure sessions; plot most-valued activities from each life domain upon hierarchy, from least to most worrisome.	Joint session: same content; encourage parent to share any valued activities that are not listed on PHODA for inclusion as needed.
5	Introduction of WILD scale & Exposure Action Plan	Review completed hierarchy and rationale for exposures, as needed; discuss use of WILD scale; conduct mini-exposure with least worrisome activity; modify activities and offer support as needed; plan Home Based-Exposures (HBEs)	Joint Session: Same Content Parent observes adolescent exposure session, participating as appropriate. Psychology offers further explanation and rationale, as well as support to parent.

6	Graded Exposure with Behavioral Experiments-1	Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan Home Based-Exposures (HBEs)	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
7	Graded Exposure with Behavioral Experiments-2	Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan Home Based-Exposures (HBEs)	Parent observes adolescent exposure session, participating as appropriate. Psychology offers further explanation and rationale, as well as support to parent. Psychology provides feedback to parent about any naturally occurring responses to adolescent during exposure.
8	Graded Exposure with Behavioral Experiments-3	Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan Home Based-Exposures (HBEs)	Parent meets separately with psychologist; discuss strategies for increasing distress tolerance, promoting activity engagement and independence, and conveying confidence in adolescent
9	Graded Exposure with Behavioral Experiments-4	Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan Home Based-Exposures (HBEs)	Parent observes adolescent exposure session, participating as appropriate. Psychology offers further explanation and rationale, as well as support to parent. Psychology provides feedback to parent about any naturally occurring responses to adolescent during exposure.
10	Graded Exposure with Behavioral Experiments-5	Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan Home Based-Exposures (HBEs)	Parent meets separately with psychologist; discuss strategies for increasing distress tolerance, promoting activity engagement and independence, and conveying confidence in adolescent
11	Graded Exposure with Behavioral Experiments-6	Review HBEs; continuing progressing exposures as appropriate; modify activities and offer support as needed; plan Home Based-Exposures (HBEs) *Exposure sessions may occur for 3 – 9 sessions depending on patient needs.	Parent observes adolescent exposure session, participating as appropriate. Psychology offers further explanation and rationale, as well as support to parent. Psychology provides feedback to parent about any naturally occurring responses to adolescent during exposure.
12	Relapse Prevention, Termination & Future Goals	Review HBEs; review general progress and accomplishments; discuss importance of relapse prevention and planning for future; target potential obstacles with Hot Seat cognitive-restructuring and problem-solving activity Review accomplishments; assist adolescent in developing long-term goals; identify "lessons learned" throughout treatment; present graduation certificate.	Joint session: same content.

Typical Pain Management (TPM) is a treatment intervention that is representative of current standards of care in a multidisciplinary pain clinic setting. We calculated historical PPMC treatment data for patients who met enrollment criteria (Mean sessions: Psychology=5 and PT=4). To ensure dose equivalency, we increased this to 6-Psychology/6-PT with 3 parent-only sessions. The CBT has been adapted from published manual for CBT treatment

of pediatric chronic pain and depressive symptoms [52] and the PT sessions are based on Guide to Physical Therapy Practice 3.0[51].

Overview. The protocol consists of approximately 12 sessions, 1-hour each, delivered twice a week, on average for 6 weeks. Patient and parent will complete daily diaries and patients will wear the Actigraph throughout the duration of treatment. Sessions will alternate between psychological CBT sessions and Physical Therapy sessions, as outlined in Table 2 below. 3 Parent-only CBT sessions with the pain psychologist will be included to address parental coping skills.

Cognitive Behavioral Therapy (CBT). CBT will consist of 6 patient sessions and 3 parent-only sessions with a licensed pain psychologist focused on biopsychosocial model education, goal setting, coping skills training, and cognitive restructuring. The final CBT sessions with the psychologist will focus on relapse prevention, long term goals, reviewing of accomplishments during treatment.

Physical Therapy (PT). PT will consist of 6 sessions with a licensed physical therapist based on Guide to Physical Therapy Practice 3.0[51] consisting of 1) therapeutic exercise, 2) balance and proprioception, 3) strength training, 4) use of modalities (e.g., heat/cold pack).

Discharge will consist of a second biomechanical motion analysis (**Michael Orendurff, PhD;** Motion and Sports Performance Laboratory at SCH), and exit interview, and self-report questionnaires completed by patient and parent.

Follow-up will occur 3 and 6-months post-discharge assessment. During the follow-up period, patients and parents will be asked to complete 7-days of daily diaries and complete self-report questionnaires.

Table 3. Typical Pain Management Sessions

Session	Topic	Adolescent Content	Parent Content
1	Rapport Building, History	Build rapport; obtain patient history. Discuss goals for treatment.	Joint Session: Same content
2	PT Session 1	Adolescent in Physical Therapy	N/A
3	Biopsychosocial Model Education	Biopsychosocial model of pain; gate control theory of pain; stress-pain connection	Joint Session: Same content
4	PT Session 2	Adolescent in Physical Therapy	N/A
5	Setting Treatment Goals	Discuss SMART goals; assist adolescent in completing goals.	N/A
6	PT Session 3 Treatment Goals (Parent only)	Adolescent in Physical Therapy	Parent meets separately with psychologist; Discuss SMART goals with the parent that focus on enhancing adolescent coping; assist parent in completing goals.
7	Coping Skills training	Learn and rehearse relaxation techniques (e.g., breathing, progressive muscle relaxation, imagery)	N/A

8	PT Session 4 Coping Skills Training 1 (Parent only)	Adolescent in Physical Therapy	Parent a review of evidence supporting relaxation techniques (e.g., breathing, progressive muscle relaxation, imagery) that are being taught to the patient and how to encourage the patient to use these skills at home.
9	Cognitive Restructuring	Introduction to fundamental cognitive-behavioral strategies including active coping, distraction, and cognitive restructuring	N/A
10	PT Session 5 Coping Skills Training 2 (Parent Only)	Adolescent in Physical Therapy	Parent introduction to fundamental cognitive-behavioral strategies taught in the adolescent session including active coping, distraction, and cognitive restructuring
11	Relapse Prevention, Termination & Future Goals	Review accomplishments; assist adolescent in developing long-term goals; identify "lessons learned" throughout treatment; present graduation certificate.	Joint Session: Same content
12	PT Session 6	Adolescent in Physical Therapy	N/A

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5.1.2 Compensation

All patients will be closely monitored by the PI, Laura Simons, as well as the treatment and research team. Patients are compensated for their time and contribution to this study, with increased compensation for the 3-and-6-month post-discharge follow-up. The following is the compensation timeline for all patients in the study:

- **Timepoint 1:** $30.00 Amazon.com gift code at the start of treatment after baseline completion of questionnaires and daily diaries;
- **Timepoint 2:** $30.00 Amazon.com gift code after completion of treatment, daily diaries, and end of treatment questionnaires;
- **Timepoint 3:** $50.00 Amazon.com gift code at the 3 month post-discharge follow-up for completion of questionnaires and 7-day daily diary
- **Timepoint 4:** $50.00 Amazon.com gift code at the 6 month post-discharge follow-up for completion of questionnaires and 7-day daily diary

5.2 Handling of Study Interventions

The GET Living Intervention will be delivered jointly with a Pain Psychology Therapist (PSY) and Physical Therapist (PT). Sessions will involve both patient and parent.

The Typical Pain Management intervention will be delivered with a Pain Psychology Therapist (PSY) and Physical Therapist (PT) separately. Sessions will involve the patient and 3 parent-only sessions held by the therapist.

5.3 Concomitant Interventions

N/A

5.3.1 Allowed Interventions

We ask all patients enrolled in the study to not partake in outside interventions such as other Physical Therapy or psychology sessions that may interfere with active treatment related to the study.

5.3.2 Required Interventions

Adherence to treatment group and intervention will be necessary throughout the study.

5.3.3 Prohibited Interventions

N/A

5.4 Adherence Assessment

In a pilot study for the GET Living intervention conducted at Boston Children's Hospital by Laura Simons, a total of 78 patients were referred for the GET Living treatment study with a 45% enrollment rate. A total of 37 patients (Mean age=13.7; 77% female) consented for treatment. Of the **34** patients who began treatment (3 dropped out during baseline), 26 completed treatment (**18%** attrition rate). One patient was lost to follow-up (**96%** follow-up retention rate). To account for the observed attrition rate in the pilot study, we aim to recruit 74 patients for this exploratory clinical trial.

Patients will be closely monitored by the PI, Laura Simons, as well as the treatment and research team. Patients are compensated for their time and contribution to this study, with increased compensation for the 3 and 6-month follow-ups. Follow-up will occur at 3 and 6-months for both treatment groups. They will be asked to complete 7-days of daily diaries and self-report assessments.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Table 4.

Assessment	Recruitment	Baseline Assessment	Pre-Treatment Period	Treatment Sessions	Discharge Assessment	3 mo Follow-up (Online)	6 mo Follow-up (Online)
Screening	x						
Medical Chart Review (i.e., diagnosis, current medications, current treatments, etc.)	x				x	x	x
Enrollment: Informed Consent & Assent Forms		x					
Demographics		x					
Randomization			x				
Self-Report Questionnaire Measures		x			x	x	x
Biomechanical Motion Analysis		x			x		
Child Daily Diary		x	x	x		x	x
Parent Daily Diary		x	x	x		x	x
Actigraphy		x	x	x			
Exit Interview					x		
Adverse Events		x	x	x	x	x	x

6.2 Description of Evaluations

The Schedule of Evaluations will include Recruitment (i.e., screening, demographics, preliminary medical chart review), a Baseline Visit (i.e., informed consent/assent, enrollment in study, baseline assessment (i.e., completion of self-report questionnaires, biomechanical motion analysis, report of adverse events), Pre-treatment Baseline Period (i.e. Daily Diaries, Actigraphy), Treatment randomization allocation, Treatment Sessions (i.e., Daily Diaries, Actigraphy, reports of any adverse events during treatment), Discharge Assessment (i.e., self-report questionnaires, biomechanical motion analysis, exit interviews, reports of any adverse events), and 3 and 6-month follow-up (i.e., medical chart review, self-report questionnaires, Daily Diaries, and reports of any adverse events post-treatment).

6.2.1 Screening Evaluation

Screening

Clinicians will complete the "Clinician Referral: Eligibility Checklist" (Supplemental Materials I – CRF Templates) to indicate if a patient may be eligible for the GET Living study. Once potential participants are identified for participation at SCH, a brief screening phone call will be made by a study staff member to confirm general eligibility requirements (see Supplemental Material II for Phone Screening Form). At this point, the research team will conduct a secondary screening assessment to determine if the patient's scores on the FOPQ and FDI meet cut-offs for the clinical trial.

Screen Failures

Participants will be considered a screen failure if they do not meet <u>all</u> of the inclusion criteria listed in section 4.1 or if they meet <u>any</u> of the exclusion criteria listed in section 4.2.

Consenting Procedure

Before obtaining formal written assent/consent from patients and their parents, clinical providers at the PPMC and Kaiser will obtain verbal consent to be approached by members of the research team.

Study staff, which will include a research coordinator (RC) or postdoctoral fellow trained by Dr. Laura Simons, will conduct the consent and assent procedure. Eligible participants will be educated about study procedures or any changes in those procedures. Signed consent/assent forms will be kept in a locked filing cabinet in Dr. Simons' office.

6.2.2 Enrollment, Baseline, and Randomization

Enrollment

Study consenting/assenting and enrollment will take place at the initial study visit. All procedures will be completed by a research coordinator (RC) and/or postdoctoral fellows.

Consenting Procedure for Enrollment

This study will follow the *Informed Consent Process for Research* according to the Stanford University Research Compliance Office. Each participant's consenting process will be recorded by the study RC in the "Screening and Enrollment Log" (MOOP Supplemental Materials I) within an online REDCap CRF. The signed consent/assent documents will be stored in a locked cabinet in the PI, Dr. Laura Simons', office.

The informed consent process will take place in a private office, and participants will have the opportunity to choose their seating, read the consent form, and ask any questions they may have

at the beginning of the data collection session. Signed consent/assent forms will be stored in a locked file. Participants will be reminded that their involvement in this study is completely voluntary, and that they can withdraw it any time without any negative repercussions whatsoever (e.g., with regard to clinical care or healthcare access). They will also be explicitly told that they may leave any question blank for questionnaires or unanswered for the clinical interview if they do not feel comfortable answering. See Supplement Material for the consent and assent form.

Non-English Speaking Participants – Individuals who do not speak or understand English will not be recruited to the study. While we recognize the limitations of this approach, practical considerations necessitate the inclusion of only those who are able to speak or understand English.

Enrollment date will be recorded in the "Screening and Enrollment Log" ECRF, which will also include documentation of inclusion/exclusion criteria.

Baseline Assessment (BAS):

During the initial study visit, a baseline biomechanical assessment will be conducted and self-reports questionnaires will be completed by the child and parent.

- Child & Parent Baseline Self-Report Measures:

  See Supplemental Materials III for baseline self-report measures

- Patient Biomechanical Assessment – Motion analysis will be assessed by Dr. Michael Orendurff, PhD, of the Motion and sports Performance Laboratory of Stanford Children's Health. Gait (stride length and velocity) [37], drop jump landing[37], and dynamic postural control[41] tasks will be performed by the patient.

Pre-Treatment Baseline Period

During the Pre-Treatment Baseline period, patients will complete the following:

- Child and parent will complete daily diaries collected via REDCap to monitor daily fear of pain, avoidance, acceptance, catastrophizing and pain ratings.
- Actigraphy data will be collected to track daily physical activity and sleep.

The pre-treatment baseline period will last an average of 2-weeks.

See Supplemental Materials III for child and parent daily diaries

Randomization

After a 2-week (on average) pre-treatment daily diary, adolescents will be randomized to either GET Living or TPM and stratified on fear (moderate/high) and disability (moderate/high). A block randomization strategy (**Table 5**) will be used with randomly generated blocks of 2 and 4 to assure near equal distributions across arms as well as to minimize the probability of predicting the next assignment. A randomization spreadsheet with four strata will be created by the study biostatistician, Dr. Derek Boothroyd.

Table 5. Fear and Disability Stratification

High Fear + High Disability	High Fear + Moderate Disability	High Disability + Moderate Fear	Moderate Disability + Moderate Fear

*Fear based on the FOPQ-C; Disability based on FDI – high fear = 50-96; moderate fear = 35-49; high disability = 30-60; moderate disability = 13-29

6.2.3 Blinding

Blinding of treatment arms will not be possible for patients, their parents, and the healthcare professional providing administering active treatment. Dr. Michael Orendurff, who will be assessing the biomechanical motion analysis during Baseline and Discharge visits for patients will be blinded to the treatment arm allocation of each patient.

6.2.4 Treatment Measures

The following measures will be collected during Treatment:

- Child Daily Diary
- Parent Daily Diary
- Actigraphy Monitoring

See Supplemental Materials III for child and parent daily diaries

6.2.5 Discharge Session

At the Discharge Session for GET Living or TPM, child and parent will complete self-report measures, along with an exit interview.

- Child & Parent Self-Report Questionnaires Measures:

  See Supplemental Materials III for discharge self-report measures

- Patient Biomechanical Assessment – Motion analysis will be assessed by Dr. Michael Orendurff, PhD, of the Motion and sports Performance Laboratory of Stanford Children's Health. Gait (stride length and velocity) [37], drop jump landing[37], and dynamic postural control[41] tasks will be performed by the patient.

- Exit Interview: patient and parent will be asked questions about their treatment experience.

  See Supplemental Materials III for exit interview materials

6.2.6 Follow-Up Assessments

A set of self-report measures will be completed by **all participants** (child & parent) after 3 and 6-months post-discharge.

See Supplemental Materials III for follow-up assessment measures

7. SAFETY ASSESSMENTS

As the study is being conducted within a healthcare facility all normal monitoring of safety will be in place. There are few additional safety risks introduced as part of the involvement in the study procedures. If any risk arises as part of being interviewed, completing measures, or participating in the treatment, there are clinical psychologists and medical personnel immediately available to

assess the situation and provide assistance.

7.1 Specification of Safety Parameters

N/A

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

N/A

7.3 Adverse Events and Serious Adverse Events

For the purposes of this study, the following AE definitions are used:

Adverse Event (AE): Any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated treatment interventions, regardless of whether it is considered related to the treatment. AEs are categorized according to the following scale:

Severity Ratings
Adverse Events (AEs) will be rated on the following three-point scale, to the determine the severity of

- ***Mild***: An experience that is transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities.
- ***Moderate***: An experience that is alleviated with simple therapeutic treatments. This experience impacts usual daily activities. Includes laboratory tests alterations indicating injury, but without long-term risk.
- ***Severe***: An experience that requires therapeutic intervention unrelated to clinical trial treatment intervention. The experience interrupts usual daily activities. If hospitalization is required for treatment, this will be classified as an SAE.

Relatedness Ratings
Adverse Events (AEs) will be rated on the following three-point scale, to the degree to which the event appears to be related to the study intervention:

- 0, ***Unrelated***
- 1, ***Possibly Related***
- 2, ***Definitely Related***

Expectedness Ratings
Adverse Events (AEs) will be assessed as to wither they were *expected* to occur or *unexpected*, meaning not anticipated based on current knowledge found in the protocol or based on the treating clinician's experience:

- ***Unexpected***: the nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, or clinician's experience
- ***Expected***: the event is known to be associated with the intervention or condition under study.

Unanticipated Problem (UP): an unanticipated problem involving risk to human participants or others, is one that (1) was unforeseen at the time of its occurrence, (2) is related or possibly related to participation in the research, and (3) indicates that participants or others are at an increased risk of harm.

Serious Adverse Events (SAE*)*: Any AE that result in any of the following outcomes:

- Death
- Suicide/Homicide Attempt
- Life-Threating event
- Event requiring inpatient hospitalization
- Persistent or significant escalation of disability/incapacity

There is no evidence that participation in this treatment trial will increase risk of a serious adverse event (SAE).

7.4 Reporting Procedures

AEs will be identified at any time during participation in this treatment study. Reports of AEs to the Get Living Study team will be assessed and noted. The study team will be informed to notify the PI of any AEs identified during treatment or throughout the duration of enrollment in the study. Parents of patients will also be asked to notify the study team if an AE has occurred. During follow-up contact, the study staff will ask patient and parent if any AEs have occurred since the end of treatment. The known potential risks will be described in informed consent documents and protocol.

All AEs and SAEs will be monitored on a continual basis and documented, by participant, in the respective eCRFS (MOOP Appendices B-C) on REDCap. All AEs and SAEs will also be collated across participants into a Master Sheet for presentation to the Safety Monitoring Committee (SMC) at quarterly meetings. In addition, all SAEs and UPs are reported according to the Stanford Medical IRB reporting guidelines (within 10 working days of occurrence). Follow-up remediation will occur within five days of the IRB's response or decision. All AEs will be reviewed quarterly by the PI and SMC.

SAEs and specific treatment intervention-associated AEs will be reported to the PI, Dr. Laura Simons, and responsible study staff within 24 hours. All SAEs and UPs will be reported to the NIAMS within 48 hours of the investigator becoming aware of the event. There are no SAEs anticipated for this research study.

7.5 Follow-up for Adverse Events

All AE's will be reported to the IRB of record within five days. Follow-up remediation will occur within five days of the IRB's response or decision.

7.6 Safety Monitoring

Oversight of this clinical trial is provided by the Principal Investigator (PI), Dr. Simons. The Study Monitoring Committee (SMC) will involve the following individuals:

- Lonnie Zeltzer, MD (Medical Expertise) – Mattel Children's at UCLA
- Soumitri Sil, PhD (Clinical Psychology Expertise) – Children's Healthcare of Atlanta
- Tarcisio De Campos, PT (Physical Therapy Expertise) – Macquarie University

As this is a single-site clinical trial involving low risk, the individuals listed above, along with the PI, Dr. Simons, and the Stanford University Institutional Review Board (IRB) will be responsible for the duties involved with this DSMP.

8. INTERVENTION DISCONTINUATION

Patients and their parents have the right to withdraw consent/assent or discontinue participation at any time without penalty or any impact on the child's care. Because this is an exploratory clinical trial, we will not discontinue participation based on missed attendance to treatment sessions. There will be no temporary discontinuations from treatment or study participation. The PI may withdraw a patient/parent dyad from the study for one or more of the following reasons:

- Failure to follow instructions of the PI or study staff.
- The PI decides that continued participation would be harmful (e.g., patient reports increased emotional or physical distress from exposure therapy)

Patients and parents will be asked permission to use data collected form the study if they are asked to discontinue or decide to withdraw from the study.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Aim 1a: *To evaluate pain-related fear outcomes between GET Living and TPM. Hypotheses: Compared to TPM, the GET Living group will (1) have significantly less pain-related fear avoidance (adolescent, parent) at discharge, with continued gains at 3 and 6-month follow-up; Exploratory: (2) have fewer number of days to achieve pain-related fear improvement, assessed via daily diaries.*

Aim 1b: *To evaluate disability and parent responses to pain outcomes between GET Living and TPM. Hypotheses: Compared to TPM, adolescents receiving GET Living will have (1) significantly less functional disability and protective parent responses at discharge, with continued gains at 3 and 6-month follow-up; Exploratory: (2) fewer number of days to achieve decreased functional disability and protective parent responses, assessed via daily diaries; (3) significantly better adolescent joint kinetics at discharge, assessed via motion analysis; and (4) demonstrate significantly greater increases in daily physical activity levels at discharge via actigraphy. We will also examine treatment response correlates: age, pain, gender, diagnosis, and readiness to change.*

Aim 1 Analysis Plan. GET Living vs. TPM. Linear mixed effects models will be used to compare GET Living to TPM. The outcome of interest for H_{1a} will be FOPQ-C and PFOPQ total scores. For $H_{1b,}$ outcomes are FDI and ARCS-Protect scores. Exploratory endpoints. Daily Diary (DD): We will use a randomization test (https://tamalkd.shinyapps.io/scda/)[53] to assess the difference between baseline (BAS) to discharge (END) and BAS to 3 and 6-month follow-up (FU)[21,54]. We will also examine at what point during treatment significant improvements occur using delayed effect lags (one effect equals 1 day) until p-value 0.05 is reached. Actigraphy: Actilife software will be used to extract data and calculate mean and peak daily activity. Published data reduction methods will be used[43]. 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 BAS to END will also be examined using DD method. Biomechanical assessment: Full body joint kinematic (motion) and kinetic (force) data will be collected with a 20-camera Vicon system (Centennial, CO, USA) with 5 integrated force plates (Bertec; AMTI). Markers will be placed on each participant according to the 3D Plug In Gait model (Vicon) with data recorded and processed in Nexus 2.6.1. Participants will walk, complete the Star excursion balance test and drop jump task[37,41]. Biomechanical variables (stride length; peak hip and knee extensor moments; peak ankle plantarflexor moment; Star excursion balance score) will be extracted using Event Analyser (Vicon) for error free data reduction. We will model biomechanical variables using mixed 2 (time) x 2 (group) ANOVAs. We will also examine treatment response correlates: age, pain, gender, diagnosis, and readiness to change.

Aim 2: *To characterize feasibility of GET Living to inform implementation of a large multi-site RCT. Hypotheses: GET Living participants will have (1) high treatment satisfaction ratings (mean score ≥ 40 of 60; reflective of satisfied or very satisfied); Secondary: (2) ≥ 80% sessions completed on-schedule, ≤ 20% attrition rate, ≥ 80% adolescent and parent daily diary adherence; Exploratory: (3) fewer health care costs at 3 and 6-month follow-up compared to TPM.*

Aim 2 Analysis Plan. Satisfaction. We will examine mean satisfaction scores. Adherence/Retention. We will examine mean parent and adolescent adherence to daily diary completion, percent of patients who dropout prior to treatment completion, and percent of sessions completed on-schedule. Health care costs. We will examine mean costs across arms at 3 and 6-month follow-up.

9.2 Sample Size and Randomization

We chose the largest feasible study size to obtain as precise estimates as possible of improvement in adolescent disability while ensuring adequate power for the treatment difference in the improvement in adolescent pain-related fear. This gave us a starting total sample size of 74 (37 in each arm). Based on pilot data, we expect roughly 19% attrition during treatment to a total of 60 and further attrition to 58 at end of follow-up.

Power calculations were first performed using the simplified approach of paired t-tests for the change from baseline to 3 and 6-months on those with 3 and 6-months data. For this approach, we used means and standard deviations of observed changes in pilot data. We then simulated data from our analytic model using the standard deviations at each time point and standard deviations of change to calculate correlation and hence the random effect and error variances. The mixed models simulation allowed us to use more data and yielded slightly higher power estimates.

Primary Outcome: In our primary power calculation, we assumed that the improvement in adolescent pain-related fear at 3 and 6-months would be 22.4 in GET Living and 5 in TPM, a difference of 17.4, with a standard deviation for change of 21. Under this scenario we will have power of 87% with 58 (29 in each arm) at end of study. Under more conservative assumptions, we still have power of 80% with only 52 at the end of study and a treatment difference of 16.6. With a smaller standard deviation of 18.9, we will have power of 80% with 50 at end of study and a treatment difference of 15.4.

Other Outcomes: For parent pain-related fear, our estimated treatment difference at 3 and 6-months is 13 with an estimated standard deviation for change of 8.5. This would give us power close to 100% for 58 at end of study and we would still have 90% power with a treatment difference of only 8 and only 50 left at end of study.

For adolescent disability, our estimated treatment effect at 3 and 6-months is 7 with a standard deviation for change of 11.2, yielding power based on the t-test of 65% assuming 58 at end of study. We also created 5000 simulated datasets using a mixed effects model with standard deviations of 11.2 for change and 12.6 at each time point and estimated power by the fraction of simulated datasets in which the treatment difference at 3 and 6-months was significant at level 0.05. This provided a slightly higher power estimate of 67% and an estimated power of 79% if the treatment difference is 8 (1 point larger than expected).

Treatment Assignment Procedures

After a 2-week pre-treatment baseline period, patients will be randomized to either GET Living or TPM and stratified on fear and disability scores (see **Table 6** for scoring criteria). A block

randomization strategy will be used with randomly generated blocks of 2 and 4 to assure near equal distributions across arms and minimize the probability of predicting the next assignment. A randomization spreadsheet with four strata will be created by the study biostatistician, Dr. Derek Boothroyd (please see **Table 5** in section 6.2.2 for fear and disability stratification).

Patients will be randomized by an un-blinded research coordinator or postdoctoral fellow. Those who are randomized to the TPM group can opt to participate in GET Living after their study assessments are complete (6.5 months after baseline). They will no longer be considered a participant of this study at that time.

9.3 Definition of Populations

We do not plan to differentiate ITT and per protocol populations for the analyses.

9.4 Interim Analyses and Stopping Rules

When we reach 50% of our planned sample of treatment completers, we will conduct an interim analysis. The intent of this interim analysis is to implement stopping rules for either overwhelming efficacy or futility.

In order to maintain power at full planned enrollment (in the case that the interim analysis does not stop the study) without adding subjects while also accounting for the additional look at the data, we will use O'Brien-Fleming significance levels (0.0054 for the interim analysis and 0.0492 for the final analysis). For futility, we propose a conditional power approach where we will stop for futility if the conditional power is below 10%. Adding a futility rule for stopping does not require further reduction of significance levels since it decreases the chance of a type I error.

9.5 Outcomes

Please refer to Section 9.1. Analysis and outcomes will be reviewed by PI, Co-Is, and consultants as needed.

9.5.1 Primary Outcome

The primary outcome is pain-related fear (adolescent and parent). This will be measured through the Fear of Pain Questionnaire (FOPQ-C, FOPQ-P) measure collected at Baseline, treatment study Discharge, and 3 and 6-month post-discharge follow-up time points. The Photographs of Daily Activities (PHODA-YE) will also be used to measure pain-related fear outcomes at Baseline and treatment study Discharge.

9.5.2 Secondary Outcomes

The secondary outcome is disability. This will be measured with the Functional Disability Inventory (FDI) measure at Baseline, treatment study Discharge, and 3 and 6-month post-discharge follow-up time points.

9.5.3 Additional Outcomes

Additional outcomes of interest include parent responses to pain and school functioning. These will be collected at Baseline, treatment study Discharge and 3 and 6-month post-discharge follow-up time points with the following measures: Adult responses to Child's Symptoms (ARCS), Helping for Health Inventory (HHI), Parent Psychological Flexibility Questionnaire (PPFQ), Chronic Pain Questionnaire (PPAQ), and Pediatric Quality of Life – School Functioning Subscale (PedsQL).

9.5.4 Exploratory Outcomes

Physical Activity (Actigraphy), Daily Diary (Child and Parent), and Biomechanics (motion analysis) are exploratory outcomes. Actigraphy will be measured during 2-week pre-treatment baseline throughout active treatment. The Daily Diary will be administered for an average of 14 days during the initial baseline period through treatment, and again for 7 days at the 3 and 6-month follow-up time points. Motion analysis will be conducted at Baseline and Discharge sessions.

9.5.5 Feasibility Measures

Feasibility will be measured in terms of treatment satisfaction, acceptability, adherence, fidelity, and healthcare use/cost. Treatment satisfaction will be evaluated by mean satisfaction of the Pain Service Satisfaction Test (PSST)[60] scores completed by child participants in both intervention groups. Treatment Acceptability will be measured by the Treatment Expectancy and Creditability measure (TEC-C, TEC-P)[61], along with exit interviews collected at the discharge session. Adherence and Retention will be examined through mean parent and patient adherence to daily diary completion, percent of patient who drop out prior to treatment completion, and percent of sessions completed on schedule. A trained research assistant will listen to audio/video recordings of treatment sessions and complete treatment fidelity checklists for content and process, for both parents and child sessions (See Supplemental Materials I for checklists). Healthcare use/cost will be measured at the Baseline and 3 and 6-month follow-up time points with the Healthcare Cost Diary[62].

Table 6. Assessment Measures

Outcomes & Correlates	Questionnaires & Tests	DD	Full version
Aim 1			
Primary Outcome			
Pain-related Fear Avoidance	Fear of Pain Questionnaire (FOPQ-C; PFOPQ) FOPQ-C: low [0-34] moderate [35-49] high [50-96]; Photographs of Daily Activities for Youth English (PHODA-YE)	x	BAS, END, FU3, FU6
Secondary Outcome			
Functional Disability	Functional Disability Inventory (FDI) mild [0-12] moderate [13-29] severe [30-60]	x	BAS, END, FU3, FU6
Additional Outcomes			
Protective Behaviors	Adult Responses to Child's Symptoms (ARCS), Helping for Health Inventory (HHI)	x	BAS, END, FU3, FU6
Parent Flexibility	Parent Psychological Flexibility Questionnaire (PPFQ-10)	x	BAS, END, FU3, FU6
Pain Acceptance	Chronic pain acceptance questionnaire (CPAQ-A; PPAQ)	x	BAS, END, FU3, FU6
School Functioning	Pediatric Quality of Life – School Functioning Subscale (PedsQL)		BAS, END, FU3, FU6
Exploratory Outcomes			
Biomechanics	Gait (stride length, velocity), vertical drop landing, dynamic postural control		BAS, END
Physical Activity	Daily mean and peak activity via Actigraphy	x	

Correlates			
Pain Severity	Numerical Rating Scale (NRS)	x	BAS, END, FU3, FU6
Pain Catastrophizing	Pain Catastrophizing Scale (PCS-C, PCS-P)		BAS, END, FU3, FU6
Medical History	Pain Questionnaire: Time since onset, previous treatments (Pain-C, Pain-P)		BAS
Demographics	Age, sex, socioeconomic status (Caregiver History)		BAS
Readiness to change	Pain Stages of Change Questionnaire (PSOCQ-A; PSOCQ-P)		BAS, END, FU3, FU6
Depression	Children's Depression Inventory-2 (CDI-2)		BAS, END, FU3, FU6
Anxiety	Multidimensional Anxiety Scale for Children (MASC)		BAS, END, FU3, FU6
Feasibility Measures			
Treatment Acceptability	Treatment satisfaction (PPST); mean score 40 of 60; satisfied to very satisfied		END, FU3, FU6
Treatment Acceptability	Treatment Expectancy & Credibility (TEC-C; TEC-P);		S1
Treatment Acceptability	% drop-out; Exit Interview (patient/parent feedback)		END
Treatment Adherence	% adherence to daily diary, at-home tasks, sessions completed on-schedule		END
Treatment Fidelity	Process (e.g., reflective listening), Content (session outline adherence)		**
Healthcare Use/Cost	Cost diary		BAS, WK, FU3, FU6

**To be assessed by ongoing coding of audio/video recordings of treatment sessions

BAS=Baseline, DD=Item Generation for Daily Diary; WK= Weekly during treatment, END=End of treatment, FU3=3-month follow-up, FU6=6 month follow-up, S=Session.

9.6 Data Analyses

Our statistician, Derek Boothroyd, PhD, will conduct analyses. Linear mixed effects models will be used for Aim 1. We chose the largest feasible study size to obtain as precise estimates as possible of treatment difference in our primary outcome, adolescent pain-related fear. With a starting sample of 74 (37/37), we expect 58 at follow-up (18% discharge attrition, 5% at 3 and 6-month follow-up). Using GET Living pilot data (see Table 2), we used a mixed model simulation using the standard deviations at each time point and standard deviations of change to calculate correlation and hence the random effect and error variances. In our primary power calculation, we assumed that the improvement in adolescent pain-related fear at 3 and 6-months would be 22.4 in GET Living and 5 in TPM[19], a difference of 17.4, with a standard deviation for change of 21. Under this scenario we will have 87% power with 58 (29 in each arm) at study end. Under more conservative assumptions, we still have power of 80% with only 52 at the end of study and a treatment difference

of 16.6. With a smaller standard deviation of 18.9, we will have power of 80% with 50 at end of study and a treatment difference of 15.4.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

REDCap (Research Electronic Data Capture), the free, secure, HIPAA compliant web-based application, will be used to collect, store, and manage data. Vanderbilt University, with collaboration from a consortium of academic and non-profit institutional partners, has developed this software toolset and workflow methodology for electronic collection and management of research and clinical study data. Data will be maintained in private, non-shared, protected folders stored on central computers at Stanford University School of Medicine. The hospital system provides nightly backup of files stored on its server. Only approved research staff will have access to these files. Identifying information will not be entered or stored on the computer with the behavioral data; thus, all relevant data other than separated consent forms will be de-identified. Documentations of clinical treatment sessions from the Screening and Treatment Delivery team will be collected weekly and stored in a study file for the participant by the study coordinator.

10.2 Data Management

All questionnaire data collected for the study will be exported into SPSS, SAS or R via REDCap. Databases for all data collected for the purposes of this research study will be stored in a password protected SPSS file which only research staff will have access. Datasets related to this clinical trial will only be accessed by Dr. Simons (PI) and research team as needed. The database will be stored on a password protected, secured and encrypted server maintained by Dr. Simons and Stanford University IT.

The Photographs of Daily Activity (PHODA) is a data collection platform that will be maintained by the study coordinator and administered to all patients at baseline and discharge sessions. Biomechanical data and analysis will be collected and maintained by the Motion and Sports Performance Laboratory (MSPL) at SCH and verified by the communications with the study coordinator on a weekly basis.

Actigraphy data will be collected using ActiLife software and maintained by the study coordinator.

Scheduling and enrollment data will be stored in an excel spreadsheet within a PHI-safe folder on Stanford Medicine Box – a secure, HIPAA compliant cloud-based data storage platform.

Treatment session audio/video recordings will be collected digitally and saved on the secure, private drive on the server and only personnel associated with the study will have access to the files. After completion of the study, all audio and video recordings will be destroyed.

10.3 Quality Assurance

10.3.1 Training

All staff will complete the human participants protection training required by Stanford University. The University uses the "CITI" training program (Collaborative Institutional Training Initiative; https://www.citiprogram.org/). All staff must pass required tests on each module. A refresher course must be passed every 24 months.

Per NIH requirements, all staff will be trained in Good Clinical Practice (GCP), consistent with

principles of the International Conference on Harmonisation (ICH) E6 (R2). The research coordinator will be responsible for maintaining documentation of all CITI and GCP training certifications.

An outpatient team consisting of a pain psychology therapist (PSY) and physical therapist (PT) provide GET Living treatment, both trained in this modality of treatment by Laura Simons, PhD with ongoing consultation from Johan Vlaeyen, PhD (lead innovator of GET in adults) and Rikard Wicksell (lead innovator in CBT and ACT in adolescent chronic pain). Training for GET Living will involve outpatient team being exposed to treatment session videos from pilot patients (n=16).

10.3.2 Quality Control Committee

The PI and research coordinator will be hold primary responsibility for study data quality control. To address quality control methods, chart data will utilize standardized collection forms. For data entry of study information, a portion of files will be re-entered by a separate person, to check for consistency. If consistency is low, the entire data set will be re-entered.

10.3.3 Metrics

All self-report outcome measures have demonstrated psychometric soundness, including reliability and validity.

10.3.4 Protocol Deviations

Each protocol deviation (PD) will be captured and documented, by participant, in the Protocol Deviation Tracking Log eCRF (MOOP Appendix E). All PDs will be collated and reviewed by the research coordinator and study PI.

A major protocol deviation or violation includes any procedure that differs from the IRB-approved protocol that was intended to eliminate an immediate hazard to the participant, was harmful, or is possible serious or continue non-compliance by a study staff member.

Major protocol deviations will be communicated to the PI immediately. All events will be communicated to the NIAMS (through KAI) within 48 hours of the PI becoming aware of the event.

Protocol deviations/violations that occur but do not affect participant safety will be submitted as part of the quarterly reports distributed to the SMC and subsequently shared with the NIAMS.

10.3.5 Monitoring

The study will be monitored by the research coordinator regularly throughout the collection of data. Oversight of this clinical trial is provided by the Principal Investigator (PI), Dr. Simons and a Study Monitoring Committee (see section 7.6).

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (MOOP Supplemental Materials II) and any subsequent modifications will be reviewed and approved by the Stanford IRB responsible for oversight of the study.

11.2 Informed Consent Forms

A signed consent form will be obtained from each parent participant, and a signed assent form for each child participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g., person with power of attorney), this individual must sign the consent form. The

consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIAMS, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIAMS, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

Steering committee – Study PI, Co-Investigators, and Research Coordinator for this study will meet monthly to discuss study progress relative to milestones, coordinate efforts, and review any protocol deviations or other issues requiring adjustment.

Safety Monitoring Committee – The Study PI and Study Monitoring Committee (Section 7.6) will meet quarterly to review study accrual, status of enrollment, adherence to data regarding study visit and intervention, and adverse events.

13. PUBLICATION OF RESEARCH FINDINGS

As an NIH-funded Clinical Trial this study will be registered at, and will submit summary results information to, ClinicalTrials.gov for public posting. Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee.

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