Agile Development of a Digital Exposure Treatment for Youth with Chronic Musculoskeletal Pain

Study Protocol and Statistical Analysis Plan

NCT05079984

October 6, 2020

RESEARCH STRATEGY

Significance

Chronic musculoskeletal (MSK) pain affects the lives of over a quarter of youth[1 2 15], with societal costs exceeding $19.5 billion dollars in the U.S. each year[4]. Chronic MSK pain in childhood predicts symptom continuity across the life span[5] and is a documented risk for opioid misuse, the effects of which have been deemed a public health crisis[6]. Further, chronic MSK pain impacts multiple domains including social, emotional, and behavioral functioning, and negatively impacts parent and family functining[16-18]. **Particularly, pain-related fear and avoidance of activities** negatively impact pain outcomes for youth and significantly interfere with treatment engagement (e.g., pain coping, physical therapy)[19 20]. This results in **continued high healthcare utilization without symptomatic improvement**[21] and highlights the need for an interdisciplinary treatment approach that targets pain-related fear and physical activity[21-24]. While a recent review supports such behavioral health interventions for youth with chronic pain[21], accessibility is undermined by a shortage of services outside of urban areas, significant treatment-related costs, and long provider waitlists[4 7]. These barriers underscore the critical need to develop digitally delivered behavioral interventions for youth with MSK pain, drastically increasing the reach of these interventions. Graded exposure[10] is a theoretically-driven[11] (**Figure 1**), individually-tailored, and evidence-based[12-14] behavioral intervention for individuals with chronic pain. Graded exposure targets pain-related impairment by exposing patients to previously feared and avoided activities. *Having adapted an interdisciplinary outpatient graded exposure intervention into a prototype digital solution (iGET Living), this proposal seeks to further develop and evaluate the feasibility and preliminary effectiveness of iGET Living in adolescents with chronic MSK pain. The proposal incorporates a sequential, replicated, randomized single-case experimental design (SCED) to support a rapid and agile development process coupled with innovative methods for remote biomechanical assessment and daily physical activity monitoring.*

Scientific premise for graded exposure treatment. Functional improvement is the ultimate goal of pain management, and decades of science demonstrates that pain-related fear and avoidance are critical barriers to functional recovery[10-12 14 19 20 25 26]. Exposure-based treatment has robust effect sizes in adults[12] and our group has demonstrated these same outcomes among adolescents (GET Living[14]). GET Living is jointly delivered by a psychologist and physical therapist, adding to the emerging evidence base for the feasibility and efficacy of interdisciplinary interventions delivered at the outpatient level of care[13 27 28]. Dissemination of GET Living would be drastically enhanced by digitization.

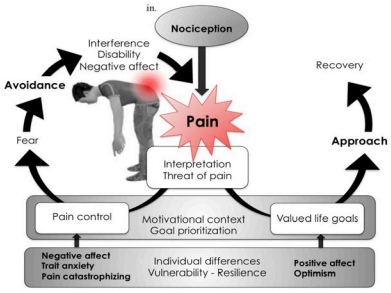


Figure 1: Fear Avoidance Model

Scientific premise for the agile development of a digital solution utilizing SCED methodology. There is a substantive collection of high-quality behavioral health interventions that have been digitalized, with similar outcomes for digital interventions for youth with chronic pain compared to conventional in-vivo treatment[29]. Despite great potential and the proliferation of research[30-40], only 28% of Internet or smartphone application tools are disseminated adequately or timely, leading to suboptimal health care innovation and significant research waste[41]. Digital health interventions developed within academia are theory-driven and evaluated scientifically[42], but methods such as RCTs are time-consuming and costly, often preventing rapid dissemination and implementation in health care. This highlights the inflexibility of the academic approach compared to industry development, which utilizes repeated, rapid cycles of fine-tuning based on user feedback[43]. However, most digital health interventions developed within industry lack theory-based strategies known to drive behavior change[44-46], evidence-based content[47-50], and systematic efficacy testing[51]. SCEDs are experimental designs aimed at testing the effect of an intervention using a small number of patients (also termed N=1 trials[52 53]), using repeated measures, sequential randomized introduction of an intervention, and method-specific data analysis[53]. SCED provides the opportunity to rapidly and pragmatically evaluate treatment effectiveness in small cohorts[54 55], making it ideally suited for the agile development process of digital interventions. Further, digital solutions provide the opportunity to collect large amounts of individual data on a continuous basis, pairing well with SCED analytic methods[56 57]. To bridge the gap between academia and industry, the current study leverages the mHealth Agile Development and Lifecycles model[3] utilizing SCED methodology.

Scientific premise for remote biomechanical assessment and physical activity monitoring within a digital solution. Adolescents with diffuse MSK pain demonstrate greater variability in lower extremity mechanics during gait assessment and drop landing[58], as well as lower mean and peak activity levels compared to healthy controls[59]. Musculoskeletal modeling and dynamic simulation have emerged as powerful tools to uncover the biomechanical causes of movement abnormalities and to design improved treatments. Incorporating innovative remote biomechanical assessment derived from 2D video combined a digital intervention focused on improving functioning will provide objective data related to physical functioning and activity across time points. Not only will

these data provide insight to improvements in kinesthetics at post-intervention and be used to evaluate the effectiveness of the intervention, but assessment of biomechanical functioning prior to and during the intervention could also help inform treatment targets within the context of active treatment.

Innovation

This proposal outlines the agile development of *iGET Living*, a graded exposure intervention for youth with chronic MSK pain incorporating aspects of behavioral psychology and physical therapy delivered via a digital solution. The development of iGET Living will enhance dissemination of exposure-based treatment, providing a low-burden interdisciplinary intervention known to improve functional outcomes within this population. This application shifts current research and clinical practice in three ways: **(1) Harnessing digital solutions for innovative assessment and intervention.** Consistent with the tenants of a precision medicine approach, the development of efficient and effective targeted treatments is critical, with its success contingent on the collection of data across domains. Digital health has the potential to integrally contribute to both data collection and intervention and is at the core of the current proposal. **(2) Utilizing the mHealth Agile Development and Lifecycle model[3]** to combine the rapid, iterative development process used in industry with behavioral change theories of academia to produce a useable, efficacious, widely disseminated digital solution. Per NIH reports, it is estimated that over $2.8 billion federally funded dollars have been invested in pain research over the last 5 years, of which millions of dollars have been awarded to develop digital behavioral interventions. Despite this proliferation, time-and-cost barriers exist and prevent theory-driven, efficacious, interventions from rapid development and dissemination. This project seeks to overcome this barrier by applying the Agile mHealth Lifestyle Developmental model to the development of our digital intervention. Agile research methods will allow for a rapid, iterative development and evaluation of the intervention, yielding a clinically useful, evidence-based digital solution. **(3) Innovative methods for remote biomechanical assessment and daily physical activity monitoring.** Purposefully capturing objective data (kinematics, actigraphy) will inform clinical decision-making and support tailored, point of care decisions that result in science-forward, targeted, and effective interventions.

Approach

Preliminary Studies. My prior research experience, along with the expertise of my mentorship committee and ease of access to required tools and techniques at Stanford University, provide an ideal foundation for successful execution of this proposal. This section summarizes preliminary data building toward the current proposal.

Digital Behavioral interventions are effective for adults and youth with chronic pain. **Advisor Dr. Wicksell** and his team at Karolinska Institutet have developed Acceptance and Commitment Therapy (ACT) interventions for adults and youth with chronic pain. An internet version (iACT) demonstrated acceptability and feasibility in reducing pain interference for adults with chronic pain. Utilizing the mHealth Agile Development & Evaluation Lifecycle model[3], iACT was refined into a smartphone-based intervention (ACTsmart)[60]. ACTsmart showed equally strong effects sizes (pain interference, *d*=1.01) up to 12-months after treatment. ACTsmart was modified for youth with an added parent component[61 62]. Pilot results for adolescents with chronic pain (*n*=29) demonstrated strong effects for adolescent pain interference (*d*=1.034) and parent pain reactivity (*d = 0.70)*[61]. *Taken together, these studies provide support for digitally delivered behavioral interventions for chronic pain and demonstrate specialized expertise on my advisory team.*

Intervention underlying iGET Living is effective. The proposed digital intervention (iGET Living) is based on in-person graded exposure treatment for youth with chronic pain (entitled GET Living). Large effects for functional disability (partial η^2=0.53), school functioning (partial η^2=0.46), pain-related fear (partial η^2= 0.29), and avoidance (partial η^2 = 0.47) were observed[14]. Moreover, SCED results demonstrate GET Living effectiveness on fear, avoidance, catastrophizing, acceptance, and pain that maintain over time (case example in **Figure 2**)[14]. GET Living is currently being evaluated in a two-arm RCT led by my co-mentor **Dr. Simons** at the Pediatric Pain Management Clinic (PPMC) at Stanford Children's Health (SCH)[63].

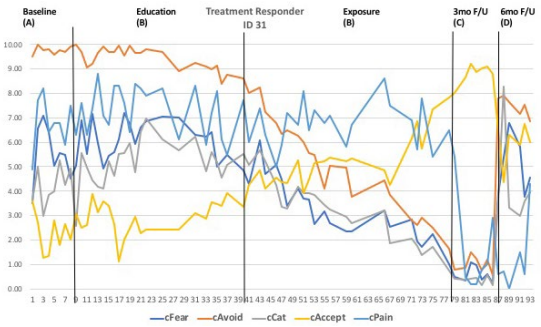


Figure 2. Daily diary example baseline to follow-up.

GET Living delivered via Telehealth supports remote enrollment, biomechanical assessment, and treatment delivery (Shear, Harrison, et al., *in preparation*)**.** The COVID-19 pandemic required swift adaptation to remote recruitment, assessment, and treatment delivery of our RCT[13]. All active patients transitioned to telehealth with the added benefit of remote treatment increasing access. The Motion and Sports Performance Lab (MASPL) at SCH created a remote biomechanical assessment (6 Minute Walk Test, single-leg squat, double-

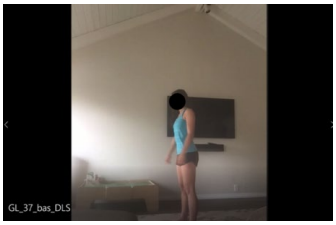


Figure 3a. Zoom Video squat task.

leg squat) conducted via Zoom (baseline and discharge). Participants stand such that the camera has a sagittal view (**Figure 3a**). The video data is exported to MaxTraq 2.0 (Innovation Systems, Columbiaville, MI) for data processing (**Figure 3b**). Unique to GET Living is the focus on activity exposures, which are enhanced in the virtual format as patients now complete exposures in their home environment (vs. a rehabilitation gym), allowing for guided practice of activities within their daily environment (e.g., completing chores, riding bike, going on hike with a dog). *These data demonstrate the feasibility of remote delivery of exposure treatment, remote assessment biomechanical outcomes and provide guidance to enhance assessment and treatment via a digital solution.*

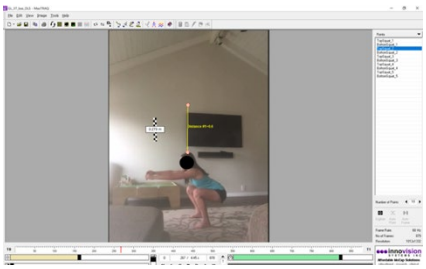


Figure 3b. Squat task in MaxTraq 2.0.

A digital prototype of iGET Living demonstrates preliminary acceptability. With funding from the Drotar-Crawford Postdoctoral Fellow Research grant, I developed an alpha version of iGET Living. iGET Living extracts fundamental concepts from GET Living, integrates audio files and animations, and restructures content for daily (vs. bi-weekly) engagement. Initial cognitive interviews conducted with a mix of teens with pain and no pain (*N*=6; 50% female, ages 10-14) provided module-by-module feedback assessing acceptability, clarity, and satisfaction. After viewing all of the content, participants reported e.g. "[it's a] tool for kids struggling with chronic pain to learn to live with it and work through it and finally be able to do the things they haven't been able to do in a long time" and "[the purpose is] to give people a higher quality of life without having pain get in the way." After each module, participants were also asked about changes or improvements, resulting in suggestions to tailor the content by age groups (e.g., 10-13 and 14-17). Also, a majority of the comments focused on improving interactivity of the content and enhancing visual aesthetics. These user experience data support preliminary acceptability of the iGET Living content as well as the feasibility of the user-centered focus groups and will be used to inform the further development and alpha testing of the treatment content. *Results from this preliminary alpha testing warrant the proposed study aimed to further develop systematically evaluate the feasibility and preliminary effectiveness of iGET Living in adolescents with chronic MSK pain utilizing a SCED. Our track record of productive research collaborations, capacity to leverage resources, and successful execution of NIH-funded studies makes this team and the Stanford University environment ideal.*

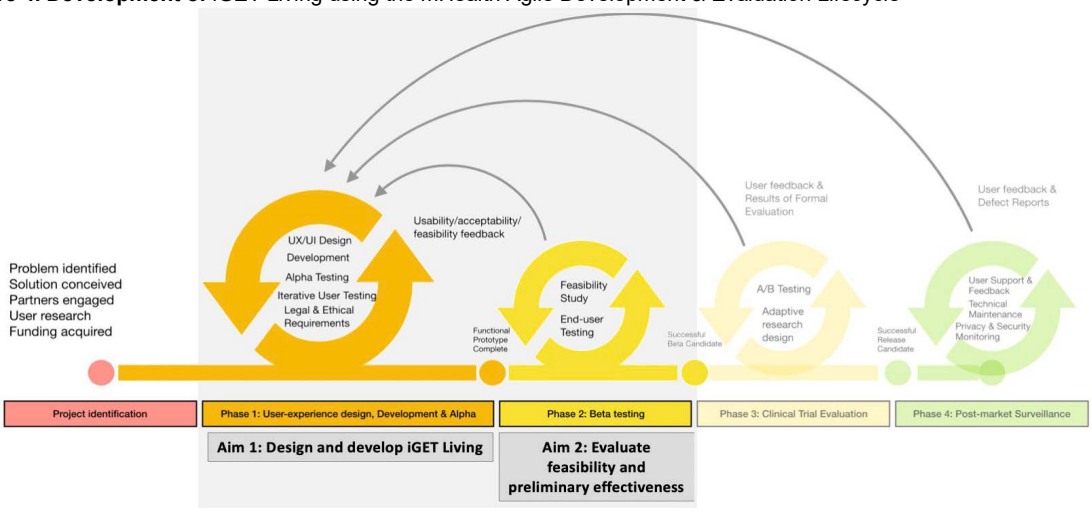
Proposed Intervention

iGET Living is structured to be completed in roughly 6-weeks. Youth content is organized into 30 separate sessions, each lasting 15 minutes or less, with patients completing ~five sessions per week. Week 1 is focused on pain education and an introduction to skills will be used during the program (e.g., goal setting, exposures). Weeks 2-5 are structured similarly and focus on values-based goal setting and activity exposures. Week 6 reviews progress and plans for long-term success. The prototype of iGET Living is built on a secure flexible platform that can be used on any device, including smartphone (BASS4; https://ki.se/en/research/internet-delivered-interventions). BASS4 is available through the KI e-Health Core Facility who provides maintenance and technical support and has been successfully used for other internet-based behavioral interventions with adolescents and adults, including iACT[64-66]. Parent content will be developed and refined as part of this project.

Study Overview

The overall objective is to develop a digital solution that is user-friendly, flexible, effective, accepted by the users, solicits retention, and is designed for continuous data collection. Focusing on Phase 1 (**Aim 1**) and Phase 2 (**Aim 2**) of the mHealth Agile Development & Evaluation Lifecycle (**Figure 4**) will promote continuous development, fine-tuning of treatment content, and data driven decision-making during development[3 60]. Development of the digital solution will be based on a series of short iterations, with

Figure 4. Development of iGET Living using the mHealth Agile Development & Evaluation Lifecycle[3]



alpha testing (**Aim 1**) on a small sample of end-users followed by multiple re-iterations and re-testing. After this, beta testing (**Aim 2**) will involve a sample of naïve end-users. Successful execution will allow us to scientifically evaluate and optimize iGET Living to make it a clinical trial ready solution for a future R21 submission.

Methods

Participant Recruitment. Patients evaluated in the PPMC and a primary caregiver will be recruited. ***Inclusion criteria***: (1) youth 10-18 years old; (2) have a diagnosis of chronic MSK pain (>3 months); (2) have moderate to high pain interference (PROMIS Pain Interference[67] ≥ 61); (3) English literate; and (4) have access to a computer, smartphone, or tablet with internet connection. ***Exclusion criteria:*** (1) significant cognitive impairment (e.g., brain injury); (2) significant medical or psychiatric problems that would interfere with treatment (e.g., seizures, psychosis, suicidality). ***Recruitment:*** All patients presenting to the PPMC complete Peds-CHOIR[68] and indicate if they would like to participate in research. More than 650 patients have expressed interest in research, with the database continually growing with ~ 300 new patient evaluations conducted each year. Dr. Simons has extensive experience leveraging this registry for recruitment, which will easily support recruitment goals of *n* = 15 (**Aim 1)** and *n* = 20 (**Aim 2**). Patients and their parent who meet eligibility criteria will receive a recruitment phone call from a research assistant to introduce the study and confirm eligibility (patients may only enroll in one phase). Clinicians (*n*=15) will be recruited via emailed announcements to relevant listservs (e.g., the Society of Pediatric Psychology, Pediatric Pain Special Interest Group, the International Society for Pediatrics Pain) and through Dr. Simons' collaborators and contacts. Experts will have 1) specialized training in chronic pain in adolescents, 2) may have experience in development of digital solutions for pediatric populations, and 3) hold faculty positions at universities or medical centers that house pain treatment clinics. ***Incentive***: Aim 1: youth participants (n = 15) will receive a $[redacted] Amazon gift code for up to 3-hours of qualitative data collection (user feedback interviews). Aim 2: youth participants (*n* = 20) will receive $[redacted] gift codes at baseline, discharge, and $[redacted] gift codes at 3-month follow up. **Power Considerations:** This study uses SCED, therefore traditional power and sample size considerations do not apply. The design of this study was based on previous work done in adults (n= 6[12]; n=8[69] [70]) with chronic pain applying the same treatment approach and study design. We aim to recruit 20 participants for aim 2 to ensure adequate sample size and sufficient feasibility data.

Measures. All measures utilized in this study have established reliability and validity (**Table 1**). The Qualitative Interview for stakeholders is a standardized, semi-structured interview developed by this team to elicit qualitative and quantitative feedback that will be analyzed and used to modify intervention content. ***Daily Measures.*** Daily Diaries will be delivered to the adolescent and parent to assess outcomes within the last 24-hours[14]. ***Nondaily Measures.*** Full versions of the measures will be completed at baseline, discharge, and 3-month follow-up.

Table 1

Outcomes & Correlates	Questionnaires & Tests	DD	Full version
Aim 1			
Acceptability	Qualitative Interview+		
Aim 2a			
Treatment Satisfaction	Treatment satisfaction[71]; mean score ≥ 40 of 60; satisfied to very satisfied		END, FU
Treatment Acceptability	Treatment expectancy & credibility[72]; % drop-out; Feedback from stakeholder interview (e.g., *patients, parents, clinicians)*		BAS, END, FU
Treatment Adherence	% adherence to daily diary, modules completed, # of messages to the therapist		END
Aim 2b			
Primary Outcome: Functional Disability			
Functional Disability	Functional Disability Inventory (FDI)[73]	x	BAS, END, FU
Secondary Outcomes: Pain-related distress and behavior			
Pain-related distress	Fear of Pain Questionnaire, child report, short form (FOPQ-C[74]); Parent Fear of Pain Questionnaire (PFOPQ)[18]; Pain Catastrophizing Scale (PSC-C[75]; PSC-P[17])	x	BAS, END, FU
Psychological Flexibility	Chronic Pain Acceptance Questionnaire for Adolescents (CPAQ-A8)[76]; Parent Psychological Flexibility Questionnaire[77]	x	BAS, END, FU
Protective Behaviors	Adult Responses to Child's Symptoms (ARCS)[78]	x	BAS, END, FU
Correlates			
Pain Severity	Numerical Rating Scale (NRS)[79]	x	BAS, END, FU
Medical History	Time since onset, previous treatments		BAS
Demographics	Age, sex, socioeconomic status		BAS
Exploratory			
Biomechanics	Gait (stride length, velocity)[58]; dynamic postural control[80]		BAS, END
Physical Activity	Daily mean and peak activity via Actigraphy[59]	x	

Note: DD = Daily Diary; BAS=baseline; TX = once weekly, during treatment; END=Discharge; FU = 3-month follow up; + = during viewing of content

Aim 1: Design and develop iGET Living for adolescents with chronic pain and their parents.

Aim 1 Procedures. Utilizing the mHealth Agile Development & Evaluation Lifestyle model, the Alpha test phase will elicit stakeholder feedback (experts and patients) to inform an iterative, user-centered development process. *Patient and parent feedback*: Patient and parent feedback sessions will be conducted remotely via Zoom, independent of each other, and will utilize best practices for qualitative and cognitive interviewing for research[39]

[40 81] (*Goal 5 of Training Plan*). Consent and assent will be obtained via REDCap. Each patient will be given a log-in and password enabling them to access the BASS4 platform. Youth will pilot various functions (e.g., audio files). The time taken to complete each module will be recorded. While viewing treatment content, they will be prompted to think aloud about likes, dislikes, and difficulties with the content. Likert-scale-rated and open-ended questions related to acceptability, ease of use, comprehensibility, and suggestions for improvement will also be administered. Questions will be asked after each module, as well as at the conclusion of viewing all of the content. All interviews will be recorded and transcribed. Usability testing sessions will continue until data saturation is reached (i.e., no data are generated that have not already been categorized). Once data saturation is reached, all usability issues from a single iterative cycle will be considered to have been identified[82 83], and iGET Living content will be modified accordingly. *Clinician Feedback*: Clinicians will be given user- and provider-facing access to the platform. Data will be captured via numeric ratings assessing preference and acceptability of materials, as well as typed responses to standardized, open-ended questions administered online via REDCap. Specific data on how providers would integrate into practice, who they would refer, and potential barriers will also be collected[84]. *Sample Size considerations*: Review of the literature and previously conducted usability testing studies indicates that prototype refinement is typically achieved within 2 to 3 cycles of testing[82 83]. Additionally, data saturation can usually be reached with samples as small as 5 to 7 participants per usability cycle[85]. Therefore, we aim to recruit 15 adolescents ages 10-18 years for 2 to 3 cycles of usability testing.

Aim 1 Analysis Plan. *In an iterative process with a user-experience design, we will collect data on comprehensiveness and acceptability of treatment content and structure during qualitative interviews from patients (n = 15), parents (n = 15), and clinicians (n = 15) to refine the digital solution. Data collection will proceed in iterations of n = 5 until the goal is met.* **Hypothesis:** Patients and parents will rate iGET Living as satisfactory and easy to use, and user insights will provide guide further development and improvements to optimize clarity and user friendliness. *Qualitative data extraction*: All video recorded interviews will be transcribed verbatim. Transcripts (audio and typed feedback) will be uploaded into NVivo 12. Framework matrix analysis will categorize emergent themes, yielding specific, recurring information. Modifications to content will be made after each iterative cycle of testing, guided by **Drs. Wicksell and Stinson**, who have extensive experience in user-centered design and development. Developing expertise in qualitative methods will be supported by **Dr. Stinson**. *Quantitative analyses*: Descriptive statistics will be used to examine Likert-scale ratings of acceptability.

Aim 2. Evaluate feasibility and preliminary effectiveness of iGET Living.

Aim 2 Procedures. Patients and parents recruited for this Beta-testing phase will complete a remote baseline study visit with a research assistant via Zoom. Prior to the baseline visit, an Actigraph will be mailed to each participant via USPS priority mail, and they will be instructed to begin wearing the device immediately following their remote baseline visit. *Baseline:* Consent, assent, and self-report measures will be collected via REDCap, and youth will complete a remote biomechanical assessment (iWalkAssess, 2D video). Patients will be randomly assigned to a baseline (BAS) period of 10-21 days, after which the patient begins the intervention. On the day they are scheduled to begin the intervention, the patient will be provided with a username, password, and hyperlink which will be used to access the BASS platform. *Intervention:* Patients are encouraged to engage with the program daily. Each daily module should take no more than 15 minutes to complete. Parents also receive their own login, which allows them to access parent-only modules. *Discharge:* At the end of treatment, the patient and parent will attend a discharge visit via Zoom, complete an exit interview and biomechanical assessment, and complete measures via REDCap. Daily Diaries are discontinued at this time and they will be provided with instructions and materials for returning the Actigraph. *Follow-up:* All non-daily assessments will be administered again at 3-month follow-up. Youth and parent will complete the daily diaries for a 7-day period.

Aim 2 Analysis Plan. Aim 2a Feasibility. *We will determine (a) feasibility of smartphone treatment delivery and daily assessment of youth and parents, (b) acceptability of iGET Living as indicated by retention rates, treatment satisfaction ratings, and interviews with stakeholders (patients, parents, providers) and (c) rates of adherence to daily diaries and iGET Living modules.* **Hypotheses:** iGET Living participants will have (1) high treatment satisfaction ratings (mean score $\geq$ 40 of 60; reflective of satisfied or very satisfied), (2) $\geq$ 80% of modules completed, (3) $\leq$ 20% attrition rate, (4) $\geq$ 80% daily diary adherence. **Analysis Plan:** We will examine mean treatment expectancy, credibility and satisfaction scores, and patient dropout percentage. For adherence, we will examine mean adolescent and parent daily diary completion and treatment module completion.

Aim 2b Preliminary Effectiveness. *We will examine (a) SCED effect sizes for changes from baseline to treatment phases and time to improvement via daily diaries, (b) response rate on measures of functional disability and pain-related distress (>30% improvement from baseline), and (c) maintenance of gains at 3-month follow-up.* **Hypotheses:** iGET Living will be superior to a (no treatment) baseline phase, with improvements in daily diary and measures of functional disability and pain-related distress. **Analysis Plan:** *Daily Diaries*: We will

present descriptive and model-based inference analyses, based on single-case reporting guidelines[86] and recommendations for reporting on several replicated SCED cases[57 87]. Using the Shiny app for Single-Case Data Analysis[88], we will calculate effect sizes for each individual on each outcome comparing phases (AB, BC, AC, where A = Baseline, B = Treatment, C = 3-month follow-up) using the non-overlap of all pairs (NAP) test statistic. *Non-daily measures*: Criterion of 30% improvement from BAS will be considered clinically significant change[14]. Developing expertise in SCED analyses will be supported by **Dr. Boothroyd**. **Exploratory Hypotheses:** Patients will demonstrate (1) improvement in joint biomechanics at discharge, assessed via 2D video; and (2) increased daily physical activity levels at discharge via actigraphy. **Analyses.** *Actigraphy:* Actilife software will be used to extract data using published data reduction methods[59]. We will model physical activity (mean, peak) at two time points using mixed ANOVAs. Rate of change in physical activity from A to B will also be examined using daily diary method. *Remote biomechanical assessment*: assessment of physical functioning will include stride length, peak hip and knee extensor moments, peak ankle plantar-flexor moment, and balance will be collected via wearable sensors and video. 2D Video data is extracted from the remote biomechanical session and analyzed using MaxTraq 2.0 and OpenPose[89]. We model biomechanical variables using mixed ANOVAs. If biomechanical variables differ by pain site (upper, trunk, lower, diffuse) this will be included as a covariate. We will examine correlates: age, pain, gender, diagnosis, physical activity. Developing expertise with remote biomechanical assessment and analysis will be supported by **Dr. Delp.**

Potential Problems and Solutions.

Monitoring adverse events (AE). Oversight of this study will be provided by the PI, **Dr. Lauren Harrison**. Study conduct (i.e., accrual, drop-outs, protocol modifications, protocol deviations) will be reviewed on a quarterly basis. Adverse events will be reviewed in real-time and in aggregate on a monthly basis (see Data Safety Monitoring Plan in Human Subjects documentation). **Consistent engagement with the content.** Extensive support will also be provided during the onboarding phase to ensure families are able to access the intervention. If a participant displays difficulty with daily engagement (2+ days no progress), the provider will reach out to the family via the messaging feature in the platform and problem-solve barriers to engagement. **Patient engagement in co-occurring treatments.** We will recommend that patients not start any new treatment or intervention (including medications) while enrolled in iGET Living. In order to track this more systematically, we will have parents complete a weekly healthcare cost diary[90], which will allow us to track other healthcare utilized (e.g., physical therapy, massage) and other costs associated with healthcare (e.g., money spent on gas to travel to and from other appointments) that the patient engaged in over the previous week. **Technology issues with the software.** The KI e-Health Core Facility provides maintenance and technical support should technical issues, malfunctions, and/or glitches occur in the iGET Living software over the course of this trial.

Implications, Dissemination Plan, and Future Directions

This proposal outlines the development of an innovative, digital exposure intervention for youth with chronic MSK pain (iGET Living). Based on key findings of feasibility and preliminary effectiveness, an Exploratory Clinical Trial (R21) grant application will be submitted to NIAMS mid-Year 4. The R21 will allow for evaluation of iGET Living as an exploratory RCT, providing data for a more robust clinical trial. Ultimately, we believe that iGET Living could significantly improve functioning in youth with chronic MSK pain and greatly reduce barriers to treatment access. Long-term efforts will seek to test the intervention across developmental groups. The career award will establish a strong foundation to support my goal of developing an independent, extramurally-funded, line of research harnessing the *agile development of effective digital behavioral solutions that can be widely disseminated and integrated into healthcare, optimizing nonpharmacologic management of MSK pain in youth.*

Timeline and Milestones

Regulatory Approval: Y1 Q2. *First Subject Enrollment:* Y1 Q2(Aim 1), Y2 Q3(Aim 2). *Complete Primary and Secondary Endpoint Analysis*. Y4 Q3. SCED analysis when each patient discharges. *Grant submission*. Y4 Q4.

Table 2. Project Timeline and Milestones

		Year 1				Year 2				Year 3				Year 4				Year 5			
	Quarter	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Aim 1	Submit IRB and Study Start-up																				
	Recruitment & Enrollment																				
	Focus groups & Iterative refinement																				
	Abstract & manuscript prep																				
Aim 2	IRB & study prep																				
	Recruitment & Enrollment																				
	iGET Living BL +Treatment																				
	3-month follow-up																				
	Data analysis																				
	Abstract & Manuscript prep																				
	R21 plan, write, revisions																				