Study Protocol

Title: Building Adaptive Coping and Knowledge to Improve Daily Life (Back2Life): A Pilot Feasibility Clinical Trial for Youth With Chronic Sickle Cell Pain

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
V. 2	5-11-20	Misc. details for IRB submission
V. 3	6-9-20	Clarification regarding the use of verbal consenting, clarification regarding subject recruitment, changes to participant compensation, updated version and date, added study team info
V.4	8-17-21	Addition of opt-in portion of the study involving blood sample to coincide with assessment time points

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1.0 Study Summary

Study Title	Building Adaptive Coping and Knowledge to Improve Daily Life (Back2Life): A Pilot Feasibility Clinical Trial for Youth with Chronic Sickle Cell Pain
Study Design	Single-Arm, Uncontrolled Behavioral Clinical Trial
Primary Objective	Conduct a pilot proof-of-concept clinical trial to evaluate the feasibility, acceptability, and preliminary efficacy of Back2Life with youth with chronic SCD pain and their parents
Secondary Objective(s)	Refine intervention content and delivery based on participant qualitative feedback; Evaluate a biological response to intervention
Research Intervention(s)/Interactions	The treatment program includes 6-sessions of standard cognitive-behavioral therapy (CBT) treatment (delivered to all participants) and 1-4 tailored sessions to address common co-morbidities associated with chronic pain (sessions assigned based on results of baseline assessment). The treatment manual leverages existing evidence-based interventions into a treatment package that will be tailored to individual patient and family needs.
Study Population	Children with sickle cell disease (SCD) aged 10-18 years old and their parent(s)
Sample Size	25 parent-child dyads
Study Duration for individual participants	8 months
Study Specific Abbreviations/ Definitions	Back2Life: Building Adaptive Coping and Knowledge To improve daily Life CBT: cognitive-behavioral therapy
Funding Source (if any)	NHLBI

2.0 Objectives*

2.1 Primary Aim: Conduct a pilot proof-of-concept clinical trial to evaluate the feasibility, acceptability, and preliminary efficacy of Back2Life with youth with chronic SCD pain and their parents (n=25). We will use an adaptive treatment approach with 6-10 module-based treatment sessions selected on the

basis of baseline assessment (rather than a fixed treatment approach) to allow flexibility in tailoring treatment components to meet individual family needs.

2.2 Hypothesis 1: It is expected that the Back2Life treatment program will be feasible and acceptable as demonstrated by high levels of treatment engagement (≥80% attendance of treatment sessions) and high ratings of treatment satisfaction.

2.3 Hypothesis 2: Participants who complete the Back2Life treatment program will report reductions in pain interference and pain symptoms (intensity and frequency) at post-treatment and 6-month follow-up. Preliminary efficacy will be defined as clinically significant (≥30%) reductions in pain interference and pain.

2.4 Exploratory hypothesis 1: We will explore reductions in secondary outcomes related to healthcare use for pain (inpatient hospitalizations, ED visits, and opioid use) at 6-month follow-up.

2.5 Exploratory hypothesis 2: The Back2Life treatment program will result in measurable reductions in inflammatory biomarkers from baseline to 3-month and 6-month follow-up.

3.0 Background*

3.1 Pediatric sickle cell disease (SCD) is a genetic disorder of the hemoglobin in which the course of acute pain from vaso-occlusion and its sequelae vary widely across genotypes and individual patients. SCD pain often begins during childhood and can progress to chronic pain for approximately 23% of children and adolescents1. Youth with chronic SCD pain, that is pain that is present on most days per month and persists for at least 6 months2, report high levels of functional disability, elevated depressive and anxiety symptoms, and reduced quality of life relative to youth with SCD without chronic pain1. The complex, multifactorial nature of chronic SCD pain can also contribute to increased healthcare utilization for pain1,3-5. The most effective management and treatment of chronic SCD pain likely requires individualized, multimodal, multidisciplinary treatments that go beyond pharmacological management alone6. A range of evidence-based non-pharmacological treatments, such as behavioral health, complementary, and integrative health approaches, are recommended for chronic pain management and are gaining greater awareness and integration into comprehensive chronic pain care6,7)

3.2 Behavioral health treatment, such as cognitive-behavioral therapy (CBT) for pain, focuses on improved daily functioning and coping through several core treatment components such as psychoeducation about how the body processes pain, relaxation skills training, and cognitive strategies8. CBT is effective for youth with a variety of chronic pain conditions, including chronic headache, recurrent abdominal pain, fibromyalgia, and recurrent sickle cell pain, in reducing pain intensity immediately following treatment and reducing pain-related

disability post-treatment and up to 12 months later9. CBT has been shown to reduce proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), interleukin-1β (IL-1 β), and interleukin-6 (IL-6), in adult patients with stroke, cardiovascular disease, cancer, depression, and anxiety. Interventions that reduce inflammation are especially needed for youth with SCD, for whom the propagation of inflammatory activity is a central mechanism that triggers vaso-occlusive episodes and long-term disease complications, such as organ damage. The few existing randomized clinical trials (RCTs) of CBT for acute or recurrent SCD pain in pediatrics are primarily limited by small sample sizes, poor treatment engagement, and inadequate randomization, stratification, or blinding; further, no clinical trials have yet to specifically target chronic SCD pain10.

3.3 Youth with chronic SCD pain need an evidence-based, culturally informed, adaptive treatment. Behavioral treatments that are tailored to patient and family needs are beneficial when patients may require different levels of care11. Tailored or adaptive treatments align with a stepped care model that moves from lower (screening) to higher (intervention) levels of care in a cost-effective manner12. Adaptive treatments have been successful for a variety of pediatric chronic conditions, such as asthma13, depression14, anxiety15, and adults with chronic pain and co-morbid psychological disorders16-18. Adaptive designs are more effective in improving health outcomes, satisfaction with treatment, and reducing healthcare use than standard protocols where patients receive a fixed "one size fits all" treatment that is not personalized to their needs; adaptive designs are also recommended for tailoring evidence-based interventions with culturally diverse populations19-21. Adaptive treatments can integrate evidence-based strategies to address common co-morbid problems associated with chronic pain, such as elevated anxiety or depressive symptoms or sleep disturbance14,16,22,23 . Teaching parents problem-solving skills can reduce caregiver stress among families managing chronic pain and illness13,24,25.

3.4 We will utilize an adaptive behavioral treatment to target psychosocial risk factors for youth with chronic SCD pain as a first step towards developing a stepped care model for SCD pain. The proposed treatment, called Back2Life, is innovative because it is culturally informed by families' and patients' feedback regarding their treatment preferences and targets psychological co-morbidities that are often excluded in clinical trials. The overarching hypothesis driving the proposed intervention is that disrupting the complex interacting psychosocial factors that can exacerbate chronic SCD pain will prevent and/or reduce poor health outcomes in children and adolescents with SCD.

4.0 Study Endpoints*

4.1 Primary study endpoints include markers of treatment feasibility, acceptability, and preliminary efficacy related to pain interference, pain characteristics (burden, intensity, frequency), and pain coping efficacy. Secondary

outcomes will include healthcare use for pain (admissions, ED visits, opioid use) and inflammatory biomarkers (e.g., proinflammatory cytokines).

5.0 Study Intervention / Design

A proof-of-concept trial is a cost-effective method to determine if the treatment package can achieve a clinically significant improvement in outcome in a small, select sample26. As a single-arm trial, a proof-of-concept determines whether the treatment merits rigorous and costly testing using an RCT or requires further optimization, thereby minimizing waste of resources and first ensuring clinically significant improvements can be achieved under optimum conditions.

A manualized treatment protocol, including intervention content, delivery style, and materials were adapted for optimization based on analyses of qualitative feedback from qualitative interviews and theater testing (i.e., pre-testing the intervention with the target audience to examine attitudes towards the format, content, etc). The treatment program includes 6-sessions of standard treatment (delivered to all participants) and 1-4 tailored sessions to address common co-morbidities associated with chronic pain (sessions assigned based on results of baseline assessment). The treatment manual leverages existing evidence-based interventions into a treatment package that will be tailored to individual patient and family needs.

6.0 Procedures Involved*

6.1 Patients and parents who provide consent/assent will participate for 8 months (between 12-17 study visits). The study involves a combination of 1) assessments (4 study visits), 2) treatment sessions (6-10 study visits), 3) booster sessions (1 study visit), and 4) a qualitative interview (combined with a post-treatment assessment).

6.2 Baseline Assessment: Parents and teens will complete an assessment of surveys at a baseline study visit. We will ask parents and teens to complete brief questionnaires about the teen's pain, sleep, mood, physical functioning, and interest in participating in the program (see Measures below). Parents will also complete a brief questionnaire about stress related to parenting. Teens will complete a 1-week daily diary to record pain ratings, school attendance, sleep quality, and medication use.

6.3 Treatment Program: All teens will receive the standard 6-session pain coping skills training program (learning ways to cope with and manage chronic sickle cell pain). The standard program includes topics that were identified by teens with chronic sickle cell pain and their parents as important skills for all teens with chronic pain and sickle cell disease. Research staff will use the information from the baseline assessment to tailor the treatment program to the needs of each teen and family. In addition to the standard 6-session program,

teens may receive an additional 1 to 4 sessions that may help with specific problems and/or co-morbidities related to pain. For example, additional sessions may include topics such as difficulty sleeping, bad moods, or parenting stress. Patients and parents who do not screen into the additional tailored sessions based on their baseline assessment scores will still have the option to participate in any of the additional sessions. Please see Appendix A for Back2Life Treatment Session Overview.

6.4 Treatment Sessions: The treatment sessions will be conducted in-person at a CHOA hospital campus or via telehealth using HIPPA-compliant platform (e.g., Zoom). An in-person study visit for the first treatment session is strongly encouraged to promote optimal therapeutic rapport, and all remaining treatment sessions may be conducted in-person or via telehealth, based on patient/family preference. Treatment sessions will begin 1 week following the completion of baseline assessment. Each session will last about 1 hour, once a week. A treatment session window of +/- 14 days will allow flexibility to support adherence. Each session will focus on teaching a new skill or strategy to improve chronic pain management. Sessions will be led by a psychology provider (PhD student, post-doctoral fellow, psychologist). Teens will be asked to practice the coping skills at home between sessions and keep a brief diary of their practice, pain symptoms, school attendance, and medication use. At least one parent or guardian is required to attend with their teen. However, all interested family members (parents, grandparents, siblings) are encouraged to attend sessions with their teen. Parents will also receive education and training in the skills their teen will be learning along with behavior management strategies to support teen's use of skills at home. One booster session will be offered 2 months after completing the program. The booster session will focus on problem-solving any difficulties teens or parents may have had with using the skills at home or school. The booster session will be conducted either in-person, telehealth, or by phone, depending on family preference. Intervention content will be sensitive to developmental differences. For example, parents of school-aged children will be guided to coach their children's use of coping strategies. Parents of adolescents will be guided to provide monitoring and oversight of adolescent self-management and communication with providers to promote independence. Sessions may be audio recorded and will only be reviewed by research staff to make sure that the content of the training program is being provided accurately and thoroughly to all participants. Between sessions, follow-up by phone or during inpatient admissions will allow for opportunities to problem-solve integration of strategies. Make-up sessions will be built into the treatment session timeline to allow flexibility and treatment adherence.

6.5 Follow-Up Assessments: All teens and parents will complete the same assessment of surveys after completing the standard 6-session program (post-treatment evaluation). Parents will also report on any changes to their teen's medical treatment plan since the last assessment. All teens and parents will

complete the assessments at 3-months and 6-months follow-up from baseline. All assessments can be completed in-person, at home using online or paper-and-pencil questionnaires, or by telehealth (video or phone) depending on teen and parent preference. An assessment window of +/- 2 weeks will allow flexibility to support recruitment and adherence.

6.6 Blood Sample Collection: As an optional component of the study, all teens will have the option to consent to blood sample collection at three assessment visits: baseline, 3-month follow, and 6-month follow-up. Blood sample collection will occur at or close to each time point allowing at least 2 weeks following an acute care visit for pain to ensure steady disease state collection. To enhance clinical implementation and acceptability, efforts will be made to coordinate blood sample collection during routine medical visits to minimize blood draws. Each sample will be about 4 teaspoons (about 20 milliliters) of blood, which will be drawn in the clinic or hospital, and will only take a few seconds. Collected blood samples will be immediately transported to Dr. Sheehan's laboratory for labeling, processing, storage, and analysis.

6.7 Qualitative Interview: At the end of the treatment program, parents and teens will be asked for feedback in a one-on-one interview lasting about 30 minutes. Feedback may include how they liked the program, what they thought about the content of the program, and any suggestions or changes to the materials or format. Information from these interviews will be used to refine and modify the Back2Life program. Interviews can be conducted in-person or by telehealth (video and/or phone). Interviews will be audio recorded as digital files and transcribed for analysis by advanced psychology PhD students or trained study members. Audio recordings will be saved for up to 6 years following completion of the study and saved via password-protected computer that is only accessible to the PI to ensure security. No audio recordings will be used for educational or presentation purposes. The research design does not require subjects to be deceived.

6.8 Intervention fidelity. Written intervention manuals will promote quality assurance and include materials for training, supervision, and fidelity monitoring. All sessions may be audio recorded; a random sampling of 25% of sessions from each family will be reviewed with mentors to monitor protocol adherence. Fidelity checklists will be completed independently by 2 reviewers (PhD students). Participant homework completion will be routinely assessed.

6.9 Measures

Study measures are described below. Based on PedIMMPACT guidelines29, the primary treatment outcomes will be pain interference, pain characteristics (burden, intensity, frequency), and pain coping efficacy. Secondary outcomes will include healthcare use for pain (admissions, ED visits, opioid use). Questionnaires will be completed online using REDCap or paper-and-pen, depending on

participant preference. Children and their parents will complete their questionnaires separately. The total time for the full battery of child and parent questionnaires is approximately 20 minutes. We will monitor changes in medical or psychiatric treatment during the study through medical chart review.

6.10 Treatment Feasibility

1) Study recruitment and enrollment statistics
2) Treatment adherence as demonstrated by drop-out rate, session completion, missed/rescheduled treatment sessions, therapist ratings of participants' homework completion
3) Completion of study assessments
4) Participant ratings on whether they thought the Back2Life program is a reasonable approach for chronic pain management, if the program was helpful, could be integrated into their lifestyle, and description of barriers in implementing the program.

6.11 Treatment Acceptability

Treatment Evaluation Inventory, Short Form will be completed at immediate post-treatment. It includes 9 items adapted to be specific to pediatric pain. Items are rated on a 5-point Likert scale ranging from 1 to 5. Total scores range from 9-45. Scores ≥ 27 indicate "moderate" treatment acceptability30.

6.12 Primary Treatment Outcomes

1) PROMIS Pediatric Short Form-Pain Interference, Self- and Parent-Proxy Report is an 8-item self-report measure that will assess functional interference due to pain in the past 7 days. PROMIS Pediatric measures have been well validated among youth with SCD and chronic pain in inpatient and outpatient settings31-34. (2-3 mins)

2) Sickle Cell Pain Burden Interview for Youth, Self--Proxy Report is a brief, validated measure of pain burden in 7-21 year olds. It demonstrated strong reliability and validity among youth with SCD from inpatient and outpatient settings35. Patient self-report and parent-proxy report of total pain days in the past month and duration of chronic pain will also quantify pain frequency1,35. (2-3 min)
3) PROMIS Pediatric Short Form-Pain Behaviors, Parent-Proxy Report is an 8-item measure completed by parents that assesses pain behaviors displayed by their child in the past 7 days. PROMIS Pediatric measures have been well validated among youth with SCD in inpatient and outpatient settings (2-3 min)

4) Child Self-Efficacy Scale, Self- and Parent-Proxy Report is a well-established, 7-item measure of self-efficacy for functioning despite pain for 8-19 year olds36. It demonstrated good internal consistency and validity among youth with a variety of pain problems37. (2-3 min)

6.13 Secondary Treatment Outcomes

1) Healthcare utilization will be extracted from the medical record to document the total number of emergency department (ED) visits and admissions for pain for 6-months and 12-months pre- and post-treatment.

2) Opioid use will be calculated based on participant completion of daily diaries for 1-week at each assessment visit. Participants will record opioid use daily (presence/absence). Opioid use also will be documented on daily diaries throughout the course of treatment.

3) Inflammatory biomarkers, including but not limited to, proinflammatory cytokines and markers, such as interleukin -1β (IL-1β), interleukin – 6 (IL-6), interleukin – 8 (IL-8), tumor necrosis factor – alpha (TNF-α), c-reactive protein (CRP), brain-derived neurotrophic factor (BDNP), and interferon gamma (INF-y) will be analyzed. Plasma concentrations for each biomarker will be determined by a custom multiplex kit (e.g., FirePlex-384 Multiplex Assay by abcam), an immunoassay panel detected by flow cytometry used for simultaneous quantitative measurement in a single sample with high sensitivity and high throughput capacity. All samples will be analyzed in triplicate.

6.14 Psychosocial Measures - Tailoring Variables and Predictors of Treatment Success

Based on baseline assessment of the following measures, additional sessions will be tailored to each family's needs.

1) Pediatric Inventory for Parents, Parent Report is a 42-item parent-reported measure of caregiver stress related to child chronic illness. It has shown high internal consistencies among caregivers of youth with SCD38,39. Total scores that are ≥ 1 SD above the mean will be eligible for tailored sessions on caregiver stress. (5-7 mins)
2) Adolescent Sleep Wake Scale (ASWS), Adolescent Report is a 28-item patient-reported describing the occurrence and frequency of various behavioral sleep characteristics over the past month. It is a commonly used measure of sleep in pediatric pain with good psychometric reliability and validity40,41. Total scores that are ≥ 1 SD above the mean will be eligible for tailored sessions on behavioral sleep strategies. (3-5 mins)

3) PROMIS Pediatric Short Form - Depressive Symptoms, Self- and Parent-Proxy Report. An 8-item measure designed for youth to assess self-reported symptoms of depression, and has been utilized among a wide array of pediatric chronic illness, including chronic pain and SCD32,42. Teens reporting T-Score ≥ 65 will be eligible for tailored sessions focused on managing depressive symptoms. (1-2 mins)
4) Pain Catastrophizing Scale-Child and Parent Report is a 13-item well-validated self-report and parent-report measure of worried thoughts about pain. It is widely used in chronic pain and demonstrated strong internal consistency in SCD28,43. Total scores ≥26 by parent or child report will be eligible for tailored sessions focused on managing anxiety and fear of pain. (2-3 mins)

5) Pain Stages of Change Questionnaire- Adolescent and Parent Report is a 30-item measure designed to evaluate parent and adolescent perceptions of readiness to adopt a self-management approach to pain44,45. (5 mins)

6.15 Compensation

Parents and teens will be compensated for their time and participation for each completed study visit. Participants who do not finish the study will be paid for the visits they have completed. Parents and teens will each receive between $435 to $595 total, if they complete all study visits. Reimbursements are detailed below.

Baseline and Follow-up Surveys: Parents and teens will each receive $25 for completing the baseline study visit, $30 for end of treatment assessment, $35 for 3-month assessment, and 40 for 6-month assessment.

Treatment and Booster Sessions: To reimburse transportation costs for attending each treatment session or to offset the costs for cellular data or WiFi usage for telehealth sessions, parents and teens will each receive $40 for every attended session (between 7-11 sessions).

Qualitative Interview: Parents and teens will also each receive $50 for completing the qualitative interview at the end of the program.

Blood Sample Collections: Teens will receive $30 for completing each blood sample collection at the baseline study visit, 3-month assessment, and 6-month assessment.

7.0 Data and Specimen Banking*

7.1 N/A

8.0 Sharing of Results with Participants*

8.1 As a clinical service to participants, patients and parents may elect to receive aggregate data on the study findings at the completion of the study.

9.0 Study Timelines*

9.1 Patients and parents who provide consent/assent will participate for 8 months (between 12-17 study visits). The study involves a combination of 1) assessments (4 study visits), 2) treatment sessions (6-10 study visits), 3) booster sessions (1 study visit), and 4) a qualitative interview (combined with a post-treatment assessment).

10.0 Subject Population*

10.1 Inclusion Criteria: Youth will be eligible for inclusion if they are (a) 10-18 years old, (b) diagnosed with SCD (any genotype), (c) report chronic pain, (d) speak and read English, and (e) have not initiated new disease modifying-treatments (e.g, hydroxyurea, Endari, voxeletor, crizanlizumab, chronic transfusions) or significantly increased dosages (mg/kg) of any disease-modifying treatments in the past 3 months. As in our prior work1,28, chronic pain classification will be based on pain frequency and persistence: 1) patient reports ≥ 12 pain days per month, and 2) pain frequency persisted for ≥ 3 months. Parents or caregivers will be eligible if they speak and read English.

10.2 Exclusion Criteria: Youth will be excluded if they (a) have comorbid medical conditions typically associated with pain but unrelated to SCD (e.g., rheumatologic disorders or inflammatory bowel disease); (b) are receiving chronic transfusion indicated for central nervous system risks and/or complications, previous overt strokes, or significant cognitive or developmental limitations, as per their healthcare provider or parent, that would impair completion of self-report measures or engagement in treatment sessions; and (d) received ≥ 3 sessions of outpatient psychological therapy for pain management in the 6 months prior to screening to ensure inclusion of patients and families who are naïve to CBT for pain. Parents or caregivers will be excluded if they have significant cognitive limitations or severe psychiatric conditions, as per the child's healthcare team or history, that would impair completion of self-report measures or engagement in treatment sessions.

10.3 25 child-parent dyads will be recruited from CHOA SCD clinics. Participants will include parents and children with SCD aged 10-18, which represents the developmental period when chronic pain is prevalent among youth27. Patients who are 18 years old may participate without a parent or caregiver, although parent participation is preferred.

10.4 Community Participation (if applicable)

- *N/A*

11.0 Vulnerable Populations*

11.1 The research involves children under 21 who have not attained the legal age for consent to treatments or procedures involved in research. This study involves no greater than minimal risk to children. It presents the prospect of

anticipated direct benefit to individual participants by teaching coping skills that may help improve pain management. Parental permission of one parent will be obtained and assent will be obtained from children to ensure voluntary participation. Parental permission, parental consent, and child assent will be documented.

12.0 Local Number of Participants

12.1 25 parent-child dyads

13.0 Recruitment Methods

13.1 Eligible patients will be identified for the study from new or existing SCD patients being seen through the CHOA Comprehensive Sickle Cell Program. We will use multiple recruitment strategies used in past studies. Describe the source of participants.

13.2 Participants in our research database who have agreed to be contacted for future studies will be contacted with a letter describing the study in a "who, what, where, and why" format and/or a personal phone call to the family to describe the study in further detail and determine interest and eligibility. Patients and parents expressing interest in the study will be provided the option to complete web-based or paper baseline measures at home, during their next scheduled outpatient clinic appointment, or during/following their inpatient admission. Verbal consent with the parent will be completed over the phone for participants from the existing study cohort. The research team will call participants to follow-up about baseline survey completion.

13.3 Second, all eligible patients will be approached and screened during their routine outpatient SCD appointment or inpatient admission. Parents or legal guardians of patients must provide written consent for their child to be eligible for inclusion, and youth will provide written assent. Parents will be invited to participate as well and must provide written consent for their own participation. How will eligibility be determined? Provide a detailed description of any eligibility screening done prior to enrolling subject (including whether any identifiers will be recorded – note that IP address is an identifier)

13.4 Third, parents and youth with SCD who meet the inclusion criteria and did not attend their scheduled outpatient appointment will be contacted by a letter describing the study. Approximately one week after the letter is mailed, a member of the research team will call the family, describe the study in further detail, and ask if they are interested in participating. Families who express an interest or agree to participate will complete verbal consent and assent over the phone and will be mailed a packet of questionnaires or a link to complete questionnaires online via a secure CHOA REDCap site, based on their preference and access to internet. The progress of the study in terms of recruitment will be monitored via a data tracking system that will allow the PI to review subject enrollment by age, gender and race.

14.0 Withdrawal of Participants*

14.1 Participants have the right to leave the study at any time without penalty. If participants choose to go off the study treatment or leave the study before the final planned study visit, participants may be asked to have some final study procedures completed including but not limited to follow-up surveys at the planned end of the program, and follow-up surveys at 3-months and 6-months after the program.

14.2 Study personnel may stop participant involvement in the study without participant consent for any reason to maintain the best interest of the participant or if participants object to any future changes that may be made in the study plan.

15.0 Risks to Participants*

15.1 Assessments: The risks for participation in the study are minimal. Study questionnaires contain potentially sensitive questions concerning pain, psychosocial functioning, and sickle cell disease, which may elicit emotional discomfort. Completion of questionnaire assessments may produce fatigue in some participants and burden related to length of assessments will be kept at a minimum.

15.2 Treatment Sessions: The potential risk to participants is minimal. Potential risks for participants include feelings of emotional discomfort when discussing their/their child's experiences with sickle cell disease and pain management and loss of confidentiality. Some participants enjoy talking about their symptoms and functioning and learning about self-management approaches. Participants may obtain more information about their pain condition and gain confidence in their ability function despite pain. Procedures to protect against these risks are detailed in the Protections Against Risk section below. Overall, the focus group discussions do not significantly increase the participants' risk of harm beyond those risks that are inherent in ordinary daily living.

15.3 Blood Draws: Children and adolescents have the option to consent to blood sample collection. Participation in the assessments and treatment sessions will not require consent for blood sample collection. If they consent to this opt-in portion of the study, teens will have a needle stick to get the required blood. This may cause pain, bruising, bleeding, or infection at the site of the needle stick. There should be minimal discomfort related to blood draws.

16.0 Potential Benefits to Participants*

16.1 General: To help reduce any uneasiness or discomfort about answering questions about their health, the research protocol includes standardized measures that have been widely used in other research of youth in this age range with SCD without adverse effects. Participants will be allowed to skip any

questions that they do not feel comfortable answering, will be allowed the freedom to leave during treatment sessions or the qualitative interview at any time, and will have opportunities for breaks to minimize fatigue. Participants will be informed of their right to terminate their participation in any part of data collection at any time and will be given phone numbers of the PI as well as the Emory IRB if they would like to issue a complaint or desire any additional information regarding the study. Participants will receive financial compensation for the time commitment necessary for their study participation. Participant compensation will be provided in the form of Visa cash cards. To ease the travel burden associated with transportation, participants also will be provided with gas cards.

16.2 Blood draws: To help minimize discomfort from blood draws, every effort will be made to coordinate study visits with clinic visits to minimize repeated blood draws and reduce the amount of time needed for additional sample collection. Well-trained phlebotomists at CHOA are experienced in conducting blood draws with minimal risk. Child life specialists are available to offer coping support to children and adolescents, if needed.

16.3 Depression Screening: In the event that one of the procedures reveals indicators of significant depressive symptoms or suicidal ideation, a standard suicide-risk plan will be implemented. Dr. Sil and her research staff are already trained in a standard risk assessment protocol that has been successfully implemented in Dr. Sil's prior studies. Research staff will already be reviewing baseline assessment measure to determine the need for tailored sessions. The treatment program will be delivered by highly trained psychology postdoctoral fellows supervised by the PI. In the event that a participant endorses clinically significant depressive symptoms, suicidal ideation, or reveals a history of abuse on questionnaires or during treatment sessions, a risk assessment will be conducted by the psychology fellows under Dr. Sil's supervision. Dr. Sil is a licensed clinical psychologist and will be available 24 hours a day to be called via cell phone to address crisis questions. Psychiatric or other life crises that are high risk and imminent will be acted upon immediately with staff linking participants to appropriate crisis services (e.g., a referral to the ED (if necessary), community agencies for ongoing care). These are reviewed immediately with the clinically responsible PI and/or primary co-mentor (Dr. Cohen), who is also a licensed clinical psychologist. Lower risk and less imminent crises will result in an attempt to help the participant devise a plan for treatment and/or safety. For example, major stresses, availability of social supports, access to treatment, and plans for safety will be discussed in detail with the participant, and appropriate referrals for treatment will be provided. These cases will be reviewed within 24 hours by the clinically responsible PI and mentors. All actions taken will be documented on a case report form. Based on our prior experience in similar psychosocial pain research in SCD, we anticipate this risk to be very low.

16.4 Benefits to participant or future benefits. Participation in the clinical trial may or may not directly benefit participants. This study is designed to learn more about how teens with chronic sickle cell pain respond to the program and if it helps them manage their chronic pain. Although we do not know for certain whether the treatment will reduce pain, the study results will allow us to develop better treatment programs which might be used to help others in the future. This will provide critical knowledge for the further intervention refinement and testing in a controlled trial in a future study. The potential risks of participation to participants are considered to be minimal in relation to the potential gain.

17.0 Data Analysis, Management* and Confidentiality

17.1 Data Management. All data will be entered into REDCap (supported by both Emory and CHOA), a secure web-based application for managing surveys and databases online, and exported into SPSS. The first step will be to compute descriptive statistics for all measures (means, standard deviations, range and skewness). This process will allow us to determine if there are any extreme outliers and whether the variables are normally distributed. If a variable is not normally distributed, log transformations will be used in all further analyses. Bivariate correlations among demographic variables and variables of interest will be examined to identify any meaningful covariates that will need to be controlled in further analyses. Missing data will be handled by using Multiple Imputation or Maximum Likelihood methods of handling missing data.

17.2 Treatment Feasibility. Feasibility will be assessed using 4 metrics:

1) Study recruitment and enrollment statistics, such as proportion of eligible participants approached for the study who consent to participant

2) Treatment adherence as demonstrated by drop out rate, session completion, missed/rescheduled treatment sessions, therapist ratings of participants' homework completion, including the proportion of participants who attend at least 80% of sessions

3) Proportion of participants who complete study assessments

4) Participant ratings on whether they thought the Back2Life program is a reasonable approach for chronic pain management, if the program was helpful, could be integrated into their lifestyle, and description of barriers in implementing the program.

17.3 Treatment Acceptability. Acceptability of the intervention will be assessed through the Treatment Evaluation Inventory Short Form as well as qualitative interviews that will elicit perceptions about treatment content (utility, appropriateness) and format (convenience, number and length of sessions). See Appendix B for Interview Guide. Audio recordings of qualitative interviews will be transcribed for analysis. A coding system for thematic domains

and a coding scheme will be developed. Qualitative data will be analyzed using MAXQDA. Interview data will be coded by two independent reviewers to enhance confirmability and dependability of conceptual domains. Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

17.4 Preliminary efficacy will be examined by calculating standard effect sizes and 95% confidence intervals on primary outcomes (pain interference, pain, coping) at post-treatment and 3- and 6-month follow-up. Changes in primary outcomes over time will be assessed using repeated measures ANOVA. Comparisons between time points will be made using paired tests or Wilcoxon tests. In an adjusted analysis, potential control covariates (e.g., child age, number of sessions, changes in treatment) will be examined as appropriate. Based on past CBT pain trials, pain reductions typically occur from baseline to follow-up and independent of changes in pain interference9. To account for potential non-significant changes in pain intensity, we will examine individual clinically significant (≥30%) reductions in pain and interference.

17.5 Power Analysis: We are not attempting to fully power this proof-of-concept study and will only examine preliminary efficacy using exploratory analyses. Preliminary power analyses were based on meta-analysis of CBT for pediatric chronic pain. We estimate an effect size of d=.55 for pain reduction at follow-up (30% pain reduction)9. A sample size of n=25 would achieve power estimates of approximately 80%.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants*

This project is a pilot feasibility study of the Back2Life intervention. Because it involves a behavioral intervention, we recognize the need to provide a plan to ensure the scientific integrity and safeguard the well-being of study participants. The study team is highly qualified to lead the cognitive-behavioral intervention. All study staff will be trained to conduct the interventions using a manualized protocol and will monitor the comfort and safety of participants at each session. The PI and study therapists will have regular monthly meetings to monitor the progress of the study, the integrity of the treatment and safety monitoring including a review of any adverse events. The PI will report any significant study-related or unanticipated adverse events to the Institutional Review Board based upon institutional guidelines. Given that this is a feasibility study, it is felt that monitoring at the level of the PI and research team, with oversight from the IRB is sufficient.

The research team will utilize a variety of safeguards to protect the study from loss of data. Data will be collected using electronic or hard-copy versions of measures and will only be identified with the participant ID number. The codes that link the name of the participant to the study ID will be kept confidential in a secured cabinet. Collected forms will be electronically transferred or hard copies

will be transported to the Clinical Research Office. Data will be entered in the computer independently by two trained data entry staff, and discrepancies will be corrected by the PI based on source documents. The quality of the data will be monitored once per month. Data quality will be monitored by random inspection of the completed forms by the research staff and any problems detected will be discussed with the PI. Transcripts of qualitative interviews will be reviewed by an independent transcriber. Qualitative data will be coded by two independent reviewers and any discrepancies will be discussed to reach consensus during research team meetings. Research staff will receive standardized training on administration of assessments. Dr. Sheehan will oversee blood sample analysis, entry, management, quality assurance, and storage of quantified values in a de-identified database.

19.0 Provisions to Protect the Privacy Interests of Participants and Confidentiality of Participants' identifiable data

19.1 This study will have several protections in place to minimize risk to loss of participant confidentiality. The participant's identity, research records, and personal health information will be safeguarded using secure password-protected services. Primary sources of data from questionnaires and digital audio files will be stored on a secure password-protected database that is protected by the highest standards for electronic data safety. The Aflac Clinical Research Office (CRO) will be responsible for the entry, management, quality assurance, and storage of the data. The CRO and research staff will utilize a variety of safeguards to protect the study from loss of data. The staff will perform routine backup of all study files, including main study database, digital audio files, transcriptions, files created for analyses, and programs used to process and analyze data. All files will be archived on a daily basis. All data will be coded with participant ID and no personal identifiers will be associated with these data. Only the study PI and other members of the research team will be able to access participant data. The list of identifying information linking subjects to their ID numbers will be kept in a restricted electronic file. A hard copy of the list will be kept in a locked file cabinet in my office away from research databases.

19.2 Every effort will be made to assure that the data from the recorded treatment sessions and qualitative interviews are kept confidential. At the onset of each session and interview, participants will be reminded of audio recording and will be asked to refrain from revealing personal information that could result in identifying them to protect anonymity and confidentiality. The audio recordings produced from the sessions and interviews will be used only for the purposes of the study. The audio files will be stored in a password-protected computer folder accessible only to the study team. Each participant will be assigned an anonymous study code number in the transcript of the audiotape. Once transcribed, the computer data files will be password-protected, and these

data files will have no personal identifiers and contain no information linking an individual participant with their study code. These protections will be explained in the consent form.

20.0 Compensation for Research-Related Injury

20.1 N/A.

21.0 Economic Burden to Participants

21.1 N/A

22.0 Consent Process

22.1 Written or verbal informed parental consent and child assent (as participants will be ages 10-18 years old) will be obtained prior to the initiation of any study procedures. Participants will be explicitly told that their care at CHOA will not be affected whether they choose to participate in the study or decline participation. Copies of parental consent and assent forms will be given to participants at the study visit.

22.2 For patients and families who are recruited via mailed letters or phone contact, verbal consent and assent will be obtained over the phone. Following verbal consent, participants will be provided with a web link to complete the web-based questionnaires or paper-pencil forms will be mailed (based on family preference and internet access).

23.0 Process to Document Consent in Writing

23.1 Procedures in accordance with Emory IRB Policy (HRP-091) will be followed to document written consent for participants recruited in-person during routine clinic visits. For participants who are recruited and consent by phone, verbal consent will be obtained.

24.0 Setting

24.1 Patients and parents will have the option to complete assessments (either web-based measures or paper-and-pencil measures) during a routine outpatient sickle cell clinic visit at CHOA or at home. Participants will be provided the option to take home packets of paper-pencil questionnaires or have packets mailed home to them if time prohibits their participation in clinic or internet access is not available in the home. Participants across all three CHOA sites will be eligible. Treatment sessions will occur at a CHOA campus location. Describe the sites or locations where your research team will conduct the research.

25.0 Resources Available

25.1 Children's Healthcare of Atlanta is home to the nation's largest pediatric sickle cell disease program with over 2000 active patients followed annually. Approximately 1000 patients are aged 10-18 years old. Based on

prior work in chronic SCD pain, approximately 20% of age-eligible patients are expected to meet diagnostic criteria for chronic pain in SCD. Study funding further supports 75% of the PI's effort to direct towards research activities. The PI (Dr. Sil) has well-developed plans and resources to support psychological and behavioral human research (see Protections Against Risk for additional information).

25.2 Research coordinators and assistants will complete and maintain CITI certification and undergo training to use REDCap for data collection and management. The PI will train research personnel in the process of screening eligible participants, recruitment, and the consenting process. Research personnel also will receive standardized training on the administration and scoring of measures using REDCap as well as paper-pencil measures. The research staff also will be trained in a specific procedural plan for identifying potential suicidal ideation and contacting a psychologist (Dr. Sil and/or Aflac Psychology team) to conduct a risk assessment at the site of data collection. Psychology postdoctoral fellows and/or Ph.D. students will be trained in transcription and coding of qualitative data under the supervision of the PI and qualitative methods expert. Psychology postdoctoral fellows also will undergo intensive training in the treatment manual led by the PI.

26.0 Multi-Site Research* ☐

- *N/A*

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