

**Acceptability, Feasibility and Safety of a Yoga Program for Chronic Pain in Sickle Cell Disease**

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**Title:** Acceptability, Feasibility and Safety of a Yoga Program for Chronic Pain in Sickle Cell Disease

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**Abstract:** Chronic Pain is associated with substantial morbidity, functional disability and poor quality of life in patients with Sickle Cell Disease (SCD). The etiology of chronic pain in SCD is multi-factorial. While opioid-based therapy is effective for the treatment of acute pain, opioids and other pharmacological therapies may not be effective in the management of chronic pain and are associated with risks. Complementary therapies, such as yoga, have been demonstrated to be effective in patients with non-SCD chronic pain conditions and may be effective in SCD. Yoga is generally safe and well tolerated, and preliminary evidence in SCD suggests potential efficacy for SCD pain. In-person yoga classes may be prohibitive due to cost and access to these programs may be limited in minority, low-income populations. Smartphone applications available are not tailored to SCD chronic pain. In this study, we propose to study the acceptability, feasibility and safety of yoga for SCD associated chronic pain. Following completion of the study, we also aim to assess participant interest and needs in the development of a smartphone based application for yoga in SCD.

## BACKGROUND AND SIGNIFICANCE:

Chronic persistent pain with recurrent acute exacerbations is a major cause of morbidity, impaired quality of life, healthcare utilization and increased mortality in SCD <sup>1-3 4</sup>. Chronic pain in SCD is associated with higher healthcare utilization, increased work absences<sup>5</sup> and greater functional disability <sup>6</sup> with a negative impact on physical, social and emotional functioning. While opioids are used in the management of chronic pain in SCD, they are associated with substantial risks<sup>7</sup>, there is a need for safe and effective non-pharmacological methods for treatment of SCD chronic pain. Long term opioids are associated with significant risks including pharmacological and psychological dependence, drug interactions, and lethal overdose<sup>8</sup>. Long-term opioid use is also associated with gastrointestinal and endocrine dysfunction, increased risk for cardiovascular events, increased risk for fractures and increased risk for sleep disorders <sup>8</sup>. Use of opioids may paradoxically increase pain sensitivity, a phenomenon termed as opioid induced hyperalgesia<sup>9</sup>.

Mind-body therapies such as yoga can alter pain and related comorbidities. Yoga promotes the relaxation response with decreased heart rate, increased breath volume and improved physiological responses to stress <sup>10</sup> and pain as well as an increase in parasympathetic activity<sup>11</sup>. Mind-body therapies may decrease the sensory discriminative and affective-motivational aspects of pain<sup>12</sup> even when not engaged in practice. Study of yoga and mindfulness based interventions suggest that these interventions can reduce pain and comorbidities, such as anxiety<sup>13, 14</sup> depression<sup>15</sup>, and fatigue<sup>12</sup>, and multiple investigators have demonstrated the effectiveness of yoga in a variety of chronic pain syndromes<sup>16 17, 18</sup> such as low- back pain<sup>16, 19</sup>, fibromyalgia<sup>20</sup>, osteoarthritis<sup>21</sup> and chronic neck pain<sup>22</sup> as well as in functional pain syndromes<sup>23, 24</sup>. Use of complementary therapies including mind-body interventions has also reduced opioid use in a small population of patients with chronic pain<sup>25</sup>. The practice of yoga has been attributed to reduced pain, increased coping, better pain acceptance and increased control<sup>26</sup>. There is also decrease in sensitivity to laboratory induced pain with mindfulness meditation-based techniques<sup>27, 28</sup>. Yoga has also been shown to be associated with decreased cortisol<sup>20</sup> , decrease in inflammatory signaling<sup>29</sup>, in autonomous nervous system function with decreased sympathetic<sup>30</sup> and increased parasympathetic system signaling<sup>31</sup>. Pro-inflammatory biomarkers have been reported to be decreased with yoga<sup>32, 33</sup>.

Yoga is the fifth most popular complementary therapy in children and adolescents in the US<sup>34</sup>. SCD chronic pain offers several therapeutic targets that may be responsive to yoga, and limited data in SCD suggests it is well tolerated. SCD chronic pain is associated with psychological comorbidities such as anxiety, depression<sup>35</sup>, fatigue<sup>36</sup> and maladaptive coping<sup>37</sup>, as well as chronic inflammation, all of which may be impacted by yoga. Limited data suggests yoga is well tolerated in children with SCD admitted for acute pain, and a single session was reported to decrease mean pain intensity but not anxiety, length of stay or opioid use<sup>38</sup>.

Lack of awareness and access to yoga are barriers to the use of yoga, and smartphone apps may overcome this barrier. Limited health knowledge is one of the reasons for non-use of complementary therapies<sup>39</sup>, and individuals with lower educational attainment, and lower income were more likely to report lack of knowledge as a reason for non-use of these therapies<sup>39</sup>. There are increased challenges in access to yoga for minority and low-income populations<sup>40</sup>, since yoga is often a fee-based service and there may be additional limitations due to geographical access<sup>40</sup>.

While there is currently no data on the use of yoga as a Complementary and Alternative Medicine (CAM) therapy in SCD chronic pain, one study in acute SCD pain suggest that the practice was well accepted and well tolerated<sup>38</sup>. Additionally, preliminary data from a secondary data analyses of the decision aid study suggests that adult patients express a desire for non-medication based pain relief. These data indicate that patients with SCD who suffer from chronic pain, may be willing to consider CAM therapies. A customized yoga program, taking into account risks of SCD, and limitations posed by SCD-related comorbidities, including but not limited to fixed deformities, AVN, splenomegaly, lung disease, cerebral vasculopathy, retinopathy, etc.

The overarching goal of this study is to 1) determine the acceptability of yoga for chronic pain in SCD 2) determine the feasibility of a yoga program for individuals with SCD chronic pain, 3) determine the safety of a yoga program for individuals with SCD chronic pain, 4) determine the feasibility of collection of psychological and patient reported outcomes in a study of yoga for chronic pain and 5) Explore patient acceptability of yoga through qualitative interviews and conduct a needs assessment for the development of a smartphone app for yoga.

## **AIMS:**

### **Aim 1. Acceptability, feasibility and safety of a yoga program for chronic pain in SCD.**

We will assess the acceptability of yoga for chronic pain in SCD. We will also assess the feasibility and safety of a yoga program for adolescents with SCD and chronic pain.

**Rationale:** Yoga content customized for patients with SCD chronic pain, is currently not available for patients. We propose for the first time to develop routines with consideration of needs, expectations and physical limitations of SCD. The overall acceptability, feasibility and safety of such a program in SCD is yet to be studied, though data from other chronic painful and inflammatory conditions do not suggest safety concerns.

**Hypotheses:** 1a) We hypothesize that more than >50% of those with chronic pain approached to complete a survey of their attitudes and practices related to yoga, would be willing to complete a survey. 1b) At least 50% of adolescent SCD patients with chronic pain offered participation in a yoga program through in-person yoga sessions will agree to participate in the yoga program 1c) At least 80% of participants enrolled in the in-person yoga program will be

able to attend at least 6 of 8 in-person yoga sessions. 1d) Fewer than 30% of participants will have an ED visit or hospitalization for pain within 24 hours of completion of a yoga session.

**Aim 2: Feasibility of collection of psychological and patient-reported outcomes in a study of yoga for chronic pain in SCD.**

**Rationale:** Yoga content tailored and customized for patients with SCD chronic pain, is currently not available for patients. We propose for the first time to develop routines with consideration of individual needs, expectations and physical limitations. In addition to aims in Aim 1, we propose to measure health outcomes and psychological characteristics pre- and post- the yoga program, with a goal to determine the feasibility of collection of these outcomes in a larger study. Since our sample size is small, and this is a pilot feasibility study, it will not be powered to assess measurable benefit (or lack of) from the yoga program, therefore these outcomes will be exploratory. These outcomes will be collected regardless of the number of yoga sessions attended.

**Hypothesis:** 2a) We hypothesize that 70% or more of participants will complete all study assessments before, and at the end of the yoga program. 2b) We hypothesized that the proportion of participants who submit at least 4 days of pain diary data before, and at the end of the yoga program will be 70% or greater.

**Aim 3. Explore patient acceptability of yoga through qualitative interviews and conduct a needs assessment for the development of a smartphone app for yoga.**

**Rationale:** Qualitative Interviews will be used to assess aspects of acceptability and use of yoga as an adjunct therapy for SCD chronic pain. We will also use qualitative interviews format to assess participant interest and perceived needs in the development of a smartphone yoga app. Qualitative thematic analysis methods or other methods as applicable will be utilized.

**Outcome Measures:**

**The study will have the following primary outcome measures:**

- 1- Proportion of adolescent patients with SCD and chronic pain approached that consent to participate in Part A.  
*The study hypothesis is that the proportion of adolescent patients with SCD and chronic pain approached that consent to complete a survey to assess attitudes and practices related to yoga (Part A) will be 50% or greater.*
- 2- Proportion of adolescent patients with SCD and chronic pain enrolled in Part A that consent to participate in Part B.  
*The study hypothesis is that the proportion of adolescent patients with SCD and chronic pain enrolled in Part A that consent to participate in Part B will be 50% or greater.*
- 3- Proportion of participants enrolled in Part B that attend at least 6 of 8 yoga sessions.  
*The study hypothesis is that the proportion of participants enrolled in Part B that attend at least 6 of 8 in-person yoga sessions will be 80 percent or greater.*
- 4- Proportion of participants enrolled in Part B with an ED visit or a hospitalization for pain within 24 hours of completion of each yoga session.

*The study hypothesis is that the proportion of participants enrolled in Part B with an ED visit or a hospitalization for pain within 24 hours of completion of each yoga session will be 30% or less.*

- 5- Proportion of participants in Part B who complete all study assessments.  
*The study hypothesis is that the proportion of participants who complete all study assessments before, and at the end of the yoga program will be 70% or greater.*
- 6- Adherence to submission of pain diary.  
*The study hypothesis is that the proportion of participants who submit at least 4 days of pain diary data before, and at the end of the yoga program will be 70% or greater.*

**The study will have the following exploratory outcome measures (Change from baseline to end of yoga program):**

- 1- Chronic Pain Acceptance (Measured using the chronic pain acceptance questionnaire)
- 2- Fear of Movement (Measured using the Tampa Scale of Kinesiophobia)
- 3- Pain Intensity (Measured using PROMIS Pain Intensity Short Form)
- 4- Pain Interference (Measured using PROMIS Pain Interference Short Form)
- 5- Pain Catastrophizing (Measured using the Pain Catastrophizing Scale)
- 6- Expectations from the yoga program (Measured using the Modified EXPECT questionnaire)

## STUDY DESIGN

This study will be a 2-part study.

In Part A, there will be 2 groups of participants enrolled.

---Group 1 will include patients with SCD who meet inclusion criteria for the study, and do not have any exclusion criteria.

---Group 2 will include parents/guardians of patients who are in Group 1. Only one parent/guardian per participant will be enrolled.

Potential patient participants (Group 1) and their parent/guardian (Group 2) will be approached for participation in a survey based study to determine their attitudes and practices relating to yoga, and potential acceptability of a yoga based program for chronic SCD pain. They will complete the surveys as described in Part A as well as the demographics as detailed below. Medical records will be reviewed as described below for all participants in Group 1, but we will not review medical records of participants in Group 2. Both groups will separately consent to participation in the study. Parents/Guardians (Group 2) will be offered participation in Part A even if their child is 18 and older, as long as their child are enrolled in the study.

Patients in Part A Group 1 who indicate and interest and willingness to participate in a study of yoga for SCD pain will be offered Part B of the study, which will determine the feasibility and safety of a customized yoga program for SCD. The participant in Part A Group 1 does not have any commitment to enroll on Part B of the study, and does not necessarily have to express interest in participating in Part B of the study prior to participation in Part A. Participants in Group 2 will not be offered participation in Part B of the study.

**PART A: Assessment of attitudes and practices related to yoga and potential acceptability of a yoga program in adolescents with SCD and chronic pain, and their parents/guardians.**

**Inclusion Criteria for Group 1 participants:**

- 1-SCD, any genotype
- 2-Presence of chronic pain, the presence of chronic pain will be defined based on the frequency characteristic of the AAPT criteria for chronic SCD pain<sup>41</sup>, as the presence of SCD-related pain on 15 or more days of the month for the past 6 months.
- 3-Age 12-21 at time of enrollment
- 4- English speaking

**Exclusion Criteria for Group 1 participants:**

- 1- Daytime or nighttime oxygen requirement for hypoxia
- 2- Most Recent Hemoglobin< 5 or platelet count < 20
- 3- Known Pregnancy
- 4- Severe cognitive issues not allowing for understanding consent/assent and instructions
- 5-History of overt stroke with significant residual motor weakness
- 6-History of recurrent syncope
- 7- Any other comorbidities or health concerns that the treating healthcare provider or investigators feel are a contra-indication for participation in the study.

**Inclusion/Exclusion Criteria for Group 2 participants:** There are no specific inclusion/exclusion criteria for parent/guardian participants, except that their child is a participant in the study.

We have developed a survey (attached-Survey Part A) to determine attitudes and practices relating to yoga in patients with SCD chronic pain, and potential acceptability of a yoga program for chronic SCD pain. The presence of chronic pain will be defined based on the based on the frequency characteristic of the AAPT criteria for chronic SCD pain<sup>41</sup>, as the presence of pain on 15 or more days of the month for the past 6 months, and will be determined by self/parent report.

We will also collect the following questionnaires from Group 1 participants in the study: 1) Chronic pain acceptance questionnaire 2) Tampa Scale of Kinesiophobia 3) PROMIS Pain Intensity and Pain interference 4) Pain catastrophizing scale (Crombez et. al.). Surveys may be completed in person, or over the telephone, or may be mailed to participants to complete.

Medical records will be reviewed for pertinent demographic and clinical details including but not limited to those pertaining to SCD, healthcare utilization for pain, other pertinent details about pain phenotype, presence of fixed damage such as AVN, SCD complications, pertinent medical complications, medications, transfusions, and pertinent laboratory values such as (but not limited to) hematological parameters and markers of hemolysis. Since psychological diagnosis are often associated with chronic pain, we will review available psychological and mental health records for co-existing psychological diagnoses. Medical records will also be reviewed for inclusion and exclusion criteria. Note: Only medical records of patient participants (Group 1) will be reviewed; medical records of parent participants (Group 2) will not be reviewed.

We will also obtain demographic information including but not limited to age, sex, race, ethnicity, family income, insurance status, parent and child education status, family composition and parent marital status, religious affiliation, availability of transportation and distance from the

proposed yoga site. If participants indicate they have previously practiced yoga, we will also gather the following: when yoga was first practiced, number of months/years' yoga has been practiced, frequency of practice and time of most recent practice of yoga. For Group 1 participants, this form may be completed by the parent/guardian for those <18, and by the participant if >18, with or without assistance from the research coordinator. For Group 2 (parent) participants, this will be completed by the parent themselves, with or without assistance from the research coordinator.

At the end of Part A, Group 1 participants will be asked if they are interested in learning about participating a study of yoga for chronic SCD pain. If they answer yes, then they will learn more about the proposed program, and Part B of the study will be offered to them. In addition to the research coordinator discussing the Part B yoga program, we will use written materials to help participants become familiar with what they may expect in part B (attached with this protocol), which will include pictures of sample yoga and breathing routines. Participants may take the Part B consent form with them to think over if they wish to consider this prior to enrolling or refusing participation in Part B. If participants are not interested in a pilot study of yoga or do not wish to enroll/are unable to enroll on Part B, investigators will request and document reason for refusal (if provided), and participant will not have to complete additional study procedures. The proportion of those who complete Part A but do not wish to consent for Part B will be recorded. Group 2 participants will not be offered Part B.

It is anticipated that this introduction and pictures for part B will take approximately 10-15 minutes.

### **PART B: Feasibility and Safety of a yoga program for SCD.**

Part B will assess the feasibility and safety of a yoga program for SCD. This program will comprise of 8 instructor-led group yoga sessions. We will measure psychological factors implicated in chronic pain and pain-related patient reported outcomes, and assess the feasibility of collection of these outcomes. We will also explore patient acceptability of yoga through qualitative interviews and conduct a needs assessment for the development of a smartphone app for yoga.

Participants who express interest in learning more about participating in a study of yoga in Part A will be offered this portion of the study.

Prior to enrollment in Part B, the investigators will confirm with their treating provider that the patient does not meet any exclusion criteria for the study. If any concerns are noted at this point, then patient will not be enrolled on Part B of the study, and this will be documented.

#### **Inclusion Criteria:**

- 1-SCD, any genotype
- 2-Presence of chronic pain, the presence of chronic pain will be defined based on the frequency characteristic of the AAPT criteria for chronic SCD pain<sup>41</sup>, as the presence of SCD-related pain on 15 or more days of the month for the past 6 months.
- 3-Age 12-21 at time of enrollment
- 4- English speaking

#### **Exclusion Criteria:**

- 1-Daytime or nighttime oxygen requirement for hypoxia
- 2-Most Recent Hemoglobin< 5 or platelet count < 20
- 3- Known Pregnancy

- 4- Severe cognitive issues not allowing for understanding consent/ assent and instructions
- 5- History of overt stroke with significant residual motor weakness
- 6-History of recurrent syncope
- 7- Any other comorbidities or health concerns that the treating healthcare provider or investigators feel are a contra-indication for participation in the study.

The presence of the following conditions will be assessed from the medical record but are **NOT** exclusion criteria: 1) Presence of splenomegaly, 2) presence of asthma 3) presence of AVN 4) Presence of cerebral vasculopathy 5) retinopathy, 6) presence of symptomatic pulmonary HTN. The assessment of the study investigators and the treating team will determine if any of these or any other co-morbidities require for modification of or pose as potential contraindications for participation in a yoga program.

If prospective study participants are enrolled on other clinical trials that do not allow for concurrent enrollment in this study, they will not be enrolled on this study. The PI/study staff will confirm eligibility for enrollment with PI's/study staff of the respective clinical trials regarding patient eligibility for enrollment.

#### **In-person yoga sessions:**

Patients will be offered a yoga program consisting of 8 in-person instructor-led group yoga sessions. Yoga sessions are likely to be held at CHOA campuses or at ECC, depending on availability of space. Based on number of participants enrolled and participant convenience/logistical issues, study cohort may be split into 2 or more groups, but a participant may only attend a total of 8 sessions. Sessions are currently planned to be weekly, however there may be variations in schedule to accommodate situations including but not limited to major holidays, school breaks, instructor illness, etc.

- i. During the sessions, participants will be monitored by a study investigator and the yoga instructor. An investigator who is an MD familiar with care of SCD patients will be present, and a RN may also be present, both of whom will monitor patient safety at each session.
- ii. Yoga instructor is certified and have expertise in teaching yoga. Instructor will be Dr. Cooley. A physical therapist (Marlysa Sullivan), who is also a certified yoga instructor, will also assist in developing the class routine, and may be present during the session.
- iii. The yoga instructors, with the guidance of SCD clinical experts, will develop a customized set of restorative yoga poses, breathing exercises, and guided relaxation routines with consideration of needs, expectations and physical limitations of SCD.
- iv. During guided yoga sessions the yoga instructor will carefully observe the participants for any sign of discomfort or suitability. Yoga instructors will modify particular poses to be suitable for the participant. The yoga sessions will be geared towards increased incorporation of breathing techniques and mindfulness and some 'asanas' (poses). Props may be utilized for yoga poses.
- v. Timing of yoga sessions will likely be in the evenings or on weekends, to accommodate participant's ability to attend these sessions. Participants will be asked regarding their preferred times. Every effort will be made to accommodate participants.
- vi. Proposed Yoga protocol (45-60 minutes), but this may be modified as yoga instructor deems necessary to suit patients with SCD. The sequence below is only to serve as a guide, and only lists representative elements, and instructor may move around the order. The final yoga protocol may be modified in-real time per instructor discretion, and to maintain safety, based on ongoing feedback and response to classes. It is possible that some elements of the yoga sessions may change as classes progress.

- a) Opening and Pranayama (breathing exercises)
  - b) Gentle warm up
  - c) Predefined set of standing and poses
  - d) Surya (Sun), Chandra (Moon) and earth series of poses
  - e) Pranayama (Breathing exercises)
  - f) Guided relaxation or 'yoga nidra'
- vii. During, and at the end of each session, feedback will be obtained from participants as a group, and will be recorded. Future yoga sessions may be modified as necessary based on participant feedback.
- viii. Email or phone reminders for upcoming yoga sessions will be sent to participants at the email address/phone numbers provided. If participants miss or are unable to attend sessions, study staff may follow up to attempt to determine reason for non-attendance.
- ix. Study staff will also record ED visit or hospitalization that occurred in the 24 hours following the yoga session. This will be assessed 24 hours after, but prior to the start of the subsequent session.

**Assessments:**

- 1- Surveys (**2 assessments, pre and post**). The following surveys will be completed: 1) Chronic pain acceptance questionnaire 2) Tampa Scale of Kinesiophobia 3) PROMIS Pain Intensity and pain interference 4) Pain catastrophizing scale 5) Modified EXPECT questionnaire, to assess individual expectation from the yoga program. Surveys may be completed in person, or over the telephone, up to 4 weeks before the anticipated start of the yoga sessions, and up to 4 weeks after completion of the last yoga session.
- 2- Qualitative Interviews (one assessment, after completion of yoga sessions): A qualitative interview will be conducted, either in person or over the telephone. These interviews will explore participant experience with the yoga study, including perceived benefits, perceived complications/harms, challenges, barriers to successful participation, feedback on yoga classes and content, and other related themes. We will also evaluate participant beliefs and acceptability of yoga and other complementary therapies before and since the intervention. We will also assess aspects of acceptability and use of yoga as well as potential barriers as an adjunct therapy for SCD chronic pain. We will also use qualitative interviews format to assess participant interest and perceived needs in the development of a smartphone yoga app. There may be other questions that the interviewer may ask based on participant responses. Interviews may take up to 20-30 minutes. Interviews will be audio recorded and identified with the unique subject number for the study. Audio files will be transferred to the secured Hematology/Oncology share drive at Emory or CHOA. All audio recordings will be transcribed verbatim by a member of the research team. An interview script has been uploaded with the protocol, but as with all qualitative methodology, it is an iterative process, thus the interview guide may be modified based on emerging themes to better understand those themes.
- 3- We will review medical records for demographic and clinical characteristics as described earlier in the protocol.
- 4- Pain diary (2 assessments, pre and post): Participants will complete a multi-dimensional pain diary (MDP diary) for up to one week prior to and following the period of in-person yoga sessions. The pain diary is accessible via a password protected website, which is also currently used to collect pain data for other large clinical trials in SCD. Data entry will occur two times per day, morning and evening and will take less than 3 minutes to fill out at each time point. The diary can be completed up to 4 weeks prior to the anticipated start of the yoga program, and may be started up to 4 weeks following the completion of the last yoga session.

- 5- We will also obtain demographic information from patient/family including but not limited to age, sex, race, ethnicity, family income, insurance status, parent and child education status, family composition and parent marital status, religious affiliation, availability of transportation and distance from the proposed yoga site. As with Part A, if participants indicate they have previously practiced yoga, we will also gather the following: number of months/years' yoga has been practiced, frequency of practice and time of most recent practice of yoga. This would already have been gathered at the start of Part A but may be collected again if necessary.
- 6- Study staff may send email or phone reminders for completion of study assessments, and may follow up to obtain completed study assessments.
- 7- We will also follow healthcare utilization for pain during and up to 6 months after completion of the yoga program.

After the sessions have ended, and the participant has attended at least one session, all surveys will be repeated and a qualitative interview will be conducted to evaluate participant acceptability and perceived benefits/risks of yoga, as well as the perceived needs in the design of a smart-phone accessible yoga app; as described above.

The goal will be to obtain these assessments within one month prior to the planned start of Part B, and within one month of completion of the last yoga session.

#### **Total number of participants:**

*Part A, Group 1: Up to 40 adolescent patients who meet inclusion/do not meet exclusion criteria. Patient participants will be enrolled on Part A (up to a max of 40 patient participants) until 20 patient participants enroll on Part B.*

*Part A, Group 2: Up to 40 parents/guardians of adolescent patients in Group 1. The number of Group 2 participants will be determined by the number of Group 1 participants. Only one parent/guardian per Group 1 participant will be enrolled.*

*Part B, We anticipate enrolling up to 20 patients in Part B of the study.*

#### *Total Duration of Participation in Part B*

Up to 18 months.

#### **Recruitment Methods:**

Potential participants will be recruited from Children's Healthcare of Atlanta (Egleston, Scottish Rite and Hughes Spalding locations).

Pre-screening of potential study participants who seek care at CHOA will be done using medical record review. We may also identify patients from the existing SCD clinical database maintained by Dr. Peter Lane to identify patients with frequent healthcare utilization for pain or those who potentially may have chronic pain identified through clinical care or prior/ongoing other research studies. This is to limit burden of approaching those patients who are likely to not meet criteria for chronic pain. Participants may also be referred to the study by their treating healthcare providers. If medical records or healthcare provider report/database indicate a possible diagnosis of chronic pain, a research team member will approach the patient/parent to introduce the study and also determine if patient meets eligibility criteria. Patients may be approached for the study either in the inpatient or the outpatient setting. The study staff may also introduce the study in person-or over the telephone to discuss patient interest in the study. If eligible, and the individual is interested, the consent will be reviewed, including expected study activities, and

potential risks and benefits. A copy of the consent may be provided for review based on patient and family preference, either in person or e-mailed/mailed to the potential participant, if so requested. The individual will have an opportunity to discuss it with significant others, including caregivers and other family. The individual will also be given the opportunity to discuss it with his/her hematologist or healthcare provider, if they wish to. This may be done in-person or if the family wishes to, due to time constraints at clinic or hospital visits, over the telephone. Once a potential participant has reviewed consent and all questions have been answered, consent will be obtained in-person.

Specific attention will be given during the consenting process for the potential for increased discomfort and/or pain as a result of the yoga poses. These may result in increased use of medication, or potentially a ED visit, or hospitalization.

All questions will be answered by a member of the research team and/or the PI. If the individual agrees to participate, he/she will be consented/assented in person. A copy of the signed consent will be given to the participant.

Participants will be consented for Part A and Part B separately. For those who are enrolled in part B of the study, investigators will confirm that patients don't have exclusion criteria prior to proceeding with the first yoga session.

Flyers may be posted in the sickle cell clinics and at community sites, or in on-line patient forums, with study coordinator contact information.

#### **Monitoring of Potential adverse outcomes:**

**Pain:** There is a potential for increased discomfort and/or pain as a result of the yoga poses, even though the program is designed to be gentle. The potential for increased pain will be discussed with the participant during the consenting session and if needed, prior to each in-person yoga session, so the patient and their family are fully informed of the potential risks. Pain may result in increased use of medication, or potentially a ED visit, or hospitalization. We will also track healthcare utilization for pain, and if  $\geq 30\%$  of participants present with increased pain resulting in an ED visit or hospitalization, we will halt yoga sessions and reassess if any changes need to be made to the protocol. Since participants have chronic pain, it may be difficult to determine if the yoga program was the cause of increased pain, so we will go by patient self-report to determine if yoga program was believed to be causative. If this is the case, the participant may opt to discontinue the research study or a physician researcher may opt to withdraw the participant. We also anticipate that those who perceive an increase in pain following the program will self-discontinue from the study. Monitoring during yoga sessions will make every effort to ensure participants do not exceed their limitations.

**Other risks:** There is a possibility of muscle strain, of aggravation of an existing injury, which may cause discomfort or pain, increased medication use, need for medical treatment, increased time off work or school, or financial loss.

As with all research studies, there is also a risk of loss of confidentiality of participant data.

#### **Anticipated results and Potential problems, alternate strategies:**

We may encounter difficulties with enrollment of participants. Participants may be uninterested in complementary therapies or may believe that they may not help with chronic pain. They may not want to pursue yoga as a complementary therapy due to concerns that this may be in

conflict with their religious beliefs. There may be cultural barriers to acceptability of yoga. The yoga instructors or investigators, who are familiar with addressing concerns about yoga, will be available to answer any questions they may have about the practice of yoga itself and if potential participants have any concerns regarding yoga as a spiritual practice.

Once enrolled in Part A, participants may not complete survey, though we expect that this non completion rate will be low. Once enrolled on part B, participants may decide not to participate further in the study, or may have a medical complication between enrollment and participation in the yoga sessions that may not allow them to participate in the study. Participants may not attend one or more in-person yoga sessions. We will attempt to determine the causes for individuals dropping out of the program.

There may also be discontinuation of the program due to increased pain, or perceived increased pain, and this will also be noted as a reason for discontinuation. Systematic reviews have not shown increased risk of severe adverse events by the use of yoga in the management of chronic pain syndromes. In addition, there may be changes in health status that may prevent safe continuation of the yoga program. These aims will generate critical data on the feasibility acceptability, reach and maintenance of yoga in adolescents with SCD and chronic pain.

### **Analytic Methods:**

Part A: Descriptive statistics will be used to determine the proportion of patients with chronic pain who are willing to consider yoga and participate in a yoga program. We will also determine predictors of acceptability of yoga such as, but not limited to, age, gender, pain phenotypes, medical comorbidities, attitudes towards complementary therapies, fear of movement and pain catastrophizing. There may be additional analyses that may be conducted once these are completed.

Part B: This aim will also determine the feasibility of attendance at in-person yoga program, and safety. As in part A, we anticipate descriptive statistics will be utilized, and we will look for characteristics associated with feasibility of attendance at in-person yoga sessions. Qualitative analysis will also help indicate wider issues related to acceptability of yoga and barriers to use of yoga and other complementary therapies. Qualitative analyses will also analyze participant needs for development of a yoga app.

We will monitor for adverse effects following the in-person yoga session. If the research coordinator receives reports of increased pain in participants following a yoga session, that are perceived to be related to the yoga session, then these will be recorded. We will also record any ED visits or admissions for pain that occur within 24 hours of the yoga session. We will monitor for drop out from the study due to perceived increase in pain.

Pain diary data and quality-of-life survey and PROMIS will interrogate improvement in pain, quality-of-life from the use of yoga application program. Given the pilot nature of this study, we do not expect we will be adequately powered to detect differences in health outcomes like pain intensity and pain interference or psychological factors between pre- and post treatment values. There may be additional analyses that may be conducted once these primary analyses are completed.

### **Human Subjects:**

#### *Protected Health Information*

Name, address, telephone number, and email address will be recorded to facilitate contact with study subjects, send reminders for completion of study procedures and to mail gift

cards. Medical records and PHI will be reviewed as described in this protocol. Other data gathered will include but not be limited to sickle cell genotype, type and frequency of pain medication utilization, intensity and frequency of in-patient and emergency department treatment for vaso-occlusive crisis, and co-morbidities.

If we uncover information about the participant during this study that study investigators feel believe may impact their care, they may discuss this with the participants' healthcare providers.

#### *Third Party Information*

Data Warehouse Consultants (DWC) which is an agent of Emory University that will manage the pain diary. DWC will have access to participants' phone number, email address, IP Address and data that is entered in the pain diary application.

#### *Potential Risks*

There is a risk of breach of confidentiality. All electronic data will be kept on a secure server. Paper documents will be retained in a locked file cabinet in a locked office. Consent forms will be kept separate from research data.

There is a risk of discomfort with qualitative interviews. Participants are free to refuse to answer any questions that make them feel uncomfortable. The interview may be stopped at any time.

There is a potential for increased discomfort and/or pain as a result of the yoga poses. These may result in increased use of medication, or potentially a ED visit, or hospitalization. Since participants have chronic pain, it may be difficult to determine if the yoga program was the cause of increased pain, so we will use patient self-report to determine if yoga program was believed to be causative. If this is the case, the participant may opt to discontinue the research study or a physician researcher may opt to withdraw the participant. The potential for increased pain will be discussed with the participant during the consenting session and if needed, prior to each in-person yoga session, so they and their family are fully informed of the potential risks. Medical personnel expert in sickle cell disease will be present at the yoga sessions to monitor for discomfort.

**Other risks:** There is a possibility of muscle strain, of aggravation of an existing injury, which may cause discomfort or pain, increased medication use, need for medical treatment, increased time off work or school, or financial loss.

Given the minimal risk of the pain diary, we do not anticipate concerns with its use. Participants will be consented and informed that pain data collection via MDP diary is not a means of communicating with provider but only as a reporting tool for the study. A disclaimer is present in the consent form indicating that the data collected in the study is only for reporting purposes and not as a means to inform their healthcare provider, seek or provide medical attention. Data from pain diary may be reviewed periodically, and participants may be contacted if the study team believes they have concerns. This will not be to provide medical advice but to ensure that participants have sought care for pain related or other concerns with their healthcare provider.

#### *Potential Benefits*

There is a potential benefit of participation in this study as performing yoga may help decrease or control chronic pain though there is no guarantee, and there is a potential for pain to not improve/worsen. This is indicated on the consent form.

#### *Data and Safety Monitoring Plan*

Research staff directly involved in the study will have access to data collected during this study. Paper documents will be filed in a locked filing cabinet in a secure office setting. Electronic data will be maintained on a secure Hematology/Oncology share-drive with limited access behind a secure firewall at Emory University or at CHOA. Participant data will be identified with a unique number. The key connecting the participant to the ID number will be maintained separately from the study data and will be destroyed upon completion of the study, to include dissemination of findings. The ID key will be accessible only to members of the research team. All audio recordings will be identified on the recording with the unique participant identification number. All transcripts will be identified using the participant identification number and names of parents and health care providers will be indicated with "XXX" in the transcription.

The data and safety monitoring team will include the Principal Investigator, co-Investigators and the study coordinator. Meetings will occur every 2 weeks from time of first yoga session, until 2 weeks after completion of the last yoga session. Investigators will discuss any concerns with yoga protocols utilized and if any modifications are needed for patient safety. All study data reviewed and discussed during these meetings will be kept confidential. Any breach in confidentiality will be reported to the IRB and regulatory agencies.

#### *Withdrawal from Study*

The participant may withdraw from the study at any time by notifying the PI and/or the research team. All data collected up until the point of withdrawal may be included in data analysis. Reason for withdrawal will be noted if provided. No further data will be collected after withdrawal.

*Recruitment of Women and Minorities as Research Subjects:* Majority, if not all, of the patients will be of minority ethnic origin because of the demographics of distribution of SCD. It is possible that more females may be enrolled, as chronic pain is more common in females. The racial, gender and ethnic characteristics of the proposed subject population is expected to reflect the demographics of patients in the CHOA clinic. No exclusion shall be based on race, ethnicity, or gender.

#### **COMPENSATION:**

Participants will be compensated as follows:

Part A: \$ 25 for completion of study procedures.

Part B: \$25 for completion of surveys, 2 time points = \$50

1. \$25 for qualitative interview, 1 interview = \$25
2. \$25 to cover costs of transportation and parking for each yoga session, up to 8 yoga sessions = max of \$200
3. \$1 for completion of pain diary at each time point, twice daily for 7 days X 2 time-points = max of \$28

Total possible compensation for Part B \$303.

Note that payments will be prorated based on study procedures completed.

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