# MULTIsite feasibility of MUSIc therapy to address Quality Of Life in Sickle cell disease (MULTI-MUSIQOLS)

# PREFACE

*The Clinical Intervention Study Protocol Template is a suggested format for clinical trials sponsored by the National Center for Complementary and Integrative Health (NCCIH). Investigators are encouraged to use this format, as appropriate, when developing protocols for their studies. Large multi-site observational studies will also benefit from this protocol template.*

*Note that instructions and explanatory text are indicated by italics and should be replaced in your protocol with appropriate text. Section headings and template text formatted in regular type should be included in your protocol document as provided in the template.*

*The goal of this template is to provide a general format applicable to all single- and multicenter clinical intervention trials (e.g., drug, surgery, behavioral, nutritional, device, etc).*

*As you can see the version number and date are on the bottom of each page. When making changes to an approved and "final" protocol, please provide a summary of the changes, with the date, at the front of the protocol.*

# MULTIsite feasibility of MUSIc therapy to address Quality Of Life in Sickle cell disease (MULTI-MUSIQOLS)

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## Tool Revision History

Version Number: 4
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Summary of Revisions Made:

1) Changed timing of iPad handoff to following randomization
2) Added that study team has the option to provide transportation assistance to help participants attend the baseline consent visit if needed.

Version Number: 3
Version Date: 12Sep2024
Summary of Revisions Made:

1) Removed the REDCap referral option. Providers will use email to refer patients to the study because this method is more likely to be used

2) Add Mind/Body pain management and transportation questionnaire to gauge and document inclusion exclusion criteria not captured elsewhere and to document the need for transportation assistance

3) Change MyChart to MyCAP because MyCAP is more accessible and has more features that the study team would like to utilize

4) Added that Prisma will use a paper consent as per their institutional requirements

Version Number:
Version Date:
Summary of Revisions Made:

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Summary of Revisions Made:

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## PRÉCIS

### Study Title

MULTIsite feasibility of MUSIc therapy to address Quality Of Life in Sickle cell disease (MULTI-MUSIQOLS)

### Objectives

The objectives of this study are to (1) conduct a feasibility randomized control trial (RCT), to examine the data collection processes, and intervention (in-person music therapy [InMT], hybrid MT [HybMT], and hybrid health education [HybHE]) implementation overall and across 2 sites (University Hospitals/Case Western Reserve University [site 1] and Prisma Health/University of South Carolina [site 2]); and (2) evaluate the implementation of the InMT, HybMT, and HybHE interventions using both quantitative data (study records, stakeholder surveys) and qualitative data (interviews).

**Design and Outcomes**

This is a multi-site, multi-visit feasibility RCT of music therapy (MT) among adolescent and adult patients (aged 14 and older) with sickle cell disease (SCD).

Subjects will be randomized into one of three groups, either (1) InMT: 6 visits of in-person MT; (2) HybMT: 1 visit of in-person MT and 5 visits of virtual MT; or (3) HybHE: 1 visit of in-person health education and 5 visits of virtual health education.

Cohorts of 15 participants (10 at site 1 and 5 site 2) will be recruited each quarter for 6 quarters to reach 90 participants. Cohorts will maintain a semi-structured recruitment, consenting, assessment, and intervention schedule.

**Interventions and Duration**

Three wellbeing programs for individuals with SCD will be compared: (1) InMT, (2) HybMT, and (3) HybHE. Each intervention includes 6 sessions. The treatment period for each group will be 6 to 8 weeks. Each weekly session will last up to one hour in all arms of the study. MT sessions in the InMT and HybMT arms will include the topics of SCD education and MT rationale, breathing exercises, relaxation, imagery, music making, and review and creation of a coping plan for future challenges. The HybHE group will use an adapted version of Project Patients Empowered and Educated Providers (PEEP). Covered topics include: science of SCD, identifying barriers in the Emergency Department, tools for navigating the healthcare system, healthcare based communication, and review and planning for future challenges.

Semi-structured qualitative interview topics will focus on participants' perceptions of the interventions, perceived benefits and burdens of the interventions, and other barriers and facilitators to in-person and hybrid delivery.

**Sample Size and Population**

A total of 90 subjects will be randomized to either InMT, HybMT, or HybHE (1:1:1 allocation). Patients must:

(1) Be aged 14 years or older;

(2) Have a diagnosis of SCD present in their electronic health record (EHR);

(3) Meet Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy (AAPT) criteria for chronic SCD pain which includes:

(3a) A diagnosis of SCD confirmed by laboratory testing (present in EHR per eligibility criteria 2)

(3b) Reports of ongoing pain present on most days over the past 6 months either in a single location or in multiple locations (to be obtained at screening)

(3c) Displaying at least one of the following signs on clinical exam (to be obtained from providers' clinical notes in the EHR

- Palpation of the region of reported pain elicits focal pain or tenderness;
- Movement of the region of reported pain elicits focal pain;

- Decreased range of motion or weakness in the region of reported pain;
- Evidence of skin ulcer in the region of reported pain;
- Evidence of hepatobiliary or splenic imaging abnormalities (e.g., splenic infarct, chronic pancreatitis) consistent with the region of reported pain; or
- Evidence of imaging abnormalities consistent with bone infarction or avascular necrosis in the region of reported;

(3d) There is no other diagnosis that better explains the signs and symptoms (to be obtained from providers following referral and pre-screening)

(4) Be able to speak and understand English;

(5) Have an email address and access to mobile device with a functioning data plan

(6) Reporting that pain interfered with daily activities at least 1-2 days in the past week

Patients will be unable to participate if they:

(1) Have a significant visual, hearing, or cognitive impairment

(2) Have previously participated in the MUSIQOLS single-site pilot study at University Hospitals in 2018

(3) Are currently engaging in mind-body therapies under the supervision of a healthcare professional specifically for pain management

(4) Have a planned major medical event in the next 14 weeks such as (but not limited to) childbirth, orthopedic surgery, gene therapy, or stem cell transplant (These criteria do not include blood transfusions, exchange transfusions, or other pharmacologic pain treatment).

Qualitative interviews will be conducted with 24 participants who received the interventions (with equal numbers across the InMT, HybMT and HybHE groups). Participants will be purposively sampled to include both sexes, younger and older participants, and distribution across sites in proportion to recruitment.

Stakeholder surveys and qualitative interviews will be conducted among 20 relevant staff stakeholders (10 per site), including healthcare providers & staff, music therapists and HybHE interventionists.

## 1. STUDY OBJECTIVES

### 1.1 Primary Objective

The primary objective of the study is to examine the feasibility of completeness of data collection, participant recruitment and rate, participant retention, as well as assessment of hybrid intervention implementation and home practice using study records across the two sites.

### 1.2 Secondary Objective

This study will include a secondary objective of conducting qualitative interviews to assess feasibility of implementation.

## 2. BACKGROUND AND RATIONALE

### 2.1 Background on Condition, Disease, or Other Primary Study Focus

***Sickle Cell Disease (SCD) in the United States:*** Approximately 100,000 individuals live with SCD in the United States. SCD disproportionately affects minority populations, with 1 out of every 365 Black or African American births carrying the genetic condition.[1, 2] Emergency department (ED) and inpatient admissions among individuals with SCD account for approximately $2.4 billion dollars in annual spending, exceeding ED-associated expenditure rates among individuals with congestive heart failure, HIV, and asthma.[3]

***Pain in SCD:*** In addition to enduring unpredictable acute vaso-occlusive pain crises throughout their lives, many adults with SCD also suffer from chronic pain, defined as the presence of pain on most days in the past 6 months in one or more locations.[4, 5] Chronic SCD pain often emerges in adolescence as a result of physiological complications including chronic sickle cell vaso-occlusion, inflammation, increased red blood cell adhesion, central sensitization, and opioid-induced hyperalgesia.[5, 6] In the Pain in Sickle Cell Epidemiology Study (PiSCES), a longitudinal etiologic study of 232 adults with SCD, 54% reported having pain, pain crises, or utilization on more than half (51%) of 31,017 analyzed patient-days. Estimates of chronic pain prevalence among adults with SCD range from 29% to 100%, with a weighted mean of 65% within seven studies.[7] Among 170 adults with SCD and chronic pain, 57.1% reported Grade III (highly disabling–moderately limiting) or Grade IV (highly disabling–severely limiting) chronic pain that was significantly associated with higher pain catastrophizing and lower chronic pain self-efficacy.[8]

***Health-Related Quality of Life (HRQoL) in SCD:*** These physical and psychological challenges contribute to impaired HRQoL. In PiSCES, patients with SCD scored significantly worse than national norms on all HRQoL subscales except mental health.[9] Specifically, HRQoL was equal to or worse than patients with other significant chronic conditions in many domains, and the more pain patients with SCD experienced, the worse their reported HRQoL.[9] More recently, an integrative review of 22 studies also found that adults with SCD report worse HRQoL than the general population.[10] Adults with SCD enrolled in a recent randomized controlled trial (RCT) of a web-based decision aid reported PROMIS pain interference, anxiety, depression, fatigue, and physical function scores 0.5–1 SD worse than population norms and worse than reference norms of PROMIS scores for individuals with cancer.[4] Thus, new interventions are needed to improve overall HRQoL for individuals with SCD in addition to pain outcomes.

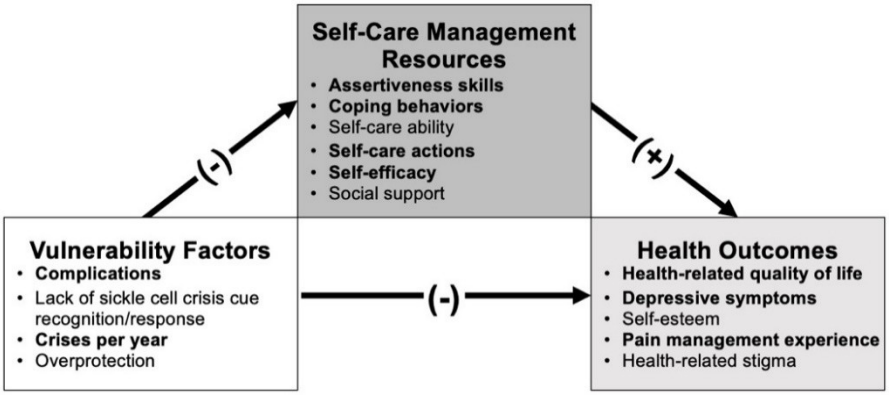
***Need for Non-pharmacologic Pain Management:*** In their 2020 guidelines for pain management in SCD, the American Society of Hematology acknowledged that

pharmacologic approaches have limited effectiveness and that non-pharmacologic integrative approaches are beneficial but may have limited accessibility for individuals with SCD. These guidelines identified research priorities including determining which non-pharmacologic therapies are most acceptable and developing manualized, accessible, and developmentally appropriate interventions for chronic SCD pain.[5] In a qualitative study exploring chronic pain and self-management, adults with SCD expressed (1) a preference for non-pharmacologic strategies, (2) that pain medications were not always effective and limited their ability to perform daily activities, and (3) a desire to learn new pain management strategies.[11]

***Music Therapy (MT) for Pain Management and HRQoL:*** MT is the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved MT program.[12] MT has demonstrated effectiveness for managing pain in patients with cancer,[13-15] patients with chronic pain,[16-18] and patients receiving palliative care.[19, 20] A recent clinical effectiveness study comparing the MT experiences of Black and White patients with cancer found that Black patients with moderate-to-severe pain reported clinically meaningful pain reduction (2.1 units on the Edmonton Symptom Assessment Scale).[14] Importantly, MT can be tailored to the unique cultural preferences of adults with SCD and provide opportunities for active engagement with music, a factor shown to be associated with reduced pain intensity among adults with acute pain.[21] Our prior work described below has demonstrated the preliminary efficacy of MT for addressing acute pain, mood,[22] and HRQoL[23] among adults with SCD.

***Importance of Self-efficacy:*** Self-efficacy is a significant factor influencing health outcomes and self-care activities for individuals with SCD.[24] A meta-analytic review of 86 studies examining its relationship to chronic pain outcomes found that self-efficacy had negative overall correlations with impairment, affective distress, and pain severity and identified it as an important protective factor for individuals with chronic pain.[25] Self-efficacy is related positively to fewer physical and psychological symptoms[26, 27] and improved quality of life[28, 29] among individuals with SCD. In a recent study of 170 adults with SCD and chronic pain, investigators observed a negative relationship between chronic pain self-efficacy and chronic pain intensity ($p = 0.026$) and chronic pain disability ($p < 0.001$).[8] Furthermore, self-efficacy has been shown to improve in response to MT interventions among Black/African American individuals with chronic pain.[16, 18, 23]

**Figure 1. Theory of Self-Care Management for Sickle Cell Disease (Jenerette et al.) Applied to MT**




The revised Theory of Self-Care Management for Sickle Cell Disease (Fig. 1[30, 31]) guides the proposed study. Dr. Jenerette's (study MPI) theory focuses on vulnerability factors and

self-care management resources influencing health outcomes. In Figure 1, vulnerability factors (lack of SCD crisis cue recognition/response, number of acute pain episodes per year, and overprotection) negatively influence health outcomes (pain management experience, depressive symptoms, self-esteem, and perceived health-related stigma). Self-care management resources (self-efficacy, coping behaviors, social support, self-care ability, self-care actions, and assertive communications skills) positively mediate the relationship between vulnerability factors and health outcomes.

*Our proposed study conceptualizes MT as a self-care management resource that can mediate the relationship between vulnerability factors and health outcomes.* The proposed study conceptualizes pain interference as a vulnerability factor approximating pain crises. As noted in the theory, **self-efficacy** will be the self-care management resource measured. Finally, **HRQoL** will be measured as a health outcome. Based on our previous work[22, 23] as Preliminary Data immediately below, MT can be considered a coping behavior that positively influences HRQoL.

**Critical gaps in the current evidence that necessitate additional research**. To date, there is not enough quality evidence on non-pharmacologic treatments for chronic SCD pain, including treatments that are patient-centered, culturally relevant, and accessible.[5] Few studies examined the impact of MT on HRQoL and self-efficacy for individuals with complex chronic pain. Prior studies investigating the feasibility and impact of MT among predominantly Black/African American patients with chronic pain lacked an active attention-control condition and post-intervention follow-up outcome measures.[16, 18]

## 2.2 Study Rationale

***Pilot Study 1: RCT of a Single MT Session for SCD:*** In a three-arm RCT comparing (1) MT, (2) music listening, and (3) no music (control), we enrolled participants with SCD who received a single 20-minute electronic music improvisation session. Subjects were more likely to report a significant improvement in pain intensity (mean = -1.92 ± 1.88 units; OR = 5.12, p = 0.035) and mood (OR = 11.60, p = 0.005) compared to the control group, whereas participants who received music listening were more likely to report mood improvement only (OR = 5.76, p = 0.040). Qualitative data from this study supported the acceptability and feasibility of a single MT intervention for addressing pain intensity during an acute care SCD clinic visit.[22]

***Pilot Study 2: Music Use Survey:*** In a cross-sectional study of 100 adults with SCD conducted in preparation for Pilot Study 3 (below), we found that adults with SCD (1) face significant challenges related to pain interference (mean = 61.13); (2) perceive music as being helpful for managing challenges, including mood (57%), sleep (48%), stress (47%), and pain (37%); (3) purposefully engage in music listening to manage pain (74%); and (4) would be interested in participating in MT services in inpatient (88%) and outpatient (81%) settings. The most common need reported in our study population was for reducing pain (47%), followed by helping with relaxation and sleep (44%). Additionally, there was a moderate positive correlation ($r_s$ = 0.516, p <

.001) between the number of strategies used alongside music and the perceived helpfulness of music for reducing pain.[32]

***Pilot Study 3: RCT of a 6-session MT Intervention for SCD*:** Mr. Rodgers-Melnick, Drs. Dusek, and Jenerette recently conducted a pilot study designed to determine the feasibility, acceptability, and preliminary efficacy of a 6-session MT intervention as compared to waitlist control (WLC) for adults with SCD and chronic pain. Adults with SCD (ages 21–57; mean age 32.33) were randomized (1:1) to either (1) a 6-session in-person MT intervention (n = 12) or (2) WLC (n = 12). All participants completed measures of self-efficacy, HRQoL, and coping skills before and after their assigned study condition to explore preliminary efficacy. MT participants received in-person MT and were taught music exercises accessed via smartphone and subsequently interviewed to determine feasibility and acceptability. The enrollment rate in this study was 89%. All outcomes were completed at the 2-week follow-up (100%). Interviews revealed two overall themes related to MT participants' experience: (1) participants learned new self-management skills and (2) MT improved participants' ability to cope with pain. MT participants demonstrated 100% attendance. In preliminary analyses, MT participants demonstrated significant improvements (means ± SD) in self-efficacy (5.42 ± 5.43, p = 0.008, d = 1.20), PROMIS sleep disturbance (−1.49 ± 6.68, p = 0.023, d = −0.99), PROMIS pain interference (−2.10 ± 4.68, p = 0.016, d = −1.06), and ASCQ-Me social functioning impact scores (2.97 ± 6.91, p = 0.018, d = 1.05) compared to WLC participants.[23] We found across all six MT sessions that most MT participants reported using music exercises at home almost every day (40%) or every day (35%). Fewer MT participants reporting using music exercises once or twice per week (12%), never (10%), or more than once per day (3%). See Figure 2 below for a demonstration of the recruitment feasibility and preliminary efficacy from this study.

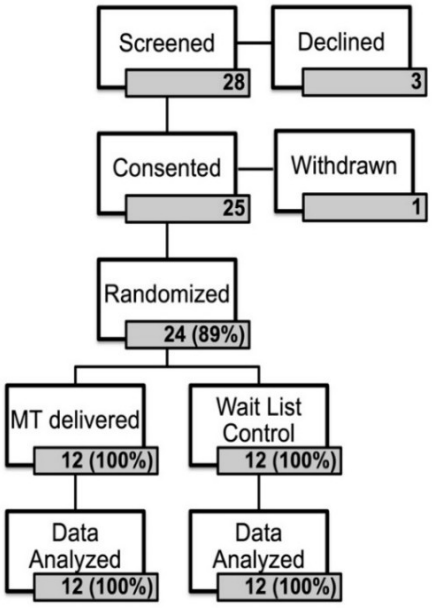



**Figure 2. Demonstration of Feasibility and Preliminary Efficacy from Preliminary Study.**

| Outcome | Music Therapy Mean ± SD | Waitlist Control Mean ± SD | p-value[b] | Effect size[c] |
|---|---|---|---|---|
| **Sickle Cell Self-Efficacy Scale** | 5.42 ± 5.43 | -0.50 ± 4.38 | 0.008 | 1.20 |
| **PROMIS Sleep Disturbance[a]** | -1.49 ± 6.68 | 4.63 ± 5.58 | 0.023 | -0.99 |
| **PROMIS Pain Interference[a]** | -2.10 ± 4.68 | 4.30 ± 7.12 | 0.016 | -1.06 |

| | | | | |
|---|---|---|---|---|
| **ASCQ-Me Social Functioning Impact[a]** | 2.97 ± 6.91 | -4.28 ± 6.93 | 0.018 | 1.05 |

[a] T-scores [b] Student t-test comparing change scores between groups [c] Cohen's *d* comparing change scores between groups

***Other Preliminary Data:*** Recent multi-session interventions with urban African Americans with chronic pain have revealed positive effects of vocal MT on pain self-efficacy and participants' ability to participate in social activities.[16, 18] A meta-analysis of 14 RCTs found that music interventions were effective for reducing self-reported chronic pain and depressive symptoms, and patient-preferred music was more effective than music chosen by the research team.[33]

***Virtual and/or Hybrid Delivery of Integrative Therapies:*** Due to the COVID-19 pandemic, the UH MT program has been adapted for virtual delivery, with several virtual MT sessions being provided to adults with SCD.[34] Other cancer centers have also described successful MT adaptations to the virtual environment.[35, 36] A recent study exploring the feasibility of a mindfulness-based MT intervention for adolescents and young adults with cancer that transitioned from in-person to virtual delivery found significant improvements in perceived stress and non-significant changes in anxiety. Additionally, a greater number of virtual MT group participants (n=17) completed all four sessions (76.5% vs. 29.4%) than in-person MT group participants (n=17).[37] Other virtual MT approaches have been utilized to reduce barriers to accessing services within military veteran populations,[38-41] parents of hospitalized infants in neonatal intensive care units,[42] and teens with Asperger's Syndrome who lacked access to in-person services due to residing in remote or rural communities.[43, 44]

Ezenwa and colleagues conducted a pilot RCT of a 12-minute tablet-based guided audio-visual relaxation among 28 adults with SCD, and found that guided relaxation significantly reduced pain index scores, 96.4% of participants completed the study protocol and questionnaire items, and participants shared benefits of using tablets to collect research data and access the intervention.[45] Ezenwa conducted a follow up RCT with all 30 participants completing the study, and 83% of participants in the experimental group reported enjoying the study.[46] As a co-investigator, Dr. Ezenwa will bring her knowledge on virtual delivery for both the HybMT and HybHE intervention delivery.

## 3. STUDY DESIGN

Type/design of trial

This is a multi-site, multi-visit feasibility RCT of three wellbeing interventions among patients aged 14 and older with SCD.

Specific unit(s) of assignment and unit(s) of observation

The unit of assignment is at the patient level. Specifically, patients with SCD enrolled from SCD centers will be randomly assigned to either InMT, HybMT or HybHE. The unit of observation is the patient.

Primary and secondary outcomes

The primary objective is to refine procedures for conducting a future fully-powered multi-site RCT. The secondary objective of the study is to examine the feasibility of completeness of data collection, participant recruitment and rate, participant retention, as well as assessment of hybrid intervention implementation and home practice using study records across the 2 sites. This study will include qualitative interviews to assess feasibility of implementation.

Study population and groups/arms including sample size

(1) The study population will be ninety (60 from site 1, 30 from site 2) individuals who (1) are aged 14 and older; (2) are diagnosed with SCD (3) meet AAPT Diagnostic Criteria for Chronic SCD Pain as evidenced by (3a) a diagnosis of SCD confirmed by laboratory testing; (3b) reporting ongoing pain present on most days over the past 6 months either in a single location or in multiple locations; (3c) displaying at least one of the following on clinical exam from a provider: palpation of the region of reported pain elicits focal pain or tenderness, movement of the region of reported pain elicits focal pain, decreased range of motion or weakness in the region of reported pain, evidence of skin ulcer in the region of reported pain, evidence of hepatobiliary or splenic imaging abnormalities (e.g., splenic infarct, chronic pancreatitis) consistent with the region of reported pain, or evidence of imaging abnormalities consistent with bone infarction or avascular necrosis in the region of reported pain; (4) are able to speak and understand English; (5) have an email address and access to a mobile device with a functioning data plan; and (6) report that pain interfered with daily activities at least 1-2 days in the past week. Individuals who (1) have significant visual, hearing, or cognitive impairments; (2) previously participated the in MUSIQOLS single-site pilot study at University Hospitals in 2018; (3) are currently engaged in mind-body therapies under the supervision of a healthcare professional specifically for pain management or (4) have a planned major medical event in the next 14 weeks such as (but not limited to) childbirth, orthopedic surgery, gene therapy, or stem cell transplant (these criteria do not include blood transfusions, exchange transfusions, or other pharmacologic pain treatment) will be ineligible for study participation.

Allocation of the study participants will be as follows:

| | InMT | HybMT | HybHE | Total |
|---|---|---|---|---|
| UH/CWRU | 20 | 20 | 20 | 60 |
| Prisma/USC | 10 | 10 | 10 | 30 |

(2) Twenty-four participants (equal numbers across the InMT, HybMT and HybHE groups) will be contacted for brief qualitative interviews within 2-3 weeks of intervention completion.

(3) Twenty relevant staff stakeholders (SCD providers and staff, music therapists and HybHE interventionists), 10 at each site, will be contacted to participate in a brief survey and qualitative interviews approximately 16-26 weeks after enrollment begins.

Study location

Randomized Control Trial

Subjects will be recruited from: UH Seidman Cancer Center Adult SCD Clinic or UH Rainbow Babies and Children's Hospital Sickle Cell Anemia Center (site 1) and Prisma Health Lifespan Comprehensive SCD Program (site 2). Interventions will be conducted at:

- **InMT**: SCD center main campus, satellite campus, or another location preferred by the participant (e.g., community center) for all sessions.
- **HybMT**: SCD main campus, satellite campus, or another location preferred by the participant (e.g., community center) for session 1. Secure telehealth platform (i.e., Zoom Health Professional) for sessions 2 – 6.
- **HybHE**: SCD main campus, satellite campus, or another location preferred by the participant (e.g., community center) for session 1. Secure telehealth platform (i.e., Zoom Health Professional) for sessions 2 – 6.

Qualitative Interviews

Participant qualitative interviews will be conducted via a HIPAA-compliant secure telehealth platform (e.g. Zoom Health Professional or Doxy.me) or over the phone and will be audio and/or video recorded. Video recordings will be immediately deleted, and audio recordings will be transcribed. SCD providers and staff, music therapist, and HybHE interventionist interviews will happen via a HIPAA-compliant secure telehealth platform (e.g. Zoom Health Professional or Doxy.me) and will be audio and/or video recorded. Video recordings will be immediately deleted, and audio recordings will be transcribed. Investigators will stop conducting the qualitative interviews in each arm AFTER 8 interviews are completed.

Approximate duration of enrollment period and follow-up

Randomized Control Trial

Subjects will be enrolled for 12 to 14 weeks (6 – 8 weeks for the intervention and 6 weeks for the final follow-up measures). Each site will enroll for ~18 months.

Cohorts of up to 15 participants (10 at site 1 and 5 at site 2) will be recruited each quarter for 6 quarters to reach the goal of 90 participants. Cohorts will maintain a semi- structured recruitment, consent, assessment, and intervention schedule.

Qualitative Interviews

Participant interviews will take place during their 12 to 14 weeks of enrollment, approximately 2-3 weeks after their last intervention session. Provider enrollment will begin when they express interest in participating in the interview and will end after they complete their interview and survey.

Description of intervention and administration

Parent/guardians of minor participants will be encouraged to remain on site during the minor participants' in-person sessions at the SCD center main campus, satellite campus or another location preferred by the participant (e.g., community center). However, the parent/guardian will be asked to remain outside of the session space.

*Music Therapy Conditions (InMT and HybMT)*

Participants in the InMT and HybMT conditions will receive either 6 in-person MT sessions (InMT) or 1 in-person and 5 virtual sessions (HybMT) over 6 weeks (see Table 1 below for descriptions of each session). Each MT session will last no longer than one hour. This 6-week treatment period may be extended to up to 8 weeks if a scheduling conflict prevents a participant from receiving the 6 MT sessions over 6 consecutive weeks. In-person sessions will be delivered one-on-one at the SCD center main campus, satellite campus, or another location preferred by the participant (e.g., community center). Virtual sessions will be delivered over secure telehealth platform (e.g. Zoom Health Professional). If participants lack their own tablets, computers, or home internet, they will be provided with iPads preconfigured with data plans and headphones to facilitate receiving the intervention.

To begin each session, the interventionist will determine ability to participate (see form B.3.3) in a session by asking and documenting “Do you feel able to engage with us now, or would you like to try to participate at a later time/date?” If the participant says “No”, the session will not continue and will be rescheduled. If the participant says “Yes”, the session will continue. At the start and end of each MT session, the participant will complete 0-10 numeric rating scale measures of pain, stress, anxiety, and fatigue (see below for description). Each MT session will include (1) setting an agenda, (2) an explanation of the music exercise, (3) a demonstration of the music exercise in which the MT-BC will engage the participant in practicing the music exercise (e.g., breathing, progressive muscle relaxation, imagery), (4) time to process the participant’s response to the exercise, (5) time for the MT-BC to electronically deliver the music exercise to the participant and ensure that the participant has all materials necessary to use the exercise at home, and (6) a homework assignment for the participant to practice the music exercise taught in that session at least once per day until the following MT session. The genres of each music exercise (i.e., music-based breathing exercise, progressive muscle relaxation, imagery, and active music making) will be personalized to participants’ preferences (e.g., hip-hop, gospel, R&B, jazz, rock, and/or soul) based on the music preferences disclosed in the first session. Each music exercise lasts an average of 10.9 minutes. As the music exercises are being demonstrated, the MT-BC will simultaneously record the exercise using GarageBand for MacOS. Participants will record their use of the music exercises in weekly REDCap surveys delivered via text message. We will also use REDCap surveys or MyCap to remind participants about upcoming MT sessions and prompt them to confirm their upcoming attendance.

Participants will be provided with all necessary materials (e.g., instruments, audio files, headphones) needed to practice the music exercises at home, including instructions and personalized audio recordings of music exercises delivered via a secure Box® folder, email, and/or Airdrop® depending on the functions of the participant’s mobile device. Participants will not have to purchase their own musical or electronic materials to participate in the MT interventions. Participants will be able to contact the music therapist via secure message in MyCap or via email if they have any questions about using the music exercises during the study.

**Table 1. Description of MT Sessions.**

| Session | Description |
|---|---|
| **1) Education** | Explain pain mechanisms in SCD and rationale for how music helps to reduce pain |
| **2) Breathe** | Teach deep breathing exercise with music |
| **3) Relaxation** | Teach guided progressive muscle relaxation (PMR) exercise with music |
| **4) Imagery** | Teach music-based imagery exercise |
| **5) Music Making** | Teach active music making exercise |
| **6) Conclusion** | Review previous MT exercises and make plan for coping with future challenges |

*Hybrid Health Education (HybHE)*

The HybHE attention control condition will be adapted from Project PEEP: Patients Empowered and Educated Providers. The Sickle Cell Community Consortium developed Project PEEP with a grant from Global Blood Therapeutics. Project PEEP addresses unmet needs directly identified and prioritized by a collective of patients with SCD, caregivers, and community-based organizations. The objective is to provide the tools and resources to improve communication and increase positive patient-provider interactions to receive quality, timely care. For the proposed study, we will use modules from the curriculum developed for patients living with SCD. All modules were developed with input from individuals living with SCD. Dr. Bailey was a critical developer of the Project PEEP curricula, and she will serve as a consultant to assist with its use in this R01 feasibility pilot RCT.

Participants in the HybHE condition will receive 1 in-person health education session at the SCD center main campus, satellite campus, or another location preferred by the participant (e.g., community center) and 5 virtual sessions over secure telehealth platform (e.g. Zoom Health Professional). The 6 HybHE sessions will occur over 6 weeks (see Table 2 below for descriptions of each session). Each HybHE session will last no longer than one hour. This 6-week treatment period may be extended to up to 8 weeks if a scheduling conflict prevents a participant from receiving the 6 HybHE sessions over 6 consecutive weeks. If participants lack their own tablets, computers, or home internet, they will be provided with iPads preconfigured with data plans and headphones to facilitate receiving the intervention. Participants will be given iPads to receive the intervention and complete outcome measures.
As in the MT conditions, to begin each session, the interventionist will determine capacity to participate in a session by performing and documenting a modified global assessment including: (1) Is the subject alert and able to communicate with the investigator/study team? (2) Is the subject sufficiently comfortable as to be able to communicate? and (3) Is the subject reporting a current pain level that would prevent them from participating in today's session? Each HybHE session will include (1) setting an agenda, (2) an explanation module, (3) time to review the module, (4) time for the HybHE interventionist to answer any questions, and (5) a homework assignment for the participant to reflect on the module and reflect on how the content

can be used to improve care-seeking. Participants will record their use of HybHE content in weekly REDCap surveys delivered via text message. We will also use MyCap to remind participants about upcoming HybHE sessions and prompt them to confirm their upcoming attendance.

Participants will be provided with all necessary materials to fully engage in HybHE (e.g., manual of modules) needed to practice the content of the modules at home. These materials will be delivered via a secure Box® folder, email, and/or Airdrop® depending on the functions of the participant's mobile device. Participants will not have to purchase electronic materials to participate in the HybHE interventions. Participants will be able to contact the HybHE interventionist via secure message in MyCap or via email if they have any questions about using the HybHE content during the study.

**Table 2. Description of HealthED Sessions.**

| Session | Description |
|---|---|
| **1) Science of SCD** | Reviews the science of SCD, focusing on blood, organs affected, labs, and the biology behind vaso-occlusive crises. |
| **2) Identifying Barriers in the Emergency Department** | Introduces common barriers (supported by research) that patients with SCD experience in the ED. |
| **3) Tools for Navigating the Healthcare System** | Explores the healthcare infrastructure, chain of command, documenting care (both positive and negative) and the process of filing a complaint in a constructive and effective manner. |
| **4) SBAR: Healthcare Based Communication for Patients (Part 1)** | Introduces Situation, Background, Assessment, Recommendation (SBAR) and as an effective form of communication for patients when accessing medical care and covers Situation (S) and Background (B) of SBAR. |
| **5) SBAR: Healthcare Based Communication for Patients (Part 2)** | Reviews SBAR and covers Assessment (A) and Recommendation (R) of SBAR. |
| **6) Conclusion** | Review content from sessions 1-5 and make a plan to address future challenges. |

Following the post-test assessment, the participants randomized to HybHE will receive access to a library of recordings from the MT intervention. Participants randomized to InMT or HybMT will receive access to the health education content. All participants will not be required to complete any additional assessments or perform any study activities during the time following the 6-week post-intervention assessment.

Remuneration

As acknowledgement of the participant's time, participants will receive:

- $20 for baseline data collection;
- $20 for participating in session 1;
- $10 for sessions 2, 3, 4, and 5;
- $20 for session 6;

- Those who complete at least 4 of 6 sessions will receive a $25 bonus;
- $25 for completing follow-up data collection at post-intervention;
- $25 for interview participation; and
- $25 for completing follow-up date collection at 6-weeks post-intervention.

Thus, participants will be eligible to receive a possible maximum of $175-$200 per patient, given via ClinCard prepaid debit card.

If the participant does not already have one, a ClinCard prepaid debit card will be issued during the participant's enrollment session by the study staff. Study staff will register the participant to the card and distribute a physical or virtual card to the participant. Participants will be provided with a Frequently Asked Questions guide, Cardholder Agreement, and Cardholder Information Sheet. Study staff will load funds onto the participant's ClinCard according to the schedule above.

Randomization, blinding and any restrictions on randomization

A total of 90 subjects (60 from site 1, 30 from site 2) will be randomized to either InMT, HybMT or HybHE (1:1:1 allocation). Random assignments will be made by the study statistician in permuted blocks of size 3 and 6. The block size will also be randomly generated to minimize correct prediction of assignments and preserve approximate balance between groups, using the rand function in SAS. Administrative personnel from the Data Coordinating Center will prepare the randomization module using REDCap.

Study personnel that will be blinded to participant data, unless they will be involved with fidelity monitoring, are the MPIs, co-investigators, site PIs, DCC PIs, study biostatistician, and research assistants recruiting participants and following up to collect patient-reported outcomes. The MSC/site coordinator at UH will be unblinded for quality assurance. Prisma's site coordinator and all interventionists will be unblinded to the randomization of the participants. However, they will be blinded to patient-reported outcomes (e.g., NRS, PROMIS-29 or PROMIS-25, and ASCQ-Me). Unblinded staff will not have access to data outside the session logs that they document and no involvement in data monitoring and analyses.

## 4. SELECTION AND ENROLLMENT OF PARTICIPANTS

### 4.1 Inclusion Criteria

Participants must meet all of the inclusion criteria to participate in this study.

**A. Randomized Control Trial**

| | **Inclusion Criteria** |
|---|---|
| 1. | ≥14 years of age |
| 2. | Have a diagnosis of SCD present in their EHR |
| 3. | Meet AAPT criteria for chronic SCD pain, which includes:<br>a) Diagnosis of SCD confirmed by laboratory testing (eligibility criteria 2) |

| | |
|---|---|
| | b) Reporting ongoing pain present on most days over the past 6 months either in a single location or in multiple locations (upon screening)<br>c) Provider EHR documentation of at least one of the following signs<br>a. Palpation of the region of reported pain elicits focal pain or tenderness<br>b. Movement of the region of reported pain elicits focal pain<br>c. Decreased range of motion or weakness in the region of reported pain<br>d. Evidence of skin ulcer in the region of reported pain<br>e. Evidence of hepatobiliary or splenic imaging abnormalities (e.g., splenic infarct, chronic pancreatitis) consistent with the region of reported pain<br>f. Evidence of imaging abnormalities consistent with bone infarction or avascular necrosis in the region of reported pain<br>d) Per provider documentation, there is no other diagnosis that better explains the signs and symptoms |
| 4. | Ability to communicate in English |
| 5. | Has an email address and access to mobile device with a functioning data plan |
| 6. | Reporting that pain interfered with daily activities at least 1-2 days in the past week |

**B. Qualitative Interviews**

| | **Inclusion Criteria** |
|---|---|
| 1. | **Participants:** Individuals who participated in the RCT |
| 2. | **Participants:** Access to the internet and a device with videoconferencing capabilities |
| 3. | **Providers/Staff:** Clinical providers in the SCD centers for at least 6 months including the study period at University Hospitals or Prisma Health (physicians, nurse practitioners, physician assistants, and registered nurses) OR music therapist and HybHE interventionist involved with the MULTI-MUSIQOLS study for at least 6 months |
| 4. | **Providers/Staff***:* 18 years of age or older |

### 4.2 Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation.

**A. Randomized Control Trial**

| | **Exclusion Criteria** |
|---|---|
| 1. | Currently engaging in practicing mindfulness, meditation, MT, or other mind-body practices under the guidance of a healthcare professional for the purposes of pain management |
| 2. | A planned major medical event within 14 weeks of the screening date, which could include: childbirth, orthopedic surgery, gene therapy trial, or stem cell transplant (these criteria do not include blood transfusions, exchange transfusions, or other pharmacologic pain treatment). |
| 3. | Having a significant visual, hearing, or cognitive impairment |

| | |
|---|---|
| 4. | Previously participated in MUSIQOLS single-site pilot study (STUDY20180101) |

**B. Qualitative Interview**

| | **Exclusion Criteria** |
|---|---|
| 1. | **Participants:** N/A |
| 2. | **Providers/Staff:** N/A |

### 4.3 Study Enrollment Procedures

**Recruitment Methods**

Randomized Control Trial: Patients will be referred by members of the outpatient SCD team at participating sites (UH Seidman Cancer Center Adult SCD Clinic or UH Rainbow Babies & Children's Pediatric Sickle Cell Anemia Center [site 1] and Prisma Health Lifespan Comprehensive SCD Program [site 2]). Providers will be able to email patient information to a secure research email monitored by the site's study staff, comprised of the site's study coordinator (SC) and research assistant (RA) or meet with study staff to review patient lists for upcoming outpatient clinic visits or inpatient care. Following the patient referral, the study staff from the respective SCD center will review the patient's paper and/or electronic health record (EHR) to verify the patient's initial eligibility (age, understanding of English language, and diagnosis of SCD). After meeting these initial criteria, the study staff will enter the patient information in the screening log in REDCap. The study staff will prepare Participant Eligibility Source Document forms for each initially eligible patient arriving for an appointment or who has been admitted to the hospital for that day. During daily huddles, weekly meetings, or while in the SCD center, study staff will meet with providers to complete the Participant Eligibility Source Document form for determining patient's signs of SCD and AAPT category. The study staff will approach eligible patients, and their parent/guardian when necessary, at a convenient time during their next (1) regularly scheduled visit to the outpatient SCD center, (2) visit to an infusion center, or (3) inpatient admission prior to discharge.

If the patient and parent/guardian has time to discuss the study right then, the study staff will continue with recruiting procedures. If the patient and parent/guardian do not have time during their appointment, the study staff will return at a more convenient time that day or ask to set up another time to meet to discuss the study in person.

After a brief explanation of the study and patient approval, the study staff will continue to determine eligibility by (1) asking about duration, frequency, and interference related to their pain, and (2) confirming the patient's access to an email address and mobile phone with a functioning data plan. If the patient meets all eligibility criteria and expresses interest in participating in the study the SC or RA will seek to obtain informed consent from adult patients and parents of minors, as well as signature from minors. If the adult patient is not interested in participating in the study or refuses to provide/confirm their phone number and email for follow up assessments and scheduling, a reason for refusal will be documented in REDCap by the study staff. If the minor patient is not interested in participating in the study or

they or their parent/guardian refuses to provide/confirm their phone number and email for follow up assessments and scheduling, a reason for refusal will be

documented in REDCap by the study staff.

Qualitative Interview: *Patient Participants:* The consent will inform the patient that if they are randomized to receive InMT, HybMT, or HybHE a study team member may contact them to ask if they would like to participate in an additional interview, and that they may refuse to participate in the interview portion of the study without affecting their participation in the other portion of the research. They will be informed that the interview will be recorded and transcribed and that a study information sheet will be shared and reviewed with them prior to the start of the interview. Study staff will contact the patients who expressed interest in participating in the interview via phone and/or email within 2-3 weeks of their final session. Participants may decline to participate in the interview when contacted to schedule the interview without penalty of withdrawal.

*SCD Provider & Staff, Music Therapist, and HybHE Interventionists:* We will use staff rosters to identify physicians, advance practice providers, nurses and SCD center staff who have been employed by the SCD center at one of the two sites during the data collection period and to identify MULTI-MUSIQOLS music therapists and HybHE interventionists performing the intervention as part of the study. Stakeholders will be presented with a study information sheet explaining the interview objectives, procedures, benefits and risks. A verbal consent will be obtained to continue with the interview. Study staff who have been trained to conduct the qualitative interviews will contact these providers and staff by email, followed by phone, to invite them to participate.

**Documentation of Reasons for Ineligibility**

We will maintain a screening and enrollment log to document ineligibility reasons and non-participation of eligible candidates in REDCap.

**Informed Consent Process**

Randomized Control Trial: During the initial approach, the study staff will give a brief explanation of the study, the time commitment and answer any preliminary questions from the patient. If the patient and parent/guardian, when appropriate, is/are willing to continue with the recruitment procedures, at this point, study staff will complete the screening process by asking the patient about pain duration, frequency, and interference in relation to their SCD, and access to WiFi, devices and data plans. If eligibility is confirmed between 2 and 6 weeks away from each cohort's intervention start date, study staff will set up an appointment with the patient (and parent/guardian, when necessary) at the SCD center or another location preferred by the participant (e.g., community center) to obtain consent/assent and baseline assessments within 2 weeks of the cohort intervention start date. If the eligibility is confirmed within 2 weeks of the cohort start date, study staff will continue directly to the consent/assent and baseline assessment process, time permitting. If a patient/parent/guardian does not have time during their screening visit to complete the consent and baseline assessments, an appointment will be scheduled to complete these documents at the patient/parent/guardian's convenience within 2 weeks prior to the cohort intervention start date. If the patient/parent/guardian cannot meet within 2 weeks of the cohort intervention start date, study staff will attempt to schedule the consent/baseline assessment appointment within the first weeks after the cohort intervention start date. If the patient/parent/guardian still cannot meet

during that time, then their recruitment will be held over to a subsequent cohort. If this delay occurs during the final study cohort, then the patient will not be able to participate in the study. If needed, the study staff will provide the patient with transportation assistance to attend the consent and baseline assessment visit.

Study staff at University Hospitals and Prisma will obtain electronic signature on the eConsent from the adult patient or the minor's parent/guardian and the minor patient.

The Informed consent process will occur in a private treatment room or consult room out of the earshot of others to maintain privacy. Patients and parents/guardians will be provided with a hard copy of the consent form along with an identical electronic version to read along with the SC or RA. Patients, parent/guardians, and study staff will read through the informed consent document together at this time. The study staff will answer any questions the adolescent or adult patient or parent/guardian may have about the study and allow time for the patient and parent/guardian to summarize the study procedures to confirm understanding. If the patient or parent/guardian would like more time to consider participation in the study, they can take the consent form home to review and consider and then bring it to their next visit to the SCD Clinic. The adult patients ready to consent, will sign the electronic consent form in REDCap by "making their mark" on the signature line to indicate that they understand the document. After this is documented in REDCap by the study staff, the minor patient and the parent/guardian of the minor will sign the electronic consent form in REDCap by "making their mark" on the signature line to indicate that they understand the document.

A partial waiver of consent will be used to review the medical charts for pre-screening purposes. This waiver will only be used to access patients' PHI following the referral and prior to obtaining written informed consent. Patients will still be fully informed of study details prior to giving written consent and participating in research.

Qualitative Interviews: *Participant Interviews Consent Process:* Participants who are consented to participate in the RCT will be informed as part of that consent process that we may approach them to invite them to participate in an interview. The consent form will include language informing the patient that the interview will take place via a HIPAA-compliant commercial tele-health platform: (e.g. Zoom Health Professional or Doxy.me) and will be recorded and transcribed. There will also be an option for the participant to opt out of being contacted for the interview. Study staff will contact participants within 2-3 weeks after their final session to schedule the interview and to share the study information sheet to review. Participant contact with the research staff for qualitative interviews will be documented in REDCap with up to 5 attempts to schedule the qualitative interview. At the time of the interview, the interviewer will review the study information sheet with the participant. This document will explain that the interview will be recorded and transcribed, and will reiterate the voluntary nature of participation. The document will explain that if the participant continues with the interview, they are agreeing that they have read the information and that they voluntarily agree to participate and to be recorded for transcription purposes.

*Provider/Interventionist Interview Consent Process:* Identified providers/staff and interventionists will be contacted by study staff via email followed by phone and invited to participate in the interview. They will schedule the interview at the providers' convenience. A study information sheet will be shared via email with the provider ahead of the interview, and will be reviewed at the beginning of the

scheduled interview. This document will explain that the interview will be recorded and transcribed, and will reiterate the voluntary nature of participation. The document will explain that if the participant continues with the interview, they are agreeing that they have read the information and that they voluntarily agree to participate and to be recorded and transcribed.

**Randomization**

*Randomized Control Trial: Randomization to Group*

Random assignments will be made by the study statistician in permuted blocks of size 3 and 6. Randomization will be stratified by site and by group. The block size will also be randomly generated to minimize correct prediction of assignments and preserve approximate balance between groups, using the rand function in SAS. Administrative personnel from the Data Coordinating Center (DCC) will prepare the randomization module using REDCap. The SC or RA will enable randomization in REDCap for each participant after completion of the informed consent and baseline data collection.

After a patient completes the consent/assent and baseline assessment process, study staff will inform the respective site study coordinator (sSC). The sSC will randomize the participants into their intervention group using the REDCap tool. Once randomized, the sSC will contact the participant/parent/guardian to schedule the initial intervention session.

*Qualitative Interview*

During the informed consent process for the randomized trial, all participants will be asked if they would be willing to participate in a 30-to-60-minute qualitative interview via secure Zoom within 2-3 weeks of completing their assigned intervention.

We seek to enroll 24 participants equally across the 3 groups ($n$ = 8 per group), and a comparable number by sex (males vs females), age group (≥30 vs < 30), and site (16 from UH and 8 from Prisma).

# 5. STUDY INTERVENTIONS

## 5.1 Interventions, Administration, and Duration

*HybMT and InMT*

Randomized participants will be assigned to a single music therapist for the duration of their study intervention (6-8 weeks). At each site, two music therapists will be trained to provide the study intervention, with one therapist providing the HybMT interventions and the other providing the InMT interventions. We expect the distribution of participants to be:

At Prisma/USC

- For 20 MT participants (10 InMT and 10 HybMT), one music therapist will provide the InMT interventions and the other will provde the HybMT interventions.

At UH/CWRU

- For 40 MT participants (20 to InMT and 20 HybMT), one music therapist will provide the InMT interventions and the other will provde the HybMT interventions.

*HybHE*

Randomized participants will be assigned to a single HybHE interventionist for the duration of their study intervention (6-8 weeks). At each site, two graduate nursing students will be trained on the HybHE intervention, one being the primary interventionist and the second as a back-up to provide flexibility in coverage. We expect the distribution of participants to be:

At Prisma/USC

- For 10 HybHE participants, the primary HybHE interventionist will be a dedicated interventionist to this study group.

At UH/CWRU

- For 20 HybHE participants, the primary HybHE interventionist will be a dedicated interventionist to this study group.

To minimize the burden on study interventionist, cohorts will be recruited quarterly (i.e., 15 participants per quarter [Qtr]).

*UH/CWRU (n = 10/Qtr)*

Music therapist(s) providing 36 – 48 sessions/Qtr

- InMT (*n* ~ 3 – 4, max = 4) x 6 sessions = 18 – 24 sessions/Qtr
- HybMT (*n* ~ 3 – 4, max = 4) x 6 sessions = 18 – 24 sessions/Qtr

Graduate nursing student providing 18 – 24 sessions/Qtr

- HybHD (*n* ~ 3 – 4, max = 4) x 6 sessions = 18 – 24 sessions/Qtr

*Prisma/USC (n = 5/Qtr)*

Music therapist(s) providing 12 – 24 sessions/Qtr

- InMT (*n* ~ 1 – 2, max = 2) x 6 sessions = 6 – 12 sessions
- HybMT (*n* ~ 1 – 2, max = 2) x 6 sessions = 6 – 12 sessions

Graduate nursing student providing 6 – 12 sessions/Qtr

- HybHD (*n* ~ 1 – 2, max = 2) x 6 sessions = 6 – 12 sessions/Qtr

Receiving either intervention (i.e., InMT, HybMT, or HybHE) will not affect the patient's usual care in that any medications, infusions, or most services will continue to be available under the direction of the patient's care provider team. Study participants will be asked to refrain from receiving mindfulness, meditation, MT, or other mind-body practices for the purposes of pain management under the guidance of professionals not affiliated with the study while participating in the study interventions. Study participation will be noted in the patient's EHR (i.e., flagged in Epic). Other MT providers within the departments at UH and Prisma will be advised to look for this notation and not approach study participants for additional services

while they are actively participating in the study.

Parent/guardians of minor participants will be encouraged to remain on site during participant's in-person sessions at the SCD center or another location preferred by the participant (e.g., community center). However, the parent/guardian will be asked to remain outside of the session space.

The study music therapists will adhere to the following approach:
Participants in the MT condition (either InMT or HybMT) will receive 6 MT sessions over 6 weeks (see Table 1 below for descriptions of each session). Each MT session will last no longer than one hour. This 6-week treatment period may be extended to up to 8 weeks if a scheduling conflict prevents a participant from receiving the 6 MT sessions over 6 consecutive weeks. The first session will be delivered one-on-one in-person at the SCD center main campus, satellite campus, or another location preferred by the participant (e.g., community center). The focus of this session will include building rapport, goal setting, understanding participants' music preferences, providing education on pain and music analgesia, and providing education on how to engage in future virtual sessions.

For participants randomized to the InMT arm, subsequent sessions will take place at the SCD center main campus, satellite campus, or another location preferred by the participant (e.g., community center). For participants randomized to the HybMT arm, subsequent sessions will occur virtually via a secure telehealth platform (e.g. Zoom Health Professional). If participants lack their own tablets, computers, or home internet, they will be provided with iPads preconfigured with data plans and headphones to facilitate receiving the intervention.

At the start and end of each MT session, the participant will complete 0-10 numeric rating scale measures of pain, stress, anxiety, and fatigue (see section 6.1 for description). Each MT session will include (1) setting an agenda, (2) an explanation of the music exercise, (3) a demonstration of the music exercise in which the MT-BC will engage the participant in practicing the music exercise (e.g., breathing, progressive muscle relaxation, imagery), (4) time to process the participant's response to the exercise, (5) time for the MT-BC to electronically deliver the music exercise to the participant and ensure that the participant has all materials necessary to use the exercise at home, and (6) a homework assignment for the participant to practice the music exercise taught in that session at least once per day until the following MT session. The genres of each music exercise (i.e., music-based breathing exercise, progressive muscle relaxation, imagery, and active music making) will be personalized to participants' preferences (e.g., hip-hop, gospel, R&B, jazz, rock, and/or soul) based on the music preferences disclosed in the first session. Each music exercise lasts an average of 10.9 minutes. As the music exercises are being demonstrated, the MT-BC will simultaneously record the exercise using GarageBand for MacOS. Participants will report their use of the music exercises at the beginning of MT sessions 2-6, and the music therapist will note this in REDCap. We will also use REDCap surveys to remind participants about upcoming MT sessions and prompt them to confirm their upcoming attendance.

Participants will be provided with all necessary materials (e.g., instruments, audio files, headphones) needed to practice the music exercises at home, including instructions and personalized audio recordings of music exercises delivered via a secure Box® folder, email, and/or Airdrop® depending on the functions of the participant's mobile device. Participants will not have to purchase their own musical or electronic materials to participate in the MT interventions. Participants will be able to contact the music therapist via secure message in MyCap or via email if they have any questions about using the music exercises during the study.

**Table 1. Description of MT Sessions.**

| Session | Description |
|---|---|
| **1) Education** | Explain pain mechanisms in SCD and rationale for how music helps to reduce pain; receive devices for hybrid session, as needed |
| **2) Breathe** | Teach deep breathing exercise with music |
| **3) Relaxation** | Teach guided progressive muscle relaxation (PMR) exercise with music |
| **4) Imagery** | Teach music-based imagery exercise |
| **5) Music Making** | Teach active music making exercise |
| **6) Conclusion** | Review previous MT exercises and make plan for coping with future challenges |

The HybHE interventionists will adhere to the following approach:
The HybHE control will be adapted from Project PEEP: Patients Empowered and Educated Providers. The Sickle Cell Community Consortium developed Project PEEP with a grant from Global Blood Therapeutics. Project PEEP addresses unmet needs directly identified and prioritized by a collective of patients with SCD, caregivers, and community-based organizations. The objective is to provide the tools and resources to improve communication and increase positive patient-provider interactions to receive quality, timely care. For the proposed study, we will use modules from the curriculum developed for patients living with SCD. All modules were developed with input from individuals living with SCD. Dr. Bailey was a critical developer of the Project PEEP curricula, and she will serve as a consultant to assist with its use in this R01 feasibility pilot RCT.

Participants in the HybHE condition will receive 6 HybHE sessions over 6 weeks (see Table 2 below for descriptions of each session). Each HybHE session will last no longer than one hour. This 6-week treatment period may be extended to up to 8 weeks if a scheduling conflict prevents a participant from receiving the 6 HybHE sessions over 6 consecutive weeks. Like the HybMT group, the first session will be delivered one-on-one in person at the SCD center main campus, satellite campus, or another location preferred by the participant (e.g., community center). The focus of this session will include building rapport, goal setting, understanding the HybHE intervention, and providing education on how to engage in future virtual sessions.

For participants randomized to the HybHE arm, subsequent sessions will be delivered virtually via Zoom. If participants lack their own tablets, computers, or

home internet, they will be provided with iPads preconfigured with data plans and headphones to facilitate receiving the intervention. Participants will be given iPads to receive the intervention and complete outcome measures.

Each HybHE session will include (1) setting an agenda, (2) an explanation module, (3) time to review the module, (4) time for the HealthED interventionist to answer any questions, and (5) a homework assignment for the participant to reflect on the module and reflect on how the content can be used to improve care-seeking. Participants will report their use of HybHE content to HybHE interventionists at the beginning of session 2-6. We will also use MyCap to remind participants about upcoming HybHE sessions and prompt them to confirm their upcoming attendance.

Participants will be provided with all necessary materials to fully engage in HybHE (e.g., manual of modules) needed to practice the content of the modules at home. These materials will be delivered via a secure Box® folder, email, and/or Airdrop® depending on the functions of the participant's mobile device. Participants will not have to purchase electronic materials to participate in the HybHE interventions. Participants will be able to contact the HybHE interventionist via MyCap or via email if they have any questions about using the HybHE content during the study.

**Table 2. Description of HybHE Sessions.**

| Session | Description |
|---|---|
| **1) Science of SCD** | Reviews the science of SCD, focusing on blood, organs affected, labs, and the biology behind vaso-occlusive crises; receive devices for hybrid sessions, as needed. |
| **2) Identifying Barriers in the Emergency Department** | Introduces common barriers (supported by research) that patients with SCD experience in the ED. |
| **3) Tools for Navigating the Healthcare System** | Explores the healthcare infrastructure, chain of command, documenting care (both positive and negative) and the process of filing a complaint in a constructive and effective manner. |
| **4) SBAR: Healthcare Based Communication for Patients (Part 1)** | Introduces Situation, Background, Assessment, Recommendation (SBAR) and as an effective form of communication for patients when accessing medical care and covers Situation (S) and Background (B) of SBAR. |
| **5) SBAR: Healthcare Based Communication for Patients (Part 2)** | Reviews SBAR and covers Assessment (A) and Recommendation (R) of SBAR. |
| **6) Conclusion** | Review content from sessions 1-5 and make a plan to address future challenges. |

## 5.2 Handling of Study Interventions

To ensure HybMT and HybHE participants will have access to a reliable means of study engagement, we plan to purchase up to 36 iPads that these participants will use during their study participation (if needed) and return at the end of their

intervention period (i.e., after session 6). These iPads will be equipped with cellular capacity to provide data bandwidth for engaging in videoconferencing in the absence of a stable WiFi connection if needed. The sSC will track the distribution of iPads within REDCap.

The participant's need for a device will be assessed at recruitment by asking questions regarding (1) what devices they have access to at home, (2) whether they have reliable WiFi internet at home, (3) whether they currently have a data plan for their smartphone (if applicable), and (4) whether they have engaged in video conferencing at home before. The person conducting the informed consent visit will distribute the iPad (if needed) following randomization.

We will plan to purchase 2-month LTE data plans as needed to provide to participants whose WiFi and/or limited data plans prevent or hinder engagement in videoconferencing at home. The sSC will track the distribution of data plans within REDCap. The iPads will be pre-configured with these data plans when they are provided to participants during HybMT or HybHE session 1.

We will purchase 90 closed back-headphones equipped with microphones for all study participants to ensure consistent audio delivery. The sSC or RA will distribute headphones during the consenting and baseline assessment appointment.

We will provide HybMT patients with a small diatonic xylophone to facilitate participation in session 5 (music making) at home while engaging in the session virtually. This will be provided to HydMT participants during their in-person MT session and collected following their final HybMT session.

To alleviate the burden on participants traveling to participate in in-person consenting and in-person sessions, local bus passes, rideshare assistance, or mileage reimbursement and parking passes will be distributed as needed. If a patient/parent/guardian needs a bus pass to attend a consenting and baseline assessment appointment, passes will be provided during the recruitment session. During the consenting and baseline appointment, bus passes or rideshare assistance will be available to those who express a need in order to attend the first in-person session for all study arms. During the first session, those who have been randomized to the InMT arm will receive bus passes based on their need or discuss the rideshare assistance and mileage reimbursement process. Site SC will track the disbursement of bus passes in REDCap.

## 5.3 Concomitant Interventions

### 5.3.1 Allowed Interventions

There are no restrictions for participants' care teams to prescribe or administer medications or refer to most services. Participants have the ability to continue any SCD interventions in place prior to enrollment except when prohibited (see section 5.3.3).

### 5.3.2 Required Interventions

For participants randomized into the InMT or HybMT arms, the 6-session MT intervention is required.

For participants randomized into the HybHE arm, the 6-session HybHE intervention is required.

### 5.3.3 Prohibited Interventions

Participants will be asked to not engage in a new practice of mindfulness, meditation, MT, other mind-body practices under the guidance of professionals for the purposes of pain management during their time participating in the study.

## 5.4 Adherence Assessment

Recruitment proportion will be deemed successful if 35% of eligible approached patients enroll in the study. Recruitment rate will be successful if we can recruit 10 participants at site 1 and 5 participants at site 2 per quarter.

Individual attendance will be acceptable if a given participant attends 4 of 6 sessions in 8 weeks. These 4 sessions must include the first session and any 3 out the 4 sessions between sessions 2-5. We anticipate a 70% attendance rate in each arm. We will consider retention to be successful if we retain 70% of participants until the final survey time point (6-week follow-up).

Individual session attendance will be deemed complete if the participant attends 2/3 of the session including (1) the introduction (discussing experience with the MT or HybHE exercise over previous week, providing education on rationale for intervention); (2) setting of the agenda; and (3) the main intervention (e.g., co-creating the music for the intervention, customizing the place and imagery to participants' preferences, experiencing and recording the intervention). The last third of the intervention includes verbally processing the participant's experience of the intervention, delivering the digital file, and providing directions for use in the future. If this last third is not provided in the live session, the music therapist or HybHE interventionist will provide this information via email.

Home practice will be considered sufficient if 70% of participants practice intervention exercises at least once per week.

We will consider data quality/completeness to be successful if data completeness exceeds 90% in quality control review.

# 6. STUDY PROCEDURES

## 6.1 Schedule of Evaluations

Randomized Control Trial

Participants will enter their responses to the patient reported outcome (PRO) measures detailed below directly into REDCap using an iPad provided by the RA or SC (baseline) or using their own devices (post-intervention and 6-week follow-up). The study staff will hand the patient a tablet for confidential self-administration. Once

the patient completes the questionnaires, the answers will be masked so the research staff will not have access to the scores. The numeric rating scale (NRS) is a validated measure for acute pain intensity.[47] It has been widely used within studies of integrative therapies[48] and found to be more reliable than the visual analog scale in clinical trials, especially among patients of low socioeconomic status.[48] Investigators in previous studies have also used the 0-10 NRS to measure other domains including anxiety in clinical effectiveness studies of nonpharmacologic interventions (e.g., acupuncture, massage therapy, and meditation)[49-51] and stress in a randomized controlled trial of music therapy.[52] Prior research among adults with sickle cell disease has also demonstrated that acceptability of the Edmonton Symptom Assessment Scale measures of fatigue and anxiety for outpatient symptom monitoring (0 – 10 scale).[53] For all scales, questions will be phrased as "How much (stress, pain, anxiety, or fatigue) are you having right now?" with 0 signifying "none" and 10 signifying "worst possible."

| Variable | Measure source | Data Collection Time Point | | | | |
|---|---|---|---|---|---|---|
| | | Screening & Baseline | Pre + post-session | Post intervention | Post-intervention exercise use | 6-week follow up |
| **Treatment outcomes** | | | | | | |
| Pain interference (primary) | Pain interference items from the PROMIS-29 Profile (if age ≥ 18) or PROMIS-25 Pediatric Profile (if age < 18) | X | | X | | X |
| HRQoL[a] | PROMIS-29 Profile (if age ≥ 18) or PROMIS-25 Pediatric Profile & PROMIS Pediatric Sleep Disturbance 4a (if age < 18) ASCQ-Me | X | | X | | X |
| Self-efficacy | SCSES | X | | X | | X |
| Pain intensity | NRS | | X | | | |
| Stress | NRS | | X | | | |
| Anxiety | NRS | | X | | | |
| Fatigue | NRS | | X | | | |
| **Baseline variables** | | | | | | |
| Participant and emergency contact information | EHR and self-report | X | | | | |
| Demographics[b] | EHR and self-report | X | | | | |
| Music use | Music use assessment[c] | X | | | | |
| **EHR review** | | | | | | |
| Clinical characteristics[d] | EHR | X | | | | X |
| **Implementation outcomes** | | | | | | |
| Acceptability | Likert scale | | | X | | |
| Use of MT exercises/HybHE assignments at home *during intervention* | Self-report to interventionists (at beginning of session) | | X | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Use of MT exercises/HybHE assignments at home *post-intervention* | REDCap surveys | | | X | X | X |

[a]HRQoL domains include (1) PROMIS-29 Profile measures of physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference and pain intensity OR PROMIS-25 Pediatric Profile measures of physical function, anxiety, depression, fatigue, peer relationships, pain interference and pain intensity and PROMIS Pediatric Sleep Disturbance 4a; and (2) ASCQ-Me measures of pain impact, emotional impact, and social functioning impact. [b]Demographic variables include age, gender, education level, religious background, income, employment status, race, ethnicity, and marital status. [c]Music use will be assessed using the survey developed by Rodgers-Melnick et al.[32] [d]Clinical characteristics include age, SCD type, insurance type, SCD complications (e.g., history of stroke, avascular necrosis), healthcare utilization (i.e., hospital admission, emergency department visit, or same-day pain infusion) at any hospital in last 12 months (baseline) and since randomization (6 weeks post-intervention), SCD treatment, and opioid prescriptions in last 14 weeks (baseline) and since randomization (6 weeks post-intervention)

*Please see attached **Screening Log** to be reviewed during the screening process.*

*Please see attached **Screening Questionnaires** to be completed during the screening process.*

*Please see attached **Informed Consent** documents*

*Please see attached **Study Information Sheets** for participant and provider interviews*

*Please see attached **Demographics Questionnaire** to be collected after subject agrees to participate.*

*Please see attached **Baseline, Post-Intervention and 6-weeks Post-Intervention** questionnaire**s** to be collected at each time point, including **Music Use Assessment** at Baseline and **Treatment Acceptability** at 6-Weeks*

*Please see attached **Pre + Post Session** for NRS measures*

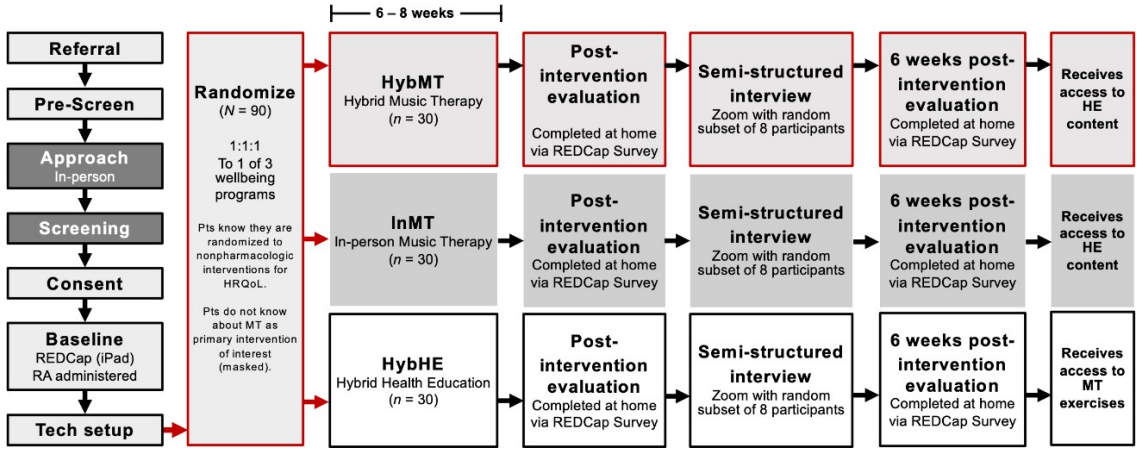
*Please see attached **Post-intervention Exercise Use** to be collected weekly.*

*Please see attached **Interview Guides** for semi-structured participant, provider and interventionist qualitative interview guides.*

## 6.2 Description of Evaluations

### 6.2.1 Screening Evaluation

At each site, the study staff will work with the SCD center staff and providers to identify patients who may be eligible for the study. Study staff will be embedded in the SCD centers up to 4-5 days per week during active recruitment periods. As the schematic below shows, study staff will use the EHR to evaluate patient eligibility for patients on the clinic roster or referred through provider referral.




The study team will procure a Participant Eligibility Source Document form for each patient that pre-screens as eligible to obtain patient's signs of SCD and AAPT category from SCD providers (i.e., hematologist or advanced practice provider). For patients who continue to be eligible, study staff will approach the patient at their next (1) regularly scheduled visit to the outpatient SCD center, (2) visit to an infusion center, or (3) inpatient admission prior to discharge. Study staff will approach the patient and give brief details about the study, the time commitment, and answer any initial questions from the patient.

If the patient/parent/guardian has time to discuss the study right then, the study staff will continue with recruiting procedures. If the patient/parent/guardian do not have time during their appointment, the study staff will return at a more convenient time that day or ask to set up another time to meet to discuss the study in person.

After a brief explanation of the study and patient approval, the study staff will continue to determine eligibility by asking the patient to complete a REDCap survey assessing (1) duration, frequency, and interference related to their pain, and (2) the patient's access to an email address and mobile phone with functioning data plan. If the patient meets all eligibility criteria and expresses interest in participating in the study, the SC or RA will seek to obtain informed consent from adult patients and parents of minors, as well as written assent from minors. If the adult patient is not interested in participating in the study or refuses to provide/confirm their phone number and email for follow up assessments and scheduling, a reason for refusal will be documented in REDCap by the study staff. If the minor patient is not interested in participating in the study or they or their parent/guardian refuses to provide/confirm their phone number and email for follow up assessments and scheduling, a reason for refusal will be documented in REDCap by the study staff.

### Consenting Procedure

During the initial approach, the study staff will give a brief explanation of the study, the time commitment and answer any preliminary questions from the patient. If the patient and parent/guardian, when appropriate, is/are willing to continue with the recruitment procedures, at this point, study staff will complete the screening process by asking the patient about pain duration and frequency in relation to their SCD and access to WiFi, devices and data plans. If eligibility is confirmed between 2 and 6 weeks away from each cohort's intervention start date, study staff will set up an

appointment with the patient (and parent/guardian, when necessary) at the SCD center main campus, satellite campus, or another location preferred by the participant (e.g., community center) to obtain consent/assent and baseline assessments within 2 weeks of the cohort intervention start date. If the eligibility is confirmed within 2 weeks of the cohort start date, study staff will continue directly to the consent/assent and baseline assessment process, time permitting. If a patient/parent/guardian does not have time during their screening visit to complete the consent and baseline assessments, an appointment will be scheduled to complete these documents at the patient/parent/guardian's convenience within 2 weeks prior to the cohort intervention start date. If the patient/parent/guardian cannot meet within 2 weeks of the cohort intervention start date, study staff will attempt to schedule the consent/baseline assessment appointment within the first 2 weeks after the cohort intervention start date. If the patient/parent/guardian still cannot meet during that time, then their recruitment will be held over to a subsequent cohort. If this delay occurs during the final study cohort, then the patient will not be able to participate in the study.

UH and Prisma study staff will obtain an electronic signature on the eConsent from the adult patient or the minor's parent/guardian and assent from the minor patient.

Prisma study staff will obtain a wet ink signature on their paper consent from the adult patient or the minor's parent/guardian and assent from the minor patient.

Informed consent will occur in a private treatment room or consult room out of the earshot of others to maintain privacy. Patients and parents/guardians will be provided with a hard copy of the consent form along with electronic version to read along with the SC or RA. Patients, parent/guardians, and study staff will read through the informed consent document together at this time. The study staff will answer any questions the adolescent or adult patient or parent/guardian may have about the study and allow time for the patient and parent/guardian to summarize the study procedures to confirm understanding. If the patient or parent/guardian would like more time to consider participation in the study, they can take the consent form home to review and consider and then bring it to their next visit to the SCD Clinic. Once ready to consent, the adult patients will sign the electronic consent form in REDCap by "making their mark" on the signature line to indicate that they understand the document. The minor patient and the parent/guardian of the minor will sign the electronic consent form in REDCap by "making their mark" on the signature line to indicate that they understand the document.

A partial waiver of consent will be used to review the medical charts for pre-screening purposes. This waiver will only be used to access patients' PHI following the referral and prior to obtaining written informed consent. Patients will still be fully informed of study details prior to giving written consent and participating in research.

**Screening**

All screening activities must be completed before consent and study enrollment. All screening activity will take place 1-6 weeks prior to the cohort intervention start date.

| | **Inclusion Criteria** | **When Screening Occurs** |
|---|---|---|
| 1. | ≥14 years of age | Pre-screening |
| 2. | Have a diagnosis of SCD present in their EHR | Pre-screening |

| | | |
|---|---|---|
| 3a. | Per provider, the patient displays at least one of the following signs:<br>• Palpation of the region of reported pain elicits focal pain or tenderness<br>• Movement of the region of reported pain elicits focal pain<br>• Decreased range of motion or weakness in the region of reported pain<br>• Evidence of skin ulcer in the region of reported pain<br>• Evidence of hepatobiliary or splenic imaging abnormalities (e.g., splenic infarct, chronic pancreatitis) consistent with the region of reported pain<br>• Evidence of imaging abnormalities consistent with bone infarction or avascular necrosis in the region of reported pain | Pre-screening/ Study staff obtains information from provider |
| 3b | Reporting ongoing pain present on most days over the past 6 months either in a single location or in multiple locations | Patient facing |
| 3c | Per provider documentation, there is no other diagnosis that better explains the signs and symptoms of pain | Pre-screening/ Study staff obtains information from provider |
| 4. | Ability to communicate in English | Pre-screening |
| 5. | Have an email address and access to mobile device with a functioning data plan | Patient facing |
| 6. | Reporting that pain interfered with daily activities at least 1-2 days in the past week | Patient facing |

| | **Exclusion Criteria** | **When Screening Occurs** |
|---|---|---|
| 1. | Currently engaging in practicing mindfulness, meditation, MT, or other mind-body practices under the guidance of a healthcare professional for the purposes of pain management | Pre-screening |
| 2. | Having a significant visual, hearing, or cognitive impairment | Pre-screening |
| 3. | Previously participated in MUSIQOLS single-site pilot study (STUDY20180101) | Pre-screening |
| 4. | Have a <u>planned</u> major medical event in the next 14 weeks such as (but not limited to) childbirth, orthopedic surgery, gene therapy, or stem cell transplant (these criteria do not include blood transfusions, exchange transfusions, or other pharmacologic pain treatment) | Pre-screening |

### 6.2.2 Enrollment, Baseline, and/or Randomization

**Enrollment**

Subjects are considered enrolled once all screening criteria are met and the informed consent document has been signed. Only one electronic informed consent document will be used, as we have requested a partial HIPAA waiver for screening. The date of enrollment will be the date the consent form is signed.

**Baseline Assessments**

- The Patient Reported Outcomes Measurement Information System Adults: (PROMIS-29 Profile): PROMIS-29 measures include physical function (4 questions), anxiety (4 questions), depression (4 questions), fatigue (4 questions), sleep disturbance (4 questions), ability to participate in social roles and activities (4 questions), pain interference (4 questions), and pain intensity (1 question). Adolescents: (PROMIS Pediatric Profile-25): PROMIS-25 measures include physical function (4 questions), anxiety (4 questions), depressive symptoms (4 questions), fatigue (4 questions), peer relationships (4 questions), pain interference (4 questions), and pain intensity (1 question) and PROMIS Pediatric Sleep Disturbance 4a. Most PROMIS measures elicit participant responses based on the 7 days prior using 5-point response options ranging from ‘‘never’’ to ‘‘always’’ in most measures and from ‘‘without any difficulty” to ‘‘unable to do” for physical functioning measures. Higher scores indicate greater severity of anxiety, depression, fatigue, sleep disturbance, and pain interference; greater ability to participate in social roles and activities; and less severity for physical function impairment. PROMIS measures are scored on a general population-based T-score metric with a mean of 50 and a standard deviation of 10.[54, 55] Different PROMIS measures have been validated in the adult and pediatric populations and have been evaluated in patients with SCD.[56-58]
- Sickle Cell Self-Efficacy Scale (SCSES): Self-efficacy will be measured using the Sickle Cell Self-Efficacy Scale (SCSES). The SCSES is a nine-item Likert scale originally developed for adults with SCD[59] and revised in a follow up study for adolescents using a sample of 131 individuals age 11-19.[27] Clay and Telfair reported a Cronbach’s alpha of 0.87 for the nine items, indicating good internal consistency as well as a significant association with personal health care items showing convergent validity.
- Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me): ASCQ-Me is a patient-reported outcome measurement system that addresses the physical, social, and emotional impact of SCD. This study will utilize the ASCQ-Me 5-item short forms for pain impact, emotional impact, and social functioning impact. ASCQ-Me is a valid measure and highly reliable for use with adults and adolescents with SCD.[60-62] ASCQ-Me scores are calculated in the direction of overall health, with higher ASCQ-Me scores indicating better health.
- Numeric rating scale: Participants will complete 0-10 (0 = none, 10 = worst possible) numeric rating scale (NRS) measures of pain, stress, anxiety, and fatigue prior to and following each session using a REDCap survey sent to their own devices via Twilio. These scores will be used to understand participants’ symptoms pre-session, post-session, and longitudinally over the course of the study; and determine which MT exercises are most beneficial for MT participants’ symptoms. Intervention facilitators will be blinded to participants’ NRS scores.
- EHR Review: Study staff will conduct an EHR review that includes age at the time of recruitment, insurance type, SCD type, SCD complications, emergency department utilization in the past 12 months, hospital admissions in the past 12 months, same-day pain treatment at infusion center in the past

12 months, current disease modifying therapies, and detailed description of pain medications prescribed in the past 14 weeks.

- Access to technology and contact information: Study staff will collect access to technology information from participants including (1) cell phone number (2) cell phone carrier, (3) mobile device type, (4) email address, and (5) emergency contact information.

- Mind/Body pain management and transportation questionnaire to gauge and document inclusion exclusion criteria not captured elsewhere and to document the need for transportation assistance.

**Provide Technology**

Immediately following the baseline assessment the study staff will (1) enroll the participant in MyCap, for communication between the study team and the participant, if the patient is not already enrolled, (2) demonstrate to the participant how to communicate with study personnel using chat features within MyCap, (3) provide the participant with headphones, (4) ensure the participant has a means by which to access Zoom, (5) ensure the participant can access the Box folder designated to them during their study participation, and (6) provide the participant with transportation assistance (if needed) to attend their first in-person session.

**Randomization**

Random assignments will be made by the assistant study statistician in permuted blocks of size 3 and 6. The only role of the assistant study statistician will be to handle the randomization. Accordingly, s/he will be aware of group assignment. Importantly, the primary study statistician will remain blinded to group assignment until all analyses are complete. Randomization will occur within 2 weeks of the cohort intervention start date. Site SC will be notified when the participant has signed the consent form. The sSC will complete randomization using the REDCap tool. The sSC will contact the participant to inform them of their study arm and set up their initial session.

### 6.2.3 Blinding

Study personnel that will be blinded to participant data, unless they will be involved with fidelity monitoring, are the MPIs, co-investigators, site PIs, DCC PIs, study biostatistician, and research assistants recruiting participants and following up to collect patient-reported outcomes.

The MSC/site coordinator at UH will be unblinded for quality assurance. Prisma's site coordinator and all interventionists will be unblinded to the randomization of the participants. However, they will be blinded to patient-reported outcomes (e.g., NRS, PROMIS-29 or PROMIS-25, and ASCQ-Me). Unblinded staff will not have access to data outside the session logs that they document and no involvement in data monitoring and analyses.

### 6.2.4 Follow-up Visits

| MT Session | Session Description | Evaluations completed |
|---|---|---|
| **1) Education** | Explain pain mechanisms in SCD and rationale for how music helps to reduce pain; receive devices for hybrid session, as needed | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey) |
| **2) Breathe** | Teach deep breathing exercise with music | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey)<br>• Music exercise use in past week (asked by interventionist) |
| **3) Relaxation** | Teach guided progressive muscle relaxation (PMR) exercise with music | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey)<br>• Music exercise use in past week (asked by interventionist) |
| **4) Imagery** | Teach music-based imagery exercise | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey)<br>• Music exercise use in past week (asked by interventionist) |
| **5) Music Making** | Teach active music making exercise | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey)<br>• Music exercise use in past week (asked by interventionist) |
| **6) Conclusion** | Review previous MT exercises and make plan for coping with future challenges | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey)<br>• Music exercise use in past week (asked by interventionist) |

| HybHE Session | Session Descriptions | Evaluations completed during the session |
|---|---|---|
| **1) Science of SCD** | Reviews the science of SCD, focusing on blood, organs affected, labs, and the biology behind vaso-occlusive crises; receive devices for hybrid sessions, as needed. | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey) |

| | | |
|---|---|---|
| **2) Identifying Barriers in the Emergency Department** | Introduces common barriers (supported by research) that patients with SCD experience in the ED. | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey)<br>• Health education assignment use in past week (asked by interventionist) |
| **3) Tools for Navigating the Healthcare System** | Explores the healthcare infrastructure, chain of command, documenting care (both positive and negative) and the process of filing a complaint in a constructive and effective manner. | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey)<br>• Health education assignment use in past week (asked by interventionist) |
| **4) SBAR: Healthcare Based Communication for Patients (Part 1)** | Introduces Situation, Background, Assessment, Recommendation (SBAR) and as an effective form of communication for patients when accessing medical care and covers Situation (S) and Background (B) of SBAR. | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey)<br>• Health education assignment use in past week (asked by interventionist) |
| **5) SBAR: Healthcare Based Communication for Patients (Part 2)** | Reviews SBAR and covers Assessment (A) and Recommendation (R) of SBAR. | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey)<br>• Health education assignment use in past week (asked by interventionist) |
| **6) Conclusion** | Review content from sessions 1-5 and make a plan to address future challenges. | • Ability to Participate<br>• Pre- and post-session NRS: pain; stress; anxiety; fatigue (completed via REDCap survey)<br>• Health education assignment use in past week (asked by interventionist) |

Post-intervention evaluation for all arms

Post intervention evaluations will be obtained 1-7 days post session 6 in each arm via REDCap (Twilio text). Participants will complete these evaluations at home:

- PROMIS-29 (if age ≥ 18) or PROMIS-25 Pediatric Profile & PROMIS Pediatric Sleep Disturbance 4a (if age < 18)
- Sickle Cell Self Efficacy Scale
- ASCQ-Me: Pain Impact, Emotional Impact and Social Functioning Impact
- Treatment acceptability

### 6.2.5 Completion/Final Evaluation

6-Week Post-intervention evaluation for all arms

The 6-week post intervention evaluations will be obtained 42-49 days post session 6 in each arm via REDCap (Twilio text). Participants will complete these evaluations at home:

- PROMIS-29 (if age ≥ 18) or PROMIS-25 Pediatric Profile & PROMIS

Pediatric Sleep Disturbance 4a (if age < 18)
- Sickle Cell Self Efficacy Scale
- ASCQ-Me: Pain Impact, Emotional Impact and Social Functioning Impact
- MT and/or mind/body intervention engagement outside of the protocol during the study

An EHR and prescription monitoring program review will be collected by study staff. The following data will be collected using the participant's EHR:

- Emergency department utilization since randomization date;
- Hospital admissions since randomization date;
- Same-day pain treatment at infusion center since randomization date; and
- Detailed description of pain medications prescribed since randomization.

Early Termination

The study doctor or the sponsor can stop a subject's participation at any time without their consent for the following reasons:

- If it appears to be medically harmful to them;
- If they fail to follow directions for participating in the study;
- If it is discovered that they do not meet the study requirements;
- If the study is canceled; or
- For administrative reasons, including competitive enrollment (e.g. the target number of subjects has entered the study.)

### 6.3 Provider Feasibility Assessment and Interview

A recruitment email will be sent via REDCap. Providers, staff, and interventionists who are interested will click a link to the feasibility study information sheet. Those who wish to participate in the interview will click "yes" and be directed to the survey. We will also distribute a recruitment flyer to be posted in charting areas and workspaces at each SCD center, inviting providers and staff to participate. The flyer will include a QR code that links directly to the study information sheet. Those who wish to participate will click "yes" and be directed to the survey. Feasibility surveys will be completed online by interested participants at their convenience.

- Demographic information including: gender, ethnicity, race, age, how long they have worked in the SCD center, occupation, contact with the MULTI-MUSIQOLS study and in what context
- Suitability of the intervention to the applicable population
    - To what degree do you view the MT (or HealthED) intervention as useful or suitable for this population?" (1-very inappropriate—5-very appropriate)

## 7. SAFETY ASSESSMENTS

The investigative team will monitor the data for security, integrity, and patient safety. The study teams will meet at least every 2-4 weeks to assess for adherence to the protocol and review any safety events.

There is a slight risk a participant may not like the music interventions included in the study. In that event, they may leave the session space during an MT intervention or choose not to participate in the rest of the intervention. It is possible that the participant may not be comfortable wearing headphones used for the music

interventions. If this occurs, the participant may ask the investigator to remove them.

There is a slight risk a participant may not be comfortable with the content of the HybHE intervention during one or more sessions. In this event, the participant may request skipping the topic or ending the session early.

If a participant experiences a serious adverse event (e.g., active suicidal ideation, stroke, loss of consciousness, etc.), during the HybMT or HybHE intervention, away from a medical facility, the interventionist will immediately call the local suicide prevention hotline (e.g., Frontline Cuyahoga County for site 1 or 988 Suicide and Crisis Lifeline for site 2) and/or 911 and notify dispatch of the participant's condition and location. Suicide prevention help lines will be contacted in the event of suicidal ideations and 911 will be contacted in the event of other medical emergencies. The interventionist will then notify the study coordinator via REDCap reporting who will also notify the participant's clinical team (i.e., SCD team).

If a participant experiences a serious adverse event (e.g., active suicidal ideation, stroke, loss of consciousness, etc.), while in a medical facility, the interventionist will initiate the local site's intervention protocol by contacting the clinical team at that site immediately. The interventionist will then notify the study coordinator of the adverse event via REDCap reporting. The study coordinator will also notify the participant's clinical team (i.e., SCD team) if this is not the clinical team at the medical facility.

If a participant displays or reports other physical or psychological challenges during or related to a session, the individual will be referred to their respective healthcare provider. In all cases, the interventionist will notify the appropriate clinical team (e.g., SCD team) and report the adverse event (AE).

If any of the 4 items on the PROMIS-29 or PROMIS-25 Depression 4a scale completed during baseline, post-intervention, and/or 6-week post-intervention assessments are reported as "often" or "always," then a suicidality assessment (i.e., PHQ-9 item #9) will be triggered to populate in the REDCap instrument. If any of the first 3 items on the ASCQ-Me Emotional Impact scale completed during baseline, post-intervention, and/or 6-week post-intervention assessments are reported as "often," "always," "quite," or "very" then a suicidality assessment (i.e., PHQ-9 item #9) will be asked. If the participant affirms suicidal ideation (i.e., PHQ-9 item #9 ≥1), they will immediately receive a screen referring them to call 911 in case of emergency or contact their local suicide prevention hotline. An automatic text or email message will notify the sickle cell team at the participant's site (including physicians, nurses, and social workers) of the participant's score for the team to reach out and make further assessments. The study team (i.e., study coordinator, principal investigator) will be notified immediately via automatic text or email notification for AE reporting.

Monitoring of the study for AEs will be continuous throughout the study. In the event of an AE or serious adverse event (SAE), it will be reported to the UH IRB in compliance with UH IRB standards. The MSC will be conducting weekly quality assurance checks for the first two months of enrollment and then monthly for remaining months of enrollment.

There is no guarantee of direct benefit during the interventions. Those who participate in InMT or HybMT may enjoy listening to music or having MT delivered during sessions. Those who participate in HybHE may learn more about SCD.

Participants may experience reduced symptoms of pain, anxiety, and stress after sessions.

There is no guarantee of direct benefit from participating in the qualitative interviews. The insights provided from the responses will help to improve design and implementation of the music therapy intervention.

The only alternative to participation is to not participate.

## 7.1 Specification of Safety Parameters

N/A

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

N/A

## 7.3 Adverse Events and Serious Adverse Events

An adverse event (AE) is generally defined as any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these regardless of relationship to participation in the study.any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention.

A serious adverse event (SAE) is generally defined as any event that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related"

means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and,

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

## 7.4 Reporting Procedures

RESPONSIBLE INDIVIDUALS

The site Principal Investigator (PI) is responsible for assessing all AE and SAEs. The site PI will monitor AE reporting and complete the AE PI Report in the MULTI-MUSIQOLS REDCap for events reported during the study enrollment period as reported in the EHR. Study staff and interventionists are responsible for reporting and documenting the events determined to be an AE or SAE, including any adverse events occurring during a session or reported by a subject's physician, in the MULTI-MUSIQOLS subject AE Log and reporting these events to the Clinical Coordinating Center within the required timelines.

PROCEDURES

*Reporting Adverse Events:* The PI or their delegated research staff will review reported events to determine if they qualify as an AE/SAE and assign causality and severity/intensity in REDCap. Research staff will document AE on the MULTI-MUSIQOLS Subject AE and External AE Summary logs after becoming aware of the event. Subject AE logs will be stored in the individual subject's REDCap record. The External Summary AE log must be provided to the Clinical Coordination Center upon request, including for Quality Assurance, sIRB Continuing Review, and Study Close Out.

Reporting Serious Adverse Events: Research staff will document SAE on the MULTI-MUSIQOLS Subject AE log after becoming aware of the event. The PI, or their delegated research staff, and a study physician will review, sign off on SAE and assign causality, and severity/intensity and determine if the event was unanticipated. Those evaluating SAEs will use the OHRP standards to identify unanticipated events and the definitions of AE/SAEs to characterize the event. If the event satisfies the UHCMC IRB requirements for reporting SAEs, it will be reported to the UHCMC IRB;

a. Serious
b. Unanticipated, and
c. Related to study product or study procedures

If the event is clarified as an SAE and deemed reportable to the IRB, delegated research staff will report event to the IRB within 5 days of being notified of event via the University Hospital's Cleveland Medical Center's (UHCMC) IRB's "Reportable New information Smart Form" (RNI). If more information becomes available regarding the SAE, delegated research staff will inform and follow-up with IRB.

ANTICIPATED ADVERSE EVENTS

The study team anticipates study participants may experience medical, financial and/or emotional events during their enrollment period. Examples of these events may include:

- Severe medical event not related to study intervention necessitating long admission to ICU
- Financial issues effecting housing, data access, device access, disruption to transportation access
- Emotional response during sessions, feeling uncomfortable answering survey or interview questions, feeling overwhelmed with participating

### 7.5 Follow-up for Adverse Events

Delegated research staff are responsible for all follow-up associated with AEs and SAEs and reporting this information to the IRB until the AE occurs.

### 7.6 Safety Monitoring

The NCCIH requires that all Human Subjects research studies undergo independent monitoring, and NCCIH Program Officials will provide specific guidelines to the PI for the study. Accordingly, an Independent Monitoring Committee will be assembled by the MPIs with approval required by the NCCIH.

## 8. INTERVENTION DISCONTINUATION

Early Termination

The study doctor or the sponsor can stop a subject's participation at any time without their consent for the following reasons:

- If it appears to be medically harmful to the participant;
- If they fail to follow directions for participating in the study;
- If it is discovered that they do not meet the study requirements;
- If the study is canceled; or
- For administrative reasons, including competitive enrollment (e.g. the target number of subjects has entered the study.)
- If the patient's clinical condition worsens emergently as determined by physician.

## 9. STATISTICAL CONSIDERATIONS

### 9.1 General Design Issues

#### Primary Objective

The primary objective is to refine research procedures for conducting a future fully-powered multi-site RCT

The study will examine the feasibility of the following across 2 sites:

1) data quality/completeness
2) screening rate
3) recruitment
4) retention
5) individual attendance
6) home practice

### Secondary Objectives

This study will include qualitative interviews of patients and providers/staff to assess feasibility of implementation.

## 9.2 Sample Size and Randomization

Sample Size Justification

The aim of the R01 is to examine feasibility and acceptability across sites to inform a future, full-scale trial, rather than to power the proposed study for detecting statistical differences. The Adult Sickle Cell Disease (SCD) Clinic at University Hospitals (UH) Seidman Cancer Center provides comprehensive care to over 344 active adult patients residing in Northeast Ohio. There are 66 pediatric patients between the ages of 14-17 at UH. The Prisma Health Lifespan Comprehensive SCD Program provides comprehensive care to over 213 active adult patients with SCD in South Carolina. At Prisma, there are 50 pediatric patients between the ages of 14-17. By including children aged 14 and older, we would have 673 individuals eligible for participation.

Our screening success rate will be successful if we can enroll 35% of those approached for the study. To meet that rate, we would need to approach ~28 participants at UH per quarter and ~14 at Prisma per quarter. In other words, over the course of the study we expect that

- The research team at UH will need to approach 170 individuals to enroll 60 participants (60/170 = 35%).
- The research team at Prisma will need to approach 86 individuals to enroll 30 participants (30/86 = 35%).

Therefore, our proposed recruitment goal of 90 subjects will require enrollment of 60 at UH (10 per quarter) and 30 at Prisma (5 per quarter) over the 6 quarters (18 months) of recruitment.

Recruiting over 18 months provides the opportunity to modify recruitment procedures (if necessary) and assess the impact of such modifications on attaining recruitment goals. Statistical differences in outcome variables between groups will not be investigated. However, preliminary investigation of the distribution of within-group changes will be assessed. Specifically, obtaining estimates of the standard deviation of change (from baseline) in clinical outcome measures (e.g., self-efficacy and pain interference) will be useful for power calculations for the subsequent trial. However, per published literature[63-66] and NCCIH guidance,[67] we will be using clinically important differences from the literature to calculate the sample size for the future, multi-site RCT (UG3/UH3).

Randomization

Randomization will occur within 2 weeks of the cohort intervention start date. Study staff will contact the sSC when the participant has signed the consent form. The sSC will complete randomization using the REDCap tool. The sSC will contact the participant to inform them of their study arm and set up their initial session

## 9.3 Definition of Populations

As this is a multi-site feasibility study, the intent is not to assess statistical significance across the three study groups. As such, the feasibility outcomes will be assessed with patients actually receiving their assigned intervention. Thus, an intent-to-treat population will not be used in this study.

## 9.4 Interim Analyses and Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

## 9.5 Outcomes and Data Analysis

Implementation and Treatment Outcomes
All data analyses will be preceded by extensive data checking and verification to identify and resolve the reasons for any missing values, inconsistencies, and out-of-range values. Although we anticipate little missing data based on our experience, we will carefully examine whether missingness is completely at random, at random or informative. Models proposed for analysis can handle incomplete data but do require at least that missingness be at random.

Descriptive statistics of primary and secondary outcomes will be calculated to assess their distribution overall and by sites as well as demographic characteristics (e.g. sex, age group, SCD type, household income, among others). The variables will be summarized using descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for continuous variables and by the number and percentage of patients for categorical variables.

**Primary Outcomes. Evaluate the feasibility of research procedures.**

*Data quality and completeness.* We will track completeness of data collection, and patterns and proportions of missing data at each time point. We will compare these proportions overall, across sites, and by demographics.

*Recruitment and retention.* Using study records and administrative data, we will track recruitment (proportion of eligible patients recruited), document recruitment rates (accrual per quarter), and rates of retention. To assess recruitment, we will track the number of eligible patients being referred from the SCD centers and the proportion who agree to participate. Basic demographics will be collected for all eligible patients, allowing us to identify subgroups who are more or less likely to participate. Similar approaches will be used to assess variation in rates of loss to follow-up at all data collection points.

We will measure aspects of recruitment, including percentage of enrollees out of the total number of patients invited to participate, the average time of recruitment, and the clinic from which participants are recruited. Retention in the study, attending the respective program, and completion of outcome measures at all time-points will also be measured. Reasons for study dropout will be tracked.

1. **Data quality/completeness** is **90%** in quality control review.

2. **Screening rate** is **35%**. This is defined as those who were enrolled (i.e., provide written informed consent) divided by those approached for the study who met eligibility criteria.

3. **Recruitmen**t is **90%.** This translates into *randomizing* 81 of 90 (90%) participants who provided written informed consent

4. **Retention** is **70%.** The number of participants retained until the final survey time point (6-week follow-up).

5. **Individual attendance** is **70%**. We will consider individual attendance to be acceptable if a given participant attends 4 of 6 sessions in 8 weeks. These 4 sessions must include the first session and any 3 out of the 4 sessions between sessions 2-5. Individual **session attendance will be deemed complete if the participant attends 2/3 of the session** including (1) the introduction (discussing experience with the MT or HybHE exercise over previous week, providing education on rationale for intervention); (2) setting of the agenda; and (3) the main intervention (e.g., co-creating the music for the intervention, customizing the place and imagery to participants' preferences, experiencing and recording the intervention).

6. **Home practice** is **70%**. If a given participant practices intervention exercises at least once per week, this will be coded as engaging in the minimum dose of home practice.

**A final determination of "feasibility" for the study will be met if any 4 of the 6 metrics *described above are met.***

**Secondary Aim.** Evaluate the **implementation of the InMT, HybMT, and HybHE interventions,** using both quantitative data (study records, stakeholder surveys) and qualitative data (interviews).

**2a. Assess implementation outcomes:** feasibility, appropriateness, and acceptability using administrative, survey, and qualitative data as appropriate.

*Feasibility* is defined as the degree to which the intervention can be successfully implemented in the clinic, community, or home setting (in-person or virtual). This is operationalized as **recruitment**; and **attendance** (the proportion of recruited participants who completed at least 4 of 6 InMT, HybMT or HybHE sessions which must include the first session and any 3 out of the 4 sessions between sessions 2-5). This outcome will be measured by a single question assessment: *"Did participant receive four of six complete sessions which included the first session and any 3 out of the 4 sessions between sessions 2-5?"*).

We will compare feasibility metrics between InMT and HybMT to determine which is more favorable and resulted in higher attendance proportion. Feasibility of the study will also be assessed qualitatively, through stakeholder interviews focusing on barriers and facilitators to implementation.

*Appropriateness* is defined as the perceived **suitability** of the intervention to the applicable population. Patient providers will be asked: *"To what degree do you view the InMT, HybMT or HybHE intervention as useful or suitable for this population?" (1-very inappropriate—5-very appropriate).* Perceptions of appropriateness will also be explored through qualitative interviews.

*Acceptability* is defined as perceptions of the palatability of an innovation, or satisfaction by stakeholders with aspects of an innovation. It is more specific than overall satisfaction with a service.[68] For this study, acceptability among the adult SCD team is operationalized in our quantitative assessment as satisfaction with the InMT, HybMT and HybHE as delivered. Enrolled **participants** will be asked to answer two questions at treatment completion and at 6-week follow up: *"How satisfied are you with how **your pain was managed** during your participation in the*

*study"* on the 5-point Likert scale (1-strongly dissatisfied—5-very satisfied). A second question is *"Overall how satisfied are you with your treatment during your study participation?*" on the same 5-point Likert Scale. Acceptability of the intervention will also be explored through in-depth semi-structured stakeholder interviews with InMT, HybMT and HybHE participants.

**2b. Assess implementation processes, strategies, and barriers/facilitators to implementation using semi-structured stakeholder interviews (healthcare providers, MT and HealthED subjects, music therapists, and HealthED interventionists).**
To further explore influences on implementation outcomes, including stakeholder experiences, processes, strategies, and barriers and facilitators to implementation of the intervention, we will use qualitative methods. We will conduct qualitative interviews with a broad range of relevant staff stakeholders.

The success of program implementation depends on many factors, as described in Damschroder, et al's influential Consolidated Framework For Implementation Research (CFIR) framework.[69] The CFIR includes 5 'domains' influencing implementation: the intervention, inner and outer setting, individuals, and processes. We will use the CFIR domains to structure our inquiry and to make sure that our qualitative data collection instruments, coding system, and interim reports reflect the complex multiple levels of influence that will shape the conduct and outcomes of the MT intervention.

**Qualitative Interviews**. We will develop stakeholder lists with contact information, following consultation with local project leadership, then conduct 20 qualitative interviews with 10 stakeholder participants per site. This will include a broad range of relevant staff stakeholders, including SCD providers, staff, and music therapists In addition, 24 participants who received InMT, HybMT or HybHE (16 from UH and 8 from Prisma) will be purposefully sampled to include multiple presenting complaints, both sexes and older and younger participants (< 30 vs ≥30). Interviews will be conducted via Zoom and focus on perceptions of the intervention, burden, feasibility, and other barriers and facilitators. Participants will receive $25 for interview participation. Interview recordings will be stored on a secure server immediately after each interview. Interviews will be professionally transcribed.

***Qualitative Analysis.*** To analyze qualitative interview data, we will use QSR's NVivo, a computer program that facilitates (1) the rapid organization and retrieval of thematically linked data; and (2) the use of quantitative grouping variables to classify cases and generate complex comparisons. Briefly, the Implementation analysis team will first conduct thematic analysis through an iterative process of coding subsets of data. Analytic memos will be created for each interview describing the major themes emerging in the transcript. Memos will be used to determine the emergence of data saturation. Next, the coded data will be retrieved and used to create case summaries of key themes related to implementation processes at each site. Finally, we will conduct comparative analyses both within and across sites using the matrix functionality in NVivo. Within-site analyses will include comparisons of relevant groups, including but not limited to gender and baseline self-efficacy and pain (high vs. low). In the cross-site analyses, we will examine differences in barriers, facilitators, and implementation processes across the two sites with the goal of generating inferences regarding important factors shaping differences in implementation outcomes. For example, presuming that the sites differ on rates of

recruitment, we will examine our qualitative

data to generate hypotheses regarding the causes of this documented difference.

**2c. Examine InMT, HybMT and HybHE providers' fidelity to the respective intervention.**

**'Fidelity'** in this study means that we will identify the proportion of patients who are treated in a manner consistent with the manualized InMT, HybMT and HybHE interventions. The treatment fidelity parameters will align with our previously published intervention.[23] The treatment fidelity measures will include the dose (number of sessions) and the session delivery (was the intervention delivered as planned or cut short). To ensure treatment fidelity, investigators will implement strategies consistent with the NIH Behavior Change Consortium Treatment Fidelity Workgroup. These recommendations have previously been utilized in a NIH-funded multi-site MT intervention for adolescents and young adults undergoing stem cell transplant.[70] Specifically, Mr. Rodgers-Melnick (InMT and HybMT Fidelity) and Dr. Jenerette (HybHE fidelity) will implement the following strategies detailed in the table below to ensure fidelity in interventionists' training, treatment delivery, and treatment receipt.

| Goal | Strategy |
|---|---|
| **Recruit qualified personnel** | **InMT and HybMT:** Ensure music therapists are board-certified and demonstrate core competencies in music performance, music recording, clinical documentation, and interpersonal skills.<br>**HybHE:** Ensure graduate nursing students are able to deliver the HealthED intervention. |
| **Provide standardized training** | Provide training covering study protocol, clinical needs of patients with SCD, therapeutic and technological intervention procedures, workflow and documentation procedures, and quality assurance. |
| | **InMT and HybMT:** Conduct role playing exercises until adequate therapeutic, musical, and technological skills are displayed.<br>**HybHE:** Conduct role-play educational content delivery to ensure that the students can deliver the content consistently. |
| **Ensure consistent treatment delivery** | Monitor session dosage, length, and intervention procedures using REDCap. |
| | Conduct external quality assurance (QA) monitoring of session audio recordings for the first 5 participants followed by every 5$^{th}$ participant. Investigators will complete QA checklists and review any discrepancies with music therapists/graduate nursing students. |
| | Hold bi-weekly conference calls to discuss challenges, communicate updates, and answer questions of interventionists. |
| | Monitor for therapist effects through qualitative interviews with participants. |
| **Ensure appropriate receipt of treatment** | **InMT and HybMT:** Train music therapists to use active questioning and behavioral observation to assess whether participants comprehend how to access music exercises.<br>**HybHE:** Train graduate nursing students to use active questioning and behavioral observation to assess whether participants comprehend educational content. |
| | **InMT and HybMT:** Train music therapists to encourage participants to engage in music exercises following each session. |
| | **HybHE:** Train graduate nursing students to encourage participants to review content and ask questions to reinforce and clarify content. |
| | **InMT and HybMT:** Assess music exercise utilization through REDCap surveys.<br>**HybHE:** Assess educational module completion through REDCap surveys. |

## 10. DATA COLLECTION AND QUALITY ASSURANCE

### 10.1 Data Collection Forms

Confidentiality will be maintained by collecting and storing patient data in a secure REDCap database.

| Data Collection Form | Method of Collection | Blinding |
|---|---|---|
| Screening and Baseline Questions | Study Staff enter into REDCap | Blinded |
| Demographics Questionnaire | Patient-Facing REDCap survey | Blinded |
| ASCQ-Me- Emotional Impact | Patient-Facing REDCap survey | Blinded |
| ASCQ-Me- Pain Impact | Patient-Facing REDCap survey | Blinded |
| aSCQ-Me- Social Functioning Impact | Patient-Facing REDCap survey | Blinded |
| NRS- pain, stress, anxiety, tiredness | Patient-Facing REDCap survey | Blinded |
| PROMIS-29 or PROMIS-25 + Pediatric Sleep Disturbance | Patient-Facing REDCap survey | Blinded |
| SCSES | Patient-Facing REDCap survey | Blinded |
| Treatment Acceptability | Patient-Facing REDCap survey | Blinded |
| Music Use Assessment | Interventionist enters into REDCap and interventionist assessment | Unblinded |
| Clinical Characteristics | Study Staff enter into REDCap | Blinded |

### 10.2 Data Management

The research team will build a comprehensive study management database. Our team has successfully used REDCap for multisite data collection for a number of single-site and multi-clinic studies.

Informed consents and HIPAA authorizations will be collected and stored electronically. Participant Eligibility Source Documents forms will be scanned and uploaded to the participant's REDCap record while the physical copy will be kept by the study team in individual patient binders in locked filing cabinets of a secure, badge-access location at each site.

Screening data will be collected by the study staff through EHR data extraction prior to consenting. Baseline data will be collected by study staff directly from the participants. The data collected by study staff will be entered directly into an electronic data collection tool. There will be no hard copies of this data

Baseline, post-intervention, and 6-week post intervention assessments will be collected electronically sent to participants via REDCap Twilio function. All PROs will be entered directly by the participant on a tablet via REDCap or participant's own smart device and will disappear from view once entered so neither the participant nor study staff will have access to the scores. There will be no hard copies of this data.

Use of music exercises or HybHE will be collected by the interventionist during each session. Data will be entered into individual subject's REDCap records by the interventionist. Between post-intervention and 6-week post intervention, use of music exercises or HybHE will be collected electronically by REDCap survey sent to

participants. There will be no hard copies of this data.

Clinical characteristics will be collected via EHR data extract and will be entered electronically by study staff at each site with HIPAA protected identifiers as limited datasets. The data extracted from EHR will be verified by MRN and date with our electronic platforms. EHR extracted data will include age, SCD type, insurance type, SCD complications, healthcare utilization at any hospital in last 12 months (baseline) and since randomization (6 weeks post-intervention), SCD treatment, and opioid prescriptions in last 14 weeks (baseline) and since randomization (6 weeks post-intervention).

All electronic data will be kept in password protected databases behind an electronic firewall at sites and then securely sent to the UCI Coordinating Center and maintained on password protected PCs by a designated data manager. Data in hard copy form will be stored in locked file cabinets within a secure, badge-access location at each site. Upon completion of study enrollment, members of the study team will verify the information contained within the database. After answering all queries in the database, the information contained will be locked and exported for analysis. Both the source (electronic data collection) data and exported databases will be stored as required by the respective rules and regulations (e.g., HIPAA authorizations will be maintained for at least six years).

## 10.3 Quality Assurance

### 10.3.1 Training

The site Study Coordinator (sSC) will ensure that all study personnel have completed all required institution-specific and protocol-specific trainings and that these trainings are documented appropriately on the Training Log. The sSC will also ensure that new personnel are appropriately documented on the Delegation of Responsibilities Log (DOR). While training should be completed and documented in real time, the Multi-Site Study Coordinator (MSC) will verify that all training is current and appropriately documented on a quarterly basis, as noted in section 10.3.2 below.

Institution-specific Training

All study staff will complete CITI or NIH Human Subjects training prior to commencement of study activities. The site staff is also required to receive Good Clinical Practice (GCP) training through CITI or the Society for Behavioral Health. Staff training certificates will be stored in the Regulatory Binder in REDCap and documented on the Training Log.

Protocol-specific Training

Below is a summary of required initial training by role for new study personnel.

**PI, Study Coordinators, Research Assistants and anyone recruiting patients**:

- ✓ Review and express understanding of the Site Initiation Visit (SIV) training slides
- ✓ Review and express understanding of the IRB protocol
- ✓ Review and express understanding of the NCCIH protocol
- ✓ Review and express understanding of the Informed Consents and Study Information Sheets

- ✓ Review and express understanding of the MOP

**Music Therapists and HybHE interventionists who are not recruiting patients:**

- ✓ Review and express understanding of the IRB protocol
- ✓ Review and express understanding of the Informed Consents and Study Information Sheets
- ✓ Review and express understanding of the MOP

**Statistician**

- ✓ Review and express understanding of the IRB protocol

### 10.3.2 Quality Control Committee

N/A

### 10.3.3 Metrics

Quality Assurance (QA) activities will be conducted at each subject study visit, as well as on a monthly, quarterly and annual schedule. Additional QA activities and reviews will be conducted on an as-needed basis in response to staff or process changes.

The following tools will be used to document QA activities for this study:

- MULTI-MUSIQOLS QA Essential Documents Review Tool
- MULTI-MUSIQOLS QA Monthly Consent and Eligibility Data Review Tool
- MULTI-MUSIQOLS QA Participant Data Review Tool
- MULTI-MUSIQOLS QA Quarterly Review Tool
- MULTI-MUSIQOLS QA Annual Review Tool

In addition the following checklists and reminders have been developed for this study's QA process:

- MULTI-MUSIQOLS Informed Consent Documentation
- MULTI-MUSIQOLS Study Visit checklist
- MULTI-MUSIQOLS Interview Visit Checklist
- MULTI-MUSIQOLS Protocol Deviation Log
- MULTI-MUSIQOLS Session Protocol Adherence Checklist

<u>Consenting Visit QA Activities:</u>

The following is a detailed description of the Consenting Visit QA activities:

- Prior to the consent and baseline assessment appointment, the SC or RA will verify that the most current IRB-approved study consent documents are available for use. If re-consenting is required throughout the subject's participation in the study, the study staff will verify that the most current IRB approved consent is available prior to the study visit.
- Study staff will review and complete the REDCap Eligibility Criteria form before study activities begin.
- Study staff will document the consent process using the MULTI-MUSIQOLS IC Documentation Form. Before the subject leaves the appointment, study

staff will review the consent documentation and confirm adherence to the consent processes described in the MOP.

- Study staff will document in REDCap 1) the distribution of participant's headphones; 2) participant's enrollment in MyCap; 3) review of MyCap functions; 4) Zoom account access; 5) Box account access; and 6) distribution of bus passes.

Intervention Session QA Activities:

- At the initial visit the interventionist will document in REDCap (1) download of applications, as needed; (2) review of tech functionality; and (3) review of how to download music, if needed.
- At completion of all sessions, the interventionist will complete the Intervention Visit Checklist that captures the required elements of the visit.

InMT and HybMT Intervention QA Activities:

- Interventionists will complete MT Intervention QA checklist within 24 hours of each session and upload recorded sessions to the Box account.
- The intervention monitors will complete MT Intervention QA Monitoring Checklist within 7 days of recording upload for the first 5 participants at each site and every 5$^{th}$ participant or 60 days since last external QA (whichever comes first) thereafter.

HybHE Intervention QA Activities:

- Interventionists will complete HybHE Intervention QA checklist within 24 hours of each session and upload recorded sessions to the Box account.
- The intervention monitors will complete HybHE Intervention QA Monitoring Checklist within 7 days of recording upload for the first 5 participants at each site and every 5th participant or 60 days since last external QA (whichever comes first) thereafter.

Qualitative Interviews Visit QA Activities:

- Prior to confirming subject study visits, the site interviewer will verify that the subject is scheduled for the appropriate appointment.
- During the visit, the interviewer will ensure that the subject still meets the eligibility requirements.
- The interviewer will document the consent process using either the MULTI-MUSIQOLS Consent with Signature Form for the participants after obtaining participant signature or the MULTI-MUSIQOLS Consent with Signature Waiver Documentation Form for providers after obtaining verbal consents.
- At visit completion, the interviewer will complete the Interview Visit Checklist that captures the required elements of the visit.

Monthly QA Activities

The following is a detailed description of the Monthly QA review activities, which will be documented on the QA Monthly Consent and Eligibility Data Review Tool

- Consent Process Completion and Documentation: The site PI will review 100% of the site's executed consents using the QA Participant Data Review Tool.

- Eligibility Criteria and Documentation: the site PI will review 100% of the Eligibility checklists and source documentation.

Quarterly QA Activities

The following is a detailed description of the Quarterly QA review activities, which will be documented on the QA Quarterly Review Tool.

- Consent Process Completion and Documentation: The MSC or designee will review 100% of the site's executed consents using the QA Participant Data Review Tool.
- The MSC will use the QA Participant Data Review Tool to review completion and accuracy of the source documents and the eCRFs for 100% of subjects at the site every 3 months.
- The MSC will cross-check eCRF data for accuracy and completeness every 3 months. The MSC will also review query reports to confirm that all manual and automatic queries have been resolved.
- Training Logs will be reviewed by the MSC every 3 months to verify training is current and properly documented. This will include a review for institution-specific and protocol-specific trainings.
- The Site Regulatory Binders in REDCap are updated by the sSC when changes to licenses, certifications, credentials, IRB documents or CVs are made during the study. The sSC will review the Site Regulatory Binder every 3 months to verify that all documents (paper and electronic) are maintained. This review will be documented and summarized in the MULTI-MUSIQOLS Essential Documents Review Tool. At least annually, the MSC will conduct a complete review of the each Site Regulatory Binder.

Annual QA Activities

The following is a detailed description of the Annual QA review activities, which will be documented on the MULTI-MUSIQOLS QA Annual Review Tool.

- The procedures and processes to ensure protocol adherence among the study personnel are set forth in the Manual of Procedures (MOP). The MOP is reviewed by the MSC every 12 months for applicability and accuracy.
- This QA Plan will be reviewed for applicability and accuracy and updated as necessary every 12 months by the MSC. Additional QA needs identified at a study site will be communicated to the MSC. The MSC and MPI's will evaluate the need to update the QA plan, tools, and logs.

### 10.3.4 Protocol Deviations

A protocol deviation is any alteration/modification to the IRB-approved protocol that is not approved by the IRB prior to its initiation or implementation. Protocol deviations may result in determinations of non-compliance, serious or continuing.

1. Minor Protocol Deviation: An incident involving noncompliance with the protocol but one that typically does not have a significant effect on the subject's rights, safety, welfare, or on the integrity of the resultant data.
2. Major Protocol Deviation: A more serious incident involving noncompliance with the protocol usually involving critical study parameters. Major protocol deviations generally affect the subject's rights, safety, or welfare, or the integrity of the study data. A major protocol deviation can also be called a protocol violation.

Per UH IRB, protocol deviations must be reported by the PI or their designated research staff to the IRB within 5 days for major deviations, and at continuing review for minor deviations. Deviations are reported electronically by the MSC or designee using the appropriate category on the UHCMC IRB's RNI form.

Research staff will document the protocol deviation on the MULTI-MUSIQOLS Protocol Deviation Log after becoming aware of the event. The site PI or their delegated research staff will review and sign off on the deviation and designate it as major or minor. The site PI or delegated staff is responsible for reporting the deviation to the MSC within 3 days for major deviations and quarterly for minor deviations. The MSC is responsible for all follow-up associated with protocol deviations and reporting this information to the UH IRB.

#### 10.3.5 Monitoring

Each site will maintain the QA tools/logs either in a QA binder (for paper documents) or electronic folder. Site SCs will be responsible for site-specific QA activities. The MSC will be responsible for QA activities at the lead study site and will provide oversight for QA activities for the entire study.

Each sSC will provide a Quality Assurance Summary Report to the MSC one month before the Data Safety and Monitoring Committee (DSMC) Report is due. The MSC will compile the site reports into a comprehensive, study-wide report that will be provided to NCCIH. The MSC will also summarize the information for inclusion in the DSMC Report. This summary will document the following:

- QA activities completed since the prior report submittal, including:
    - Frequency of reviews
    - Number of charts reviewed
    - Items covered by the review
- Identification of problem areas
- Corrective Action Plan(s)

In addition, the PI will propose an independent monitoring committee (requires NCCIH approval) to overview the study from a data and safety perspective.

## 11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

### 11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

### 11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. For adult patients, only the participating patients themselves will be allowed to provide consent for inclusion into the study. No legally authorized representative (LAR) may enroll an adult patient into the study. For minor patients, the minor will provide written assent to participate in the study while their parent/guardian will provide consent for inclusion in the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record.

### 11.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality.

All electronic data will be kept in password protected databases behind an electronic firewall at sites and then securely sent to the UCI Coordinating Center and maintained on password protected PCs by a designated data manager. The UCI Coordinating Center will securely share data collected at their site and those received from Case Western Reserve University (CWRU)/University Hospitals (UH), the lead site and IRB of record. Data shared with CWRU/UH will be stored in a password protected database behind an electronic firewall on a secure UH server. Data in hard copy form will be stored in locked file cabinets within a secure, badge-access location at each site. Upon completion of study enrollment, members of the study team will verify the information contained within the database. After answering all queries in the database, the information contained will be locked and exported for analysis. Both the source (electronic data collection) data and exported databases will be stored as required by the respective rules and regulations (e.g., HIPAA authorizations will be maintained for at least six years).

Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NCCIH, and the OHRP

### 11.4 Study Discontinuation

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

## 12. COMMITTEES

The proposed 3-year project is designed to conduct and evaluate a feasibility study in 2 sites, in preparation for a definitive study of MT vs health education for pain and quality of life in patients with SCD.

To pursue these aims, we have assembled an experienced multidisciplinary team.

**The Steering Committee** will consist of Drs. Dusek and Jenerette as multi-PIs, as well as Drs. Karasz, Anderson, Malik, Owusu-Ansah and Mr. Rodgers-Melnick. Ms. Segall will also join these meetings. This team will meet monthly to oversee implementation with specific insights from the site's SCD physician champions.

**Site Research Teams** will consist of the site PI, SCD physician champion, Study Coordinator, Research Assistant, HybHE trainer(s) and the study music therapist(s). These teams will meet regularly leading up to and during the implementation of the feasibility study at their site, under the direction of the site PIs.

**Data Coordinating Center (DCC)** will consist of the PI (Dr. Malik) of the DCC, the lead statistician (Dr. Ricks-Oddie), the TBD junior statistician and the DCC manager (Dr. Christodoulou).

## 13. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NCCIH prior to submission.

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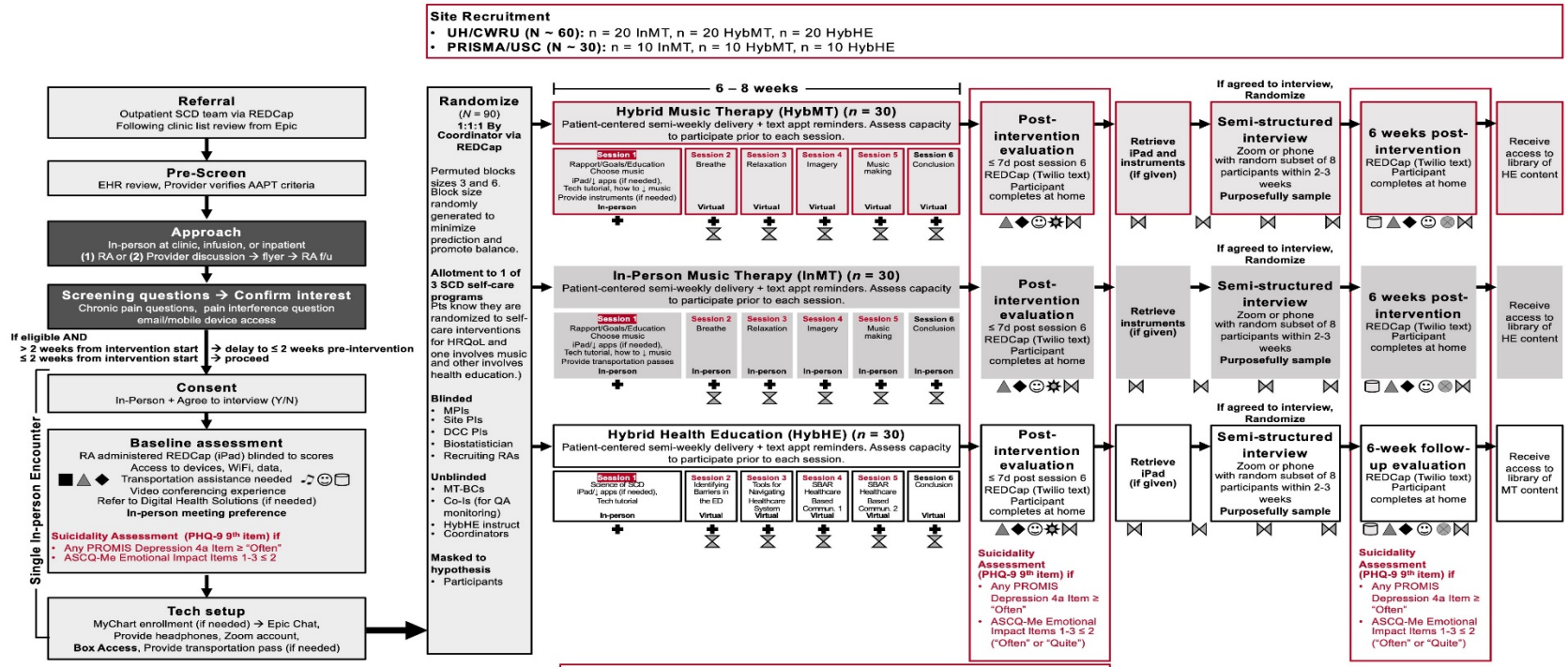
# MULTIsite feasibility of MUSIc therapy to address Quality Of Life in Sickle cell disease (MULTI-MUSIQOLS)




## Patient Eligibility Criteria

**Eligible if**

- 14 years or older
- Diagnosis of SCD present in EHR
- Meets AAPT criteria for chronic SCD pain
- Able to speak and understand English
- Has email address and access to mobile device with a functioning data plan
- Reporting that pain interfered with daily activities at least 1-2 days in the past week.

**Ineligible if**

- Significant visual, hearing, or cognitive impairment
- Previously participated in MUSIQOLS single-site pilot study (STUDY20180101)
- Engaging in mind-body therapies under the supervision of a healthcare professional specifically for pain management
- Have a planned major medical event in the next 14 weeks such as (but not limited to) childbirth, orthopedic surgery, gene therapy, or stem cell transplant. Planned major medical events do not include regular blood transfusions for sickle cell disease care.

**Implementation Evaluation**

- **Stakeholder interviews and surveys with SCD providers, staff, and MT-BCs**
- Following at least 2 cycles of intervention completion (n = 20 [~ 10 per site])

**Remuneration:**

- $20 for baseline data collection
- $20 for participating in session 1
- $10 for sessions 2, 3, 4, and 5
- $20 for session 6
- Those who complete at least 4 of 6 sessions will receive a $25 bonus
- Each participant will also receive $25 for completing follow-up data collection at post-intervention and 6-weeks post-intervention
- Totaling a possible maximum of $175 per patient, given via e-gift cards

**Measures**

- **Demographics:** gender (1); education level (1); religious background (1); income (1); employment status (1); race (1); ethnicity (1); marital status (1)
- **PROMIS-29:** physical function (4); anxiety (4); depression (4); fatigue (4); sleep disturbance (4); ability to participate in social roles and activities (4); **pain interference (4) (primary)**; pain intensity (1). PROMIS-25 + PROMIS Pediatric Sleep Disturbance 4a if Age < 18.
- **Sickle Cell Self Efficacy Scale (9)**
- **Music use assessment**
- **ASCQ-Me:** Pain Impact (5), Emotional Impact (5) and Social Functioning Impact (5).
- **EHR + prescription monitoring program review:** age; SCD type; insurance type; SCD complications; healthcare utilization @ any hospital in last 12 months (baseline) and since randomization (6wk post-intervention); SCD treatment; opioid Rx in last 14 weeks (baseline) and since randomization (6wk post-intervention)
- **Pre- and post-session numeric rating scales:** pain; stress; anxiety; fatigue
- **Treatment acceptability**
- **Music exercise/health education assignment use in past week (asked by interventionist)**
- **Post-intervention music exercise/health education assignment use in past week (completed by participant via REDCap)**
- **Music therapy and/or mind-body intervention engagement outside of protocol during study**