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CULTURALLY ADAPTED MOBILE TREATMENT OF CHRONIC PAIN IN ADOLESCENT SURVIVORS OF PEDIATRIC CANCER

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Protocol Summary

MNEMONIC and Title: ADAPTED - CULTURALLY ADAPTED MOBILE TREATMENT OF CHRONIC PAIN IN ADOLESCENT SURVIVORS OF PEDIATRIC CANCER
Principal Investigator: Tara Brinkman, PhD
IND Holder: Not applicable
Brief Overview: This study will include (1) cultural adaptation of an evidence-based mobile cognitive behavioral therapy (CBT) program for chronic pain and procedures for transcranial direct current stimulation (tDCS) and (2) a feasibility study of adapted mobile CBT paired with tDCS. Participants will be recruited from four large pediatric cancer centers: St. Jude Children's Research Hospital (SJCRH), Children's Healthcare of Atlanta (CHOA), Texas Children's Hospital (TCH), and Seattle Children's Hospital (SCH). CHOA, TCH, and SCH will provide the study brochure, and if willing, participants will complete a Consent to Contact form. SJCRH will screen, consent, and conduct all study procedures for all eligible participants for the study.
Intervention: We will conduct a series of focus groups with non-Hispanic Black and Hispanic childhood cancer survivors to obtain their input on culturally adapting a mobile CBT program for chronic pain and tDCS procedures. Once this adaptation process is completed, we will conduct a feasibility trial with non-Hispanic Black, Hispanic and non-Hispanic White childhood cancer survivors with chronic pain.
Study Design: Prospective study employing focus groups to culturally adapt CBT and tDCS procedures which will then be used for the second phase, a feasibility study. The feasibility study will assign eligible participants to either culturally adapted mobile CBT + active tDCS to the dorsolateral prefrontal cortex or culturally adapted mobile CBT + sham tDCS.
Sample Size: We anticipate approximately 60 participants for the focus groups and approximately 30 participants for the feasibility study for a total of about 90 participants.
Data Management: The Study Team at SJCRH will design forms for data collection within the electronic database. Statistical analysis will be provided locally by the Biostatistics Department at St. Jude Children's Research Hospital.
Human Subjects: The risks of participating in the study are low. This time commitment could be seen as a burden and some of the questions may make the participant uncomfortable. There may be some stress or anxiety based on the questions we will be asking. There is a risk of privacy loss, but we have taken measures to mitigate the risk, as will be detailed later in the protocol. There is low risk to participants related to active tDCS. Potential side effects include redness and slight tingling at the site of stimulation, and all side effects are transient. Recent meta-analyses show side effects to occur no more frequently than placebo conditions.

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1.0 OBJECTIVES

1.1 Primary Objective

1.1.1. To leverage stakeholder input to culturally adapt an evidence-based mobile cognitive behavioral therapy (CBT) intervention for comorbid chronic pain in non-Hispanic Black and Hispanic adolescent survivors, and to obtain input on transcranial direct current stimulation (tDCS) implementation.

Hypothesis: Stakeholder feedback will enable the cultural adaptation of intervention content and delivery for non-Hispanic Black and Hispanic adolescents through identification of tailoring variables and implementation strategies to maximize engagement.

1.1.2. To assess the feasibility of applying a culturally adapted mobile CBT and remote tDCS to a racially/ethnically and geographically diverse sample of non-Hispanic White, non-Hispanic Black, and Hispanic adolescent survivors of pediatric cancer with chronic pain (n=30).

Hypothesis: ≥60% of survivors will complete ≥75% of the mobile/remote intervention procedures.

2.0 BACKGROUND AND RATIONALE

2.1 Background

Survivors of pediatric cancer are a growing population with a high burden of morbidity: Advances in treatment and supportive care have improved 5-year overall survival for pediatric cancer to over 85%.[1] However, the intensive treatments required to achieve cure often result in a high burden of physical health morbidity for survivors.[2] It is estimated that 80% of adult survivors of childhood cancer will have at least one severe or life-threatening treatment-related chronic health condition by 45 years of age.[3] Specific to survivors of bone sarcomas, survival has increased from less than 20% to 65-75% for localized disease over the past five decades.[4, 5] Five-year survival for soft tissue sarcomas has improved from 30% to 70%, although with variability by risk status.[6, 7] Multimodal therapy for pediatric sarcomas often includes high-dose chemotherapy as well as primary tumor local control with aggressive surgery and/or high-dose radiation.[8] This aggressive therapy places survivors at risk for long-term morbidity, including chronic pain, reduced physical function, and chronic health conditions. By 35

years of age, pediatric Ewing sarcoma and osteosarcoma survivors have an average of 3.5 and 4 severe and life-threatening chronic health conditions, respectively, compared to 0.9 in community controls.[9] Long-term survivors of soft tissue sarcomas are at-risk for endocrinopathies and diseases of the nervous system, digestive organs, and urinary system.[6] Racial/ethnic differences exist in the incidence of bone sarcomas as Blacks and Hispanics have higher rates of osteosarcoma compared to Whites.[10] Similarly, soft tissue sarcoma incidence in children and young adults is higher among blacks compared to Whites.[10] Unfortunately, survivors who are members of racial or ethnic groups that have historically been underserved, mistreated, or marginalized by the biomedical community face disproportionately poor outcomes. For example, mortality is notably higher among Black and Hispanic compared to White pediatric sarcoma patients, and survival disparities by race and ethnicity in this population have grown over the past four decades.[11] Importantly, disparities in pediatric cancer incidence and survival are not limited to sarcoma patients. For example, Hispanic individuals experience increased incidence of ALL compared to non-Hispanic Whites.[10] Moreover, non-Hispanic Black and Hispanic patients with childhood cancer have worse survival for all pediatric cancers combined (leukemias and lymphomas, brain tumors, and solid tumors) compared to non-Hispanic Whites.[12]

Chronic pain is prevalent among survivors of childhood cancer: Chronic pain, defined as pain that lasts or recurs for 3 or more months,[13] has a significant economic impact in the United States (U.S.), with an estimated yearly cost of over $19.5 billion for adolescents alone.[14] A recent review of chronic post-surgical pain in children reported a prevalence of 20% (IQR, 15% to 38%) 12-months post-surgery. Because pediatric bone sarcomas often require invasive local control (amputation or limb-sparing surgery), it is not surprising that pain is prevalent in these survivors. A recent report indicated that among pediatric patients with osteosarcoma, 34.5% met criteria for chronic post-surgical pain.[15] We recently reported that long-term survivors of bone sarcoma were nearly 4 times as likely to experience moderate to severe pain that interfered with daily functioning than non-cancer controls while survivors of soft tissue sarcomas were 9 times more likely to report such pain.[16] However, data from the St. Jude Lifetime Cohort Study indicates that **all childhood cancer survivors** are at-risk for developing moderate to severe pain with daily interference compared to non-cancer community controls (e.g., Hodgkin Lymphoma OR: 3.38, 95% CI, 2.06-5.55; Non-Hodgkin Lymphoma OR: 4.13, 95% CI, 2.40-7.10; ALL OR: 3.10, 95% CI, 1.95-4.92).[17] Therefore, the experience of chronic pain is not limited to survivors of pediatric sarcoma, despite a higher prevalence in these survivors. Racial/ethnic disparities consistent with those observed in the general population also exist among

survivors across all diagnoses as Hispanic and Black survivors are more likely to report pain than white survivors.[18]

Risk factors and comorbidities associated with chronic pain: Our discussion of potential risk factors and comorbidities associated with chronic pain is structured within the World Health Organization's Commission on the Social Determinants of Health (CSDH) Framework.[19] Like other similar frameworks, including the framework developed by the National Institute on Minority Health and Health Disparities,[20] CSDH asserts that health and well-being vary across *domains* and *levels* of influence. However, CSHD reorganizes the levels of influence into two broad categories: **structural**, which exert more distal influences on health outcomes and **intermediate** which have more proximal influences on outcomes. An additional benefit of CSHD is its description of how different categories of risk factors influence each other; this allows greater conceptual clarity than frameworks that simply present a list of categories.

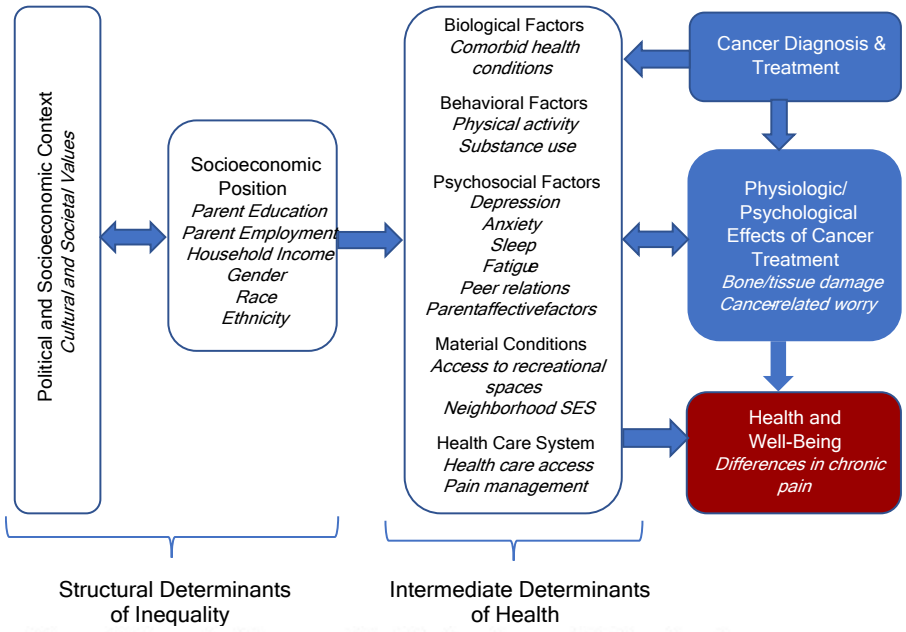


Figure 1. Conceptual framework for the development of chronic pain among adolescent survivors of pediatric bone sarcoma. Adapted from the World Health Organization's Conceptual Framework for the Action on Social Determinants of Health. 2010.

Structural determinants of inequality: The *political and socioeconomic context* (left side of Figure 1) of the U.S. is not the focus of this application. Nevertheless, we acknowledge that cultural and societal values, our economic system, and historical and persistent racism are key to setting the stage for health inequities. There is significant evidence from non-cancer populations that chronic pain is related to variables that shape an individual's *socioeconomic position*. For children and adolescents, socioeconomic position is almost entirely dependent upon the position of their parents (e.g., parental education, income). Not surprisingly, socioeconomic risk factors for chronic pain in youth are similar to those of adults and include both female sex and lower household income.[21, 22] Among adolescent survivors of childhood cancer, knowledge of how *socioeconomic position*

influences chronic pain is limited, but data from adult survivors reflect similar trends as observed in the general population with risk factors including female sex, lower educational attainment, unemployment, household income <$20,000, and Black and Hispanic race/ethnicity.[18, 23] Importantly, childhood cancer and its treatment can have a substantial negative impact on *parental* socioeconomic situation. A recent systematic review revealed a high level of disruption in parental employment, income loss, and increased perceived financial burden following a child's cancer diagnosis.[24] In addition, >30% of families reported experiencing household material hardship at least 1 year-off therapy.[25] These potential threats to parental socioeconomic position likely influence the experience of chronic pain and its management for adolescent survivors of childhood cancer.

Intermediary determinants of health: In addition to variables that shape *socioeconomic position*, intermediary determinants (middle part of Figure 1) including *behavioral* and *psychosocial factors*, *material conditions,* and *healthcare systems* may also be associated with chronic pain in childhood cancer survivors. In terms of *behavioral factors*, sedentary behavior and low cardiorespiratory fitness have been associated with increased risk of pain among children.[26] A recent study revealed that drinking to intoxication was associated with a 3-fold increased likelihood of persistent pain among survivors of childhood cancer.[27] Related to *psychosocial factors*, adolescents with chronic pain often experience mental health comorbidities[28], including anxiety[29] and depression.[30] Fatigue and sleep disturbance are common among adolescents with chronic pain.[31] Sleep is a potential mechanism underlying the transition from acute to chronic pain in youth,[32] and fatigue has been shown to mediate the relationship between pain intensity and pain-related disability in youth with chronic pain.[33] Parental affective factors, including anxiety have been associated with increased child pain intensity and analgesic use.[34] As adolescent development is characterized by greater autonomy from parents and increased emphasis on peer relations, it is not surprising that peer relationship quality moderates associations between parent and adolescent cognitive and behavioral pain responses.[35]

Studies on how *material conditions*, particularly neighborhood SES and built environment, contribute to pain are also relevant. In pediatric patients with upper extremity fractures, children living in areas with the greatest social deprivation reported worse function, mobility, pain interference, and peer relations compared to children with the least social deprivation.[36] Another study among children with chronic pain demonstrated that patients from more socially deprived areas were less likely to be referred to a chronic pain service and less likely to attend appointments.[37] In a sample of youth considered to be at-risk for chronic pain, high risk status was associated with living in neighborhoods with less walkability and

further proximity to parks.[38] These studies demonstrate the importance of considering *material conditions* in interventions targeting chronic pain in adolescents.

Even though childhood cancer survivors are at increased risk for chronic pain when compared to peers, a recent study indicated that only half of adolescent survivors of childhood cancer received follow-up *healthcare* after treatment completion.[39] It is likely that socioeconomic inequalities impact not only access to healthcare, but also access to treatment or interventions for chronic pain management in cancer survivors. Children with chronic pain whose parents are from a higher occupation level are more likely to travel a greater distance to access specialized treatment than are those from lower occupation levels,[40] and individuals from underserved populations, particularly Blacks, are less likely to receive opioids for the management of acute and chronic pain. This is despite the fact that Blacks are less likely to misuse opioids than Whites.[41] Nonetheless, overreliance on opioids has resulted in a national health crisis, with adolescents and young adults experiencing a significant increase in opioid overdose mortality.[42] This is relevant for childhood cancer survivors as they are 1.5 to 4 times more likely than age-, sex-, and region-matched peers to fill opioid prescriptions,[43] and bone tumor survivors are significantly more likely than survivors of hematologic cancers to use opioids and experience potential misuse in the first year post-therapy.[44] Among survivors, pain is associated with a more than 2-fold increased risk of opioid use cross-sectionally,[45, 46] with persistent and increasing pain over a 4-year interval resulting in a nearly 8-fold increased risk of opioid use.[47] In the general population, adolescents with chronic pain are more likely to misuse opioids as adults,[48] where treatment of chronic pain with opioids is often ineffective and may result in opioid-induced hyperalgesia[49] as well as misuse and abuse.[50] These data support the need for alternative, non-pharmacologic approaches for chronic pain.

Cancer diagnosis & treatment exposures: Most bone sarcoma patients with extremity tumors are candidates for limb sparing surgery, which usually involves en bloc removal of the tumor and involved bone, and reconstruction with endoprosthesis or allograft. This invasive surgery may result in chronic neuropathic or musculoskeletal pain.[51] In fact, data from our institution indicate that more than one-third of pediatric osteosarcoma patients treated with limb-sparing surgery report significant chronic pain.[15] We also found that among adult survivors, those who underwent limb-sparing surgery during childhood were twice as likely to report pain with daily interference than survivors who did not.[16] These data suggest a high prevalence of chronic pain among adolescent survivors of bone sarcomas that appears to persist into adulthood and, coupled with high opioid use,

indicate a clear need for non-pharmacologic pain interventions in this population. Cancer survivors are at-risk for developing cancer-related worry or fear of recurrence. A recent report indicated that 43% of adolescent and young adults survivors reported fear of cancer recurrence.[52] Given that many sarcoma patients identify pain as an early presenting symptom of their cancer diagnosis, survivors may be more hypervigilant to pain and interpret it as an indicator of cancer recurrence. This likely contributes to an ongoing pain and fear cycle, with each serving to maintain or exacerbate the other. Because pain is associated with increased risk of worry about relapse in long-term survivors,[53] cancer-related worry is an important outcome to consider in interventions targeting pain in cancer survivors.

Non-pharmacologic interventions for chronic pain: Data indicate that pain is significantly undertreated among children with cancer. This may stem, in part, to historical overreliance on opioids as well as stigma related to psychological interventions. For children with osteosarcoma, the duration of pain is significantly longer in patients who are resistant to psychological interventions.[15] Importantly, non-pharmacological approaches to pain management in adolescents with chronic pain are highly effective. ***Cognitive behavioral therapy*** (CBT), the gold standard and predominant psychological treatment for chronic pain in pediatric populations,[54] is designed to reduce negative thoughts about pain and modify maladaptive behavioral patterns in response to pain.[55] A recent meta-analysis of 24 randomized controlled trials for multiple chronic pain conditions in adolescents showed that CBT has a moderate effect on pain intensity reduction after treatment, and a modest effect on disability reduction after treatment and at follow-up.[54] Improvements in anxiety post-treatment are also reported.

Despite its efficacy, traditionally delivered CBT (i.e., face-to-face psychotherapy) is often underutilized due to limited availability and access to trained professionals, costs, stigma associated with professional psychological support, geographical distance from treatment centers, and long waiting lists.[56] These barriers are even more salient in underserved populations. To reduce access barriers and promote participation in CBT (i.e., treatment uptake), alternative delivery models have been developed. One approach is technology-delivered CBT (computer and mobile applications). A recent meta-analysis of 4 internet-delivered CBT programs for pediatric chronic pain found it produced medium to large effect sizes for reducing pain intensity.[57] The mobile CBT program for the proposed study, WebMAP, reduced activity limitations at 6 and 12 months post-intervention in 11-17 year old adolescents with multiple different sources of chronic pain.[58, 59] While mobile CBT can reduce barriers to access care, it's reach, utility, and uptake remain limited to the extent that it is sensitive and responsive to cultural

differences. Culture impacts both the content and process of psychotherapy.[60, 61] Cultural adaptation, or the "systematic modification of an evidence-based treatment or intervention protocol to consider language, culture, and context in such a way that is it compatible with the client's cultural patterns, meanings and values"(p.362)[62] increases treatment engagement and effectiveness. A meta-analysis reviewed 76 studies that employed culturally adapted mental health treatments and reported that interventions targeted to specific ethnic groups produced 4 times stronger effects than those provided to diverse ethnic groups.[63] To our knowledge, mobile CBT interventions for chronic pain have not been adapted to incorporate cultural differences and preferences for Black and Hispanic youth, who disproportionately experience chronic pain and barriers to its treatment. Although mobile CBT is attractive because it is portable and likely amenable to cultural adaptation, data indicate that it is not as effective as CBT delivered in-person.[64] The effectiveness of mobile CBT may be enhanced by a companion intervention that augments cognitive and affective processing of pain.

Transcranial direct current stimulation (tDCS) is a non-invasive method of brain stimulation and an emerging treatment for chronic pain.[65, 66] Excitatory (anodal) stimulation over the dorsolateral prefrontal cortex (DLPFC) is a common tDCS regimen for treating pain. Transcranial direct current stimulation differs from conventional interventions in that it directly stimulates specific brain regions responsible for cognitive and affective processing similar to those activated during CBT for chronic pain.[67] Transcranial direct current stimulation involves modulation of cerebral cortex excitability by direct application of low-level electric current to an anode electrode site, the current travels to a cathode electrode site stimulating brain regions that lie in the path of current flow. Studies have shown analgesic effects on reported pain intensity and improvements in quality of life after treatment,[65] as a result of local and connectivity effects within the pain processing brain network.[68, 69] Anodal tDCS of the DLPFC modulates both sensory and cognitive-affective networks[70] and reduces pain by inhibiting the maladaptive allocation of cognitive and attentional resources and, influencing emotional and motivational aspects of pain.[69] A recent integrated review and meta-analysis reported that anodal tDCS to the DLPFC produced an effect size of -0.54 (95% CI, -0.91 to -0.16).[71] A recent trial of home-based tDCS to the DLPFC demonstrated a 46% reduction in pain scores after 20 sessions.[72] Due to its dependency on brain state,[73, 74] tDCS appears to be more efficacious at augmenting effects of a *simultaneous/combined* treatment rather than inducing *de-novo* changes.[75] For example, larger benefits of CBT on psychological outcomes (e.g., depression) have been observed when administered with tDCS,[76, 77] although this treatment combination has not yet been examined in a sample with chronic pain.[78]

2.2 Rationale

Survivors of pediatric cancers are at high risk for developing chronic pain. Unfortunately, because of the limited availability of and access to evidence-based interventions, these survivors are disproportionally using prescription opioids to manage their pain. Racial and ethnic disparities exist, both with respect to the prevalence of chronic pain and its management, and these are strongly influenced by social determinants of health (SDOH). Non-pharmacological interventions are efficacious in treating chronic pain, but their uptake and efficacy is limited across diverse cultural groups. In addition, while mobile CBT has promise to transcend historical access barriers to psychological care, its impact on improving chronic pain does not appear to be as robust as traditionally delivered CBT. Therefore, we propose to pair culturally adapted mobile CBT with remotely delivered tDCS to enhance the effectiveness of CBT for improving comorbid chronic pain in adolescent survivors of pediatric cancer. The mobile CBT program does not need to be adapted specifically to cancer survivors as it has demonstrated effectiveness in adolescents with multiple pain conditions.

3.0 PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

We will enroll Hispanic and non-Hispanic Black parents of childhood cancer survivors and adult childhood cancer survivors as well as 10–17-year-old adolescent survivors for the first part of the study aiming to adapt a mobile cognitive behavioral therapy intervention for chronic pain with input on tDCS implementation. The second part of the study will be an intervention enrolling non-Hispanic Black, Hispanic and non-Hispanic White adolescents with pediatric cancer who have chronic pain These participants will use the adapted mobile cognitive behavioral therapy with tDCS.

According to institutional and NIH policy, the study will accession research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

3.1 Inclusion Criteria for focus groups

3.1.1 Adults

3.1.1.1. Hispanic or non-Hispanic Black childhood cancer survivor or parent of Hispanic or non-Hispanic Black childhood cancer survivor
3.1.1.2 18 years or older

3.1.2 Adolescents
3.1.2.1 10-17 year-old survivors of childhood cancer
3.1.2.2 At least one-year post treatment completion
3.1.2.3 Hispanic or non-Hispanic Black
3.1.2.4 Phase 4 only: History of chronic pain
3.1.2.4.1 Pain that was present for more than 3 months

3.2 Exclusion Criteria for focus groups

3.2.1 Adults/Adolescents
3.2.1.1 Inability or unwillingness of research participant or legal guardian/representative to give written informed consent.

3.3 Inclusion Criteria for feasibility study

3.3.1 Hispanic, non-Hispanic Black, and non-Hispanic White 10–17-year-old survivors of pediatric cancer
3.3.2 At least one-year post treatment completion
3.3.3. Pain present over the past 3 months and pain at least once per week
3.3.4. Pain interfering with at least one area of daily functioning

3.4 Exclusion Criteria for feasibility study

3.4.1. Limb amputation
3.4.2. History of seizure disorder or other neurological disorders
3.4.3. Presence of metallic intracranial implants (neurostimulator, Ommaya reservoir, CSF shunt, or aneurysm clip), and metallic and non-metallic cranial, excluding the bones of the face and jaw, prosthesis (implants/plates).
3.4.4. Serious comorbid psychiatric condition
3.4.5. Current substance abuse
3.4.6. History of development delay or significant cognitive impairment
3.4.7. History of brain tumor diagnosis

3.5 Research Participant Recruitment and Screening

Four institutions will collaborate in the proposed protocol: St. Jude Children's Research Hospital (SJCRH); Children's Healthcare of Atlanta (CHOA), Texas Children's Hospital (TCH); and Seattle Children's Hospital (SCH). The three sites will provide contact information only for potential participants. SJCRH will screen, recruit, and consent all eligible participants for the study.

3.6 Enrollment on Study at St. Jude

A member of the study team will confirm potential participant eligibility as defined in Sections 3.1-3.2 and complete the 'Participant Eligibility Checklist' in OnCore if required by the study team. Eligibility will be reviewed, and a research participant-specific consent form and assent document (where applicable) will be generated. The entire signed consent/assent form(s) must be scanned into the Electronic Health Record (EHR) by the study team designee.

3.7 Procedures for Identifying and Screening Participants

Prior to initiating the study, a workshop will be held by SJCRH with team members from all sites participating. The background to the study, study procedures, consent processes, data transfer, and plans to monitor intervention integrity and data quality will be the content for that workshop.

Following the workshop and preparation of sites for identifying potentially eligible research participants will begin. Eligibility of newly admitted research participants will be confirmed during daily discussions between the study investigators, research assistants, and attending physician for both the Solid Tumor and Leukemia teams.

4.0 DESIGN AND METHODS

4.1 Design and Study Overview

This study will include the (1) cultural adaptation of an evidence-based mobile CBT program for chronic pain and procedures for tDCS and (2) a feasibility study of adapted mobile CBT paired with tDCS. Participants will be recruited from four large pediatric cancer centers: St. Jude Children's Research Hospital (SJCRH), Children's Healthcare of Atlanta (CHOA), Texas Children's Hospital (TCH), and Seattle Children's Hospital (SCH). Collaborating sites will provide SJCRH with potential participant contact information and SJCRH will consent and enroll participants on the study at SJCRH.

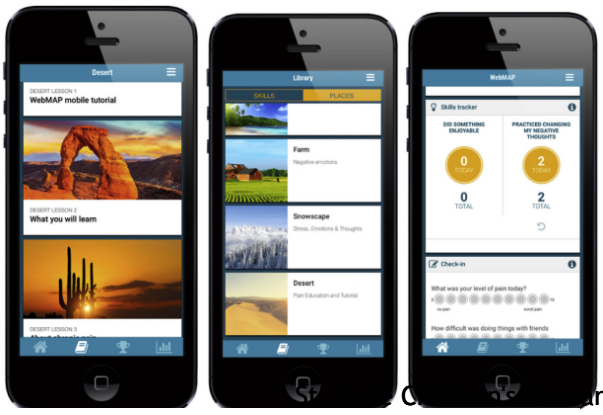


Figure 2. Screenshots from the WebMAP mobile

Mobile cognitive behavioral therapy for chronic pain: The mobile CBT program we propose to utilize, WebMAP mobile,[79] was created by Dr. Palermo (Co-I). The program is available on

Android and iOS operating systems and is an interactive, self-guided intervention with six core treatment modules. These modules focus on 1) pain education, 2) stress, emotions, and thoughts (e.g., pleasant activity scheduling, thought stopping), 3) relaxation and imagery, 4) lifestyle and school interventions, 5) staying active, and 6) maintenance and relapse prevention. Within the app, participants complete screening questions to set up a profile and evaluate the need for two supplementary treatment modules focused on comorbidities of negative mood and sleep. There are several functional components to the app, including *places and lessons* (each place has 3-5 lessons that provide education and teach pain management skills), *library* (information on skills presented through audio clips, videos), *check-in* (allowing participants to track their pain, activity, mood, and sleep), and *skills tracker* (participants record practicing specific skills such as sleep relaxation). Screen shots from the app are shown in Figure 2. Content is metered according to a time schedule, requiring youth to spend 5 days on skills practice before an assignment can be completed. Components of the program can be used daily (e.g., check in, skills practice). Total treatment duration is approximately 20 min per week over 6 to 8 weeks depending on the number of supplementary modules assigned. The app uses daily reminder notifications to encourage users to log in and complete assigned tasks. If needed, participants will be provided with a mobile device to access the intervention.

Cultural adaption of mobile CBT: A recent systematic review of cultural adaption of internet- and mobile-based interventions for mental disorders identified specific components necessary for cultural adaptation that fall under 3 key domains: content, methodological, and procedural (see Table 1).[80] For the current proposal we will culturally adapt mobile CBT, separately for Black and Hispanic survivors of childhood cancer, guided by key domains in Table 1 and identify tailoring variables that will be used to assign adapted intervention content. This will avoid the assumption of complete homogeneity within any one culture. The objective of cultural adaptation is to improve the ecological and external validity of an intervention for a culture group different than the group it was originally intended for. Nonetheless, it is important to retain core components of the program to maintain effectiveness in the target population.[81]

Table 1. Key domains and components of cultural adaption of mobile-based interventions for mental disorder[80]

Content
• Illustrations
• Language
• Mental health concepts
Methodological
• Structure of the intervention
• Functionality
• Design and Aesthetics
Procedural
• Methods used to obtain information
• Persons involved

Our cultural adaptation will include five phases: (1) expert consultation, (2) stakeholder feedback, (3) preliminary content adaptation, (4) iterative content adaptation with stakeholder feedback, and (5) finalized adaptation.

All cultural adaptation processes will occur separately, but in parallel, for non-Hispanic Black and Hispanic participants. We will use self-identification/report to determine race/ethnicity. For Phase 1 (expert consultation), experts will include Dr. Palermo (CBT, chronic pain, WebMAP creator), Dr. Brinkman (tDCS, cancer survivorship), Dr. Graetz (culture and communication, SDOH), and at least one non-Hispanic Black and one Hispanic parent of an adolescent childhood cancer survivor from the Children's Oncology Group Patient Advocate Committee and St. Jude Children's Research Hospital Patient and Family Advisory Council, and at least one Black and one Hispanic young adult childhood cancer survivor (lived experience participants). We will solicit feedback from stakeholders and lived experience participants related to the study design and conduct.

Cultural Adaptation Phases	
Phase 1 (Expert Panel) consultation to identify potential adaptations to mobile CBT program and preliminary identification of tailoring variables.	Virtual meetings with non-Hispanic Black & Hispanic parents & young adult childhood cancer survivors. **(2-3) 1-hour meetings**
Phase 2 (Stakeholder Consultation) identify adaptations of intervention content and review preliminary tailoring variables.	Virtual focus groups with non-Hispanic Black & Hispanic adolescent childhood cancer survivors. **(2-4) 45-minute sessions**
Phase 3 (Preliminary Content Adaptations) based on qualitative analysis based of stakeholder feedback.	Co-investigators make preliminary intervention content adaptations.
Phase 4 (Iterative Content Adaptation) with ongoing stakeholder feedback. Adaptations shared with survivors and additional feedback solicited.	Virtual focus groups with non-Hispanic Black & Hispanic adolescent childhood cancer survivors with chronic pain. Ongoing program content adaptation based on qualitative analysis. **(2-4) 45-minute sessions**
Phase 5 (Finalized Adaptation) with ongoing stakeholder feedback. Finalized adaptions and tailoring variables shared with survivors.	Virtual focus groups with non-Hispanic Black & Hispanic adolescent childhood cancer survivors who participated in previous sessions. Final program content adaptation based on qualitative analysis. **(2-3) 45-minute sessions**

Phase 1 will involve a minimum of two 1-hour meetings to identify possible adaptations including surface (e.g., characters, activities, language), conceptual (e.g., treatment goals, values, mental health concepts) and mobile specific considerations (e.g., amount of human guidance). Preliminary identification of tailoring variables will also be discussed. Non-Hispanic Black and Hispanic participants will meet separately.

Phase 2 (stakeholder consultation), we will recruit 8 to 12 Black and 8 to 12 Hispanic adolescent (10-17 years of age) survivors of childhood cancer who are at least one-year post-treatment completion to serve as initial stakeholders and participate in virtual focus groups. All focus groups will be conducted via an online HIPAA compliant platform, audio-recorded, and transcribed verbatim. Our team has experience conducting focus groups virtually in multiple cultures and languages.[82, 83] We will engage in purposive sampling to include representation by sex and neighborhood disadvantage as this is an important SDOH related to treatment uptake and engagement. To avoid potential saturation of our sample for the intervention phase, we will not restrict participation in the adaptation phase to bone sarcoma survivors. Focus groups will be conducted by two facilitators who will use a guide/probe structured around the 3 key domains of cultural adaptation, to solicit specific feedback about potential adaptation of the images, concepts, personal stories, daily life examples and preliminary tailoring variables identified during the expert consultation phase. If Hispanic participants indicate that they would prefer a Spanish translation of the entire program or specific components (e.g., videos) this be incorporated into the adaption process. Dr. Graetz is fluent in Spanish and has research assistants who are native Spanish speakers trained to conduct focus groups; therefore, we will be able to provide focus groups in Spanish or with staff who are bilingual, if preferred by stakeholders. We plan to hold approximately three 45-minute sessions over a at least a 3-week period to allow for sufficient time to review all program material. We will hold separate focus groups for non-Hispanic Black youth and for Hispanic youth.

Phase 3 We will make preliminary content adaptations based on results of our qualitative analysis of stakeholder feedback (see analytic description below) and create mock- ups to demonstrate these adaptations. We will show how identified culturally relevant tailoring variables (e.g., family involvement, spirituality, values, amount of guidance) can assign adapted intervention content (e.g., tailored vignettes) or functionality. For example, if religiosity is deemed an important tailoring variable, character stories will be tailored to incorporate prayer and religious social support. Any proposed changes to app functionality (e.g., amount of human guidance) will be considered at this phase.

Phase 4 This will be an iterative adaptation process where we demonstrate our proposed adaptations to stakeholders. We will refine the adaptations by eliciting rapid iterative feedback from youth in three cycles, with 5-7 Black and 5-7 Hispanic adolescent survivors of childhood cancer who have a history of chronic pain participating per cycle (n=15-21 total). This will allow us to be

informed by survivors with lived experience of chronic pain. We will again engage in purposive sampling to include representation by sex and neighborhood disadvantage. We plan to hold approximately three sessions (about 45-minutes each) with adequate time in between to work with our programming team to make modifications to app mock-ups. Importantly, because this group of stakeholders will have chronic pain, these focus groups will specifically emphasize the acceptability of adapted vignettes and pain management practice skills. This phase also will allow for refinement of tailoring variables.

Phase 5 will involve approximately two meetings with 5-7 non-Hispanic Black and 5-7 Hispanic adolescent survivors of childhood cancer who participated in earlier phases to present the adapted interventions from the results of focus groups and rapid feedback cycles. Feedback will be collected and analyzed to inform any further changes.

Figure 3. tDCS handheld control unit and preconfigured headband

Transcranial direct current stimulation (tDCS) – Mobile System: For remotely supervised tDCS stimulation, we will employ a procedure consistent with recently published professional guidelines[84] and with those utilized in our ongoing NEUROSTIM and ALLSUP studies. The mobile tDCS system is manufactured by Soterix Medical and consists of a rechargeable lithium battery pack, handheld control unit and a self-positioning headband with electrodes (Figure 3). This device is specifically designed for remote studies. It has an easy set-up and allows for precise reproduction of electrode positioning. This system allows for double-blind application of the intervention or sham treatments through the use of single-use passcodes. An anodal electrode will be placed over the dorsolateral prefrontal cortex (equivalent to F3 and F4 electrode sites) on the side of the body reported to experience the most pain, with a cathode reference electrode placed at the supraorbital region ipsilateral to the side of the body reported to experience the most pain. The electrodes are single-use and snap into pre-configured fixed locations of a flexible headband that is individualized for each participant. Participants will complete training via a telehealth platform that includes instruction on how to connect the electrodes, place the headband, and operate the device. As part of this training, participants will complete a single session of tDCS treatment.

During active sessions participants will receive 1mA direct current flow for 20 minutes. Sham sessions provide a ramp up to 1mA direct flow over a 5 second interval and return to no current flow for the remainder of the session. The tDCS unit requires a unique code for each stimulation session. Each remote session will be monitored for adherence and tDCS device connection quality. If needed, participants will be supplied with a device (iPad, laptop) to allow for video monitoring of the sessions. This methodology is consistent with the approach successfully utilized in our pilot study and ongoing studies. Cultural considerations: While the extent of cultural adaptation that can be applied to tDCS is, unfortunately, limited, we will utilize the above-described focus groups to discuss tDCS. We will conduct a 4th focus group during each phase dedicated exclusively to tDCS procedures. We will solicit feedback from stakeholders on acceptable language to describe tDCS and obtain feedback on study materials (e.g., handouts, images, instructions) and procedures (e.g., family involvement). In our ongoing study, NEUROSTIM, we have made adaptations to tDCS head straps to accommodate different hairstyles and will solicit feedback on the appropriateness of this and other adaptations across cultures.

Feasibility Study: Eligible participants will be assigned to either culturally adapted mobile CBT + active tDCS to the DLPFC or culturally adapted mobile CBT + sham. For the pilot phase, 10 participants will be enrolled from each racial and ethnic group (non-Hispanic Black, Hispanic, non-Hispanic White), and 5 participants in each group will be allocated to receive active tDCS and 5 to sham tDCS. We will alternate assignment of tDCS location within each group as participants are enrolled using an ABAB design for treatment allocation, separately for each racial and ethnic group. Because this is a feasibility study, blocked randomization and blinding is not necessary, but will be employed in a later study. Participants will complete two 20-minute stimulation sessions per week for 6 weeks. Each week, tDCS sessions will be paired with the mobile CBT program (e.g., core content, practice skills) at a time that is convenient to the participant. Two sessions will not occur within the same 24-hour period. As described above, participants will receive a unique activation code prior to each stimulation session. Each active session will be pre-programmed to deliver 1mA of direct current for 20-minutes; each sham session will be programed to provide a ramp up to 1mA over a 5 second interval and no current flow for the remainder of the session. tDCS parameters cannot be changed by participants. Adolescents will complete the outcomes measures listed below (e.g., pain intensity, functional disability) and parents will complete measures of SES, anxiety, depression, and their child's medication use at baseline and post-intervention.

Adverse event monitoring: Patient reports of AEs will be surveyed weekly, with symptoms reported for the prior tDCS sessions. Information will be collected by incident participant reporting and direct questioning using the patient report of incidence of side effects (PRISE).[85] Side effects will be assessed during weekly sessions. The PRISE assesses the presence of side effects for several biological systems. For each system (skin, nervous, eyes/ears, sleep, other), participants indicate the presence of a side effect, and if present, the tolerability of the side effect (tolerable or distressing). The PRISE includes commonly reported side effects of tDCS: tingling, itching sensation, burning sensation, pain, headache, fatigue, difficulty concentrating, and nervousness.[86] Participants will also be asked to report any other symptoms experienced during the tDCS session.

Figure 4a. Study Schema – Virtual Focus Groups

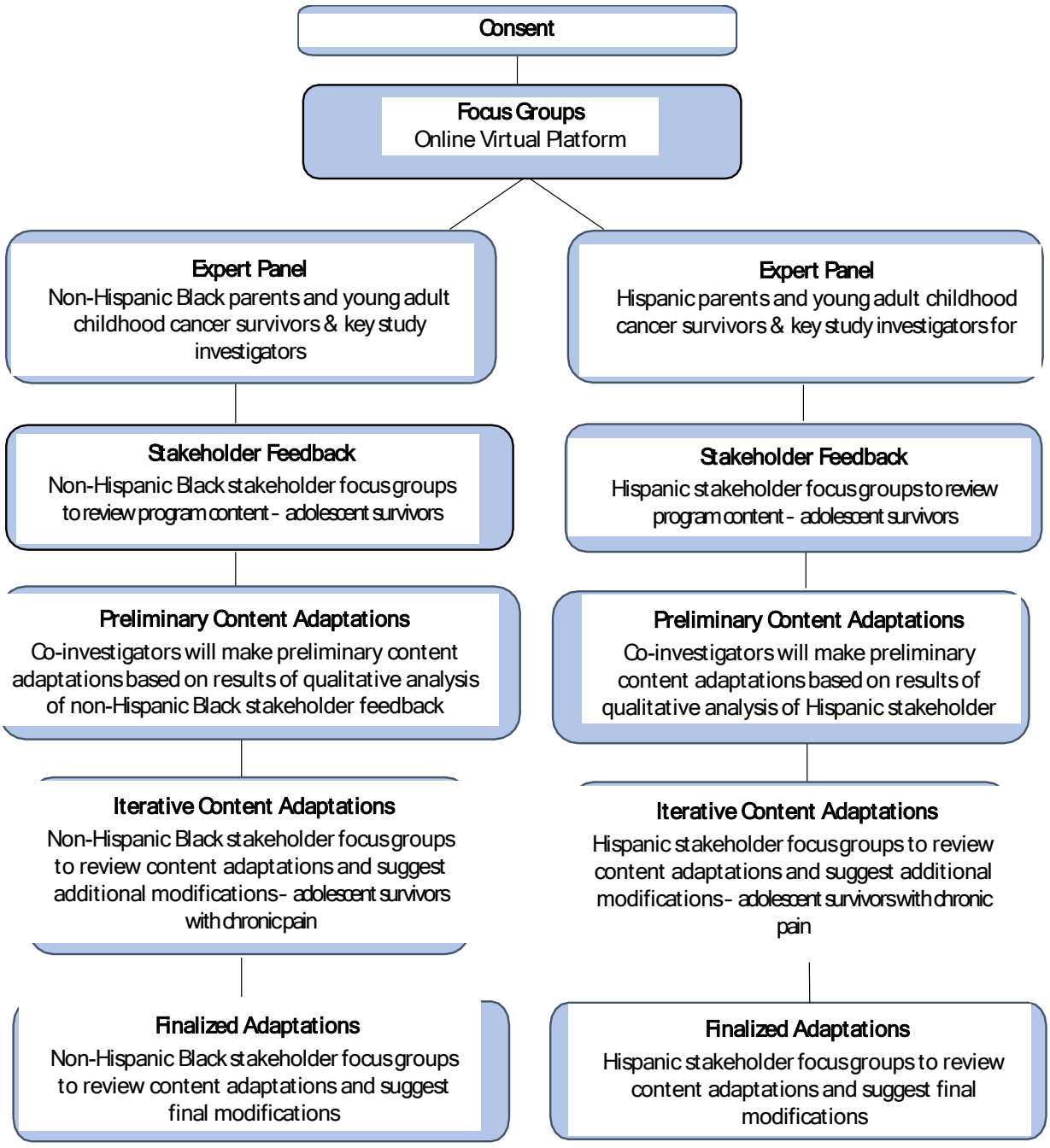
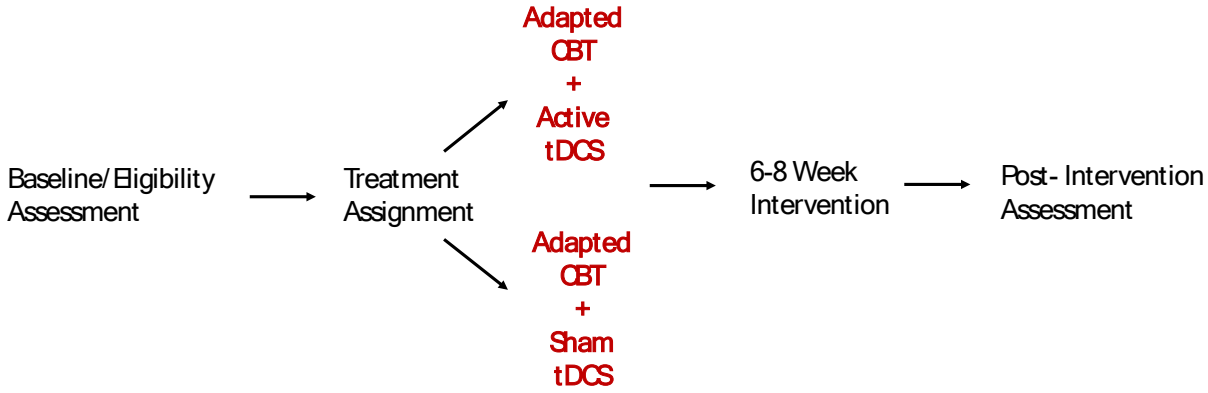


Figure 4b. Study Schema – Feasibility Pilot Study



4.2 Study Procedures:

All cultural adaptation processes will occur separately, but in parallel, for non-Hispanic Black and Hispanic participants. See detailed descriptions of procedures in 4.1 Design and Study Overview above.

Expert Panel via virtual meetings - 2 to 4 (1) hour virtual meetings with non-Hispanic Black and Hispanic parents and young adult survivors of childhood cancer and key study investigators. Sessions will be audio-recorded and transcribed verbatim.

Stakeholder Focus Group via virtual focus groups - (2-4) 45-minute sessions with non-Hispanic Black and Hispanic adolescent survivors of childhood cancer. Sessions will be audio-recorded and transcribed verbatim.

Preliminary Content Adaptations – based on results of qualitative analysis of stakeholder feedback.

Iterative Adaptation Process via virtual focus groups - (2-4) 45-minute sessions where adaptations will be presented to lived experience stakeholders (non-Hispanic Black and Hispanic survivors of childhood cancer with chronic pain). Sessions will be audio-recorded and transcribed verbatim.

Feedback meetings via virtual focus groups – (2-3) with 5-7 non-Hispanic Black and 5-7 Hispanic adolescent survivors who participated in previous sessions to review final program adaptations. Sessions will be audio-recorded and transcribed verbatim.

Mobile Cognitive Behavioral Therapy (CBT) - for chronic pain: Participants in the stakeholder focus group and the feasibility study will use mobile CBT program, WebMAP. Available on Android and iOS operating systems, this

program is interactive, self-guided intervention with six core treatment modules. These modules focus on 1) pain education, 2) stress, emotions, and thoughts (e.g., pleasant activity scheduling, thought stopping), 3) relaxation and imagery, 4) lifestyle and school interventions, 5) staying active, and 6) maintenance and relapse prevention. Within the app, participants complete screening questions to set up a profile and evaluate the need for two supplementary treatment modules focused on comorbidities of negative mood and sleep. There are several functional components to the app, including *places and lessons* (each place has 3-5 lessons that provide education and teach pain management skills), *library* (information on skills presented through audio clips, videos), *check-in* (allowing participants to track their pain, activity, mood, and sleep), and *skills tracker* (participants record practicing specific skills such as sleep relaxation).

Stakeholders in the focus groups will offer specific feedback about potential cultural adaptation of the images, concepts, personal stories, daily life examples and preliminary tailoring variables following proposed changes from the expert panel.

During the feasibility study phase eligible adolescent participants with chronic pain will be asked to use the CBT program with tDCS 20 minutes a day, twice a week for 6 weeks.

Transcranial Direct Current Stimulation (tDCS) Eligible participants will be assigned to either culturally adapted mobile CBT + active tDCS to the DLPFC OR culturally adapted mobile CBT + sham. For the feasibility phase, 10 participants will be enrolled from each racial and ethnic group (non-Hispanic Black, Hispanic, non-Hispanic White), and 5 participants in each group will be allocated to receive active tDCS and 5 to sham tDCS. We will alternate assignment of tDCS location within each group as participants are enrolled using an ABAB design for treatment allocation, separately for each racial and ethnic group. Because this is a feasibility study, blocked randomization and blinding is not necessary, but will be employed in the R33 phase. Participants will complete two 20-minute stimulation sessions per week for 6 weeks. Each week, tDCS sessions will be paired with the mobile CBT program (e.g., core content, practice skills) at a time that is convenient to the participant. Two sessions will not occur within the same 24-hour period. As described above, participants will receive a unique activation code prior to each stimulation session. Each active session will be pre-programmed to deliver 1mA of direct current for 20-minutes; each sham session will be programed to provide a ramp up to 1mA over a 5 second interval and no current flow for the remainder of the session. tDCS parameters cannot be changed by participants. Adolescents will complete the outcomes measures listed

below (e.g. pain intensity, functional disability) and parents will complete measures of SES, anxiety, depression, and their child's medication use at baseline and post-intervention.

During the stakeholders focus groups, participants will be asked to give feedback to the extent cultural adaptation can be applied to tDCS. **During the feasibility study phase** eligible adolescent participants with chronic pain will be asked to use the CBT program with tDCS 20 minutes a day, twice a week for 6 weeks.

4.3 Study Measures/Observations

Participants in both the focus group and feasibility study will be asked to fill out screening questions as described in the paragraph below.

Demographics: Participants will complete a consent to contact form and, if willing, will complete demographics questions during the screening process to obtain ethnicity, race, and other information needed to target recruitment to meet enrollment goals. If we are unable to confirm diagnosis or other screening information needed to confirm eligibility, study staff will ask the parent/guardian to sign a medical release form to obtain pertinent medical records.

Participants in the feasibility study will complete the outcomes measures listed below (e.g. pain intensity, functional disability) and parents will complete measures of SES, anxiety, depression, and their child's perception of pain and medication use at baseline and post-intervention (Table 2)

Pain intensity and pain interference: The *Brief Pain Inventory-Short Form* (BPI) includes a 4-item pain severity scale.[87] Participants rate their worst and least pain in the last week, average pain, and current pain.[88] The BPI pain intensity has good internal consistency in survivors of childhood cancer (α=0.87).[89] This measure includes a body diagram to allow participants to indicate where they experience the most pain. This will be used to inform placement of the anodal tDCS electrode (i.e., right vs. left DLPFC).[90, 91]

Pain catastrophizing: The *Pain Catastrophizing Scale, Child version* (PCS-C)[92] is a 13-item self-report measure of overly negative attitudes of pain and it consists of three scales of rumination, magnification, and helplessness. Higher scores indicate more pain catastrophizing.[93] This measure has good reliability (Cronbach's α=0.90) in a clinical sample of children and adolescents with chronic or recurrent pain.[92] The *Pain Catastrophizing Scale, Parent version* (PCS-P) is a

modified version of the PCS-C based on parent report of their own catastrophizing related to their child's pain. It assesses the same three factors of rumination, magnification, and helplessness.[94, 95]

Depression: The *PROMIS Pediatric Depressive Symptoms*[96] is an 8-item measure of self-reported symptoms of low mood in children and adolescents over the past 7 days. Higher scores indicate greater symptoms. The *Patient Health Questionnaire-2* (PHQ-2) inquires about the frequency of depressed mood and anhedonia over the past 2 weeks. A score of 3 points is the preferred cut-off for identifying possible depression (if the score is 3 or greater, major depressive disorder is likely).[97]

Anxiety: The *PROMIS Pediatric Anxiety*[96] is an 8-item measure of self-reported symptoms of anxiety symptoms in children and adolescents over the past 7 days. Higher scores indicate greater symptoms. The *Generalized Anxiety Disorder 2-item* (GAD-2) is a very brief and easy to perform initial screening tool for generalized anxiety disorder. A score of 3 points is the preferred cut-off for identifying possible cases and in which further diagnostic evaluation for generalized anxiety disorder is warranted. Using a cut-off of 3 the GAD-2 has a sensitivity of 86% and specificity of 83% for diagnosis of generalized anxiety disorder.[98]

Cancer-related worry: The *Fear of Cancer Recurrence Inventory*[99] is a 9-item measure developed specifically for survivors of childhood cancer (8-18 years) to assess the presence of fear of recurrence and perceived risk recurrence. Higher scores indicate greater cancer-related worry. Internal consistency is good (ICC=0.88).

Physical functioning: The *PROMIS Pediatric Mobility*[100] is an 8-item measure of self-reported ability at physical activities in children and adolescents in the past 7 days with higher score indicating greater ability. It has excellent test-retest reliability (ICC=0.73) and adequate internal consistency (Cronbach's α=0.73-0.74).[101] The *PROMIS Pediatric Upper Extremity*[100] is an 8-item measure of self-upper extremity function in the past 7 days with higher score indicating greater ability. It has excellent test-retest reliability (ICC=0.71) and adequate internal consistency (Cronbach's α=0.62-0.63).[101] Both measures are sensitive to change in youth with chronic pain.[102] The PedsQL™ 4.0 Generic Core Scale is reliable and valid in children and adults with cancer and includes a physical functioning scale, an emotional functioning scale, a social functioning scale, a school functioning scale, a total summary score, and both physical and psychosocial health summary scores. The instrument is available in young child, child,

adolescent, and adult versions (scales) if child/adolescent agrees and is able. All versions of this instrument are scored on a 0-100 scale.[103, 104]

Peer relations: The *PROMIS Pediatric Peer Relationship*[17] is an 8-item measure that assesses the quality of peer relationships. Higher score indicating higher quality. It has excellent test-retest reliability (ICC=0.81) and excellent internal consistency (Cronbach's α=0.83-0.84).[101]

Fatigue: The *PROMIS Pediatric Fatigue*[100] is a 10-item measure that assesses symptoms of fatigue in the past 7 days. Higher scores indicate more fatigue. It has excellent test-retest reliability (ICC=0.76) and internal consistency (Cronbach's α=0.87).[101]

Sleep: The *Adolescent Sleep Wake Scale* (ASWS) short form[105] is a 14-item measure of behavioral sleep patterns in adolescents. Internal consistency was good (α=0.74-0.84) in a pooled clinical sample of adolescents with mixed health conditions).[105] Acceptable reliability was reported in a sample of ethnically diverse adolescents from an economically disadvantage community (α=0.70-0.90).[106] We also will use the *PROMIS Sleep-Related Impairment*[107] 8-item measure to allow for assessment of sleep quality during the night as well as the impact of sleepiness on daytime function. This measure is validated for children and adolescents and assess sleep-related impairment over the past 7 days.

Global acceptability and satisfaction with treatment: Acceptability and satisfaction with treatment will be assessed using a 5-point numerical rating scale (NRS) (strongly disagree to strongly agree). The NRS has been recommended for use in pediatric pain clinical trials.[108] Two adapted questions from the modified treatment evaluation inventory will be utilized.[108, 109] We will also assess patient global impression of change using a single question to assess perceived improvement in pain.[110, 111]

Opioid Use: At each timepoint participants and/or their parents will be asked to list the names of their medications, doses taken, and the frequency with which the medications were taken over the past 2 weeks.[112] Medications will be classified as anti-inflammatory (e.g., nonsteroidal anti-inflammatory drugs); regular (daily) opioids, opioid medication as required (PRN), adjuvant pain medications (e.g., anticonvulsants). Opioid doses will be converted to morphine equivalent doses (MED) using an opioid equivalence table.[113, 114]

Parent anxiety and depression: Parental affective symptoms will be measured at each time point using the *Patient Health Questionnaire 8-item* (PHQ-8), a

measure of symptoms of major depressive disorder[115] and the *Generalized Anxiety Disorder* 7-item (GAD-7), a measure of symptoms of generalized anxiety.[116]

Table 2.

Outcome Measure	Questionnaire
Pain	Brief Pain Inventory-Short Form (BPI)
	Pain Catastrophizing Scale, Child version (PSC-C)
	Pain Catastrophizing Scale, Parent version (PSC-P)
Depression	PROMIS Pediatric Depressive Symptoms
	Patient Health questionnaire-2 (PHQ-2)
Anxiety	PROMIS Pediatric Anxiety
	Generalized Anxiety Disorder-2 (GAD-2)
Cancer-related worry	Fear of Cancer Recurrence Inventory
Physical functioning	PROMIS Pediatric Mobility
	PROMIS Pediatric Upper Extremity
	PedsQL (ages 8-12 &13-18)
Peer relations	PROMIS Pediatric Peer Relationship
Fatigue	PROMIS Pediatric Fatigue
Sleep	Adolescent Sleep Wake Scale (ASWS) short form
	PROMIS Sleep-Related Impairment
Global acceptability & satisfaction with treatment	2 adapted questions using numerical rating scale
Opioid Use	Medications Survey
	Patient Health questionnaire 8-item (PHQ-8)
Parent anxiety and depression	Generalized Anxiety Disorder 7-item (GAD-7)

4.4 Sites

All collaborating sites (Seattle Children's Hospital, Children's Healthcare of Atlanta, and Texas Children's Hospital) will identify potentially eligible participants, provide the study brochure, and provide the consent to contact form for interested participants. St. Jude will complete the remaining study activities.

5.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

5.1 Pre-Study and Study Activities

FOCUS GROUPS AND FEASIBILITY STUDY ACTIVITIES

STUDIES ACTIVITIES	Pre-Study	Focus Group Phase	Feasibility Study Phase	Off Study
Screening	X	X	X	
Consent	X	X	X	
Expert Panel – virtual meetings with stakeholders & key investigators		X		X
Stakeholder Feedback – virtual focus groups		X		X
Preliminary Content Adaptation - co-investigators only	X	X		
Iterative Content Adaptation – virtual focus groups		X		X
Finalized adaptation – virtual focus groups		X		X
Culturally Adapted CBT + active tDCS or Culturally Adapted CBT + sham for 20 min sessions twice a week for 6 weeks			X	X
Completion of Questionnaires			X	

6.0 CRITERIA FOR REMOVAL FROM PROTOCOL

6.1 Off Study Criteria

Death
Lost to follow-up
Request of the Patient/Parent
Discretion of the Study PI, such as the following

- The researcher decides that continuing in the study would be harmful
- The participant misses so many appointments that the data cannot be used in the study
- The participant's condition gets worse
- New information is learned that a better treatment is available, or that the study is not in the participant's best interest
- Study evaluations are complete

7.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

7.1 Adverse Events (AEs)

Adverse events will be monitored from the start of the study. Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. Weekly PRISE forms will be completed.

7.2 Definitions

Adverse Event (AE): Any untoward medical occurrence associated in a study participant after the beginning of the study. Adverse Events will be graded by the NCI CTC AE version 5.0. Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study.

Serious Adverse Event (SAE): Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical

intervention to prevent one of the other outcomes listed in this definition.

7.3 Handling of Adverse Events (AEs) and Deaths

Recording **of Adverse Events and Serious Adverse Events:** Adverse events of all types will be recorded in the database.

Reporting **Adverse Events and Serious Adverse Events**:
Adverse events will be surveyed weekly. Event information will be collected using a modified version of patient report of incidence of side effects (PRISE: see description above)

The St. Jude PI, upon awareness of an event, will determine the seriousness of AEs and ensure that all UPs are entered into the electronic submission system (iris) within 10 days. All (pertinent, as in *recording* above) AEs, serious or not, will be recorded in a log, spreadsheet, or report and submitted to the St. Jude IRB at the time of continuing review.

Unanticipated Problems (UPs): The St. Jude PI will refer to St. Jude Human Research Protection Program (HRPP) Policy 01.720 for definitions and specifics for reporting of unanticipated problems to the St. Jude IRB. The St. Jude IRB reports UPs to BIMO as per 21 CFR 56. The UP policy link follows: [redacted]

Collaborating sites:

Report Serious Adverse Events as defined in section 7.2 internally per your IRB of record's policy **and** to the St. Jude Principal Investigator as soon as possible.

Report Unanticipated Problems to your IRB of record per policy **and** to the St. Jude Principal Investigator within 15 days.

Sharing of SAEs:

The St. Jude PI will ensure that all unexpected, possibly related Serious Adverse Events on study are shared with all sites. Collaborative sites will

share SAEs based on guidelines of CTA SOP 28 for more details. Link:

[redacted]

Deaths: Deaths meeting reporting requirements are to be reported immediately to the St. Jude IRB, but in no event later than 48 hours after the investigator first learns of the death.

7.4 Process for Communicating Study-Wide Adverse Events

The study PI will document their plan for obtaining adverse event information from a collaborator, and for disseminating study-wide adverse event information to the collaborators.

8.0 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

8.1 Data Collection

Electronic case-report forms (e-CRFs) will be completed by the St. Jude Clinical Research Associates or the site Study Coordinator. Data from the participant's record will be entered directly into a secure study-specific database. Instructions for data entry are outlined in the database.

Data management will be supervised by the ADAPTED study team. Protocol-specific data and adverse events will be recorded in the electronic database, ideally within 2 to 4 weeks of the study procedure. All questions will be directed to the Principal Investigator, Dr. Tara Brinkman, PhD., or designee and will be reviewed at regularly scheduled working meetings.

Regular summaries of protocol events will be generated for the PI and the Department of Biostatistics to review.

8.2 Data Collection Instructions for Collaborating Sites

Collaborating sites may collect data either by using Case Report Forms or by remote electronic data entry. Timeframes for entry of study data or completion of case report forms will be outlined so that study data may be obtained in a timely and consistent manner.

When CRFs are used, they will include the name and contact information of the person to whom the forms are to be sent.

8.3 Study Monitoring- Non-Therapeutic Risk Categories

This study is considered low risk for monitoring purposes. The Principal Investigator (PI) and study team are responsible for ensuring participant eligibility and protocol compliance. The study team will hold meetings as needed to review case histories or quality summaries on participants and will generate minutes which are signed by the PI.

CTO will review up to 10% of the study participants the first year for life status, status on study, and the appropriateness of the informed consent and eligibility processes. During this monitoring, the monitor will verify regulatory documentation pertinent to the study, all Serious Adverse Event reports, and Age of Majority consenting on all study participants. St. Jude affiliates and domestic collaborating study sites will be monitored remotely, in the same method as St. Jude, by the St. Jude Monitor. If there are no unresolved issues, no further monitoring will be performed. The PI and study team will be responsible for ensuring protocol and regulatory compliance. The Monitor will generate a follow-up letter which is shared with the Principal Investigator, study team, and the Internal Monitoring Committee (IMC).

Protocol continuing reviews by the Institutional Review Board (IRB) and Scientific Review Committee (CT-SRC) will occur at least annually. In addition, Unanticipated Problems and/or Serious Adverse Event reports are reviewed by the IRB.

8.4 Confidentiality

Confidentiality will be maintained. Data forms will be kept in locked file cabinets, in locked office space, accessed only study staff on an “as needed” basis. Data files will be de-identified, linked by a participant identification number to a separate secure database. Data files downloaded for statistical analyses will not contain personal identifiers.

The medical records of study participants may be reviewed by the St. Jude IRB, FDA, clinical research monitors, etc.

9.0 STATISTICAL CONSIDERATIONS

The primary objective Qualitative analysis plan for focus groups: We will develop a codebook using *a priori* codes based on key domains and components from the literature,[80] as well as novel codes inductively derived through transcript review. Two coders will independently code focus group transcripts and meet regularly to resolve discrepancies and evaluate inter-rater reliability. Thematic content analysis will focus on identifying culturally specific adaptations and will be used to modify intervention content. MAXQDA software will be used for data management and processing. Given the iterative nature of our approach and the need for timely adaptation of the intervention, a rapid qualitative analysis technique[117] will be used to summarize and analyze transcript data. Rapid analysis is being increasingly utilized in implementation science research and has been demonstrated to yield results similar to in-depth qualitative analytic methods.[118, 119] Our analysis will focus on the 3 key domains of content, methodology, and procedure with flexibility to include additional domains or components derived from transcript review. Two qualitative analysts will pilot, revise, and utilize transcript summary templates based on these domains to identify adaptations which will be used to modify content.

Intervention feasibility: We will assess feasibility using three primary criteria: 1) proportion of approached survivors who agree to participate in the intervention trial, 2) adherence to interventions parameters (module/session completion, reasons for dropouts), and 3) acceptability of intervention procedures. For the R61 feasibility trial we aim to enroll 30 participants (10 from each racial/ethnic group: non-Hispanic White, non- Hispanic Black, Hispanic). In an ad hoc manner, if fewer than 50% of approach survivors agree to participate, the intervention will not be considered feasible (i.e., if we need to approach more than 60 survivors to enroll 30 for the feasibility trial). A participant will be considered a "completer" if he/she completes at least 75% of all the sessions (4/6 CBT and 9/12 tDCS sessions). The intervention will be considered feasible if at least 60% of the participants are completers. The feasibility will be assessed in the overall sample of 30 using exact 95% lower confidence bound (Clopper-Pearson method). Thus, the intervention will be considered feasible if 23 or more participants complete the intervention with 95% exact lower confidence bounds (0.61, 1.0). In addition, in an exploratory manner we will assess completion rates in each racial/ethnic group to see if differences are observed. We also will assess treatment acceptability. If >50% of participants report the intervention as 'unacceptable' the intervention will not be considered feasible as designed.

Finally, we will estimate preliminary effectiveness of the intervention to inform potential changes to the proposed sample size needed for the larger R33 clinical trial. We will compare mean change scores for pain intensity and functional disability in survivors who received active tDCS vs. sham using a two-sample t-test. Although we will not be powered to detect a statistically significant difference between the groups, we will use the effect estimate to inform power calculations for the R33 clinical trial. If any of the feasibility parameters including 1) participation rate, 2) adherence, or 3) acceptability do not meet our a priori defined feasibility definitions, we will re-engage stakeholders and individuals with lived experiences for input and make adaptions to the interventions based their feedback as well as data we collect from participants related to reasons drop out and unfavorable acceptability. Transition to the R33 phase will be contingent on meeting milestones defined in the Study Timeline. These include: 1) adaptation and tailoring of intervention content, 2) completion of mobile CBT program modifications, and 3) completion of the 6-week feasibility trial of culturally adapted CBT + tDCS.

9.1 Anticipated Completion Dates (elements required by CT.gov)

- **Anticipated Primary Completion Date:** October, 2024
- **Anticipated Study Completion Date** October, 2025

10.0 OBTAINING INFORMED CONSENT

10.1 Informed Consent Prior to Research Interventions

Participants will be informed that all study procedures are for research purposes only. Participants will be introduced to the study during the consent process by e-mail and phone. The consent conference for remote participation will be completed by phone. A member of the study team will explain the study and review the potential risks and benefits.

If the participant expresses interest, they will be e-mailed, faxed, or mailed/FedExed a copy of the consent form if they agree to consent conference via phone; the consent conference will occur via phone and e-mail, or e-signature will be used to document informed consent. Once the consent signature page is received the participant is enrolled on study as described in Section 3.6.

10.2 Consent at Age of Majority

The age of majority in the state of Tennessee is 18 years old. Research participants must be consented at the next clinic visit after their 18th birthday. Please refer to HRPP Policy 01.722 Legally Effective and Prospectively Obtained Informed Consent and Assent for Research and Documentation. If an affiliate or collaborating site is located in a country or state where a different age of majority applies, that location must consent the participants according to their local laws.

10.3 Consent When English is Not the Primary Language

When English is not the patient, parent, or legally authorized representative's primary language, the Social Work department will determine the need for an interpreter. This information documented in the participant's medical record. Either a certified interpreter or the telephone interpreter's service will be used to translate the consent information. The process for obtaining an interpreter and for the appropriate use of an interpreter is outlined on the Interpreter Services, OHSP, and CTO websites.

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