Cognitive Behavioral Therapy and Real-Time Pain Management Intervention for Sickle Cell Via Mobile Applications (CaRISMA)

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Statistical Analysis Plan

Study Design & Objectives. CaRISMA is a multisite, randomized, pragmatic, comparative effectiveness trial that will be conducted at 6 comprehensive sickle cell centers and 4 community-based organizations (CBOs). A total of 350 adults with SCD who report chronic pain and/or use long acting or daily opioids will be enrolled and randomized in a 1:1 ratio to receive either a digital CBT program tailored for adults with SCD (CBT) or pain and SCD education (Education) on their mobile phones for 12 weeks. Both programs will use identical mobile-based technology platforms, with the only difference being the content provided. The focus of the digital CBT program is to teach behavioral coping skills through participants' seeing and doing, whereas the pain education arm focuses on improving self-management through participants' learning and knowing more about pain and SCD.

The primary objective of the CaRISMA (Cognitive Behavioral Therapy and Real-time Pain Management Intervention for Sickle Cell via Mobile Applications) trial is to compare the effectiveness of two mobile phone–delivered programs for reducing SCD pain symptoms at the 6-month follow-up: digital CBT versus pain and SCD education (Education). We will also evaluate the sustainability of the intervention effects at the12-month follow-up. The secondary objective is to assess whether baseline depression symptoms moderate the effect of interventions on pain outcomes. We hypothesize that digital CBT will confer greater improvement in pain interference, pain intensity, and depressive symptoms at 6 months compared with Education. We also hypothesize that digital CBT will confer a greater reduction in health care use (e.g., opioid prescriptions or refills or acute care visits) over 12 months compared with Education.

Randomization. Upon completion of eligibility, participants will be randomly assigned to either digital CBT or Education. Permuted block randomization will be stratified by study center (e.g., one of the six clinical sites or from a community partner) in an effort to control for site-specific disease education and treatment approaches. The randomization schema was created by the lead statistician in the data coordinating center and integrated into the web-based data capture system.

Sample Size Calculation. For the primary test of comparative effectiveness of digital CBT versus mobile education (m-Education) for the trial, the power calculation is based on the comparison of intervention groups for the main outcome of the 6-month change in pain interference. Specifically, our sample size of 350 participants enables 80% power to detect a difference of 0.37 SDs between study arms on 6-month changes. This detectable effect is also applicable to key secondary outcomes, such as pain intensity and depression, as measured by the PHQ-9. Our calculations account for 15% attrition at 6 months.

Hypotheses. Our study hypotheses are:
H1: cCBT will confer greater benefit on pain outcomes at 6 months, compared to m-Education. The primary outcome of the proposed trial is change in pain interference at 6 months. The main secondary outcome will be change in average weekly pain intensity. We will also explore sustainability of the intervention effects at 12 months.
H2: cCBT will confer greater benefit on depressive symptoms at 6 months, compared to m-Education.
H3: cCBT will confer greater decreases in health care utilization (opioid prescriptions, acute care visits) and opioid misuse behaviors (Current Opioid Misuse Measure – COMM) over 12 months, compared to m- Education.

Analysis Sets. All analyses will be under the framework of intention-to-treat, such that all randomized participants are included regardless of initiation or adherence to interventions. However, we will conduct sensitivity analyses restricting to participants who were randomized with confirmation of sickle cell disease.

Study Outcomes.

Primary Pain Outcome: Pain Interference

Patient Reported Outcomes Measurement Information System Pain Interference assesses the effect of patient-reported pain on relevant aspects of a person's life and may include the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. This measure will only be completed at baseline and 3, 6, and 12 months.

Secondary Pain Outcome: Daily Pain Intensity

Participants will be asked to enter their daily pain via a mobile website. They will receive reminder notifications via text messages for 2-week periods at baseline and 3, 6, and 12 months. However, between these automated-reminder periods, participants will be encouraged to continue entering their pain scores on the mobile pain web app.

Other Secondary Outcomes

Painimation

Painimation is an electronic pain assessment tool that allows users to better communicate pain symptoms. Patients are provided with a selection of animations (painimations) that they use to describe the quality of their pain. The painimations can be adjusted to reflect pain intensity. Screenshots of the Painimation app illustrate the splash screen, paintable body image, and selection of painimations to indicate the quality and intensity of pain.

Medical Outcomes

For patients recruited at one of the six clinical sites, we will evaluate objectively measured opioid medication prescriptions and refills and emergency department visits or hospitalizations for pain episodes. We will work in collaboration with PCORnet to collect data retrospectively (12 months before enrollment) and prospectively (12 months after enrollment) from patients' electronic health records. These data will allow us to track opioid medication use, health care use, and laboratory values (e.g., hemoglobin level), as well as other key clinical outcomes. For patients recruited from our CBO partners or on the web, we will only evaluate their medical records to confirm their SCD diagnosis if they do not receive their SCD care at one of the participating clinical sites.

Current Opioid Misuse Measure

Current Opioid Misuse Measure is a self-report measure to monitor indicators of current aberrant drug-related behaviors in patients with chronic pain on opioid therapy. This measure will be completed only at baseline and 12 months.

Patient Health Questionnaire

PHQ-9 assesses the degree of depression severity. ThePHQ-9 total score is for nine items, all rated as 0(not at all) to 3 (nearly every day), with total scores ranging from 0 to 27. Scores of 5, 10, 15, and 20 represent cut-off points for mild, moderate, moderately severe, and severe depression, respectively. This measure will only be completed at baseline and 3, 6, and 12 months.

Generalized Anxiety Disorder Scale-7

GAD-7 evaluates the severity of anxiety. The GAD-7 total score for the 7 items ranges from 0 to 21. Scores of 5, 10, and15 represent the cut-off points for mild, moderate, and severe anxiety, respectively. This measure will only be completed at baseline and 3, 6, and 12 months.

Adult Sickle Cell Quality of Life Measurement Information System Emotional Functioning and Social Impact Scales

The ASCQ-ME emotional functioning and social impact quality-of-life measure was specifically designed for SCD and evaluates the health care experience of patients with SCD, emotional response to stress, and social relationships. These measures will only be completed at baseline and 3, 6, and 12 months.

Sickle Cell Self-Efficacy Scale

SCSES is a self-report measure to assess the ability of patients with SCD to function on a day-to-day basis and manage their SCD symptoms. This measure will only be completed at baseline and 3, 6, and 12 months.

Handling of Missing Values. We will minimize missing data by using an electronic data collection system and by contacting participants when data are not entered in a timely fashion. We will attempt to characterize the missingness mechanism (missing completely at random, missing at random, or not missing at random) by comparing rates of missingness or attrition between study arms. In addition, we will compare baseline characteristics between participants with and without missing outcome data. If we conclude that our missingness is random, then our likelihood-based approach for the primary analyses will address this. Otherwise, if the missingness can be characterized as nonignorable (not missing at random), we will use approaches such as joint modeling or shared parameter models to produce unbiased estimates of treatment effects. All reasons for dropout or other missing values will be entered by the research staff or community groups (if encountering the patient during community activities) and will be tabulated and summarized, and results will be reported using the CONSORT (Consolidated Standards of Reporting Trials) diagram. Patients who stop reporting data in the app will receive inquiry text messages or phone calls.

Statistical Analyses. All primary and secondary analyses will be preceded by descriptive analyses of the baseline and clinical characteristics. Summary statistics will include means and SDs for continuous variables and sample proportions for categorical variables. Median and IQR values will accompany nonnormal, continuous variables. The results will be presented both within and across study arms. All analyses will follow the intention-to-treat approach.

Analysis of Primary and Secondary Pain Outcomes

Linear mixed models will be employed for the primary outcome of pain interference as a function of time, study arm (digital CBT vs Education), time×study arm interaction, study site, and baseline depression level (PHQ-9≤10 vs PHQ-9>10). We will account for multiple observations for each participant by including a random effect for the subject. In addition, baseline variables with large, clinically meaningful between-arm differences will be included as covariates in the secondary analyses. Contrasts will be estimated to assess the impact of digital CBT and education intervention on 6-month improvements in pain interference. As a secondary investigation, we will use the same linear mixed models to address whether the 6-month improvements are sustainable for 12 months. The analytic strategy for the key secondary outcome of pain intensity will be identical to that of the primary outcome. As the confirmation of a sickle cell diagnosis may not be made immediately after randomization, we will conduct an a priori sensitivity analysis restricting eligible participants with the confirmation of SCD.

Analysis of Secondary Outcomes

Secondary outcomes such as PHQ-9, Current Opioid Misuse Measure, GAD-7, Adult Sickle Cell Quality of Life Measurement Information System, and SCSES will be analyzed using similar linear mixed models with time, study arm, time×study arm interaction, study site, and baseline depression level as fixed covariates and a random effect for each subject. Health care use will be compared between study arms using generalized linear models to account for count data (i.e., Poisson regression) for each of the following: the number of opioid prescriptions, number of emergency department visits, and number of hospitalizations over 12 months after study entry. Predictors will include the study arm, study site, and baseline depression level. The corresponding health care use in the 12 months before study entry will be entered as a covariate in each model. We will offset each model by the participant's time in the study.

Subgroup Analysis

We will examine the heterogeneity of the treatment effect to determine whether the intervention works better for some than for others. Our prespecified analysis plan will examine differences in pain interference between patients with high (PHQ-9>10) and low (PHQ-9≤10) depression. We will augment the primary analysis models for pain interference with relevant main effects for the baseline depression level and 2- and 3-way interactions with the study arm and time. Of primary interest is the significance of the 3-way interaction (time×study arm×baseline depression level). If significant, we will present the treatment effect estimates and 95% CIs within each subgroup. For all of the above-described models, we will focus on the 6-month outcome.

Mediation Analysis

For coping skills, self-efficacy, and program engagement or dose measures, changes in scores from baseline to 3 months and from baseline to 6 months will be tested as potential mediating variables. We will use the framework of Kraemer et al to calculate effect sizes, accounting for the impact of the potential mediator variable. In addition to modeling each mediator as a function of time, study arm, time×study arm interaction, study site, and baseline depression level (PHQ-9≤10 vs PHQ-9 >10), we will augment the original primary analytic models by including the potential mediator as a covariate.