Official Title: Clinical Decision Support for Patient Migraine Management

NCT Number: NCT03706794

IRB Number: 2015-5743

IRB Approval Date: 06/30/2021

Statistical Analysis Plan: 06/30/2021

**CDST IRB Protocol – ~~September 2020~~May 2021**

## SYNOPSIS

Little is known about who adheres to migraine management strategies, and circumstances that enhance adherence. This knowledge is required to develop patient-level interventions to improve adherence to migraine management strategies. This type of intervention is novel, long overdue, and a major step forward in the clinical care of people with migraine. The proposed project will develop and pilot the first patient level intervention designed to improve adherence to preventive and acute migraine management strategies. We plan to identify people most at risk for non-adherence to migraine management strategies. We will randomly assign the subjects to one of two groups; for one group we will develop an individually tailored clinical decision support tool (CDST) (study group), for the other we will provide general headache education (control group).

PRIMARY OBJECTIVE

The primary objective of this study is to describe and analyze how individual differences and circumstances influence adherence to preventive and acute migraine management strategies. Mobile electronic headache diaries will be used to 1) assess the roles of individual differences and conditions in adherence to preventive and acute migraine management strategies, and 2) develop and pilot a tailored clinical decision support tool (CDST) to improve adherence to preventive and acute migraine management strategies.

PRIMARY OUTCOME VARIABLES

The primary outcome variables will be **adherence to acute and preventive migraine management strategies**. All primary outcome variables will be assessed through an electronic headache diary.

## STUDY DURATION

The study will last for approximately 5 years. Phase 1 of the project began in April 2016 under the approved Einstein IRB protocol # 2015-5743. We anticipate completing data collection in 2019, and initial data analysis in 2020.

## STUDY DESIGN

This study has three phases:

1) The first phase is an **iterative qualitative design** with the purpose of developing and refining the CDST app for use in people with episodic migraine.
2) The second phase is a **prospective observational design** with the purpose of evaluating the roles of individual differences and conditions in adherence to preventive and acute migraine management strategies.
3) The third phase is a **pilot randomized clinical trial** with the purpose of evaluating the CDST app compared to a Headache Education app to improve adherence to acute and preventive migraine management strategies.

STUDY POPULATION

**Phase 1 (A & B):**

Participants will be included if they 1) have an International Classification of Headache Disorders – 3 beta diagnosis of migraine, 2) self-report between 6 to 14 headache days per month, 3) are currently prescribed a triptan for acute migraine management, 4) are between the ages of 18 and 65, and 5) self-report at least one problem with adherence to preventive and acute migraine management strategies.

Exclusion criteria are 1) probable or confirmed medication overuse headache, 2) a plan to change, or changing preventive or acute migraine medication during study participation, and 3) are pregnant or are planning to become pregnant during study involvement (as triptans are Category C medications).

**Phase 2:**

Participants will be included if they 1) have an International Classification of Headache Disorders – 3 beta diagnosis of migraine, 2) self-report and diary-confirmed 6 to 14 headache days per month, 3) are currently using one of the following treatments for acute migraine management: triptans, ditans, gepants, NSAIDs, or acetaminophen, 4) are stable on current preventive and acute treatment regimen for migraine, 5) are between the ages of 18 and 65, 6) read English, 7) have capacity to consent, and 8) complete 80% of diary recordings in the first 30 days of monitoring.

Exclusion criteria are 1) probable or confirmed medication overuse headache, 2) a plan to change, or changing preventive or acute migraine medication during study participation, 3) are pregnant or are planning to become pregnant during study involvement (as triptans are Category C medications), 4) psychiatric illness or cognitive difficulties that would interfere with participation in the study, and 4) participated in Phase 1 of the Clinical Decision Support for Patient Migraine Management protocol.

**Phase 3:**

Participants will be included if they 1) completed Phase 2 of the study, 2) completed at least 80% of diary recordings throughout Phase 2 of the study, and 3) demonstrated poor (<50%) adherence to at least one acute migraine management strategy and at least one preventive behavioral migraine management strategy during study Phase 2.

Exclusion criteria are 1) probable or confirmed medication overuse headache, 2) a plan to change, or changing preventive or acute migraine medication during study participation, 3) are pregnant or are planning to become pregnant during study involvement, 4) psychiatric illness or cognitive difficulties that would interfere with participation in the study.

NUMBER OF PARTICIPANTS

There will be a total of 394 participants.

NUMBER OF STUDY SITES

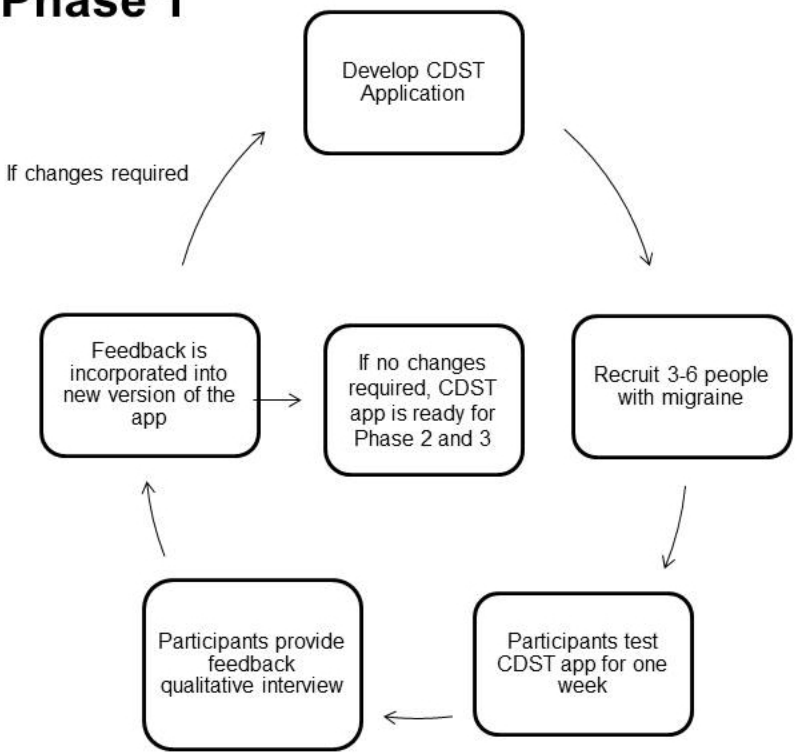
The study will be conducted at:

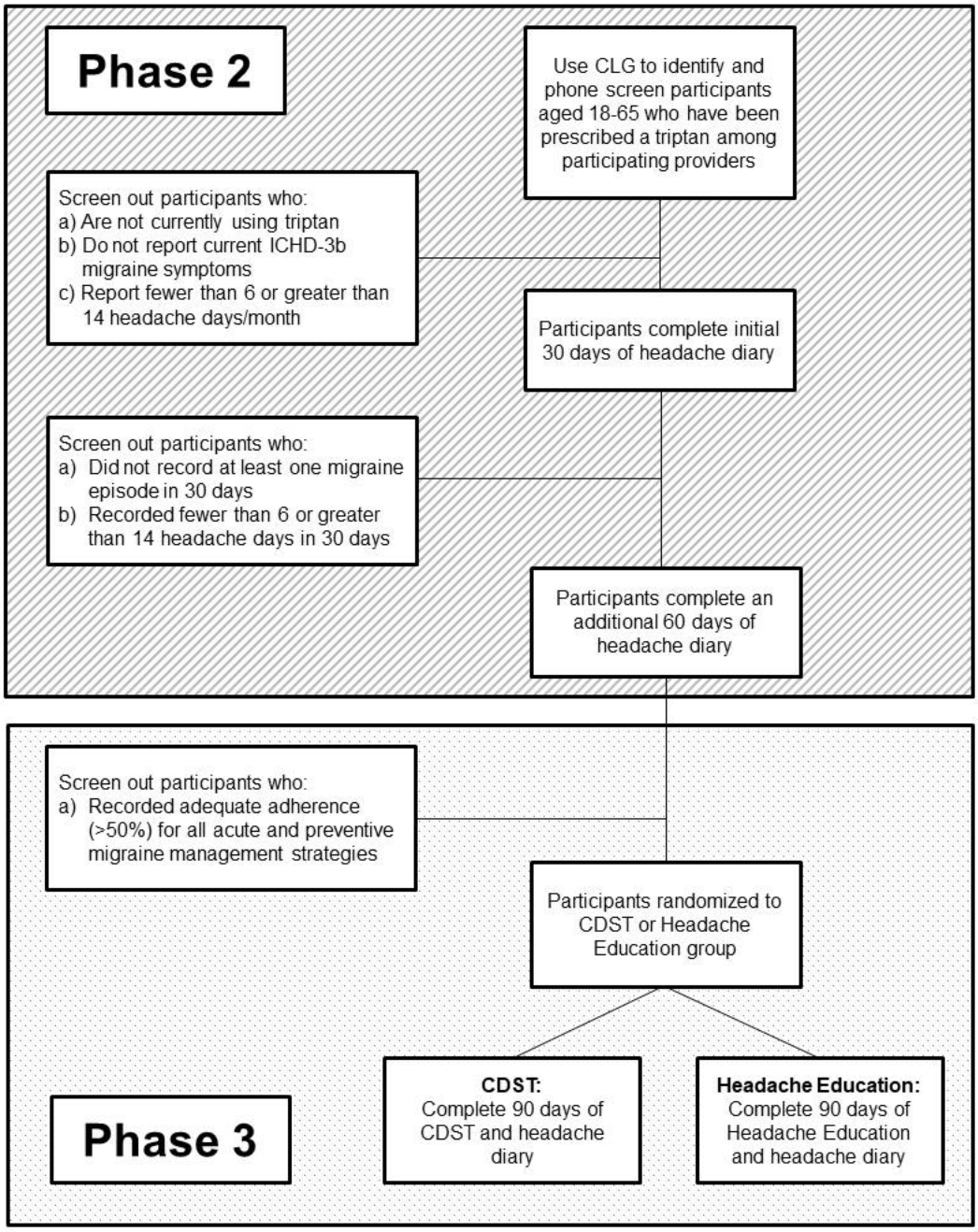
The Seng (Headache & Adherence) Lab, Van Etten Building, 1225 Morris Park Ave, Bronx, NY 10461.

The Montefiore Headache Clinic, Hutchinson Tower #2,1250 Waters Pl, Bronx, NY 10461.

STUDY FLOW CHART

# Phase 1


Develop CDST Application
If changes required
Feedback is incorporated into new version of the app
If no changes required, CDST app is ready for Phase 2 and 3
Recruit 3-6 people with migraine
Participants provide feedback qualitative interview
Participants test CDST app for one week


Phase 2
Use CLG to identify and phone screen participants aged 18-65 who have been prescribed a triptan among participating providers
Screen out participants who:
a) Are not currently using triptan
b) Do not report current ICHD-3b migraine symptoms
c) Report fewer than 6 or greater than 14 headache days/month
Participants complete initial 30 days of headache diary
Screen out participants who:
a) Did not record at least one migraine episode in 30 days
b) Recorded fewer than 6 or greater than 14 headache days in 30 days
Participants complete an additional 60 days of headache diary
Screen out participants who:
a) Recorded adequate adherence (>50%) for all acute and preventive migraine management strategies
Participants randomized to CDST or Headache Education group
Phase 3
CDST:
Complete 90 days of CDST and headache diary
Headache Education:
Complete 90 days of Headache Education and headache diary

# 1.INTRODUCTION

## 1.1 Introductory Statement

This document is a protocol for a human research study. This proposal will use mobile electronic headache diaries to 1) assess the roles of individual differences and conditions in adherence to preventive and acute migraine headache management strategies, and 2) develop a tailored Clinical Decision Support Tool to improve adherence to preventive and acute migraine management strategies. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines (CRF 21 Part 312), applicable government regulations and Institutional research policies and procedures

## 2. BACKGROUND

### 2.1 Background/Prevalence of Research Topic

Migraine is a chronic, painful condition with episodic attacks of head pain, nausea/vomiting, and sensitivity to light/sound (1). Migraine is common, affecting 1 in 7 Americans annually (2). Migraine is the most disabling neurological disease worldwide (3), and costs the U.S. healthcare system $4.3 billion annually (4). Patient adherence to migraine treatment recommendations is problematic (5-7) and can lead to increased migraine symptoms, burden, and economic cost (5, 8-10). Some people with migraine use preventive migraine management to reduce migraine frequency, and virtually all people with migraine use acute migraine management to reduce the impact of migraine attacks (11-14). Adherence to preventive migraine management strategies involves consistent use of behavioral strategies (regulating stress, sleep, and diet) (15, 16) and sometimes medication (often beta-blockers or antiepileptics). For acute migraine management, triptans, ditans and gepants are the first-line strategy for moderate-severe migraines, and non-steroidal anti-inflammatories (NSAIDs) or acetaminophen are the first-line strategy for mild-moderate migraines (14, 17-19). Acute migraine medications are most effective if taken early during a migraine episode, when head pain is still mild (11, 20-22). Most acute migraine medication use should be limited to avoid medication overuse headache, a secondary headache caused by regular overuse of acute headache medication (Triptans ≥ 10 days/ month; NSAIDs and acetaminophen ≥ 15 days/month). Thus, adherence to acute migraine management requires in-the-moment decision-making (11, 23). Little is known about who adheres to preventive and acute migraine management strategies (individual differences) and when patients adhere to these strategies (circumstances). Certain individual differences (age, gender, education, psychiatric comorbidity and patient beliefs) have been associated with retrospective reports of adherence and pharmacy refill in isolated studies (5, 8, 24-28). Changes in treatment conditions (time of day, weekly migraine frequency, variations in stress and sleep) may be implicated in adherence to acute migraine management strategies (8), but have not been empirically examined. Understanding individual variability in adherence is the foundation to targeting vulnerable populations with adherence interventions.

## 3. RATIONALE/SIGNIFICANCE

### 3.1 PROBLEM STATEMENT

Migraine is a common (29), disabling (30), and costly (31) disorder characterized by episodic, painful symptoms. Preventive treatments can reduce migraine frequency (12, 15, 16, 32, 33), and acute treatments can reduce (or eliminate) symptoms of an ongoing migraine episode (11, 14, 17). Efficacy of these treatments relies on patient adherence. Patient adherence to migraine treatment recommendations is problematic (5-8) and can lead to increased migraine symptoms, burden, and economic cost (5, 8, 9). Development of interventions to improve adherence to migraine management strategies could reduce migraine symptoms and the personal, economic, and societal burden associated with migraine(5, 8, 9). Understanding factors associated with adherence to migraine management strategies is the foundation of improving patient adherence.

### 3.2 PURPOSE OF STUDY/POTENTIAL IMPACT

A clinical decision support tool (CDST) for people with migraine would build upon commonly used daily headache diaries and offer clinical decision support to the people making clinical decisions in their daily lives: patients. Mobile electronic devices are potentially powerful tools to improve adherence to preventive and acute migraine management strategies. Electronic headache diaries are common in clinical treatment of migraine and have high adherence rates (6). Migraine is most prevalent mid-life (34), when the majority of Americans own a smartphone (35). This study will use mobile electronic headache diaries to 1) assess the roles of individual differences and conditions in adherence to preventive and acute migraine management strategies, and 2) develop a tailored CDST to improve adherence to preventive and acute migraine management strategies.

## 3.3 POTENTIAL RISKS AND BENEFITS

Study risks are minimal. Participants may feel uncomfortable answering questions about their headaches or changing lifestyle factors associated with migraine. These outweighed by the potential gains both for study participants and for people with migraine broadly.

### 3.3.1 POTENTIAL BENEFITS

Individual study participants, may experience improved knowledge about their own adherence to migraine management strategies, as well as daily variations in headache symptoms, stress and sleep. Participants may experience improvements in their adherence to migraine management strategies, and potentially experience improvements in their migraine management. Regarding societal benefits, this study will identify patterns of individual differences and circumstances associated with migraine management adherence. This will allow for tailored interventions to improve migraine management adherence in the patients who experience the most difficulty with adherence. This study will also test the feasibility and obtain initial effect sizes for a novel tailored intervention to improve patient adherence to migraine management strategies. If successful, this intervention could improve adherence to migraine management strategies, and potentially improve the effectiveness of migraine treatments.

### 3.3.1 POTENTIAL RISKS

The randomization process inhibits therapeutic choice of participants. It is possible that taking a headache diary will elicit psychological discomfort as it draws attention to each participant's headache activity and associated disability. It is also possible that participants will experience discomfort when provided with education about how their lifestyle impacts their migraine. Finally, there is a risk that a data breach could reveal private information collected as part of the study.

Protections Against Risk - If participants choose to initiate a new migraine medication during the study, they will be removed from the study, but will be offered both the CDST and Headache Education following their participation in the study. Participants randomized to receive Headache Education will be offered the CDST following their participation in the study. Participants randomized to receive the CDST will be offered Headache Education following their participation in the study. Participants will be given a random study identification number. Participants data will either be collected on paper and stored in a locked lab file cabinet, or through REDCap, a secure online data capture software, through the headache diary application. Data will be de-identified and converted to electronic databases and stored in password-protected files on a password-protected computer in the locked lab. The list linking participant names to identification numbers will be kept on paper in a locked file drawer, and destroyed immediately after the last participant information is entered in a de-identified database, no more than 6 months after the last day of data collection. The research assistant will call participants at least once per month throughout the study to assess for adverse events. The PI will also monitor each participant's recorded headache diaries monthly to assess for adverse events. If either of these procedures identify a potential adverse event, the PI will call the participant to assess the potential adverse event. If the event meets adverse event criteria, the PI will immediately inform the IRB and the NIH. If the adverse event requires medical or professional intervention, the PI will immediately contact the participant's primary clinician at the MHC and develop an intervention plan.

## 4. STUDY OBJECTIVES

### 4.1 HYPOTHESIS

Primary: We hypothesize that higher education, income and outcome expectancies, female gender, and lower rates of psychiatric comorbidities, will be associated with improved adherence to preventive and acute migraine management strategies.

Secondary: We hypothesize that the use of the CDST will increase adherence to preventive and acute migraine management strategies compared to Headache Education.

### 4.2 PRIMARY OBJECTIVE

The primary objective of this study is to describe and analyze how 1) individual differences and 2) circumstances influence adherence to preventive and acute migraine management strategies.

### 4.3 SECONDARY OBJECTIVEs (if applicable)

The secondary objective of this study is to develop and pilot a tailored clinical decision support tool (CDST) to improve adherence to preventive and acute migraine management strategies.

## 5. STUDY DESIGN

### 5.1 GENERAL DESIGN

#### 5.1.1 STUDY DURATION

The study will last for approximately 5 years. Phase 1 of the project began in April 2016 under the approved Einstein IRB protocol # 2015-5743. We anticipate completing data collection in 2019, and initial data analysis in 2020.

| | |
|---|---|
| 4/1/2016 – 2/1/2018 | Develop CDST app<br>Pilot test CDST app with up to 24 people with migraine<br><br>Set up recruitment procedures for remainder of study |
| 2/1/2018-10/1/2019 | Recruit and run up to 120 people with migraine for the 3-6 months of the study period |
| 10/1/2019-12/1/2019 | Clean data |
| 12/1/2019-4/1/2020 | Conduct primary analyses and planned secondary analyses |
| 4/1/2020-12/31/2020 | Submit primary analyses and planned secondary analyses for publication |

#### 5.1.2 NUMBER OF STUDY SITES

The study will be conducted at:

1) The Seng (Headache & Adherence) Lab, Van Etten Building, 1225 Morris Park Ave, Bronx, NY 10461.
2) The Montefiore Headache Clinic, Hutchinson Tower #2,1250 Waters Pl, Bronx, NY 10461.

### 5.2 OUTCOME VARIABLES

#### 5.2.1 PRIMARY OUTCOME VARIABLES

The primary outcome variables will be **adherence to acute and preventive migraine management strategies**. All primary outcome variables will be assessed through an electronic headache diary.

**Adherence to Acute Migraine Management Strategies.**

a) **Treat Early:** When participants record headache activity, they will record type, timing, and current pain level for each acute medication dose taken. Treating early is operationalized as taking acute medication while the pain is mild.
b) **Avoid Overuse:** Avoiding overuse is operationalized as taking fewer than 10 triptans and 15 non-specific pain medications (NSAIDs and acetaminophen) per month.

**Adherence to Preventive Migraine Management Strategies:**

a) **Adherence to Preventive Behavioral Strategies:** Each participant will record information related to a single strategy: stress management, sleep management, or consistent eating. Participants will record either 1) whether they used a stress management strategy today (assessed each evening; Yes = adherent, No = non-adherent), or 2) when they got in and rose out of bed (consistent bedtime and rise-time; assessed each morning; Within 1 hour of median = Adherent, outside of 1 hr of median = Non-

Adherent), or 3) whether they ate at least three times that day (consistent eating, assessed each evening; Yes = Adherent, No = Non-adherent).

**b) Adherence to Preventive Medication**: If a participant is taking a preventive medication, they will record whether they took preventive medication each day. Taking preventive medication = Adherent, Not taking preventive medication = Not-adherent.

### 5.2.2 SECONDARY OUTCOME VARIABLES

**Migraine Symptoms**

a) **Headache days** per 30 days as assessed by daily headache diary.
b) **Average head pain** severity as assessed by daily headache diary.

**Distress and Disability**

a) **Migraine-Related Disability** as assessed by the Migraine Disability Assessment (MIDAS) (36).
b) **Migraine-Specific Quality of Life** as assessed by the Migraine-Specific Quality of Life Questionnaire (37).
c) **Pain Interference** as assessed by the PROMIS-Pain Interference (38).
d) **Depression symptoms** as assessed by the PROMIS-Depression Short Form (39, 40).
e) **Anxious symptoms** as assessed by the PROMIS-Anxiety Short Form (39, 40).

**Psychological Factors**

a) **Stress** as assessed by:
    a. The Perceived Stress Scale (41).
    b. The Daily Stress Inventory (42).
    c. Daily ratings of perceived stress on a 0-10 numeric rating scale.
b) **Sleep** as assessed by:
    a. The PROMIS Sleep Disturbance (43).
    b. A daily rating of sleep quality on a 5-point Likert-type scale ranging from “Very Poor” to “Very Good.”
    c. A daily rating of sleep hours.
c) **Headache Management Self-Efficacy** as assessed by the Headache Management Self-Efficacy (HMSE) scale (44)
d) **Acute Medication Self-Efficacy** as assessed with the Acute Medication Self-Efficacy – Headache (AMSE-H) (45)
e) **Study-Specific Self-Efficacy** as assessed by items based on the HMSE and AMSE-H, assessing self-efficacy for study-specific lifestyle and preventive medication adherence.
f) **Outcome Expectancies** as assessed by items based on items used in other studies (46) to assess each preventive and acute migraine management strategy.
g) **Catastrophizing** as assessed by the Pain Catastrophizing Scale (47, 48).
h) **Locus of Control** as assessed by the Headache-Specific Locus of Control Scale (49).
i) **Mindfulness** as assessed by the Five Factor Mindfulness Questionnaire (50).
j) **Acceptance** as assessed by the Chronic Pain Acceptance Questionnaire (51).

**Feasibility and Acceptability**

a) **Patient Satisfaction** as assessed by the Client Satisfaction Questionnaire (52).
b) Perceived effectiveness of intervention as assessed by the **Program Evaluation** Survey (based on the program evaluation survey used in the Treatment of Severe Migraine Trial (33)).
c) **Adverse Events** as assessed by the adverse events check-ins.
d) **Adherence Rates** to the diary as assessed by proportion of entries completed.
e) **Education Utilization** as assessed by rates of participant viewing each education module.

### 5.3 STUDY POPULATION

The study population will include adult patients enrolled in the Montefiore Medical System for at least one year who have been prescribed a triptan within one year. Potentially eligible patients will be identified using Clinical Looking Glass.

Patients who have been prescribed a triptan, ditan or gepant, or who have taken NSAIDs or acetaminophen in the past year will be identified using Clinical Looking Glass. The research coordinator will email appropriate patients (see "Introductory email to participants" attached). There is an opt-out option included in the email and only patients who have not opted out will be called. Those who meet eligibility criteria will be consented and enrolled into the study over the phone for Phase 1 (See "CDST stamped Oral Consent Form", previously approved) and using the REDCap HIPAA-compliant data capture system for Phase 2 and 3. (Informed consent document previously approved).

Potential participants will also be recruited via internet resources such as Twitter, Facebook, and online postings (see "CDST Online Recruitment" and "CDST Online Recruitment - for Twitter" attached). The material directs potential participants to contact the study coordinator by email who will then pre-screen them.

Sampling will be stratified by gender [male = 30%; female = 70%; modeled after population migraine demographics (34)] to permit tests of the association of gender and adherence.

### 5.3.1 NUMBER OF PARTICIPANTS

There will be a total of 394 participants in this study. It will be necessary to screen 900 potential participants to meet this goal. This is a feasible goal: in the 8/2016-8/2017 period over 3,500 unique patients were prescribed a triptan across all providers in the Montefiore system.

### 5.3.2 ELIGIBILITY CRITERIA

Eligibility will be determined by a phone screen provided by a research assistant, supervised by the PI.

**Inclusion/Exclusion Criteria Phase 1 (A & B):**

Participants will be included if they 1) have an International Classification of Headache Disorders – 3 beta diagnosis of migraine, 2) self-report between 6 to 14 headache days per month, 3) are currently prescribed a triptan for acute migraine management, 4) are between the ages of 18 and 65, and 5) self-report at least one problem with adherence to preventive and acute migraine management strategies.

Exclusion criteria are 1) probable or confirmed medication overuse headache, 2) a plan to change, or changing preventive or acute migraine medication during study participation, and 3) are pregnant or are planning to become pregnant during study involvement (as triptans are Category C medications).

**Inclusion/Exclusion Criteria Phase 2:**

Participants will be included if they 1) have an International Classification of Headache Disorders – 3 beta diagnosis of migraine, 2) self-report and diary-confirmed 6 to 14 headache days per month, 3) are currently using one of the following treatments for acute migraine management: triptans, ditans, gepants, NSAIDs, or acetaminophen, 4) are stable on current preventive and acute treatment regimen for migraine, 5) are between the ages of 18 and 65, 6) reads English, 7) has capacity to consent, and 8) complete 80% of diary recordings in the first 30 days of monitoring.

Exclusion criteria are 1) probable or confirmed medication overuse headache, 2) a plan to change, or changing preventive or acute migraine medication during study participation, 3) are pregnant or are planning to become pregnant during study involvement (as triptans are Category C medications), 4) psychiatric illness or cognitive difficulties that would interfere with participation in the study, and 4) participated in Phase 1 of the Clinical Decision Support for Patient Migraine Management protocol.

**Inclusion/Exclusion Criteria Phase 3:**

Participants will be included if they 1) completed Phase 2 of the study, 2) completed at least 80% of diary recordings throughout Phase 2 of the study, and 3) demonstrated poor (<50%) adherence to at least one acute migraine management strategy and at least one preventive behavioral migraine management strategy during study Phase 2.

Exclusion criteria are 1) probable or confirmed medication overuse headache, 2) a plan to change, or changing preventive or acute migraine medication during study participation, 3) are pregnant or are planning to become pregnant during study involvement, 4) psychiatric illness or cognitive difficulties that would interfere with participation in the study.

## 6. METHODS

### 6.1 INTERVENTION

#### 6.1.1 DESCRIPTION OF INTERVENTION

Intervention occurs only in Phase 3 of the study. All data collection will occur in REDCap (Research Electronic Data Capture), a secure, HIPAA-compliant electronic data capture system hosted by the Research Informatics Core at Einstein (53). Survey collection will occur in the participant's browser. Daily diary collection will occur using an app (Status/Post) developed for this study to connect participants seamlessly to REDCap using an Apple device. Participants who do not have an Apple device will be provided with a study iPod. Interventions will be delivered through the Status/Post app.

Participants will be randomized to receive either the 1) CDST or 2) Headache Education version of the Status/Post App.

1) The Clinical Decision Support Tool (CDST) version of the Status/Post app will include several education modules with companion reminders. Education modules are individualized websites linked to the app that provide a consistent source of information about migraine management. Reminders are just-in-time notifications the participant receives in response to their adherence behaviors throughout the study that briefly remind participants about the education they received in response to their behaviors.

   All participants will receive the Medication module, designed to provide information regarding appropriate use of acute and preventive migraine medication. Participants will be assigned to one of three behavioral management education module based on their individual adherence to that behavioral management strategy during the Phase 2 of the study. The three behavioral management education modules are: Stress Management, Sleep Management, and Consistent Eating/Hydration. Each is designed to provide education about why the behavioral strategy is important for migraine management, and provide specific tools to help patients improve their behavioral migraine management adherence.

2) The Headache Education version of the Status/Post app will include several education modules available in the app designed to increase general knowledge about migraine, including 1) diagnostic criteria of migraine and other common headaches, 2) pathophysiology of migraine, and 3) common comorbidities of migraine and other headaches.

#### 6.1.2 METHOD OF ASSIGNMENT/RANDOMIZATION

A research assistant will randomize 60 people (n = 30 per group) to either the CDST Group or Headache Education Control Group, using block randomization with random size blocks using a computerized random number generator. Randomization will be stratified by gender. This research assistant will have no contact with any participant after he or she is randomized.

#### 6.1.3 Selection Of Instruments/Outcome Measures

All measures were selected using materials from the National Institutes of Neurologic Disorders and Stroke (NINDS) Common Data Elements (CDE) initiative. When possible, measures from the National Institutes of Health Patient Reported Outcome Measurement System (PROMIS) were selected. Primary outcomes were selected based on previous studies evaluating adherence to migraine management (5, 20, 27, 54, 55).

**Surveys**

All surveys to be used have been uploaded via the iRIS website.

**Demographics**

NINDS CDEs will be used to evaluate: Age; Gender; Ethnicity; Race; Sexual Orientation; Education Level; Marital/Partner Status; Employment Status; Household and Income; Overall Health; Medical History; Height and Weight.

**Migraine Symptoms**

***American Migraine Study/American Migraine Prevalence and Prevention (AMS/AMPP) Diagnostic Module.*** The AMS/AMPP Diagnostic Module (34, 56) is a survey based on the ICHD-2 criteria for migraine; migraine criteria remain unchanged in the updated ICHD-3b (1). The sensitivity and specificity for migraine are 100% and 82% respectively (56).

***Allodynia Symptom Checklist (ACS).*** The ACS is a 12-item survey designed to assess cutaneous allodynia in people with migraine (57). Items assess frequency of allodynia symptoms, with response options ranging from none to ≥ 50% of the time. Scale development identified here factors: thermal, mechanical static, and mechanical dynamic. Initial development indicated good psychometric qualities (57).

**Medications**

***Preventive.*** Preventive medication name, dose, frequency and timing of administration, route of administration, and start date will be evaluated using the NINDS CDE for medications taken on a regular basis.

***Acute.*** Acute medication name, dose, frequency, route of administration, and start date will be evaluated using the NINDS CDE for medications taken on an as-needed basis.

**Literacy**

***Newest Vital Sign.*** The Newest Vital Sign is a 6-item survey that measures health literacy (58). Participants respond to open-ended questions about a nutrition label, which are coded as correct or incorrect. It has demonstrated reliability and validity in primary care and electronic health settings (58, 59)

***eHEALS.*** The eHEALS is an 8-item survey measure of eHealth literacy designed to evaluate knowledge, comfort, and participant self-evaluation of skills at finding, evaluating and applying electronic health information (60). The measure has demonstrated reliability and validity (60, 61)

**Disability/Quality of Life**

***Migraine Specific Quality of Life Questionnaire (MSQL) v 2.1.*** The MSQL (37) is a commonly-used 14-item survey measuring quality of life in people with migraine. Items comprise three subscales (Role Restriction, Role Prevention, and Emotion Function) which have demonstrated adequate reliability and validity in a number of studies with migraine (37, 62).

***Migraine Disability Assessment (MIDAS).*** The MIDAS (36, 63) is a commonly-used 5-item survey measuring disruption experienced due to migraine. Items target role functioning and ask about lost days of house-work, job-work, and non-work activities. Each item is an open question, allowing entry of number of days lost over 90 days). Total scores are categorized into four, graded levels of disability severity. Several studies have shown the test to have good internal consistency, reliability and construct validity (63, 64).

***PROMIS Pain Interference – Short Form (PROMIS-PI).*** The PROMIS-PI (38) is an 8-item survey selected from a 41-item bank developed using Item Response Theory to evaluate the amount pain interfered

with daily activities and enjoyment of life in the past 7 days using a normative sample. Response options range from 1 (Not at all) to 5 (Very Much). The measure is commonly used to evaluate pain interference and has demonstrated reliability and validity in a number of studies (65).

**Sleep**

***Pittsburgh Sleep Quality Index (PSQI).*** The PSQI (66) is a commonly-used, reliable and valid measure of sleep quality that includes 19 self-rated items and 5 items rated by one's bed partner; the first four self-rated items evaluate self-reported bed time, time to sleep onset, rise time, and hours of sleep per night, and are used in this study to evaluate sleep behavior.

***Berlin Questionnaire (Berlin).*** The Berlin (67) is a 10-item survey evaluating risk factors for sleep apnea, including snoring (Category 1), waketime sleepiness and/or fatigue (Category 2), and the presence of obesity and hypertension (Category 3). Qualifying as "high risk" in two of the three categories is considered "high risk" for sleep apnea. Items within categories demonstrated good internal consistency, and adequate sensitivity and specificity across categories of sleep apnea severity (67).

***PROMIS Sleep Disturbance – Short Form (PROMIS – SD).*** The PROMIS-SD is an 8-item survey (43) selected from a 27-item bank (68) developed using Item Response Theory to evaluate sleep disturbance using a normative sample. The first item assesses perceived sleep quality, with response options on a 5-point Likert scale ranging from very poor to very good; the remainder of the items evaluate the extent to which participants endorse problems with sleep, with response options on a 5-point Likert scale ranging from not at all to very much. It has demonstrated validity related to other measures of sleep disturbance, including actigraphy (43, 68).

**Stress**

***Perceived Stress Scale (PSS).*** The PSS (41, 69) is a 10-item survey evaluating frequency of perceptions of stress (feeling life is unpredictable, uncontrollable, or overloaded) in the past month, with response options on a 5-point Likert scale ranging from never to very often. The PSS is the most commonly used survey of stress, has normative data from the United States, and has demonstrated reliability and validity for a two-factor model in numerous patient samples (70, 71).

***Daily Stress Inventory (DSI).*** The DSI (42) is a 53-item survey evaluating whether 53 common daily hassles (e.g., performed poorly at task, ignored by others) occurred (Response options: Yes/No), and the extent to which hassles that occurred were appraised as stressors, with response options on a 7-point Likert Type scale ranging from "occurred but was not stressful" to "caused me to panic." The scale has demonstrated concurrent and construct validity (42), and has been associated with headache onset in people with chronic migraine and chronic tension-type headache (15).

**Psychiatric Symptoms**

***PROMIS Depression Short-Form (PROMIS-D).*** The PROMIS-D (39) is an 8-item survey selected from a 28-item bank assessing severity of depression symptoms in a normative sample. Items assess frequency of depression symptoms ("I felt worthless") in the past 7 days with response options on a 5-point Likert scale ranging from "never" to "always." The PROMIS-D has demonstrated validity and increased utility in providing information about depression symptoms compared to other self-report measures (39, 40, 65)

***PROMIS Anxiety Short-Form (PROMIS-A).*** The PROMIS-A (39) is an 8-item survey selected from a 29-item bank assessing severity of anxiety symptoms in a normative sample. Items assess frequency of anxiety symptoms ("I felt nervous") in the past 7 days with response options on a 5-point Likert scale ranging from "never" to "always." The PROMIS-D has demonstrated validity and increased utility in providing information about depression symptoms compared to other self-report measures (39, 40, 65).

**Psychological Variables**

***Pain Catastrophizing Scale (PCS).*** The PCS (47) is a 13-item survey designed to assess the extent to which a participant utilizes maladaptive, catastrophic cognitive styles in response to painful experiences. Items comprise three subscales (Rumination, Magnification, and Helplessness) with response options on a 5-point Likert scale ranging from "not at all" to "all the time." The current study utilizes the headache version, which has demonstrated reliability and validity in people with headache (48).

***Headache Management Self-Efficacy (HMSE).*** The HMSE (44) is a 25-item survey designed assess the extent to which a person with headache is confident in their ability to change their behavior to manage headache episodes. Response options are on a 7-point Likert scale ranging from "strongly disagree" to "strongly agree." The HMSE has demonstrated excellent internal consistency and validity in samples with headache and migraine (44, 72).

***Acute-Medication Self-Efficacy – Headache (AMSE-H).*** The AMSE-H (45) is a 7-item survey designed to assess the extent to which a person with headache is confident they can take his or her acute headache medication optimally. Response options are on an 8-point Likert scale and range from "strongly disagree" to "strongly agree." The AMSE-H has demonstrated adequate internal consistency and construct validity (45).

***Study-Specific Self-Efficacy.*** The study-specific self-efficacy survey includes three items that evaluate confident to adhere to each behavioral self-management strategy evaluated in this study (manage stress, sleep consistently, and eat and drink consistently), with response options on a 7-point Likert scale and range from "strongly disagree" to "strongly agree." Items were developed using guidelines recommended by Bandura for self-efficacy scale development (46).

***Outcome Expectancies.*** The study-specific outcome expectancies survey includes 7 items that evaluate the extent to which a participant believes that adhering to the specific migraine management strategies evaluated in this study will lead to a reduction in headache symptoms. Items were developed using guidelines recommended by Bandura (46) and items developed for other studies evaluating outcome expectancies for treatments for migraine and osteoporosis (45, 73)

***Headache-Specific Locus of Control (HSLC).*** The HSLC (49) is a 33-item survey designed to assess the extent to which individuals with recurrent headache expect the occurrence, worsening, and improvement of their headaches are influenced primarily by their own behavior, by chance or fate, or by the actions of medical professionals. Items are coded on a 5-point Likert-type scale ranging from "strongly disagree" to "strongly agree." It contains three subscales, which include Internal, Chance, and Medical Professionals. Each subscale demonstrated good internal consistency ($\alpha$s = 0.80-0.89) and adequate 3-week test-retest reliability (*r*s = 0.72-0.78). Subscales also demonstrated significant expected relationships with related measures (49).

***Five Factor Mindfulness Questionnaire (FFMQ).*** The FFMQ (50) is a 39-item survey designed to evaluate the extent to which participants engage in mindfulness. Items comprise five subscales: Observing, Describing, Acting with Awareness, Non-Judging of Inner Experience, and Non-Reactivity to Inner Experience and are rated on a 5-point Likert scale ranging from "never or rarely true" to "very often or always true." The FFMQ has demonstrated adequate internal consistency and construct validity (50).

***Chronic Pain Acceptance Questionnaire (CPAQ).*** The CPAQ (51) is a 20-item survey designed to assess pain-related acceptance that was developed with patients suffering from chronic pain. Items comprise two subscales (Pain Willingness and Activity Engagement) and are rated on a 7-point Likert scale ranging from "never true" to "always true." The current study uses the headache version. The CPAQ has demonstrated acceptable internal consistency ($\propto$ = 0.78–0.82) and construct validity in pain and migraine samples (51, 74)

**Patient Satisfaction**

***Client Satisfaction Questionnaire (CSQ).*** The CSQ (52) is an 9-item survey designed to measure users' general satisfaction with human service programs. The CSQ is commonly used in treatment and program evaluation and has demonstrated excellent internal consistency (52).

***Program Evaluation.*** The Program Evaluation survey is an 8-item, study-specific survey that evaluates the extent to which participants deemed the app to be effective (with response options on a 5-point Likert scale ranging from "not at all effective" to "very effective") and the extent to which participants are likely to recommend the app to a friend with migraine (with response options on a 5-point Likert scale ranging from "not at all likely" to "very likely"). Items were based on the program evaluation survey from a previous clinical trial evaluating preventive medication and behavioral migraine treatments (33).

**Daily Diary**

***Morning.*** The morning diary will include measures assessing a) **Menstruation**, b) **Headache Symptoms** using ICHD-3b migraine criteria (1), c) **Acute Medication Usage** with items used in other headache medication adherence studies (54), and d) **Sleep Behavior**, using selected items from the Consensus Sleep Diary (75).

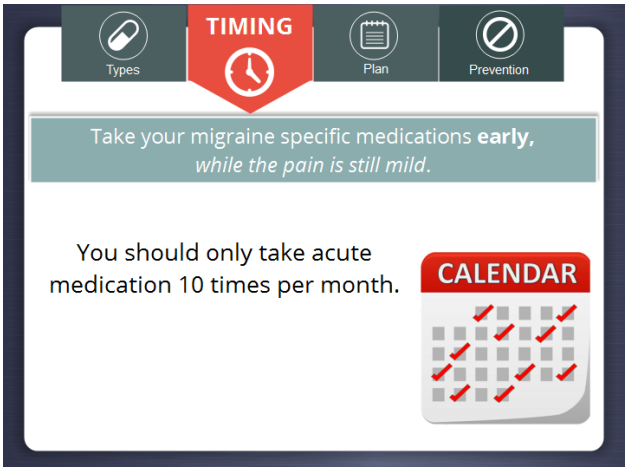
***Afternoon.*** The afternoon diary will include measures assessing a) **Headache Symptoms** using ICHD-3b migraine criteria (1), and b) **Acute Medication Usage** with items used in other headache medication adherence studies (54).

***Evening.*** The evening diary will include measures assessing a) **Preventive Medication Usage** with an item used in other headache medication adherence studies (54), b) **Headache Symptoms** using ICHD-3b migraine criteria (1), c) **Acute Medication Usage** with items used in other headache medication adherence studies (54), d) **Eating and Hydration Behavior** using one item asking participants to check off each hour during which they consumed food in the past 24 hours, and one item asking participants how many glasses of liquids they consumed in the past 24 hours, e) **Stress Level and Management** using a 0-10 Visual Analog Scale to rate stress level and a single item assessing stress management, and d) **Migraine Disability** using an abbreviated daily version of the MIDAS (36).

### 6.1.4 Intervention Administration

During Phase 1, the CDST or Headache Education version of the app will be administered to participants for one week. During Phase 3, the CDST or Headache Education version of the app will be administered to participants for 3 months. In both Phases, participants will download the app to their personal Apple device, or to a study-provided Apple device. Participants will receive a series of education modules (Figure 6.1.4), and for participants in the CDST group, notifications in the app tailored based on diary entries, which occur three times daily.

Figure 6.1.4




Treatment fidelity is conceptualized as the app providing the education and reminders at the allocated times. The app will monitor this information internally during both Phase 1 and 3.

### 6.1.4 Reaction Management

The expected risk of the CDST intervention is increased headache activity due to inhibition of therapeutic choice of participants. This risk is considered minimal. Participants may reach out to the research coordinator at any time if they experience discomfort or distress related to the study. The research coordinator will proactively assess participant reactions to the study in bi-weekly check-ins. The unblinded research assistant will also monitor participant's headache diary recordings to evaluate reactions to the study. Participants who report, or are suspected to have, clinically significant discomfort or distress during the study will immediately be reported to the PI, Dr. Elizabeth Seng, Ph.D., clinical psychologist. Dr. Seng will assess the reaction and determine whether further action is warranted, such as an intervention plan or referral for treatment. If Dr. Seng is unavailable, or if her role as PI would interfere with her ability to assess and intervene with participant distress, Dr. Elizabeth Hirky, Ph.D., clinical psychology and Director of Clinical Training at Ferkauf Graduate School of Psychology, Yeshiva University (anne.hirky@mail.yu.edu) will assess and determine the best course of action in the case of participant distress.

## 6.2 Assessments

### 6.2.1 Efficacy

The primary outcome variables will be **adherence to acute and preventive migraine management strategies**. All primary outcome variables will be assessed through the daily electronic headache diary, collected through the Status/Post app and captured by the REDCap system.

**Adherence to Acute Migraine Management Strategies.**

| | When assessed | Question asked | Indication of adherence | Indication of non-adherence |
|---|---|---|---|---|
| Stress | each evening | whether they used a stress management strategy today | Yes | No |
| Sleep | each morning | when they got in and rose out of bed | Within one hour of median | Outside of one hour of median |
| Eating | each evening | whether they ate at least three times that day | Yes | No |

**Treat Early:** When participants record headache activity, they will record type, timing, and current pain level for each acute medication dose taken. Treating early is operationalized as taking acute medication while the pain is mild.

**Avoid Overuse:** Avoiding overuse is operationalized as taking fewer than 10 triptans and 15 NSAIDS/acetaminophen per month.

**Adherence to Preventive Migraine Management Strategies:**

**Adherence to Preventive Behavioral Strategies:** Each participant will record information related to a single strategy: stress management, sleep management, or consistent eating. Participants will record either 1) whether they used a stress management strategy today (assessed each evening; Yes = adherent, No = non-adherent), or 2) when they got in and rose out of bed (consistent bedtime and rise-time; assessed each morning; Within 1 hour of median = Adherent, outside of 1 hr of median = Non-Adherent), or 3) whether they ate at least three times that day (consistent eating, assessed each evening; Yes = Adherent, No = Non-adherent).

**Adherence to Preventive Medication**: If a participant is taking a preventive medication, they will record whether they took preventive medication each day. Taking preventive medication = Adherent, Not taking preventive medication = Not-adherent.

### 6.2.1 Safety

Safety will be evaluated by:

1) Tracking adverse events reported by participants, and collected proactively in bi-weekly check-ins conducted by the research coordinator, as described below; and,
2) The unblinded research assistant will monitor symptoms recorded in participant's headache diaries for any unexpected changes in symptoms. Potential adverse events or any other situation requiring reaction management will immediately be reported to the PI. If Dr. Seng is unavailable, or if her role as PI would interfere with her ability to assess and intervene with participant distress, Dr. Elizabeth Hirky, Ph.D., clinical psychology and Director of Clinical Training at Ferkauf Graduate School of Psychology, Yeshiva University (anne.hirky@mail.yu.edu) will assess and determine the best course of action in the case of participant distress.

The unblinded research assistant will collate data regarding adverse events and changes in symptoms by group and provide these data to the Data Safety Monitoring Committee monthly.

#### 6.2.1.2 Adverse Events Definition And Reporting

An adverse event (AE) is any troublesome medical occurrence in a subject during participation in the clinical study. An AE can include a sign, symptom, abnormal assessment, or any combination of these. A serious adverse event (SAE) is any AE that results in one or more of the following outcomes: death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly or birth defect, or an important medical event based upon appropriate medical judgment. We will use the HHS/NIH/NCI Common Terminology Criteria for Adverse Events (Version 4.0) grading scale; for reference, we have provided the criteria for headache AEs (Grades 1-3): Grade 1: Mild (mild headache pain); Grade 2: Moderate (moderate headache pain that limits instrumental activities of daily living); Grade 3: Severe or medically significant but not immediately life threatening (severe headache pain that limits self-care activities of daily living); Grade 4: Life-threatening consequences; Grade 5: death related to AE. When present, each AE will be categorized according to the likelihood that they are related to the CDST on a 4-point scale, ranging from definitely unrelated, possibly related, probably related, to definitely related. The expected risk of the CDST intervention is increased headache activity due to inhibition of therapeutic choice of participants. This risk is considered minimal.

The research coordinator will assess adverse events in bi-weekly check-ins with participants. The unblinded research assistant will assess headache activity bi-weekly and provide reports to the Data Safety Monitoring Committee (DSMC) at minimum every 6 months. The research assistant will call participants at least once per month throughout the study to assess for adverse events. The PI will also monitor each participant's recorded headache diaries monthly to assess for adverse events.

If any of these procedures identify a potential adverse event, the participant will be called immediately to assess the potential adverse event. Participants who disclose potential adverse events to any study staff at any point during the study will immediately be reported to the PI, Dr. Elizabeth Seng, Ph.D., clinical psychologist. If Dr. Seng is unavailable, Dr. Elizabeth Hirky, Ph.D., clinical psychology and Director of Clinical Training at Ferkauf Graduate School of Psychology, Yeshiva University (anne.hirky@mail.yu.edu) will assess and determine the best course of action in the case of immediate participant distress. If the adverse event requires medical or professional intervention, the PI or Dr. Hirky will immediately contact the participant's primary clinician at the MHC and develop an intervention plan and referral if necessary. If a participant experiences an adverse event, he or she will be given an opportunity to leave the study. Any SAEs that are possibly related to the study intervention will be reported to the IRB and NIH within 7 days. All AEs will be compiled and reported to the Einstein IRB and NIH in accordance with the Einstein IRB requirements.

The Data Safety Monitoring Committee (DSMC) will consist of Drs. Andrea Weinberger, Ph.D., Assistant Professor of Psychology, and Frederick Foley, Ph.D., Professor of Psychology, at Ferkauf Graduate School of Psychology, Yeshiva University. The DSMC has final authority regarding making decisions regarding continuation, revision or discontinuation of the research project. The DSMC will meet every six months. The unblinded research assistant will provide reports of adverse events and diary-recorded symptoms by group to the DSMC at minimum every six months. The DSMC will provide minutes of each meeting to the PI, including attendance, summary of the discussion, and any findings. The PI will be responsible for implementation of this Data Safety Monitoring Plan and will report directly to the Einstein IRB and the NIH.

### 6.3 Study Procedures

#### 6.3.1 Study Schedule

**Phase 1A**

**Screening and Enrollment**: Up to 50 potential participants will be screened to identify 24 participants eligible and interested in the study. Potential participants will be contacted by phone or email by the research coordinator to be screened for inclusion criteria. If participants meet inclusion criteria and are interested in study participation, the research coordinator will provide informed consent over the phone (see "CDST stamped Oral Consent Form", previously approved).

**Study Procedures:** Participants will then receive an email from the research coordinator (see "CDST - App download email" attached) with instructions to download the study app. Participants will download the study app onto their device and will receive either the CDST or Headache Education version of the app. Participants will use the app, including three daily diary entries, for one week. After one week, the PI will have conduct a focus group interview with each participant (see "Focus Group Seed Questions 11.10.15" previously approved. Once the focus group is completed, the research coordinator will send the participant a thank you email (see "CDST - Thank you emails "attached) with an attached gift card compensation ($30).

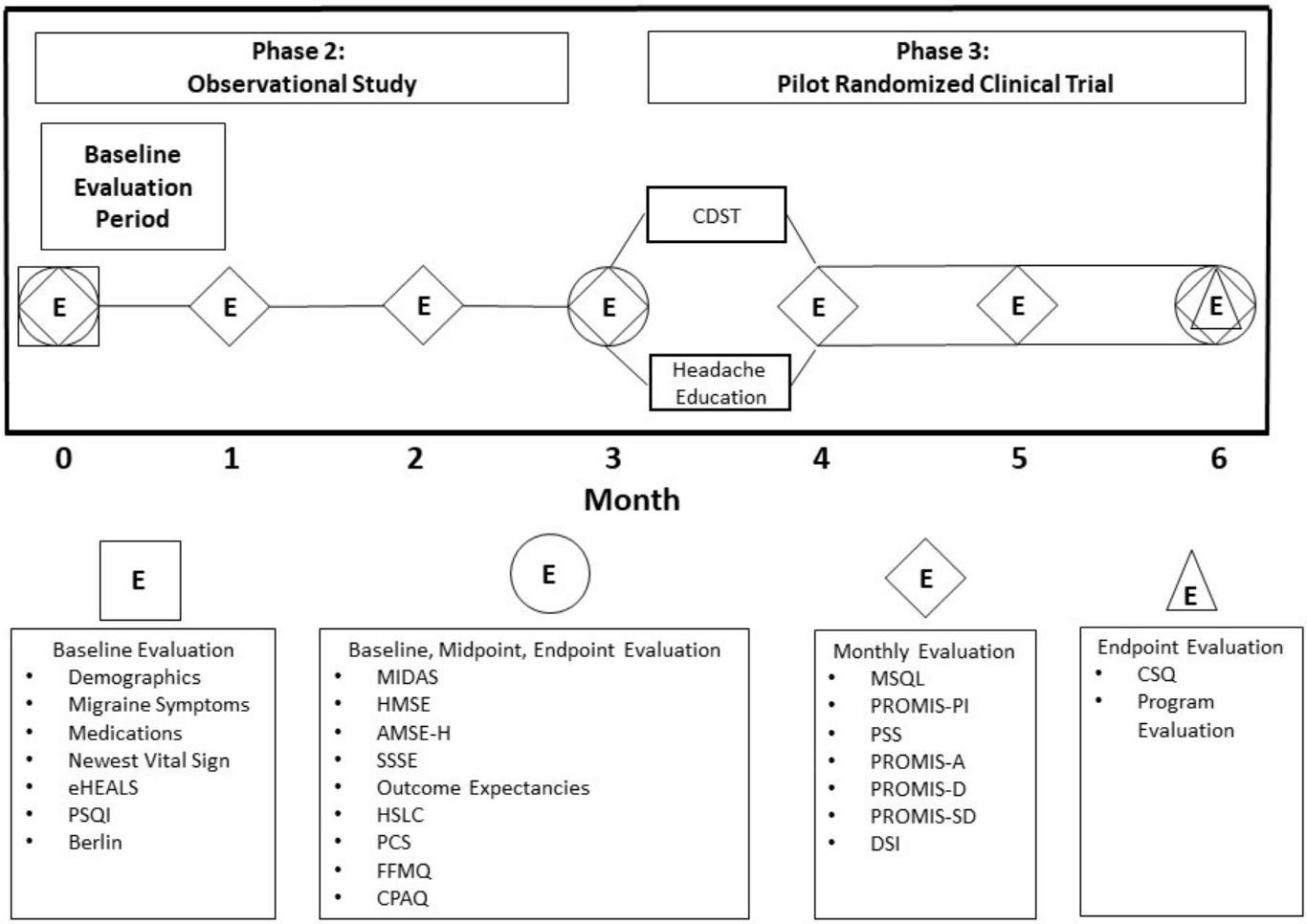
**Phase 1B**

**Screening and Enrollment**: Up to 500 potential participants will be screened to identify 250 participants eligible and interested in the study. Potential participants may be contacted by phone or email by the research coordinator to be screened for inclusion criteria. If participants meet inclusion criteria and are interested in study participation, they will provide informed consent via the REDCap app.

**Study Procedures:** Participants will then receive an email from the research coordinator (see "CDST - App download email" attached) with instructions to download the study app. Participants will download the study app onto their device. Participants will use the app, making one daily diary entry, for one month. After one month, the PI may conduct a focus group interview with each participant (see "Focus Group Seed Questions 11.10.15" previously approved). Once participation completed, the participant will be entered in a raffle for one of three $200 gift cards as compensation.

**Phase 2 and 3**

Figure 6.3.1. Phase 2 and 3 Study Schedule




**Screening**: Up to 350 participants will be screened to identify 120 participants who may be eligible to participate in Phase 2 of the study. The research coordinator will identify participants who may be eligible using Clinical Looking Glass. The PI will obtain permission from providers with numerous potentially eligible patients to send a letter from the provider informing them of their eligibility for the study and providing them study contact information to opt-out of further communication, or express interest in enrollment (see "CDST Recruitment Potential Participant Letter' previously approved). Participants will then be contacted by phone or email (see" CDST - Introductory email to participants" attached) by the research coordinator to set up phone screens with a research assistant, who will be supervised by the PI (see "Phase 2-3 Screening Checklist 1.8.18" attached).

**Phase 2:** Participants who are interested in study participation and self-report meeting eligibility criteria during the phone screen will be send a REDCap link to provide informed consent and complete baseline surveys (see Figure 6.3.1). Participants who provide informed consent and complete all Month 0 surveys will be sent instructions to initialize the study app for daily diary data collection ONLY (e.g., no CDST or Headache Education intervention). Participants will complete one month of daily diary collection during the Baseline Evaluation Period to assess eligibility criteria that require diary confirmation. If participants continue to meet criteria for the study, they will be invited to complete monthly and midpoint assessments and continue with the daily diary until Month 3.

The research coordinator will email each participant bi-weekly and provide feedback on diary days completed, offer troubleshooting for the application, and assess for adverse events (see "CDST - Bi-weekly email" attached). Participants will receive an additional contact from the research coordinator if they fail to record data for 2 days in a row (see "CDST - Missed entries email" attached). After the conclusion of Phase 2, the research coordinator will thank participants for their study participation (see "CDST - Thank you emails" attached) and provide a compensation gift card ($20 for Month 0 and 3 surveys, $10 for Months 1 and 2 surveys, and $0.50 for each diary entry, with total possible compensation of $105).

**Phase 3:** At the end of Phase 2, a research assistant supervised by the PI will evaluate each participant's diary data to determine eligibility criteria for Phase 3. The research coordinator will reach out to each participant and inform them of their eligibility determination for Phase 3, and assess interest in continuing in the study. Participants who are eligible and interested in participating in Phase 3 will be randomized by an unblinded research assistant, who will have no contact with participants after randomization. The rest of the study staff will be unaware of each participant's randomization status.

After randomization, the participant will be sent instructions for initialization of the intervention study app from the research coordinator. Participants will use the intervention version of the app for three months. During this time, participants will continue to complete the headache diary three times daily and complete monthly and endpoint surveys (see Figure 6.3.1).

The research coordinator will continue to email each participant bi-weekly and provide feedback on diary days completed, offer troubleshooting for the application, and assess for adverse events, and reach out if the participant fails to record data for 2 days in a row. After the conclusion of Phase 3, the research coordinator will thank participants for their study participation and provide a compensation gift card ($20 for Month 6 surveys, $10 for Months 4 and 5 surveys, and $0.50 for each diary entry, with total possible compensation of $85).

### 6.3.2 Informed Consent

**Phase 1A**

Prior to the screening call, the research coordinator will send the prospective participant an email including a copy of the oral consent form (see "CDST - Oral consent preview email" attached). During the screening call, the research coordinator will inform prospective participants that the study seeks to develop a tool embedded in a headache diary to improve patient decision making regarding migraine management adherence. They will be informed that the study will last for one week, during which time they will receive popup notifications in a 3x/day headache diary. They will also be informed that, at the end of the week, they will participate in a focus group with the PI that may last up to an hour. They will be informed about compensation for participation. The research coordinator will obtain informed consent over the phone (see "CDST stamped Oral Consent Form", previously approved) and send the participant a confirmation email (see "CDST - Oral consent confirmation email" attached).

**Phase 1B**

Prospective participants will be informed that the study seeks to develop a tool embedded in a headache diary to improve patient decision making regarding migraine management adherence. They will be informed that the study will last for one month, during which time they will receive popup notifications in a 1x/day headache diary. They will also be informed that, at the end of the month, they may participate in a focus group with the PI that may last up to an hour. They will be informed about compensation for participation. The prospective participant will electronically sign the consent form on REDCap, a secure web application for building and managing online surveys and databases. The research coordinator will send the participant a confirmation email after consent is obtained.

**Phase 2 and 3**

During the screening call, the research assistant supervised by the PI will inform prospective participants that the study seeks to understand how people manage their migraines, and what factors impact patient migraine management, using monthly surveys and a headache diary that will sound three times per day for three months. Prospective participants will also be informed that, if they meet inclusion criteria after three months, they will have the opportunity to continue in the study and be randomized to receive one of two kinds of education that will pop-up as notifications in their headache diary, with the goal of improving migraine management. Prospective participants will be informed that they would continue to take monthly surveys and a headache diary that will sound three times a day for an additional three months. Thus, the total potential length of study participation is 6 months. Participants will be informed about compensation for participation. If interested and eligible, the potential participant will be provided with an opportunity to provide online informed consent ("Informed Consent Phase 2.3" uploaded to the informed consent section of iRIS).

**6.3.3 Screening**

**Phase 1**

Participants will be screened for inclusion/exclusion criteria during a scheduled phone call by the Research Coordinator (see "CDST Screener Grid" previously approved). This call should take no longer than 20 minutes.

**Phase 2 and 3**

Participants will be pre-screened for inclusion/exclusion criteria through Clinical Looking Glass by the Research Coordinator (see "Phase 2-3 Screening Checklist 1.8.18" attached). Participants will be screened by a research assistant supervised by the PI during a scheduled phone call (see "Phase 2-3 Screening Checklist 1.8.18" attached). This call should take no longer than 30 minutes. Participants who self-report meeting study inclusion criteria will be enrolled in the study and monitored with a headache diary three times daily for 30 days. After 30 days, a research assistant supervised by the PI will confirm study inclusion criteria. If participants do not meet study inclusion criteria at this time, they will be informed and removed from the study and provided with appropriate gift card compensation (see "CDST-Thank you emails" attached).

**6.3.4 Enrollment**

**Phase 1**

After completing the phone informed consent, the research coordinator will enroll the participant in the study and assign them a random study identification number.

**Phase 2 and 3**

After potential subjects have completed the online informed consent document, the research coordinator will assign them a random study identification number and register the participant in the study in Einstein/Montefiore's EPIC medical records system.

### 6.3.5 On Study Visits

All study visits occur either over the phone or via scheduled REDCap data capture sessions, which are either accessed through the participant's email on any device, or through the study app on either the participant's personal Apple device or the study-provided Apple device.

**Phase 1A & B**

Screening
- Research coordinator will assess inclusion/exclusion criteria
- Approximately 20 minutes in length

App Testing
- Interact with CDST or Headache Education version of app 3 times daily for 7 days (Phase 1A) or 30 days (Phase 1B).
- Each diary entry will take between 1-5 minutes

Focus Group:
- At least one participant per focus group; Focus group led by the PI
- Up to 60 minutes in length
- Questions will focus on: 1) User Interface; 2) Message Content; 3) Message Delivery and Frequency, and 4) Overall Satisfaction

**Phase 2 and 3**

Screening
- Research assistant will assess inclusion/exclusion criteria with the supervision of the PI
- Approximately 30 minutes in length

Electronic Data Collection:
- App-based
- Phase 2: Month 0-Month 3
- Phase 3: Month 3-Month 6
- See schedule of assessments below

Table 6.1.3. Timing of Measures

| | |
|---|---|
| Month 0<br>~20 min. | Demographics<br>Migraine Symptoms<br>Medications<br><br>Health literacy (Newest Vital Sign)<br>E-health literacy (eHEALS)<br><br>Pittsburgh Sleep Quality Index (first 4-items)<br>Berlin Questionnaire |
| Month 0<br>Month 3<br>Month 7<br>~40 min. | Migraine Disability Assessment<br>Headache Management Self-Efficacy<br>Acute Medication Self-Efficacy - Headache<br>Study-Specific Self-Efficacy |

| | |
|---|---|
| | Outcome Expectancies<br>Headache Specific Locus of Control<br>Pain Catastrophizing Scale<br>Five Factor Mindfulness Questionnaire<br>Chronic Pain Acceptance Questionnaire |
| Monthly<br>~20 min. | Migraine Specific Quality of Life 2.1<br>PROMIS Interference<br>Perceived Stress Scale<br>PROMIS Anxiety<br>PROMIS Depression<br>PROMIS Sleep Disturbance<br>Daily Stress Inventory |
| Daily | Morning (~3-5 min.)<br>-Menstruation<br>-Headache Symptoms<br>-Acute Medication Usage<br>-Sleep Behavior<br><br>Afternoon (~1-2 min.)<br>-Headache symptoms<br>-Acute Medication usage<br><br>Evening (~3-5 min.)<br>-Preventive Medication Usage<br>-Headache Symptoms<br>-Acute Medication Usage<br>-Eating and Hydration behavior<br>-Stress Level and Management<br>-Migraine Disability |
| Month 7<br>~7 min. | Client Satisfaction Questionnaire<br>Program Evaluation |

**6.3.6 End of Study and Follow-Up**

At Month 7, participants will complete a long battery of surveys they have been completing throughout the study; additional surveys are the CSQ and Program Evaluation Surveys. If a participant is randomized to an intervention group but discontinues participation in the study for any reason prior to Month 7, they will be asked to complete the CSQ and Program Evaluation Surveys. Adverse Events are assessed by research coordinator contacts bi-weekly throughout the study. If a participant withdraws from the study early for any reason, we will complete this assessment at that time.

**6.3.7 Removal of Subjects**

**Phase 1:** Participants will be removed if they choose to voluntarily withdraw.

**Phase 2 and 3:** Participants will be removed if they choose to voluntarily withdraw. Participants will be removed if they no longer meet any study inclusion/exclusion criteria (for example, if they do not have diary-

confirmed migraine, or if they initiate a new migraine medication during the study). Participants who withdraw for any reason will be given the option of continuing to use the app if they choose.

All participants will be provided with a synopsis of their diary data to be used in their routine clinical care following the study.

### 6.4 Statistical Method

#### 6.4.1 Statistical Design

Basic descriptive statistics (e.g., means, standard deviations, frequencies) for variables of interest will be computed. Graphical approaches will be used to further explore the data where appropriate. The outcomes are either 1) repeated measures of binary adherence to each migraine management strategy [coded each day as 0 (did not adhere) or 1 (adhered)] or total number of non-adherence days for each migraine management strategy over the relevant time-frame. Longitudinal binary outcomes will be analyzed using randomized logistic models, and number of total non-adherence days will be examined using Poisson regression models. SAS 9.3 will be used in the analyses. All tests are two-sided using significance level 0.05.

#### 6.4.2 Sample Size Considerations

Based on n=30 subjects in CDST and Headache Education Control groups, and assumptions of dropout rate and correlations as described in the initial phase of the study, we will have 80% power to detect an odds ratio of 1.28 in adherence to migraine management strategies between CDST and Headache Education Control.

For Phase 1b, we would like to estimate satisfaction, usability, and attrition over the course of the month of diary use. In our previous daily diary research, approximately 60% of participants do not continue using headache diary applications after 3 days, and approximately 30% of people adhere to the daily diary for the duration of a 30-day study. Therefore, we hope to obtain information from n=60 people regarding satisfaction and usability at the end of the 30-day period.

For the main phase of the study, based on estimated proportions of 0.37 for stress management, 20% with mood disorder and 30% male, cumulative drop-out rate of 0.073, 0.172 and 0.216 at the end of 1, 2, and 3 month, respectively, from previous studies 1, and assuming correlations of no more than 0.6 among repeated daily migraine management strategies, with n=100 participants, we can detect odds ratios of 1.29 between those with and without mood disorder, 1.26 between female and male, and 1.17 corresponding to 1 SD difference in continuous predictors, with 80% power.

#### 6.4.3 Planned Analyses

##### 6.4.3.1 Primary Analyses

Primary Objective: Describe and analyze how individual differences and conditions influence adherence to preventive and acute migraine management strategies.

Phase 2 diary data will be utilized. Random effects logistic models will be used to examine the effects of individual differences (e.g., age and gender) and circumstances (headache days/last 7 days, variations in stress) on daily adherence to migraine management strategies during the initial three-month study period. The random effects logistic model is a kind of generalized linear mixed effects model which can take account of missing data due to drop outs. This type of analysis yields robust estimates even in situations when observations are missing both at random, and not at random. The total number of non-adherence days at the end of follow-up will also be obtained, and the effect of individual characteristics and conditions on the rate of non-adherence will be examined using Poisson regression model with log of length of follow-up as offset.

##### 6.4.3.2 Secondary Objectives Analyses

Secondary Objective: Develop a tailored CDST to improve preventive and acute migraine management strategies.

Phase 3 diary data will be utilized. As described above, random effects logistic models will be used to examine the effects of Group (CDST vs. Headache Education Control), Time, and Group X Time on daily adherence to migraine management strategies. Poisson regression model with log of length of follow-up as offset will be used to examine differences between the groups on total number of nonadherence days at the end of the study.

#### 6.4.3.3 Safety

Safety will be evaluated by:

1) Tracking adverse events reported by participants, and collected proactively in bi-weekly check-ins conducted by the research coordinator, as described below; and,
2) The unblinded research assistant will monitor symptoms recorded in participant's headache diaries for any unexpected changes in symptoms. Potential adverse events or any other situation requiring reaction management will immediately be reported to the PI. If Dr. Seng is unavailable, or if her role as PI would interfere with her ability to assess and intervene with participant distress, Dr. Elizabeth Hirky, Ph.D., clinical psychology and Director of Clinical Training at Ferkauf Graduate School of Psychology, Yeshiva University (anne.hirky@mail.yu.edu) will assess and determine the best course of action in the case of participant distress.

The unblinded research assistant will collate data regarding adverse events and changes in symptoms by group and provide these data to the Data Safety Monitoring Committee monthly. Any SAEs that are possibly related to the study intervention will be reported to the IRB and NIH within 7 days. All AEs will be compiled and reported to the Einstein IRB and NIH in accordance with the Einstein IRB requirements.

#### 6.4.3.4 Analysis of Subject Characteristics

Demographics (age, gender, and education) will be assessed in the initial assessment via questionnaire. Sampling will be stratified by gender (male n = 30; female n = 70; modeled after population migraine demographics) to permit tests of the association between gender and adherence. Basic descriptive statistics (e.g., means, standard deviations, frequencies) for variables of interest will be computed. Graphical approaches will be used to further explore the data where appropriate.

### 6.4.4 Subsets and Covariates

Although we hope that the randomization procedure will result in relatively equal groups, we recognize that with a pilot study with such a small sample, it is possible groups will differ on relevant variables. We will evaluate differences between randomized groups on demographics of interest: age, gender, education, and race/ethnicity. Because of the relatively low number of men participating in migraine studies, we will stratify both recruitment and randomization by gender. We will also evaluate baseline differences between randomized groups on adherence outcomes collected during Phase 2, and migraine symptoms (days and severity) collected during Phase 2. If any significant differences are found between the groups, we will run unadjusted and adjusted primary outcome analyses.

### 6.4.5 Handling of Missing Data

The random effects logistic model is a kind of generalized linear mixed effects model which can take account of missing data due to drop outs. This type of analysis yields robust estimates even in situations when observations are missing both at random, and not at random.

## 7. Trial Administration

### 7.1 Ethical Considerations

There is no deception in this study. All participants will be told that they will receive additional messages in their headache diary, and that the purpose of the study is to examine what kinds of messages improve adherence to migraine management. Each participant will receive education that could improve migraine management sent via the diary app. Some participants will receive a CDST, whereas others will receive more general Headache Education. Group assignment will be random.

Subjects will be made aware that nominal payment will be provided as compensation. Gift Cards will be sent after participation Phase 1A ($30), Phase 1B (participants will be entered into a raffle for one of three $200 Gift Cards), Phase 2 (up to $105), and Phase 3 (up to $85).

The proposed research does not target vulnerable populations and will not involve any of the following vulnerable populations: fetuses, neonates, children, pregnant women, prisoners, institutionalized individuals.

Information about patient diagnoses, medications, and health care utilization will be obtained from the MHC electronic health record. Participants will provide data through electronic surveys given either semi-monthly, monthly, or as part of a diary given 3 times daily. Participant data will be collected via REDCap, a secure online data capture software, through the headache diary application. These data, which will not contain identifiable information, will be kept in a password protected database on a password-protected file on lab computers. Only the PI, Research Coordinator and research assistant will have access to these files. Data will be de-identified and converted to electronic databases and stored in password-protected files on a password-protected computer in the locked lab. A list linking participant identification numbers will be kept in a password-protected file on the password-protected hard drive in Dr. Seng's lab, and will be destroyed immediately after all data has been entered (no more than 6 months after the end of data collection).

There is always a slight possibility that an unknown condition will be discovered during initial or follow-up interviews, or direct communication with the subject. If either of these procedures identify a potential condition, the research assistant will immediately inform the PI who will contact the participant. If the condition requires medical or professional intervention, the PI will immediately contact the participant's primary clinician. If the discovery of the condition meets adverse event criteria, the PI will immediately inform the IRB and the NIH.

There will be no information added to the subject's permanent medical file other than their participation in the study.

### 7.2 IRB Review

This study will undergo a complete IRB review by the Albert Einstein College of Medicine IRB. It will be required to have yearly renewal reviews.

### 7.3 Subject Confidentiality

Each participant will be given a random study identification number. Only the PI, Research Coordinator and research assistant will have access to identifiable private information. Participants data will be collected REDCap, a secure online data capture software, through the headache diary application. These data, which will not contain identifiable information, will be kept in a password protected database on a password-protected file on lab computers. Only the PI, Research Coordinator and research assistant will have access to these files. Data will be de-identified and converted to electronic databases and stored in password-protected files on a password-protected computer in the locked lab. A list linking participant identification numbers will be kept in a password-protected file on the password-protected hard drive in Dr. Seng's lab, and will be destroyed immediately after the last participant information is entered in a de-identified database, no more than 6 months after the last day of data collection.

### 7.4 Unanticipated Problems

If there is any medical or psychological problem discovered, the PI will call the participant immediately to assess the problem. If the problem requires medical or professional intervention, the PI will immediately contact the participant's primary clinician and develop an intervention plan and referral if necessary. If a participant experiences an adverse event, he or she will be given an opportunity to leave the study.

All adverse events, whether anticipated or not, will be compiled and reported to the Einstein IRB and NIH in accordance with the Einstein IRB requirements. Any serious adverse events, whether anticipated or not will be reported to the IRB and NIH within 7 days.

### 7.5 Data Quality Assurance

#### 7.5.1 Data Collection

There will be several types of data collected.

- Phase 1 focus group data will be collected through direct transcription during focus groups. Transcripts will be de-identified and kept in a password protected database on a password protected file on lab computers. Only the PI, research coordinator and research assistants will have access to these files.
- All Phase 2 and 3 study data will be entered directly by participants into an electronic database on participants' personal devices or study-provided devices. REDCap is a secure, web-based data capture system accessible via home computers and mobile devices. After de-identification, these data, will be kept in a password protected database on a password-protected file on lab computers. Only the PI, research coordinator and research assistants will have access to these files.
- A list linking participant identification numbers will be kept in a password-protected file on the password-protected hard drive in Dr. Seng's lab. Only the PI, Research Coordinator and research assistant will have access to this list and it will be destroyed immediately after all data has been entered (no more than 6 months after the end of data collection).

##### 7.5.1.1 Access to Source

Phase 1: De-identified data is held in password-protected Word documents. This allows for exporting the data to be analyzed by qualitative software programs. All analyses are planned to be conducted by lab members named as key personnel on this protocol.

Phase 2 and 3: Daily headache data will be entered by the participant through the daily electronic headache diary, collected through the Status/Post app and captured by the REDCap system, a secure online data capture software. The answers to all survey questions will be entered by the participant using a direct link to the REDCap system. The REDCap data capture system allows for transformation of data to a form that can be used with data analysis programs. We will export the data into a de-identified password-protected database which will be held on the lab computer. All analyses are planned to be conducted by lab members named as key personnel on this protocol.

##### 7.5.1.2 Data Storage/Security

Phase 1: Focus group transcripts will be de-identified and kept in a password protected Word Doc on a password protected file on lab computers. This allows for exporting the data to be analyzed by qualitative software programs. All analyses are planned to be conducted by lab members named as key personnel on this protocol.

Phase 2 and 3: The REDCap data capture system allows for transformation of data to a form that can be used with data analysis programs. We will export the data into a de-identified password-protected database which

will be held on the lab computer. All analyses are planned to be conducted by lab members named as key personnel on this protocol.

### 7.6 Study Records

Study Protocols
Screening Documents
Informed Consent Documents
Focus Group Transcripts
REDCap Database
Identifiable Participant List

#### 7.6.1 Retention of Records

The Identifiable Participant List will be destroyed no more than 6 months after data collection is finished. The Screening Documents will be de-identified no more than 6 months after data collection is finished, but the information will be retained to comply with reporting standards. The remaining records will be retained as per Einstein Guidelines. If permission is needed to move or destroy the records, the PI (Elizabeth Seng) should be contacted.

### 7.7 Study Monitoring

The research coordinator will assess adverse events in bi-weekly check-ins with participants. The unblinded research assistant will assess headache activity bi-weekly and provide reports to the Data Safety Monitoring Committee (DSMC) at minimum every 6 months. The research assistant will call participants at least once per month throughout the study to assess for adverse events. The PI will also monitor each participant's recorded headache diaries monthly to assess for adverse events.

The Data Safety Monitoring Committee (DSMC) will consist of Drs. Andrea Weinberger, Ph.D., Assistant Professor of Psychology, and Frederick Foley, Ph.D., Professor of Psychology, at Ferkauf Graduate School of Psychology, Yeshiva University. The DSMC has final authority regarding making decisions regarding continuation, revision or discontinuation of the research project. The DSMC will meet every six months. The unblinded research assistant will provide reports of adverse events and diary-recorded symptoms by group to the DSMC at minimum every six months. The DSMC will provide minutes of each meeting to the PI, including attendance, summary of the discussion, and any findings. The PI will be responsible for implementation of this Data Safety Monitoring Plan and will report directly to the Einstein IRB and the NIH.

### 7.8 Data Safety Monitoring Plan

An adverse event (AE) is any troublesome medical occurrence in a subject during participation in the clinical study. An AE can include a sign, symptom, abnormal assessment, or any combination of these. A serious adverse event (SAE) is any AE that results in one or more of the following outcomes: death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly or birth defect, or an important medical event based upon appropriate medical judgment. We will use the HHS/NIH/NCI Common Terminology Criteria for Adverse Events (Version 4.0) grading scale; for reference, we have provided the criteria for headache AEs (Grades 1-3): Grade 1: Mild (mild headache pain); Grade 2: Moderate (moderate headache pain that limits instrumental activities of daily living); Grade 3: Severe or medically significant but not immediately life threatening (severe headache pain that limits self-care activities of daily living); Grade 4: Life-threatening consequences; Grade 5: death related to AE. When present, each AE will be categorized according to the likelihood that they are related to the CDST on a 4-point scale, ranging from definitely unrelated, possibly related, probably related, to definitely related. The expected risk of the CDST intervention is increased headache activity due to inhibition of therapeutic choice of participants. This risk is considered minimal.

If any of the procedures described above identify a potential adverse event for an individual participant, the participant will be called immediately to assess the potential adverse event. Participants who disclose potential adverse events to any study staff at any point during the study will immediately be reported to the PI, Dr. Elizabeth Seng, Ph.D., clinical psychologist. If Dr. Seng is unavailable, Dr. Elizabeth Hirky, Ph.D., clinical psychology and Director of Clinical Training at Ferkauf Graduate School of Psychology, Yeshiva University (anne.hirky@mail.yu.edu) will assess and determine the best course of action in the case of immediate participant distress. If the adverse event requires medical or professional intervention, the PI or Dr. Hirky will immediately contact the participant's primary clinician at the MHC and develop an intervention plan and referral if necessary. If a participant experiences an adverse event, he or she will be given an opportunity to leave the study. Any SAEs that are possibly related to the study intervention will be reported to the IRB and NIH within 7 days. All AEs will be compiled and reported to the Einstein IRB and NIH in accordance with the Einstein IRB requirements.

The DSMC will meet every six months. The DSMC will provide minutes of each meeting to the PI, including attendance, summary of the discussion, and any findings. The PI will be responsible for implementation of this Data Safety Monitoring Plan and will report directly to the Einstein IRB and the NIH.

**7.9 Study Modification.**

Any modifications to the protocol will be submitted as amendments to the Einstein IRB for review. The change will be implemented after approval.

**7.10 Study Discontinuation**

The study would be discontinued if the DSMC recommends discontinuation.

**7.11 Study Completion**

We anticipate completing data collection in 2019, and initial data analysis in 2020. We will notify the IRB as soon as data collection is completed.

**7.12 Funding Source**

This study is funded by the NINDS (K23 NS093107; PI: Seng). We are currently in a no-cost extension period until March 31, 2022.

**7.13 Publication plan**

The PI (Elizabeth Seng, Ph.D.) holds primary responsibility for publishing the study results. Study results must be reported on clincialtrials.gov immediately following completion of the study according to NIH protocol. Primary objective results will also be submitted for publication in a peer-reviewed journal within one year of completion of data collection.

**7.2 IRB Review**

## References

1. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808.
2. Smitherman TA, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache. 2013;53(3):427-36.
3. Leonardi M. Higher burden of migraine compared to other neurological conditions: results from a cross-sectional study. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2014;35 Suppl 1:149-52.
4. Messali A, Sanderson JC, Blumenfeld AM, Goadsby PJ, Buse DC, Varon SF, et al. Direct and Indirect Costs of Chronic and Episodic Migraine in the United States: A Web-Based Survey. Headache. 2016;56(2):306-22.
5. Katic BJ, Krause SJ, Tepper SJ, Hu HX, Bigal ME. Adherence to acute migraine medication: what does it mean, why does it matter? Headache. 2010;50(1):117-29.
6. Ramsey RR, Ryan JL, Hershey AD, Powers SW, Aylward BS, Hommel KA. Treatment adherence in patients with headache: a systematic review. Headache. 2014;54(5):795-816.
7. Aube M. Improving patient compliance to prophylactic migraine therapy. The Canadian journal of neurological sciences. 2002;29 Suppl 2(2):S40-3.
8. Rains J, Lipchik G, Penzien D. Behavioral facilitation of medical treatment for headache part I: review of headache treatment compliance. Headache. 2006;46(9):1387-94.
9. Munakata J, Hazard E, Serrano D, Klingman D, Rupnow MF, Tierce J, et al. Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. Headache. 2009;49(4):498-508.
10. Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. Neurology. 2015.
11. Seng EK, Holroyd KA. Optimal use of acute headache medication: a qualitative examination of behaviors and barriers to their performance. Headache. 2013;53(9):1438-50.
12. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012;78(17):1337-45.
13. Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012;78(17):1346-53.
14. Silberstein S. Practice Parameter: evidence-based guidelines for migraine headache (an evidence-based review). Neurology. 2000;55(6):754-62.
15. Houle TT, Butschek RA, Turner DP, Smitherman TA, Rains JC, Penzien DB. Stress and sleep duration predict headache severity in chronic headache sufferers. Pain. 2012;153(12):2432-40.
16. Lipton RB, Buse DC, Hall CB, Tennen H, Defreitas TA, Borkowski TM, et al. Reduction in perceived stress as a migraine trigger: Testing the "let-down headache" hypothesis. Neurology. 2014;82(16):1395-401.
17. Johnston MM, Rapoport AM. Triptans for the management of migraine. Drugs. 2010;70(12):1505-18.
18. Worthington I, Pringsheim T, Gawel MJ, Gladstone J, Cooper P, Dilli E, et al. Canadian Headache Society Guideline: acute drug therapy for migraine headache. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques. 2013;40(5 Suppl 3):S1-S80.
19. Belvis R, Mas N, Aceituno A. Migraine attack treatment : a tailor-made suit, not one size fits all. Recent patents on CNS drug discovery. 2014;9(1):26-40.
20. Foley K, Cady R, Martin V, Adelman J, Diamond M, Bell C, et al. Treating early versus treating mild: Timing of migraine prescription medications among patients with diagnosed migraine. Headache. 2005;45(5):538-45.
21. Malik SN, Hopkins M, Young WB, Silberstein SD. Acute migraine treatment: patterns of use and satisfaction in a clinical population. Headache. 2006;46(5):773-80.
22. Cady RK, Sheftell F, Lipton RB, O'Quinn S, Jones M, Putnam DG, et al. Effect of early intervention with sumatriptan on migraine pain: retrospective analyses of data from three clinical trials. Clinical therapeutics. 2000;22(9):1035-48.

23. Peters M, Abu-Saad HH, Vydelingum V, Dowson A, Murphy M. Patients' decision-making for migraine and chronic daily headache management. A qualitative study. Cephalalgia. 2003;23(8):833-41.
24. Ottervanger J, Valkenburg H, Grobbee D, Pingel J, Theofanous J, Jackson D, et al. Pattern of sumatriptan use and overuse in general practice. Eur J Clin Pharmacol. 1996;50(5):353-5.
25. Hedenrud T, Jonsson P, Linde M. Beliefs about medicines and adherence among Swedish migraineurs. The Annals of pharmacotherapy. 2008;42(1):39-45.
26. Wells RE, Markowitz SY, Baron EP, Hentz JG, Kalidas K, Mathew PG, et al. Identifying the factors underlying discontinuation of triptans. Headache. 2014;54(2):278-89.
27. Cady RK, Maizels M, Reeves DL, Levinson DM, Evans JK. Predictors of adherence to triptans: factors of sustained vs lapsed users. Headache. 2009;49(3):386-94.
28. Lafata JE, Tunceli O, Cerghet M, Sharma KP, Lipton RB. The use of migraine preventive medications among patients with and without migraine headaches. Cephalalgia. 2010;30(1):97-104.
29. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. Headache. 2015;55(1):21-34.
30. Leonardi M, Raggi A. Burden of migraine: international perspectives. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2013;34 Suppl 1:S117-8.
31. Insinga RP, Ng-Mak DS, Hanson ME. Costs associated with outpatient, emergency room and inpatient care for migraine in the USA. Cephalalgia. 2011;31(15):1570-5.
32. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia. 2014.
33. Holroyd K, Cottrell C, O'Donnell F, Cordingley G, Carson B, Himiwan L. Effect of Preventive (B blocker) Treatment, Behavioral Migraine Management or Their Combination on Outcomes of Optimized Acute Therapy in Frequent Migraine: randomized Trial. BMJ. 2010(341:c4871):1-12.
34. Lipton R, Bigal M, Diamond M, Freitag F, Reed M, Stewart W. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68:343-9.
35. Center PR. Pew Research Center Internet Project Survey 2014 [Available from: http://www.pewinternet.org/fact-sheets/mobile-technology-fact-sheet/.
36. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. Neurology. 2001;56(6 Suppl 1):S20-8.
37. Martin B, Pathak D, Sharfman M, Adelman J, Taylor F, Kwong W, et al. Validity and reliability of the Migraine-Specific Quality of Life Questionnaire (MSQL Version 2.1). Headache. 2000;40:204-15.
38. Amtmann D, Cook KF, Jensen MP, Chen WH, Choi S, Revicki D, et al. Development of a PROMIS item bank to measure pain interference. Pain. 2010;150(1):173-82.
39. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger. Assessment. 2011;18(3):263-83.
40. Pilkonis PA, Yu L, Dodds NE, Johnston KL, Maihoefer CC, Lawrence SM. Validation of the depression item bank from the Patient-Reported Outcomes Measurement Information System (PROMIS) in a three-month observational study. Journal of psychiatric research. 2014;56:112-9.
41. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. Journal of health and social behavior. 1983;24(4):385-96.
42. Brantley PJ, Waggoner CD, Jones GN, Rappaport NB. A Daily Stress Inventory: development, reliability, and validity. Journal of behavioral medicine. 1987;10(1):61-74.
43. Yu L, Buysse DJ, Germain A, Moul DE, Stover A, Dodds NE, et al. Development of short forms from the PROMIS sleep disturbance and Sleep-Related Impairment item banks. Behavioral sleep medicine. 2011;10(1):6-24.
44. French DJ, Holroyd KA, Pinnell C, Malinoski PT, ODonnell FJ, Hill KR. Perceived self-efficacy and headache-related disability. Headache. 2000;40:647-56.
45. Seng EK, Nicholson RA, Holroyd KA. The Acute Medication Self-Efficacy –Headache: a scale to assess self-efficacy for optimal use of acute headache medications. Ann Behav Med. 2015.
46. Bandura A. Guide for creating self-efficacy scales. In: Pajares F, Urdan T, editors. Self-efficacy beliefs of adolescents. Greenwich, CT: Information Age Publication, Inc.; 2006.

47. Sullivan M, SR B, Pivik J. The Pain Catastrophizing Scale: Development and Validation. Psychological assessment. 1995;7(4):524-32.
48. Holroyd K, Cottrell C, Drew J. Catastrophizing response to migraines predicts impaired functioning and quality-of-life in frequent migraine. The Journal of Pain. 2006;7:S71.
49. Martin NJ, Holroyd KA, Penzien DB. The headache-specific locus of control scale: adaptation to recurrent headaches. Headache. 1990;30(11):729-34.
50. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. Assessment. 2006;13(1):27-45.
51. McCracken LM, Vowles K, Eccleston C. Acceptance of chronic pain: component analysis and a revised assessment method. Pain. 2004;107(1-2):156-66.
52. Attkisson CC, Zwick R. The client satisfaction questionnaire. Psychometric properties and correlations with service utilization and psychotherapy outcome. Evaluation and program planning. 1982;5(3):233-7.
53. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics. 2009;42(2):377-81.
54. Seng EK, Robbins MS, Nicholson RA. Acute migraine medication adherence, migraine disability and patient satisfaction: A naturalistic daily diary study. Cephalalgia. 2016.
55. Kroon Van Diest AM, Ramsey R, Kashikar-Zuck S, Slater S, Hommel K, Kroner JW, et al. Treatment Adherence in Child and Adolescent Chronic Migraine Patients: Results from the Cognitive Behavioral Therapy and Amitriptyline Trial. The Clinical journal of pain. 2017.
56. Lipton R, Stewart A, Diamond S, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001;41:646-57.
57. Lipton RB, Bigal ME, Ashina S, Burstein R, Silberstein S, Reed ML, et al. Cutaneous allodynia in the migraine population. Annals of neurology. 2008;63(2):148-58.
58. Weiss BD, Mays MZ, Martz W, Castro KM, DeWalt DA, Pignone MP, et al. Quick assessment of literacy in primary care: the newest vital sign. Annals of family medicine. 2005;3(6):514-22.
59. Noblin AM, Rutherford A. Impact of Health Literacy on Senior Citizen Engagement in Health Care IT Usage. Gerontology & geriatric medicine. 2017;3:2333721417706300.
60. Norman CD, Skinner HA. eHEALS: The eHealth Literacy Scale. Journal of medical Internet research. 2006;8(4):e27.
61. van der Vaart R, van Deursen AJ, Drossaert CH, Taal E, van Dijk JA, van de Laar MA. Does the eHealth Literacy Scale (eHEALS) measure what it intends to measure? Validation of a Dutch version of the eHEALS in two adult populations. Journal of medical Internet research. 2011;13(4):e86.
62. Cole J, Lin P, Rupnow M. Validation of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v. 2.1) for patients undergoing prophylactic migraine treatment. Quality of Life Research. 2007;21(7):1231-7.
63. Lipton RB, Stewart WF, Sawyer J, Edmeads J. Clinical utility of an instrument assessing migraine disability: The Migraine Disability Assessment (MIDAS) Questionnaire. Headache. 2001;41:854-61.
64. Stewart WF, Lipton RB, Kolodner K, Sawyer J, Lee C, Liberman J. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. Pain. 2000;88:41-52.
65. Stone AA, Broderick JE, Junghaenel DU, Schneider S, Schwartz JE. PROMIS fatigue, pain intensity, pain interference, pain behavior, physical function, depression, anxiety, and anger scales demonstrate ecological validity. Journal of clinical epidemiology. 2016;74:194-206.
66. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research. 1989;28(2):193-213.
67. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Annals of internal medicine. 1999;131(7):485-91.
68. Buysse DJ, Yu L, Moul DE, Germain A, Stover A, Dodds NE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. Sleep. 2010;33(6):781-92.
69. Cohen S, Williamson G. Perceived stress in a probability sample of the United States. In: Spacapan S, Oskamp S, editors. The Social Psychology of Health. Newbury Park, CA: Sage; 1988.

70. Nielsen MG, Ornbol E, Vestergaard M, Bech P, Larsen FB, Lasgaard M, et al. The construct validity of the Perceived Stress Scale. Journal of psychosomatic research. 2016;84:22-30.
71. Yokokura A, Silva A, Fernandes JKB, Del-Ben CM, Figueiredo FP, Barbieri MA, et al. Perceived Stress Scale: confirmatory factor analysis of the PSS14 and PSS10 versions in two samples of pregnant women from the BRISA cohort. Cadernos de saude publica. 2017;33(12):e00184615.
72. Seng EK, Holroyd KA. Dynamics of changes in self-efficacy and locus of control expectancies in the behavioral and drug treatment of severe migraine. Ann Behav Med. 2010;40(3):235-47.
73. Resnick B, Wehren L, Orwig D. Reliability and validity of the self-efficacy and outcome expectations for osteoporosis medication adherence scales. Orthopaedic nursing. 2003;22(2):139-47.
74. Chiros C, O'Brien WH. Acceptance, appraisals, and coping in relation to migraine headache: an evaluation of interrelationships using daily diary methods. Journal of behavioral medicine. 2011;34(4):307-20.
75. Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012;35(2):287-302.