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NYULH Study Number	s20-01911
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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
EUC	Enhanced Usual Care
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MBCT-T/V	Telephone/video-delivered mindfulness-based cognitive therapy
N	Number (typically refers to participants)
NIH	National Institutes of Health
NYULH	New York University Langone Health
PI	Principal Investigator
RCT	Randomized controlled trial
SAE	Serious Adverse Event/Serious Adverse Experience
TEAM-M	TrEAtment for Migraine and Mood
US	United States

1 Key Roles

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Migraine is a chronic condition with episodic attacks of head pain, nausea and/or vomiting, and/or sensitivity to light and sound. Migraine is the world's second leading cause of disability because of its high prevalence and negative impact on social and occupational functioning during a person's peak years of productivity.

A staggering 60% of people with migraine report some elevation of depressive symptoms, with 40% reporting an inability to feel pleasure. Depressive symptoms are associated with higher migraine disability (e.g., days missed of work and/or social activities), increased use of potentially harmful opioid therapies, and twice the total annual medical costs. Migraine and depressive symptoms have shared pathophysiological and neurobiological pathways and overlapping genetic profiles. Despite the significant emotional, social, and economic burden of this comorbidity, no existing treatment adequately addresses both migraine disability and elevated depressive symptoms. Development of scalable integrative treatments that address migraine disability and comorbid depressive symptoms has been identified as a major gap in migraine treatment.

Mindfulness-based cognitive therapy (MBCT) is an evidence-based, standardized treatment comprised of 8 weekly in-person classes and home practice. MBCT effectively addresses pain and depressive symptoms for a range of chronic pain conditions. Our preliminary data demonstrated that individual MBCT sessions reduced headache disability and depressive symptoms compared to treatment as usual in people with migraine. During exit interviews, participants noted that treatment delivery (in-person) and length (1.5-2.5 hour-sessions) were barriers to accessing care. Remote and abbreviated delivery can address these barriers.

2.2 Rationale

Preliminary data demonstrated that an abbreviated (1hr/week) 8-week group-based telephone-delivered MBCT protocol ("MBCT-T") is feasible and reduced depressive symptoms in people with hypertension. This MBCT-T protocol did not involve video-conferencing, which could enhance patient engagement and therapeutic benefit. However, the feasibility and acceptability of a video-conferenced-based protocol (MBCT-V) is unknown and has not been compared to MBCT-T. It is also unknown whether either abbreviated and remote-delivered versions of MBCT reduce depressive symptoms in patients with migraine.

2.3 Potential Risks & Benefits

2.3.1 Known Potential Risks

General Risks Associated with Study Participation. Participants in this study will have elevated depressive symptoms and may experience symptomatic exacerbation. All participants struggling with mood or suicidality will be counseled and referred by staff to all appropriate treatment modalities, including supportive treatment with additional psychotherapy or medications or immediate referral to psychiatric services available at local hospitals.

Remote-delivered MBCT. The physical risks of this intervention are minimal as no invasive procedures are involved. As participants will be a member of group sessions with other participants, there is a potential risk of a violation of privacy. Participants may experience escalating and/or destabilizing negative emotional experiences while practicing meditation. Also, symptomatic deterioration or the lack of response to treatment are possible risks of any clinical trial. Participants may experience emotional distress during the study given that participants have elevated depressive symptoms and engaging with and discussing negative emotions is part of the MBCT-T/V interventions. If a participant reports severe depressive symptoms or suicidal ideation at any time (e.g., during a study visit or during the intervention, either verbally or on the self-report depression inventory), the research coordinator/assistant or intervention facilitator will follow a detailed safety plan, which includes formal assessment of symptoms and, depending on the severity, providing referrals, informing the treating physician, arranging emergency care, and reporting the event to the IRB. Also, anxiety, dissociation, and depersonalization will be assessed over the course of the study as a part of our safety tracking to ensure monitoring of potential adverse reactions to MBCT-T/V. Participants with major depressive disorder will be excluded from our study at baseline. Please see Protections Against Risk for the detailed safety plan.

Enhanced Usual Care (EUC). EUC participants in this trial will be followed similarly to randomized participants but will not receive active psychological intervention from the study. Participants will receive educational information for migraine management and depression risk reduction and referrals to mental health resources. This will be in the form of 8 weekly online education modules whose content is based on education control groups used in previous behavioral migraine and depression research as described above.

Alternative Procedures. MBCT has been shown to improve pain and depression outcomes. Other forms of psycho-education, therapy, and/or medications may be used in routine clinical care for adjunctive treatment. Study participants may thus be treated with these modalities outside of the study. Risks of these modalities are likely to be very similar to those of the study treatments. We have selected MBCT as the primary study intervention because it has been shown to improve pain and reduce depressive symptoms in a range of patient samples and is likely to provide benefits to study participants. Remote-delivered MBCT has not been well-studied in patients with migraine and evidence is needed to determine its utility.

2.3.2 Known Potential Benefits

Participants in this study might benefit in a number of potential ways:

- All participants will receive information about strategies to improve migraine management and depressive symptoms. Individuals may additionally benefit from the social connections created by the group format.

- Beyond these direct benefits, participants may also benefit from knowing that the information gained from this study will be an important step in developing new treatment options for treating people with migraine and depression, and thus, may have a large impact on the health and quality of life of many individuals.

Taken together, these anticipated benefits outweigh the minimal risks to participants.

Importance of the Knowledge to be Gained

People with migraine have a high prevalence of depressive symptoms, yet accessible and scalable interventions are lacking. To our knowledge this is the first study to optimize two remotely delivered mindfulness-based cognitive therapy interventions (MBCT-T and MBCT-V) to reduce suffering among patients with migraine and with depressive symptoms. This research proposal is poised to establish strong cross-disciplinary collaborations with key experts in migraine and MBCT and will collect valuable data in preparation for the Phase III clinical trial of remotely-delivered MBCT.

3 Objectives and Purpose

Aim 1. Conduct a 3-arm, multi-site pilot RCT of MBCT-T, MBCT-V, and EUC

We propose a pilot three-arm, multi-site randomized controlled trial (n=144) of MBCT-T, MBCT-V, and Enhanced Usual Care (EUC) in people with migraine (defined by the International Classification of Headache Disorders – 3) and depressive symptoms (defined by empirical cut-offs on the Patient Health Questionnaire – 9). Quantitative and qualitative feedback from patients and facilitators will be used to optimize both MBCT-T and MBCT-V treatment quality (e.g., patient comprehension) and delivery via iterative adaption and development of treatment manuals, facilitator training protocols, and fidelity measures [MBCT-T/V Adherence & Competence Scales (MBCT-TACS) and Session Fidelity Checklists].

A. Demonstrate fidelity to MBCT-T and MBCT-V protocols across sites.

Hypothesis (H)1: MBCT-T and MBCT-V sessions (n = 96 sessions) will be administered faithfully [MBCT-TACS scores ≥ 2.5] across treatment arm (MBCT-T vs. MBCT-V) and site (n = 3).

B. Demonstrate feasibility and acceptability of MBCT-T, MBCT-V, and EUC.

H1: MBCT-T, MBCT-V, and EUC will be feasible (Primary Outcome: 75% Session Attendance) and acceptable (Primary Outcome: Client Satisfaction Questionnaire-8 (CSQ-8) score > 24) at each site.

C. Demonstrate feasibility of study procedures.

H1: Recruitment rate (Primary Outcome) will be ≥ 40% at each site.

H2: Retention rate (Primary Outcome) will be ≥ 75% at each site and in each arm.

Aim 2. Use decision rules to determine design for future fully-powered Phase III trial.

Pre-specified decision rules for fidelity, feasibility, acceptability, and clinical utility will determine the arms of the future Phase III trial evaluating remotely-delivered MBCT for migraine disability and depressive symptoms.

4 Study Design and Endpoints

4.1 Description of Study Design

This proposal aims to set the stage for a future definitive large-scale Phase III trial in patients with migraine and depressive symptoms. For this study, we propose a pilot three-arm, multi-site randomized controlled trial (n=144) of MBCT-T, MBCT-V, and Enhanced Usual Care (EUC) in people with migraine (defined by the International Classification of Headache Disorders – 3) and depressive symptoms (defined by empirical cut-offs on the Patient Health Questionnaire – 9).

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Currently meets ICHD-3 criteria for migraine using the American Migraine Prevalence and Prevention Diagnostic Module
- Self-reported 4-14 headache days per month, with at least one attack meeting migraine criteria
- Score between 5-14 on the PHQ-9
- Age ≥ 18
- Ability to read and speak English
- Capacity to consent
- Prospective diary-confirmed 4-14 headache days per month, with at least one attack meeting migraine criteria
- ≥1 year of migraine

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Meeting ICHD-3 criteria for persistent headache attributed to traumatic injury to the head (post-traumatic headache) on the American Migraine Prevalence and Prevention Diagnostic Module
- Changes in preventive migraine medication or anti-depressant medication within 6 weeks of intake
- Changes in longer-term migraine prevention (onobotulinum toxin A, injectable or oral anti-calcitonin gene related peptide treatment; neuromodulatory device) within 3 months of intake
- Changes in acute migraine treatment started within 4 weeks of enrollment
- Comorbid psychiatric illness or clinical features that would interfere with participant's ability to participate in or receive benefit from the MBCT-T intervention, including but not limited to: active suicidal ideation; recent history of psychosis or mania; borderline, histrionic or narcissistic personality disorder; cognitive impairment; sensory disabilities; bipolar disorder; obsessive-compulsive disorder, drug use
- Prior history of engaging in formal mindfulness-based interventions including: MBSR, MBCT, Acceptance and Commitment therapy, Dialectical Behavior Therapy
- Current daily meditation practice
- Inability to adhere to headache diary during baseline evaluation period (recorded fewer than 25/28 days)
- Unwilling to maintain stable current acute or preventive medication dosages for study duration
- Any condition that would prevent being a suitable candidate or interfere with medical care needs
- Inability to adhere to headache diary during baseline evaluation period (recorded fewer than 25/28 days).

5.3 Vulnerable Subjects

No vulnerable populations will be studied.

5.4 Strategies for Recruitment and Retention

Two main recruitment methods will be used to identify potentially eligible participants:

5.4.1 Referrals from Clinician Co-Investigator and NYU-Affiliated Specialist

Co-Investigators Lipton, Minen, and Wells see patients in their own neurology practices. When a Co-I identifies a potentially eligible subject during an office visit, he/she will inform them of the research study and provide them with an IRB-approved study brochure. Patients who are interested in participating will provide their permission for the Co-Is to notify the study team and grant permission to directly contact the potential subject on their behalf.

The study team will also receive referrals from Dr. Audrey Halpern, NYU-affiliated headache specialist. Dr. Halpern has referred participants to Dr. Minen's NYU IRB-approved studies in the past. Her contact details are as follows:

Dr. Audrey Halpern
Clinical Assistant Professor, Department of Neurology at NYU Grossman School of Medicine
(646) 559-4659
drhalpern@audreyhalpernmd.com
108 West 39th Street, Suite 405, Fourth floor
New York, NY 10018

When Dr. Halpern identifies a potentially eligible subject during an office visit, she will inform them of the research study and give them the IRB-approved study brochure. Patients who are interested in participating will provide their permission for Dr. Halpern to notify the study team and grant permission to directly contact the potential subject on her behalf.

5.4.2 Use of DataCore/EPIC Information for Recruitment Purposes

This study will also utilize electronic health records (EHR) to enhance recruitment. Study team will submit an online request in accordance with institutional protocols (Ex. DataCore at NYU, CLG and/or Atlas at Montefiore) at each site institutions to identify a list of patients with an ICD-10 diagnosis of headache seen in general neurology and primary care clinics affiliated with NYULH in the last 6 months.

At this point, the study team will reach out to prospective participants via an IRB-approved recruitment message communicating the reason they are being contacted. Interested participants will be invited to determine their preliminary eligibility by clicking on a REDCap-hosted link containing a study pre-screener. Potential subjects who are active in MyChart will be contacted via MyChart. Potential subjects who are not active in MyChart will be sent a [SAFE] email message containing the IRB-approved recruitment message.

If individuals request information regarding opting out of further recruitment for all research, they will be directed to research-contact-optout@nyulangone.org or 1-855-777-7858, or the equivalent opt-out procedures/contact at each study site.

Online pre-screening via REDCap will determine preliminary eligibility based on inclusion/exclusion criteria including the following (see Sections 5.1 and 5.2 for details):

- Demographic information
- Ability to consent
- Mindfulness experience
- Migraine symptoms
- Depression and other psychiatric symptoms
- Interest in the study

Participants will be directed to an online screening survey with a waiver of signed consent to assess eligibility; a phone call can be requested (if low literacy or low technology use). A cover letter will be included with the online screen that will serve as study introduction and include some consent information (due to low risk, it is not required to be signed). Participants will be asked if they are interested in future research. Contact information for individuals interested in future studies will be retained in a separate REDCap file that will not be linked to any data from the pre-screener. Individuals will be contacted after the REDCap pre-screening questionnaire to inform them of their eligibility status. Those who are preliminarily eligible will continue on to the screening phone call for further eligibility evaluation for inclusion into the study.

5.5 Duration of Subject Participation

Each subject will be involved in the study for 10-11 months, including up to 2 weeks of consent and screening procedures, a 1-month run-in period, baseline/M0 assessments, the 8-week intervention, and assessments at mid-intervention/M1, post-intervention/M2, and follow-ups M3, M6, and M9.

5.6 Total Number of Subjects and Sites

N = 144 people with migraine and mild-moderate depressive symptoms will be recruited from: NYULH (n = 48), Montefiore Health System (n = 48) and Atrium Health Wake Forest Baptist (n = 48). The n=144 will allow each site to have 2 groups within each treatment arm; for example, at the NYULH site, the total n = 48: MBCT-T (2 groups, n = 16), MBCT-V (2 groups, n = 16) and EUC (2 groups, n = 16).

5.7 Subject Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Subjects are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility
- Any condition that would prevent being a suitable candidate or interfere with medical care needs

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and/or IRB.

6 Psychological Intervention

6.1 Intervention Description

Mindfulness-based cognitive therapy (MBCT) is an evidence-based, standardized treatment comprised of 8 weekly classes and home practice. MBCT effectively addresses pain and depressive symptoms for a range of chronic pain conditions.

6.1.1 Administration of Intervention

To maintain clinical equipoise, an independent MBCT instructor will administer the remote-delivered MBCT-T and MBCT-V sessions. We will contract clinical psychologists (master's level or above) to teach MBCT who will be supervised by a certified MBCT instructor. Both MBCT-T and MBCT-V will be remote-delivered using NYULH WebEx conferencing, which allows for a 'call-in' option that does not require internet.

6.1.2 Make-Up Session Protocol

Participants who are unable to attend a session will be able to listen to the audio of the study session via a secure recording. The participant will schedule a time for the make-up and will receive a personalized REDCap link and will be required to input their study ID before proceeding to the next page. If they fail to input the correct study ID, the REDCap survey will end. The next screen of the REDCap survey will contain an embedded audio recording of the study session. The recording will only be available for a short window and the REDCap survey link will expire 2 hours after the participants have scheduled to listen to the make-up session. During the calls, participants are told to not state more than their first names and if a participant does add any additional information, the audio file will be edited to remove that information. The audio will be hosted through a private Soundcloud file that cannot be downloaded and is not publicly visible, and sessions will be deleted from the platform as soon as the make-up is completed.

6.1.3 Procedures for Training Interventionalists and Monitoring Intervention Fidelity

In accordance with recommendations in the field, the clinician will be required to have a minimum of master's level training in clinical psychology and a regular mindfulness practice of at least two years. The clinician will be licensed or will be practicing under a licensed clinician. Fidelity will be ensured by using treatment manuals, session fidelity checklists, and weekly supervision of session audio recordings to minimize drift. Treatment fidelity will be evaluated by two or more independent raters, with a minimum of 85% inter-rater reliability, using the MBCT-TACS scale.

6.1.4 Assessment of Subject Compliance with Study Intervention

Treatment Session Adherence is a measure of treatment feasibility. This measure will be assessed through electronic monitoring of the attendance logs of each treatment session. The number of MBCT-T/V treatment sessions attended will be recorded. A treatment arm will be considered feasible if participants attended/read 75% of sessions on average.

Homework assignment adherence is another measure of treatment feasibility. During the intervention period, participants in the MBCT groups will be asked to record the amount of assigned home-based practice they completed each week via REDCap Mobile or Gene Doe app.

The Gene Doe app, in addition to REDCap Mobile, will be used to administer the daily headache diary as well as monitor homework adherence during the baseline run-in period through the intervention and during the post-treatment evaluation period. Gene Doe is a mobile phone research platform that interfaces with REDCap for secure capture of patient-reported outcomes. The Gene Doe app data collection and functionality was reviewed by Russ Raymond, Patrocinio Domingo, and Rick Church at NYU-MCIT who determined this app does not require full MCIT security review and have cleared Gene Doe for use in this study.

7 Study Schedule and Procedures

7.1 Study Schedule

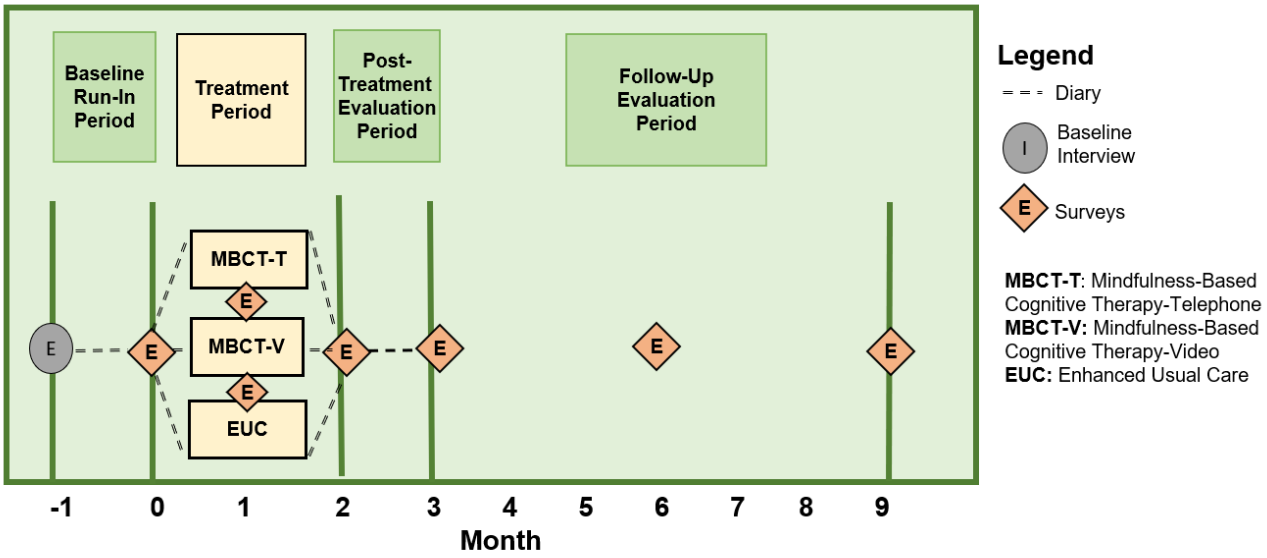

Figure 1. Study 2 Design

7.1.1 Pre-screening (online)

- Expected to take between 15-25 minutes
- Obtain pre-screener consent via REDCap
- Online screening questionnaires

7.1.2 Further Eligibility Screening (phone)

- Expected to take between 20-40 minutes within 2 weeks of pre-screener
- Obtain e-Consent via REDCap
- Further eligibility screening (verbal)

7.1.3 28-Day Baseline Run-In

- Daily diary including headache symptoms
- 28-day period to ensure inclusion/exclusion criteria for:
  - Migraine diagnosis
  - Minimal diary adherence (25/28 days)

7.1.4 Intervention Assignment & Intervention Orientation

- PI confirms final eligibility
- Participant is randomized to MBCT-T, MBCT-V, or EUC
- If randomized to MBCT-T or V, participant will be scheduled for a 30-minute orientation with the facilitator of the intervention

7.1.5 Baseline/M0

- Expected to be completed in 30-45 minutes within 5 days of the start of the intervention
- Surveys via REDCap (see section 7.2.1.5 and 7.2.1.6 for details)

7.1.6 Study Intervention

- Will begin once 6-8 participants are assigned to intervention

- Administered over 8 weeks (see section 6 for details)

7.1.7 Mid-intervention/M1

- Expected to be completed in 15 minutes halfway through the intervention
- Surveys via REDCap (see section 7.2.1.5 and 7.2.1.6 for details)

7.1.8 Post-intervention/M2

- Expected to be completed in 30-45 minutes, within two weeks of intervention completion
- Surveys via REDCap (see section 7.2.1.5 and 7.2.1.6 for details)
- A sub-sample of participants with varying levels of engagement with the study (approximately 3-4 from each cohort) will be invited to provide post-intervention individual qualitative feedback about the feasibility and acceptability of the study procedures and intervention

7.1.9 M3

- Expected to be completed in 30-45 minutes, within +/- 2-week of 3 months since baseline
- Surveys via REDCap (see section 7.2.1.5 and 7.2.1.6 for details)
- A sub-sample of participants with varying levels of engagement with the study (approximately 3-4 from each cohort) will be invited to provide post-intervention individual qualitative feedback about the feasibility and acceptability of the study procedures and intervention

7.1.10 M6

- Expected to be completed in 30-45 minutes, within +/-2-week of 6 months since baseline
- Surveys via REDCap (see section 7.2.1.5 and 7.2.1.6 for details)
- A sub-sample of participants with varying levels of engagement with the study (approximately 3-4 from each cohort) will be invited to provide post-intervention individual qualitative feedback about the feasibility and acceptability of the study procedures and intervention

7.1.11 M9

- Expected to be completed in 30-45 minutes, within +/- 2-week of 9 months since baseline
- Surveys via REDCap (see section 7.2.1.5 and 7.2.1.6 for details)
- A sub-sample of participants with varying levels of engagement with the study (approximately 3-4 from each cohort) will be invited to provide post-intervention individual qualitative feedback about the feasibility and acceptability of the study procedures and intervention

7.2 Study Procedures and Evaluations

7.2.1 Study Specific Procedures

7.2.1.1 Further Eligibility Screening

Individuals who meet pre-screening eligibility and who are interested in taking part in this study will be provided with e-Consent materials (hosted on REDCap) and will be scheduled to meet with a Research Assistant via telephone or video to review e-Consent materials, answer questions, and confirm understanding of the study procedures. If still interested, the subject will electronically sign the e-Consent and a pdf copy will be provided to them.

Individuals who meet preliminary eligibility criteria and who consent to participation in this study will stay on the call for further eligibility screening (20-40 minutes). During this eligibility interview, study staff will:

- Conduct a structured interview and then review responses with the study neurologist at each site to ascertain whether the subject meets ICHD-3 criteria for migraine using the American Migraine Prevalence and Prevention Diagnostic Module
- Administer the PHQ-9 to assess depression and suicidality
- Ask additional eligibility questions as outlined in the "Phone Screener" document

Drs. Shallcross, Seng, Lipton, Minen, and Wells will provide supervision at their respective sites on depression and migraine inclusion/exclusion criteria and will be available to address any questions regarding these criteria.

Subjects who pass this eligibility assessment will be assigned to an intervention and scheduled for a 30-minute individual orientation session with the intervention facilitator.

28-Day Baseline Run-In

Participants who meet preliminary criteria and provide informed consent will complete a 28-day baseline run-in to ensure participants meet inclusion/exclusion criteria for migraine diagnosis and the threshold for minimal diary adherence (25/28 days). During the baseline run-in, participants will complete a daily diary including headache symptoms using the REDCap Mobile App or Gene Doe app. If participants do not have a personal device, one will be provided by the research team. The application will prompt a diary entry at a time selected by the participant each evening. If a patient does not submit a daily entry, they will be alerted that the diary entry is still waiting for 12 hours. Participants will not be permitted to record retrospective data to reduce recall bias. Participants who continue to meet inclusion/exclusion criteria after the 28-day baseline run-in will be randomized to receive either 8 sessions of MBCT-T, MBCT-V, or Enhanced Usual Care.

7.2.1.2 Randomization

Randomization will be stratified by headache days [low-frequency episodic migraine (4-9 days/28 days), high-frequency episodic migraine (10-14 days/28 days)] and gender (male, female). A randomization list will be generated by the study statistician using randomization within random blocks of sizes 3 and 6. Participants will be masked to intervention options and study hypotheses. They will be informed that they will be randomized to one of three interventions that will last a maximum of 8 weeks and that will provide knowledge to help migraine and depressive symptoms. Facilitators will be unmasked. Data will be entered and coded so that group membership is known only to the project coordinator at NYULH and to research assistants who are coordinating study visits. The graduate research assistant who will be coordinating data capture across sites, as well as the investigators, will be masked to treatment condition.

7.2.1.3 8-Week Intervention Program

7.2.1.3.1 MBCT-T/V

Both MBCT-T and MBCT-V will be delivered using WebEx conferencing, which allows for a 'call-in' option that does not require internet for the MBCT-T arm. MBCT-T/V will be delivered to groups of 8 migraine patients in 8 weekly, 1-hour sessions. Smartphone devices with unlimited data plans will be available for participants who need them to participate in the study both to complete the headache diary (see below for details) and if they are randomized to either remote-delivered intervention. Our team has used the WebEx platform for three clinical trials and will ensure that all facilitators and research support staff are trained and that a comprehensive manual is available to help troubleshoot potential technical difficulties. At least one research assistant will join each weekly session to help assist with any technical difficulties participants may have. Unforeseen difficulties with the technology will provide us with additional information about the feasibility of this intervention.

Critical components of MBCT include: 1) learning mindfulness skills; 2) practicing mindfulness skills in class and at home; and 3) dialogue and inquiry. The intervention manual will be an adapted version of Dr. Shallcross' remote-delivered MBCT for chronic pain protocol (i19-00339) and Dr. Seng's in-person MBCT for migraine

protocol. All sessions will be audio-recorded. Patients will be encouraged to practice daily meditation in between group sessions for 20 minutes, 6 days per week.

As a headache diary is a core component of all headache treatments, participants will complete a daily headache diary, which will include recording of daily meditation practice. To maximize adherence and retention, coordinators will give reminder calls to patients prior to each weekly class and will contact patients who miss a weekly session to schedule a make-up session, whereby patients can listen to the audio recording of the missed session.

Table 1. Structure and Content of MBCT-T and MBCT-V

Structure	Weekly Content
• Homework review (except session 1) • In-session practice of both meditation-based and cognitive-behavioral exercises • Guided inquiry • Summary of main themes and assign at-home daily practice	1. Awareness & Automatic Pilot
	2. Awareness of the Body
	3. Thoughts are not Facts
	4. Gathering the Scattered Mind
	5. Allowing/Letting Be
	6. Awareness of Warning Signs & Reactivity
	7. Taking Care of Myself
	8. Maintenance

7.2.1.3.2 EUC

Participants randomized to EUC will receive usual care and 8 weekly online education modules whose delivery and content are based on control groups from previous behavioral migraine and depression interventions. Modules will be released on a weekly basis, which mirrors the MBCT arms. Participant engagement with each

module happens individually (not in a group) and will be tracked electronically by the secure hosting website. Participants will also complete a daily headache diary.

Table 2. Structure and Content of EUC

Structure	Weekly Content
• Online module accessed through weblink • Multi-tab structure leading participant through education • Low health literacy definitions of key concepts • Application of key concepts to the person with migraine and depressive symptoms • Vignettes depicting people with migraine and depressive symptoms demonstrating key concepts	1. What is Migraine? 2. Migraine and Depressive Symptoms 3. Migraine, Depressive Symptoms and the Brain 4. Diagnosis of Migraine and Depression 5. Treatment Options for Migraine and Depression 6. Impact of Migraine and Depressive Symptoms 7. Lifestyle Factors for Migraine and Depressive Symptoms 8. Communicating with Health Care Providers

7.2.1.4 Assessments

Please see Table 3 for an overview of assessment timeline and sections 7.2.1.6 and 7.2.1.7 for details.

Subjects will be asked to complete questionnaires online via REDCap, via REDCap Mobile App, or via Gene Doe App, (or on paper if they prefer – we will mail subjects the questionnaires).

Table 3. Schedule of Assessments

	Data collection by study personnel	**Assessments completed by participants**
Pre-Screening		Online Pre-screener
Screening	Recruitment Rate Daily Diary Completeness	Phone Screener Headache frequency
M-1^		Demographics FFMQ-15 HMSES CEQ QIDS PROMIS Off-Protocol Co-Occurring Treatment Tracking HDI MSQ Survey Acceptability Questionnaires-7
Daily Diary (M-1 - M3)		Headache frequency Average Headache Attack Pain Intensity
M0*	Survey Completeness Daily Diary Completeness	SUS-Data Capture HDI QIDS PROMIS-D MSQ

		HMSES MAIA-2 PCS HPAQ MIDAS
Weekly During Intervention	Treatment Session Adherence Fidelity Checklist Survey Completeness	Safety Tracking Homework Assignment Adherence
M1**	Survey Completeness Daily Diary Completeness Attrition	QIDS PROMIS-D HDI MSQ MBCT-HPI MAIA-2 PCS HPAQ MIDAS Survey Acceptability Questionnaires-7
M2***	MBCT-TACS Survey Completeness Retention Rate Survey Completeness Daily Diary Completeness Attrition	CSQ-8 FFMQ-15 HMSES SUS-Treatment QIDS PROMIS-D Off-Protocol Co-Occurring Treatment Tracking HDI MSQ MBCT-HPI MAIA-2 PCS HPAQ MIDAS For some: M2 Qualitative Questions (Exit interview)
M3°	Survey Completeness Daily Diary Completeness Attrition	CSQ-8 MBCT-HPI SUS-Data Capture HDI QIDS PROMIS-D MSQ MAIA-2 PCS HPAQ MIDAS Survey Acceptability Questionnaires-7
M6°°	Survey Completeness Attrition	CSQ-8 MBCT-HPI SUS-Data Capture HDI QIDS PROMIS-D MSQ MAIA-2 PCS HPAQ MIDAS
M9°°°	Survey Completeness Attrition	CSQ-8 MBCT-HPI HDI QIDS PROMIS-D

		MSQ MAIA-2 PCS HPAQ MIDAS
As Needed		BSS

^ M-1 = Month -1/Baseline; * M0 = Month 0/Pre-Intervention; ** M1 = Month 1/Mid-Intervention; *** M2 = Month 2/Post-Intervention; ° M3 = Month 3 (1 Month Post-Intervention); °° M6 = Month 6 (4 Months Post-Intervention); °°° M9 = Month 9 (7 Months Post-Intervention)

7.2.1.5 Details of Participant Assessments

Name: Online pre-screener
Type: Other
Time Frame: Pre-screening (online)
Brief Description: The online pre-screener assesses preliminary inclusion and exclusion criteria. See sections 5.1 and 5.2 as well as the attached document "PRE-SCREENER" for details.

Name: Phone Screener
Type: Other
Time Frame: Screening (verbally, post-e-Consent)
Brief Description: The Phone Screener assesses inclusion and exclusion criteria that are more nuanced than what is included in the pre-screener and require a member of the study team's training and judgment. Questions will involve assessing depressive symptoms using the PHQ-9. Other questions involve assessing migraine symptoms, many of which will be open-ended, including recent changes to headache symptoms, medications, and recent hospitalizations.

Name: Migraine Symptoms Checklist
Type: Other
Time Frame: Screening (verbally, post-e-Consent)
Brief Description: The Migraine Symptoms Checklist assesses inclusion criteria. It is a brief structured interview to guide the formal diagnosis of migraine without aura using the current International Classification of Headache Disorders – 3 criteria. The interview has 15 items to assess migraine without aura.

Name: Patient Health Questionnaire – 9 (PHQ-9)
Type: Other
Time Frame: Screening (verbally, post-e-Consent)
Brief Description: The PHQ-9 assesses inclusion criteria. It is a self-reported measure of depressive symptom severity and consists of items consistent with criteria for DSM-based diagnosis. PHQ-9 scores range from 0 to 27. Each of the 9 items can be scored from 0 ("not at all") to 3 ("nearly every day"). Cut-points of 5, 10, 15, and 20 represent the thresholds for mild, moderate, moderately severe, and severe depression, respectively. The construct validity of the PHQ-9 has been demonstrated in a wide range of patient populations.

Name: Headache Frequency
Type: Secondary
Time Frame: Headache activity is captured each day during the daily diary from Screening to M3.
Brief Description: Headache days/28 days. Each day participants will be asked, "Did you have a headache today?" with response options of "Yes," and "No." Each day on which a participant reports "Yes" will be coded as a headache day.

Name: Average Headache Attack Pain Intensity
Type: Secondary

Time Frame: The measure is administered in the daily diary from Screening through Month 3 on days during which a headache was recorded.
Brief Description: On each day when a participant reports they had a headache, participants will be asked to rate their pain on a scale from 0-10, with 0 indicating no pain, 1-3 indicating mild pain, 4-6 indicating moderate pain, and 7-10 indicating severe pain.

Name: Demographics
Type: Other
Time Frame: M-1
Brief Description: Demographics will include age, sex, income, education, race, ethnicity, marital status, family structure, and occupation.

Name: Client Satisfaction Questionnaire – 8 (CSQ-8)
Type: Primary
Time Frame: M2, M3, M6, M9
Brief Description: The CSQ-8 assesses treatment acceptability. The CSQ-8 is an 8-item self-report measure designed to assess satisfaction with mental health services. Response options are coded on a 4-point scale and summed to produce a total score ranging from 8-32. The measure has consistently demonstrated excellent reliability and validity, and is commonly used in behavioral treatment trials. For the purposes of this study, we consider “acceptable” to be a CSQ-8 score > 24 at Month 2.

Name: Five Facet of Mindfulness Scale (Short Form; FFMQ-15)
Type: Secondary
Time Frame: M0 and M2
Brief Description: The FFMQ is a measure of treatment fidelity. The FFMQ measures pre-post trait mindfulness and is assessed using 15 items that index the degree to which participants experience daily mindfulness, a central objective of the MBCT-T treatment. Each item is rated on a 5-point scale from ‘1’ = never or very rarely true to ‘5’ = very often or always true. An example item is “When I take a shower or a bath, I stay alert to the sensations of water on my body.” Scores range from 15-75, with higher scores reflecting greater trait mindfulness.

Name: Headache Management Self-Efficacy Scale (HMSES)
Type: Secondary
Time Frame: M0 and M2
Brief Description: For the EUC group, we will assess self-efficacy for headache self-management skills using the Headache Management Self-Efficacy Scale (HMSES), which is a validated instrument widely used in migraine studies. The HMSES is a 25-item scale that assess confidence in one’s ability to successfully manage migraine using behavioral strategies. Each item is rated on a 7-point Likert scale ranging from ‘1’ = Strongly Disagree to ‘7’ = Strongly Agree. An example item is, “I can prevent headaches by changing how I respond to stress.” Scores range from 25-175, with higher scores indicating higher self-efficacy.

Name: Multidimensional Assessment of Interoceptive Awareness Version 2 (MAIA-2)
Type: Secondary
Time Frame: M0, M1, M2, M3, M6, M9
Brief Description: The MAIA-2 is a 37-item questionnaire that will be used to assess body/somatic awareness and interoceptive awareness throughout the study. Body awareness is important when considering mindfulness-based interventions, which focus on nonjudgmental acceptance of body sensations and a sense of self-grounding in physical sensations in the moment. This questionnaire will be important to monitor baseline body awareness and changes in body awareness as participants experience the intervention or control.

Name: Pain Catastrophizing Scale (PCS)
Type: Secondary
Time Frame: M0, M1, M2, M3, M6, M9
Brief Description: The PCS will be used to monitor for pain catastrophizing throughout the study, which is the tendency to magnify the threat of a painful experience, feel helpless in the presence of pain, and be unable to prevent and inhibit pain-related thoughts. This is an important measure to monitor how participants experience their headache pain during the intervention or control.

Name: Head Pain Acceptance Questionnaire (HPAQ)
Type: Secondary
Time Frame: M0, M1, M2, M3, M6, M9
Brief Description: The HPAQ will be used to measure the level of acceptance participants have regarding their headache pain. Pain acceptance can have an important role in managing pain disorders and is generally considered to facilitate positive health outcomes. Head pain acceptance will be monitored throughout the study.

Name: Credibility/Expectancy Questionnaire (CEQ)
Type: Secondary
Time Frame: M0
Brief Description: The CEQ is a measure of treatment acceptability. The CEQ is a 6-item measure with two subscales: credibility and expectancy. Four of the 6 items are rated on a 9-point scale, and two items are rated from 0-100%. Items are standardized and a composite is formed for each subscale, with higher scores indicating higher credibility and expectancy.

Name: Quick Inventory of Depressive Symptomatology – Self-Report 16 ($QIDS\text{-}SR_{16}$)
Type: Secondary
Time Frame: M0, M1, M2, M3, M6, M9
Brief Description: The $QIDS\text{-}SR_{16}$ measures depressive symptom domains during the prior 7 days. Each item is scored on a scale from 0 to 3 points. Total scores range from 0 to 27. Score cutoffs are: 1–5 for no depression, 6–10 for mild depression, 11–15 for moderate depression, 16–20 for severe depression, and 17–27 for very severe depression. The QIDS-16 has been used widely in intervention studies and has sound psychometric properties, including strong internal consistency, concurrent validity, and sensitivity to symptom change. The slope of change between Month 0 and 3 represents the primary endpoint which will be used as the effect size for sample size estimation for the fully-powered trial.

Name: Patient Reported Measurement Information System – Depression (PROMIS-D)
Type: Secondary
Time Frame: M0, M1, M2, M3, M6, M9
Brief Description: The PROMIS-D measures depressive symptom domains during the prior 7 days. Each item is scored on a scale from 1 to 5 points. Scores are converted to t-scores based on normative data. The PROMIS-D is a commonly used measure of depressive symptoms and has demonstrated sound psychometric properties, including excellent internal consistency and concurrent validity. The slope of change between Month 0 and 3 represents the primary endpoint which will be used as the effect size for sample size estimation for the fully-powered trial.

Name: Off-Protocol Co-occurring Treatment Tracking
Type: Secondary
Time Frame: M0 and M2
Brief Description: This is an inventory in use in Dr. Shallcross' lab that assesses any changes in the medications or other treatments the patient is using to manage their migraine, mental

health, or any other medical symptoms. Changes to acute migraine medication, anti-depressant medications, and psychotherapy will be specifically tracked in those categories.

Name: Headache Disability Inventory (HDI)
Type: Secondary
Time Frame: M0, M1, M2, M3, M6, M9
Brief Description: The HDI is a 25-item self-report survey which assesses perceived emotional and functional impact of headache on daily activities. Sample items include, “Because of my headaches I feel restricted in performing my routine daily activities,” with response options of “Yes,” “Sometimes,” and “No.” Total scores range from 0-100, with higher scores indicating higher disability. The HDI has demonstrated excellent internal consistency and test-retest reliability in people with migraine. The slope of change between Month 0 and 3 represents the primary endpoint which will be used as the effect size for sample size estimation for the fully-powered trial.

Name: Migraine-Specific Quality of Life Questionnaire v 2.1 (MSQ)
Type: Secondary
Time Frame: M0, M1, M2, M3, M6, M9
Brief Description: The MSQ is a 14-item self-report survey which assesses quality of life over the past 4 weeks in people with migraine. Items comprise three subscales: Role Restriction, Role Prevention, and Emotion Function. Each item is scored on a Likert-type scale from 1 (“None of the time”) to 6 (“All of the time”). Total scores range from 14-84. The slope of change between Month 0 and 3 represents the primary endpoint which will be used as the effect size for sample size estimation for the fully-powered trial.

Name: MIDAS
Type: Secondary
Time Frame: M0, M1, M2, M3, M6, M9
Brief Description: The Migraine Disability Assessment (MIDAS) questionnaire is a 5-item, self-administered questionnaire designed to quantify headache-related disability. It includes five questions regarding days of activity limitations in work, chores (household work), and non-work activities (social, family and leisure activities), to score the level of disability from headaches. Total scores reflect the number of days of disability and range from 0-22+ days, with over 22 days indexing severe disability.

Name: MBCT Home Practice Inventory (MBCT-HPI)
Type: Secondary
Time Frame: M1, M2, M3, M6, M9 (MBCT groups only)
Brief Description: The MBCT-HPI is a measure of treatment feasibility. The MBCT-HPI is a log (in calendar form) that individuals use to record the amount of daily formal and informal practice (# of times and minutes of practice) of mindfulness meditation that they have completed over the past month. In addition to time practicing, participants can complete a notes section to elaborate on their experience.

Name: System Usability Scale (SUS): Treatment
Type: Secondary
Time Frame: M2
Brief Description: The SUS for Treatment is a measure of treatment acceptability. The SUS is a 10-item scale that assesses end-user perceived usability of information technology systems. For the current scale, the system being evaluated will be the WebEx system for treatment delivery for both the MBCT-T (no internet connection required) and MBCT-V arms of the study, and the online education platform used for the EUC arm of the study. Response options range from 1-5; half of the items are positively worded, and

half are negatively worded. Scores are converted to a score ranging from 0-100 with higher scores indicating higher perceived usability.

Name: System Usability Scale (SUS): Data Capture
Type: Secondary
Time Frame: M3, M6
Brief Description: The SUS for Data Capture is a measure of acceptability of study procedures. The SUS is a 10-item scale that assesses end-user perceived usability of information technology systems. For the current scale, the system being evaluated will be the mobile application used for data capture for surveys and daily diary. Response options range from 1-5; half of the items are positively worded, and half are negatively worded. Scores are converted to a score ranging from 0-100 with higher scores indicating higher perceived usability.

Name: Beck Suicide Scale (BSS)
Type: Secondary
Time Frame: As needed - the measure is administered any time an individual indicates a presence of suicidal thoughts on either the PHQ-9 or the QIDS-16 or in between assessments to anyone on the study team.
Brief Description: This is a standard 21-item scale that members of the research team have used in prior trials to assess risk of suicide. The BSS indexes current intensity of attitudes, plans, and behaviors to complete suicide. Scores over 11 and/or endorsement of a '2' on any of the following items 12, 15, 16, 18, and 21 indicate notable risk. See Appendix 1 for suicide safety protocol.

Name: Safety Tracking
Type: Secondary
Time Frame: Intervention. The measure is administered via survey and RA check-ins by telephone (mid-way through the intervention period) at Months 1 and 2. Total number of Adverse Events (AEs) and Serious Adverse Events (SAEs) will be evaluated.
Brief Description: AE and SAE data will be collected through surveys and by RAs. Surveys include standardized inventories that measure anticipated adverse events, including anxiety, flooding, depersonalization, and dissociation, as well as an open-ended question about any other troublesome medical occurrences. RA check-ins (mid-way through the intervention period) will involve inquiry about migraine and depressive symptom deterioration and suicidal ideation. An adverse event (AE) is any troublesome medical occurrence in a subject during participation in the clinical study. 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. The RA(s), neurologist Co-I and PI will work together to determine AEs and SAEs.

Name: Homework Assignment Adherence
Type: Secondary
Time Frame: Intervention
Brief Description: Homework assignment adherence is a measure of treatment feasibility. During the intervention period, participants in the MBCT groups will be asked to record the amount of assigned home-based practice they completed each day.

Name: Survey Acceptability Questions
Type: Secondary
Time Frame: M0, M1, M2

Brief Description: The Acceptability Questions are a measure of treatment acceptability and are to be administered at the end of each time point. 7 questions assess perceived acceptability of preceding surveys. Response options for questions 1-6 range from Strongly Disagree to Strongly Agree on a 4-point Likert Scale. Question 7 is open-ended to allow for free-form participant responses.

Name: Qualitative Questions
Type: Secondary
Time Frame: M2
Brief Description: Some participants (approximately 3-4 from each cohort) will be invited to provide post-intervention qualitative feedback about the feasibility and acceptability of the study procedures and intervention. Questions are open-ended and cover topics related to the questionnaires, study procedures, and intervention.

7.2.1.6 Details of Additional Data Collection by Study Personnel

Name: Recruitment Rate
Type: Primary
Time Frame: Screening/M-1
Brief Description: Recruitment rate assesses study feasibility. Recruitment rate will describe the proportion of participants who screened positive on the electronic eligibility screener (denominator) and who enroll in the study at the end of the in-person intake visit at Month -1 (numerator).

Name: MBCT-T Adherence and Competence Scale (MBCT-TACS)
Type: Primary
Time Frame: M2
Brief Description: The MBCT-TACS Adherence Scale assesses treatment fidelity. It is an adapted version of the MBCT-Adherence Scale, which has been widely used to evaluate fidelity to the 8-week in-person MBCT protocol. The MBCT-T Adherence and Competence scale was developed by Dr. Shallcross and is pending publication. Adherence (Primary Outcome) is rated separately for: a) inclusion of formal components (e.g., homework assigned, guided exercise, inquiry, etc.) and b) teaching goals (e.g., learning to place and hold attention, recognizing aversion, etc.) for each session on a 0-3 scale. Competence (Secondary Outcome) is the ability to cultivate a therapeutic group-based learning environment and capacity to embody mindfulness skills and is rated separately on a scale of 0-3. Minimal expected fidelity in order to be considered “faithful” is an average score across sessions of ≥ 2.5 for both adherence and competence.

Name: Treatment Session Adherence
Type: Primary
Time Frame: Intervention
Brief Description: Treatment Session Adherence is a measure of treatment feasibility. The number of MBCT-T treatment sessions attended will be recorded and software will record the number of EUC education modules read by each participant. A treatment arm will be considered feasible if participants attended/read 75% of sessions on average.

Name: Fidelity Checklist
Type: Secondary
Time Frame: Intervention
Brief Description: The checklists cover the rundown and activities of each mindfulness session based on content within the treatments.

Name:	Survey Completeness
Type:	Secondary
Time Frame:	M0, M1, M2, M3, M6, M9
Brief Description:	Survey completeness assesses study feasibility. Survey completeness is a person-level variable that will describe the proportion of surveys completed by each participant still enrolled in the trial at each survey administration.

Name:	Retention Rate
Type:	Primary
Time Frame:	M2
Brief Description:	Retention rate assesses study feasibility. Retention rate will describe the proportion of participants who were randomized to a treatment arm (denominator) who complete the primary clinical outcomes (Headache Disability Inventory and Quick Inventory of Depressive Symptomatology – Self-Report 16) at the primary clinical endpoint (Month 2).

Name:	Daily Diary Completeness
Type:	Secondary
Time Frame:	M0, M1, M2, M3
Brief Description:	Daily diary completeness assesses study feasibility. Daily diary completeness is a person-level variable that will describe the number of days on which participants record headache activity during each month (28-day period).

Name:	Attrition
Types:	Secondary
Time Frame:	M1, M2, M3, M6, M9
Brief Description:	Attrition assesses study feasibility. Attrition describes the proportion of individuals who have dropped out of the study at each time point.

7.2.2 Concomitant Medications, Treatments, and Procedures

All standard of care (SOC) concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this study, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.2.3 Post-Intervention Materials

After study participants have completed the Month 9 assessment, the unmasked research assistant at each site will unmask the participants to study interventions and will provide the patient manual for remote-delivered MBCT and the EUC modules to participants who did not receive these materials during the study.

8 Assessment of Safety

8.1 Specification of Safety Parameters

This trial will be conducted in compliance with the current version of the protocol, current Good Clinical Practice, the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to the IRB.

Monitoring will include regular monitoring for adverse events by the study team. In addition to reporting AEs and SAEs to the IRB according to standard guidelines, the investigators with appropriate expertise will regularly review SAEs and AEs at each weekly study meeting in order to rapidly address these events and to facilitate early recognition of any emerging patterns. Specifically, the licensed neurologist Co-I will make determinations regarding psychiatric AEs and SAEs. Additionally, the participants in this study will receive weekly depressive symptom monitoring during the intervention period. This close clinical monitoring should further facilitate early recognition of any concerning AE or SAE patterns.

All efforts will be made to keep the identities of the participants private, and participants will be reminded of the potentially sensitive matters that may be discussed and to keep these discussions private. Confidentiality and privacy will be discussed and mentioned specifically during the informed consent process. Each site's research team will be responsible for direct communication with their site's clinical patients.

We will increase safety by excluding from enrollment patients at increased risk of adverse events from study treatments (e.g., those with active suicidal ideation, psychosis, and other criteria considered contraindicated in MBCT). Off-protocol care for mental health will not be restricted for any participants, regardless of group to which they are assigned during the trial.

Dr. Shallcross was trained in suicide assessment by faculty from Thomas Joiner's Laboratory for the Study and Prevention of Suicide-Related Conditions and Behaviors at Florida State University and has extensive experience monitoring suicidal ideation and training research coordinators, assistants, and interventionists and implementing suicide safety plan from her previous clinical trials with patients with a severe history of recurrent major depressive disorder and elevated depressive symptoms.

All RAs will be required to complete a suicide assessment and prevention training sponsored by the Suicide Prevention Resource Center (https://zerosuicidetraining.edc.org/). The licensed neurologist Co-I at each site will be available to oversee psychiatric SAEs.

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient

hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Intervention

The clinician's assessment of an AE's relationship to study intervention is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study intervention assessed. In a clinical trial, the study intervention must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.*
- ***Not Related*** *– There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.*

8.2.3 Expectedness

PIs and Co-Is at each site will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained. SAEs will be followed until resolutions are reached as stated below. AEs will be followed for the duration of an individual's participation in the study. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

8.4 Reporting Procedures – Notifying the IRB

It is the investigator's responsibility at each site to report UPs to their IRB in accordance with each site's reporting policies. All UPs at sites other than NYU also need to be reported to the sIRB at NYU Grossman SOM/ NYULH.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Safety Oversight

It is the responsibility of the Principal Investigator and clinician on the study to oversee the safety of the study. Each site's PI and clinician will also provide safety monitoring at their location. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Statistical Considerations

9.1 Description of Statistical Methods

Basic descriptive statistics (e.g., means and standard deviations, frequencies and percentages, or medians and interquartile ranges) for variables of interest will be computed. Distributions of each variable will be examined. Graphical approaches will be used to further explore the data where appropriate. Differences in demographics and clinical characteristics at baseline will be evaluated across the three treatment arms. No missing data is anticipated for treatment fidelity or treatment feasibility primary outcomes. For the CSQ-8, missing data will be singly-imputed as the lowest possible score on the CSQ-8, indicating dissatisfaction with the treatment. For clinical utility responder rates, missing data will be singly-imputed as non-response to treatment. For secondary outcome analysis, missing data will be estimated as part of the mixed models procedures. Primary analyses will not be adjusted. Any significant differences on demographic variables between treatment groups will be included as covariates in secondary adjusted models of the secondary analyses described below. SPSS, SAS and R will be used to conduct the analyses. All tests will be two-tailed with alpha set at 0.05.

Aim 1A. Demonstrate fidelity to MBCT-T and MBCT-V protocols across sites.

> **Hypothesis (H)1**: MBCT-T and MBCT-V sessions (n = 96 sessions) will be administered faithfully [MBCT-TACS scores ≥ 2.5] across treatment arm (MBCT-T vs. MBCT-V) and site (n = 3).

Descriptive statistics (mean and standard deviation) will be calculated for the MBCT-TACS in total (n = 96) and across *each treatment arm* (MBCT-T, session n = 48 vs. MBCT-V, session n = 48); both treatment arms will be considered administered faithfully if mean MBCT-TACS scores are ≥ 2.5. Descriptive statistics (mean and standard deviation) will be calculated for the MBCT-TACS across *each treatment site* (NYULH, Einstein, and WFBH n = 32); a site will be considered to have administered the interventions faithfully if mean MBCT-TACS scores are ≥ 2.5.

Aim 1B. Demonstrate feasibility and acceptability of MBCT-T, MBCT-V, and EUC.

> **H1**: MBCT-T, MBCT-V, and EUC will be feasible [Primary Outcome: 75% Session Attendance] and acceptable [Primary Outcome: Client Satisfaction Questionnaire-8 (CSQ-8) score > 24] at each site.

Feasibility is assessed using Treatment Session Adherence (n = 144), which will be summed to indicate the number of treatment sessions attended. Descriptive statistics (mean and standard deviation) will be calculated for Treatment Session Adherence across each treatment arm (MBCT-T, MBCT-V, EUC) and each site (NYULH, Montefiore, WFBH). A treatment arm will be considered feasible if on average participants attended 75% of sessions, across all sites. A site will be considered to demonstrate adequate feasibility if on average participants attended 75% of sessions across treatment arms at the site.

Acceptability is assessed using the CSQ-8 at a single time-point. Descriptive statistics (mean and standard deviation) will be calculated for the CSQ-8 across each treatment arm (MBCT-T, MBCT-V, EUC) and each site (NYULH, Montefiore, WFBH). Investigators will endeavor to obtain CSQ-8 scores from all participants; if participants drop out of the study prior to Month 2 and cannot be reached to complete this measure, a total score of 8 will be imputed for these missing data, indicating dissatisfaction with the treatment across all domains. A treatment arm will be considered acceptable if CSQ-8 scores are > 24, across all sites. A site will be considered to demonstrate adequate acceptability if on average participants report CSQ-8 scores > 24 across treatment arms at the site.

Aim 1C. Demonstrate feasibility of study procedures (primary outcomes: recruitment and retention).

H1: Recruitment rate will be ≥ 40% at each site.

H2: Retention rate will be ≥ 75% at each site and in each arm.

Feasibility will be assessed using both recruitment and retention rate. Recruitment rate is the proportion of individuals who passed the online eligibility screen (denominator) who enroll in the study at the Month -1 in-person intake session (numerator). Retention rate is the proportion of participants who were randomized to treatment arm (denominator) who complete the primary clinical outcomes at Month 3 (numerator). Both recruitment and retention rates will be calculated for each site. A site will be considered to demonstrate adequate feasibility of study procedures if the recruitment rate is ≥ 40% **and** the retention rate is ≥ 75%. An arm will be considered to demonstrate adequate study feasibility if the retention rate is ≥ 75%.

Sample Size Justification and Power for Aim 1

The n = 144 will allow each site to have 2 treatment groups within each MBCT treatment arm and maintain 1:1:1 treatment arm assignment; for example, at the NYULH site, the total n = 48: MBCT-T (2 treatment groups, n = 16 per site), MBCT-V (2 treatment groups, n = 16 per site) and EUC (n = 16 per site).

Power calculations were informed by preliminary data (Ms, SDs). For Aim 1A, 100% of sessions met the benchmark in preliminary testing; within a 95% CI, we will have power above .99 to detect a mean fidelity score at or above the benchmark. For Aim 1B, 87% of participants met benchmarks for both feasibility and acceptability in preliminary testing; within a 95% CI we will have power above .89 to detect mean feasibility and acceptability score at or above the benchmarks. For Aim 1C hypothesis 1, we will be able to estimate a recruitment rate of 40% to within a 95% confidence interval of +/- 5% for the study overall (enrolled n = 144) and +/- 9% for each site (enrolled n = 48). For Aim 1C hypothesis 2, we will be able to estimate a retention rate of 70% to within a 95% confidence interval of +/- 7% for the study overall and (n = 144) +/- 13% for each site (n = 48).

Aim 2. Use decision rules to determine design for future fully-powered Phase III trial.

Decision Rules

Decision rules will be assessed using data pooled across sites to reduce multiple comparisons and discrepant findings across sites. However, we anticipate that certain sites will have strengths and weaknesses related to feasibility and acceptability outcomes. We hope to use ongoing monitoring to identify weaknesses during the study and implement procedures to improve sites falling behind on outcome parameters. We also will evaluate feasibility information at each site to determine whether to keep/remove the site for a future trial, or whether the site (and other potential sites with similar characteristics) requires different resources to be successful.

Decisions rules are based on three levels where we will consider benchmarks, clinically important differences (CIDs) between groups, and statistical significance.

Benchmarks (MBCT-T and MBCT-V): MBCT-T and MBCT-V will need to meet minimum benchmarks for primary outcomes (fidelity, feasibility, and acceptability) across treatment arm and site. Primary outcomes:

Fidelity (MBCT-TACS scores ≥ 2.5), **Feasibility of treatment** (75% Session Attendance), **Acceptability of treatment** (Client Satisfaction Questionnaire-8 (CSQ-8) score > 24), **Feasibility of study procedures** (recruitment rate will be ≥ 40%; retention rate will be ≥ 75%).

If one or more of these thresholds is not met for MBCT-T or MBCT-V for all sites, we will examine secondary outcomes to help determine the cause of suboptimal performance, make changes to the treatment arm and/or site, and/or conduct an additional pilot to rectify performance. If thresholds are not met for treatment arm, we will not move forward with a future trial with either MBCT-T or MBCT-V. If thresholds are not met for site, we will ascertain whether the identified barrier to fidelity, feasibility, and/or acceptability is modifiable. If barrier is deemed to be unchangeable, we will consider dropping the site in fully-powered trial.

Benchmarks (EUC): EUC will need to meet minimum thresholds for feasibility and acceptability indicated above. If either or both of these domains are not met, we will use secondary outcomes to improve feasibility and/or acceptability in future pilot testing prior to moving forward with the fully-powered Phase III clinical trial. If both acceptability and feasibility benchmarks are met for EUC, we will move forward with EUC in a future Phase III trial.

Clinically Important Differences (CIDs) and statistical significance

If minimum benchmarks (see above) for all arms are met, we will move forward with **both MBCT-T *and* MBCT-V vs. EUC** in a fully-powered Phase III clinical trial **so long as neither version of MBCT is superior to the other based on the following analyses**:

1) **MBCT-T/V Treatment fidelity**: MBCT-TACS is at least ≥0.2 points higher in the superior compared to the inferior arm, and this difference is statistically significant.

2) **MBCT-T/V Treatment feasibility** is at least 15% higher in the superior arm compared to the inferior arm, and this difference is statistically significant.

3) **MBCT-T/V Treatment acceptability** is at least 5 points higher in the superior arm compared to the inferior arm, and this difference is statistically significant.

4) **MBCT-T/V Clinical utility**: 50% responder rate for the HDI (10-point change from M0-M3) and the QIDS-SR (5-point change from M0-M3). No significance testing between MBCT-T and MBCT-V will be conducted for this outcome.

If one of the above criteria is met (i.e., one treatment meets threshold for being superior to the other), we will select this treatment to move forward with further testing in a fully-powered Phase III trial.

If we observe mixed results (e.g., MBCT-T is superior on feasibility but MBCT-V is superior on clinical utility) we will utilize results from secondary outcomes to further explore differences between the MBCT-T and MBCT-V treatment arms to inform the selection of treatment arms for the Phase III trial.

Analyses

Mixed effects models will evaluate whether treatment fidelity, treatment feasibility, or treatment acceptability differ significantly between MBCT-T and MBCT-V. Alpha will be set at 0.05 for all analyses.

To evaluate differences in fidelity, a multi-level linear mixed effects model will evaluate differences between MBCT-T and MBCT-V on the MBCT-TACS (72 sessions nested in 6 treatment groups). Treatment site will be included as a covariate. Repeated measures will be taken into account using session-level random effects.

To evaluate differences in feasibility and acceptability, two separate multi-level linear mixed effects model will be used to evaluate differences between MBCT-T and MBCT-V on Treatment Session Adherence and the CSQ-8 (96 participants nested in 6 treatment groups). Treatment site will be included as a covariate. Clusters

by group membership will be taken into account using random effects. **Power for Aim 2.** Using SDs and ICCs derived from preliminary data, with an n = 96 sessions and n = 96 participants, we have at least a power of .90 to detect the clinically important differences (CIDs) pre-specified in the decision rules for treatment fidelity (MBCT-TACS CID = 0.2 points; power > .99), treatment feasibility (Treatment Session Adherence CID = 15%; power > .99) and treatment acceptability (CSQ-8 CID = 5 points; power = .91).

Planned Secondary Analyses

Descriptive statistics (means and standard deviations or ns and %s) will be calculated for all secondary outcomes. Secondary outcomes for Aim 1 will be assessed via: 1) daily diary (Homework Adherence during intervention, Headache Frequency, Pain Intensity); 2) monthly survey (Headache Disability Inventory, QIDS-SR (depressive symptoms), MBCT Home Practice inventory, Migraine-Specific Quality of Life, Co-occurring Treatment Tracking, Adverse Events); or administrative data (Survey Completeness, Diary Completeness and Attrition). For secondary outcomes evaluated with daily diary, multi-level mixed effects models will evaluate changes in the outcomes at the day-level across treatment arm (MBCT-T vs. MBCT-V vs. EUC). Repeated measures (day) within person will be taken into account by using person-level random effects. Clusters by group membership will be taken into account using a random effect. Treatment site will be included as a covariate. For secondary outcomes evaluated with monthly surveys, multi-level mixed effects models will evaluate changes in the outcomes at the month-level across treatment arm (MBCT-T vs. MBCT-V vs. EUC). Repeated measures (month) within person will be taken into account by using person-level random effects. Treatment site will be included as a covariate.

9.2 Measures to Minimize Bias

9.2.1 Enrollment /Masking Procedures

Subjects will be masked to study hypotheses. They will be informed that they will be assigned to one of three interventions that will last a maximum of 8 weeks and that will provide knowledge to help migraine and depressive symptoms. The facilitators will be unmasked. Data will be entered and coded so that group membership is known only to the project coordinator at NYULH and to research assistants who are coordinating study visits. The investigators will be masked to treatment condition. After study subjects have completed the post-intervention/M2 assessment, the unmasked research assistant will unmask the subjects to study interventions.

Blinded Personnel:
Amanda Shallcross (mPI)
Elizabeth Seng (mPI)
Cuiling Wang (statistician)
YU Research Assistant (data management)
Richard Lipton (Co-I)
Mia Minen (Co-I)
Rebecca Wells (Co-I)

Unblinded Personnel:
NYU Program Coordinator (randomization scheme)
Einstein Psychology Assistant (randomization scheme)
Wake Forest Research Assistant (randomization scheme)
Interventionists at each site
YU Research Assistant - Facilitator (Einstein intervention delivery)

Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11 Ethics/Protection of Human Subjects

11.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46.

11.2 Institutional Review Board

The protocol, key information form, consent forms, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and consent materials must be

obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

11.2.1 Independent (non-NYULH, third party) certified MBCT instructors

If individuals are engaged in human subjects research based on OHRP definition, they are required to obtain their own IRB approval before human subjects research activities are performed.

If individuals are not engaged in human subjects research, PI will ensure there is an executed Business Associate Agreement (BAA) in place before any proposed work is performed by those individuals as contractors. Individuals are considered not engaged in human subjects research if they perform commercial or other services for investigators provided that all of the following conditions also are met:

- the services performed do not merit professional recognition or publication privileges
- the services performed are typically performed by those individuals for non-research purposes
- those individuals do not administer any study intervention being tested or evaluated under the protocol

11.3 Informed Consent Process

11.3.1 Consent and Other Informational Documents Provided to Participants

The following consent materials are submitted with this protocol:

- Study 2 Key Information Sheet
- Study 2 Consent Form
- Study 2 Audio Consent

11.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the subjects and their families via telephone or WebEx video-conferencing. Consent forms will be IRB-approved and individuals will be asked to read and review the document. Individuals will have the opportunity to carefully review the e-Consent materials and ask questions prior to signing in REDCap. Individuals should have the opportunity to discuss the study or think about it prior to agreeing to participate. Subjects will sign the e-Consent in REDCap prior to any procedures being done specifically for the study. Subjects may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be provided via REDCap to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

The REDCap e-Consent link will be submitted to the IRB for review in Research Navigator via Modification.

11.4 Subject and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by IRB and Institutional regulations.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

11.4.1 Research Use of Stored Data

- Intended Use: Data collected under this protocol may be used to study migraine and depression. No genetic testing will be performed.
- Storage: Data will be stored using codes assigned by the investigators. Data will be kept in NYU's REDCap system. All three research sites included in this protocol will use NYU's REDCap for data storage and management. Only investigators will have access to the data.
- Tracking: Data will be tracked using NYU's REDCap.

12 Data Handling and Record Keeping

12.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close out or 5 years after final reporting/publication. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol deviations must be reported to the local IRB per their guidelines. The PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

12.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

13 Study Finances

13.1 Funding Source

This study is financed through a grant from NIH-NCCIH.

13.2 Costs to the Subject

Subjects will incur no cost as a result of participating in the study.

13.3 Subject Reimbursements or Payments

Participants will each be compensated $15 for 7 assessment points (Intake & Months 0, 1, 2, 3, 6, and 9) ($105 total for assessments). Participants will be compensated $30 for each diary (30 days, $1/day) completed during the month-long run-in period and over the course of three months (M0-M3) ($120 total for diaries). In total, each participant will have an opportunity to be compensated up to $225 over the course of the study. Participants will be compensated with a single payment at the end of their participation in the study. If a participant withdraws from the study for any reason, they will be compensated for all completed assessment points up to the time of withdrawal. Participant compensation accrued during the study will be tracked by the study data manager and reported back to the participants throughout their participation in the study to keep them informed of the compensation accrual amount. Payments will be provided via check through the NYU PeopleSoft financials application.

14 Study Administration

14.1 Sites

Involved in Human Subjects Research:

- NYU Langone: Will oversee study administration, recruitment, data collection, and data monitoring.
- Yeshiva University: Will assist with recruitment at Montefiore Health System, data collection, and data monitoring.
- Albert Einstein College of Medicine: Will conduct recruitment at Montefiore Health System
- Atrium Health Wake Forest Baptist: Will conduct recruitment, data collection, and data monitoring.

15 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NCCIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULH investigators will follow the applicable conflict of interest policies.

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17 Appendix 1. Suicide Safety Plan

All RAs will be required to complete a suicide assessment and prevention training sponsored by the Suicide Prevention Resource Center (https://zerosuicidetraining.edc.org/). All research personnel will be trained to conduct the below protocol and will be regularly tested on their knowledge and understanding of the safety protocol.

If a participant reports being suicidal (e.g., verbally at any point during the study or endorses a "1", "2", or "3" on the survey items that ask about suicide and thoughts of hurting oneself), the research assistant (RA) will follow the procedures below.

If the participant endorses suicidal ideation via phone/video:

RA will ask the following questions to assess risk.

1. Are you currently under the care of a psychiatrist? Taking medication? Get details for physician name and medication name/how long person has been taking it, frequency of taking it.

2. Approximately how frequently each day do you find yourself thinking about suicide? Rarely, maybe 1 time. Somewhat often, maybe a couple to a few. Often, on/off most of the day.

1) Rarely = not high risk

2) Somewhat often = elevated risk

3) Often = imminent risk

3. Have you made any suicide attempts in the past? How would you describe your wish to die during your last attempt? (low, moderate, high)?

1) Low = not high risk

2) Moderate = elevated risk

3) High= imminent risk

4. Do you have a specific plan for how you may hurt yourself? If so, what is your plan? If so, when do you think you'll act on your plan? If so, how confident are you that you'll act on your plan?

1) No evidence for plan = not high risk

2) Evidence for plan wit NO timing and NO confidence = elevated risk

3) Evidence for plan with timing and confidence = imminent risk

5. Have you made preparations (e.g., writing a suicide note, buying a firearm and ammunition, etc.) for engaging in self-harm behaviors? If so, what have you done?

1) No evidence for preparations = not high risk

2) Evidence for preparations = imminent risk

6. On a scale of 1-10, '10' being very suicidal, how suicidal (how high is your wish to die) right now?

1) 1-2 = not high risk

2) 3-4 = elevated risk

3) 5 or higher = imminent risk

7. On a scale of 1-10, '10' being very likely, how likely is it that you will make an attempt in the next 24 hours?

1) 1-2 = not high risk

2) 3-4 = elevated risk

3) 5 or higher = imminent risk

8. How confident are you '10' being very confident, about keeping yourself safe for the next 24 hours?

1) 1-2 = not high risk

2) 3-4 = elevated risk

3) 5 or higher = imminent risk

9. Do you live with anyone or alone? Inquire about relationship with housemates.

If the participant endorses suicidal ideation via online survey:

Any participant who endorses the suicidal ideation item via survey is automatically routed to the BSS using branch-logic. The online survey platform will send an 'Email Trigger' to the study email address, which is monitored daily. The Email Trigger is sent with high priority and includes responses to questions on both the depression measure (e.g., QIDS-16) and the BSS. We additionally include alternative 'end of survey elements' for participants who endorse the suicide item online, whereby participants are provided a mental health resource sheet that includes the suicide hotline and referrals to local mental health services.

The RA will examine the participant's BSS. First, a total score will be calculated and a note will be made of whether or not the total score is under or over 11. Scores over 11 indicate a notable risk level. Second, 5 key items: 12, 15, 16, 18, and 21 will be closely examined. There is greater cause for concern if a participant endorses a "2" for any of these items rather than a "0" or a "1."

1. If the score on the BSS is under 11 and the above 5 items are not noteworthy, the person is not at high risk for suicide and no immediate action is needed. The participant will, however, be given a resource sheet with referral information to local mental health clinics at each site. This sheet has information about how to contact mental health resources should they feel they need to do so, including emergency suicide hotline numbers.
2. If the score on the BSS is 11 or higher and/or the 5 items are noteworthy, the RA will conduct continued risk assessment over the phone and ask the participant the following questions:
    a. Do you have a specific plan for how you may hurt yourself? If so, what is your plan? If so, when do you think you'll act on your plan? If so, how confident are you that you'll act on your plan?
    b. Have you made preparations (e.g., writing a suicide note, buying a firearm and ammunition, etc.) for engaging in self-harm behaviors? If so, what have you done?

Response to risk levels:

- **If the participant is in <u>imminent danger</u> of hurting him/herself** (i.e., has a plan, intent, means and cannot keep him/herself safe for 24 hours):
    a. The RA will confirm additional information such as the participant's location and whether they are living alone. If the participant indicates that they live with another adult, RA will acquire the name and contact information for this person.
    b. The RA will immediately notify the licensed neurologist Co-I and PI. If neither are available, the RA will contact the participant's PCP and/or treating psychiatrist to arrange for further evaluation and/or an emergency appointment.
    c. If the RA is unable to reach Co-I, PI, PCP or psychiatrist, the RA will attempt to convince the participant to voluntarily seek help from an emergency facility and will assist the participant with the process of admitting him/herself to the hospital.
    d. If the participant is uncooperative or unwilling to go to an emergency facility, the RA will call 911 for the purposes of transporting a high-risk participant to the ER for evaluation. Law enforcement will not be involved in involuntary hospital admission.
    e. In the event a participant is hospitalized, the PI and Co-I will evaluate the participant's circumstances and stability (based on length of hospitalization, need for intensive treatment, etc.) to determine whether the participant is fit to continue with the study.
    f. If a prospective participant endorses high-risk items on the BSS during pre-screening (before we have collected data on provider information) *and* is unable to be reached by phone or by email, the RA will consult the participant's health record to determine PCP contact information. If there is no PCP listed, the RA will contact the participant's psychiatrist. If neither a PCP nor psychiatrist is listed in the health record, the RA will contact the participant's neurologist to inform him/her/them about the prospective participant's suicide risk.

- **If the participant is at an <u>elevated, but not imminent</u>, risk for suicide**, the RA will call the treating physician (if applicable) and will orchestrate an amplified monitoring procedure under the supervision of the physician, PI, and Co-I. Specifically, the RA will help the participant create a coping card (i.e., an index card, to be carried with the participant at all times, that outlines several coping skills – like calling a loved one or going for a walk – that have helped the participant cope with distress in the past, and lists emergency contact numbers in the case of acute suicide risk), and arrange to call the participant 1 day later to reassess suicide risk.

The licensed neurologist Co-I will be notified of every instance of suicidal ideation, will be available for higher level suicide risk assessments, and can interface with psychiatry (in case of the need for psych ER assessment and inpatient psychiatric hospitalization).

After this response plan is implemented, a report of the event will be made to the applicable IRB and all members of the study team. In compliance with applicable regulations any unanticipated problem or serious adverse event should be reported to the IRB within 24 hours of the event.