Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

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Project Title: Does Acceptance and Commitment Therapy (ACT) Improve Disability in Chronic Migraine? A Randomized Headache Center Trial

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1. Background and Significance

Chronic migraine prevalence is 3% of the migraine population (1), though the majority of patients seen in a headache center and is often a disabling condition. Pharmacologic management has expanded and improved in recent years though it nonetheless provides incomplete control in many patients. Even the best specialty headache clinic management falls short in providing relief to some chronic migraine patients. Behavioral therapies have shown efficacy in pain conditions, including migraine. Behavioral treatments may improve disability related to headache more so than headache days, a traditional measure of headache treatment efficacy. However, reduced disability is, in the end, the most important outcome in headache management. If behavioral management, in addition to usual treatment, can improve disability outcomes in patients, an argument can be made for expanding access to these modalities in the headache clinic setting.

Acceptance & Commitment Therapy (ACT), often referred to as the “third wave of cognitive behavioral approaches,” has helped treat a variety of conditions, including depression, anxiety, and chronic non-headache pain. Mo’Tamedi and colleagues (2) performed a trial in which participants with chronic tension-type headache or CM were randomized to receive eight weekly sessions of ACT in addition to standard treatment or standard treatment only. After 8 weeks, participants reported improvement in disability, affective aspects of pain, and anxiety. More recently, Grazzi et al (3) demonstrated the positive effect of ACT in participants with high frequency migraine without aura and the benefit persisted at one year out.

ACT departs from mainstream cognitive behavioral therapy approaches in a number of respects. The most unique aspect is learning to accept one's present condition (vs. the more typical approaches that focus on direct approaches for managing and coping with a given condition). The overarching aim of ACT-based therapies for pain is to promote greater psychological flexibility by cultivating six different positive psychological capacities: acceptance, defusion, mindfulness, sense of self, values, and committed actions.

Acceptance in ACT is not merely tolerance: rather, it is the active and nonjudgmental embracing of experiences in the here and now as they are. Mindfulness is one of the ways to increase acceptance, achieve cognitive defusion and thus increase behavioral flexibility. Studies have documented the effectiveness of ACT interventions for improving disability, lessening the impact of pain, and developing resilience for varied types of recurrent non-headache pain conditions and migraine. The latter finding is particularly important as individuals with low resilience, especially those currently experiencing chronic pain, are more susceptible to emotional difficulties when exposed to stressful situations and this, in turn, gives rise to conditions such as depression or anxiety.

Studies (4,5) examining the clinical utility of mindfulness and ACT in chronic pain conditions and migraine have demonstrated how these practices help by increasing pain tolerance, reducing the need for symptomatic medications, reducing the frequency of migraine attacks as well as the course of migraine episodes, and by modulating certain personality characteristics of patients with migraine, such as anxiety, rigidity, low acceptance, and low resilience. Patients with pain can be effectively supported by nonpharmacological approaches, such as ACT, to manage their pain and the anxiety connected to pain, by improving their clinical condition, and by decreasing the likelihood of a long-term negative course. Specifically, patients with chronic migraine may benefit from attending ACT treatment not only in terms of clinical improvement, but also through reduction of the medication intake. The integration of ACT into standard care merits continued study, replication and extension to other sites to more fully identify both the strengths and limitations of this particular integrative approach

2. Specific Aims and Objectives

Hypothesis: The addition of Acceptance and Commitment Therapy to usual care will improve measures of disability in chronic migraine participants, as measured by the Headache Disability Index, comparing changes in scores from baseline to 3 months. Secondary and exploratory analyses are as noted. This is a single site randomized, open-label phase II pilot study. Participants will be randomized 1:1 with the following method using a computerized random generator into 2 groups: ACT and usual treatment. Initial ACT training requires 8 virtual group visits over 2 months. All participants will be assessed at 3, 6 and 12 months. ACT training involves 8 one-hour sessions covering six different positive psychological capacities: acceptance, defusion, mindfulness, sense of self, values, and committed actions, followed by two review sessions. The goal of ACT is to improve mindfulness. Mindfulness is one of the ways to increase acceptance, achieve cognitive defusion and thus increase behavioral flexibility which should lead to reduced disability in the migraine population.

Chronic migraine is a potentially disabling condition that requires medical management in most patients. Studying chronic migraine patients without the use of some form of standard or usual medical management would not be feasible. Restricting usual management would be unduly harsh and would limit recruitment. Thus, both groups will be offered usual or standard management. Conversely it seems clear that medical management is not a complete solution in many patients. Though many patients improve with usual treatment, many still report some level of disability. This study tests the hypothesis that ACT can improve reported disability in these patients.

As above, the expected improvement in disability justifies the intervention with ACT. ACT typically requires some training. Though other, and shorter, protocols for training ACT may prove useful and should be investigated, in this study we continue the protocol that was shown useful in studies with other migraine participants (3). It is expected that all participants will undergo all training sessions, however, if a minimum # of 6 of 8 of the training sessions are completed, individual participation in the study can continue.

A participant is considered to have completed the study if he or she has completed the baseline assessment, ACT training if so randomized and the 3-month, 6-month and 12-month follow-up assessments. Participants will be allowed to miss up to 2 sessions and miss 0 visits in order to continue in the study.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Assessment of change in disability measure	Change in the Headache Disability Index (HDI) from baseline to 3 months Scores at 3 months minus scores at baseline. Negative numbers indicate a higher reduction of headache-related disability	The HDI has good psychometric properties, and gets at both emotion and role function disability well
Secondary		
Assessment of disability measures at baseline, 3, 6, and 12 months	Headache Disability Index (HDI) at baseline, 3, 6, and 12 months 25-item survey with total scores ranging from 0-100, with higher scores indicating higher levels of disability. Headache Impact Test (HIT-6) at baseline, 3, 6, and 12 months 36-78; <50 little impact, 50-55 some 56-59 substantial, >59 severe Migraine Disability Assessment Score (MIDAS) at baseline, 3, 6, and 12 months0-270; 0-5 little/ no disability, 6-10 mild, 1-20 moderate, > 20 severe	All accepted and validated scales for their endpoints
Assessment of anxiety and depression at baseline, 3, 6, and 12 months	Hospital Anxiety and Depression Scale (HADS) at baseline, 3, 6, and 12 months	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Assessment of catastrophic thinking related to headache at baseline, 3, 6, and 12 months Assessment of mindfulness at baseline, 3, 6, and 12 months	2 scales, 0-21 each. 0-7 normal, 8-10 borderline, >= 11 significant anxiety or depression Patient Catastrophizing Scale (PCS) at baseline, 3, 6, and 12 months0-52, >= 30 significant catastrophizing Five Facet Mindfulness Questionnaire (FFMQ) at baseline, 3, 6, and 12 months 39 items	
Tertiary/Exploratory		
Abortive Medication Use, as recorded by participants	Headache Diary/ App in use daily by participants	This is a standard measure

3. General Description of Study Design

- 12-month open label study comparing two arms, participants with CM are randomly assigned to either usual treatment or usual treatment with ACT. Usual treatment is as managed by any provider in our headache center. ACT is a third wave behavioral treatment employed by patients superimposed on usual treatment after eight 1-hour weekly virtual group training sessions, conducted by research staff, to teach the modality.
- Primary Objective: To compare impact on the chronic migraine population with and without treatment with ACT
- Secondary Objectives: To assess other disability measures, the use of abortive medications, to assess work productivity and catastrophizing
- Primary Endpoint: Change in Headache Disability Index (HDI) from baseline to 3 months.

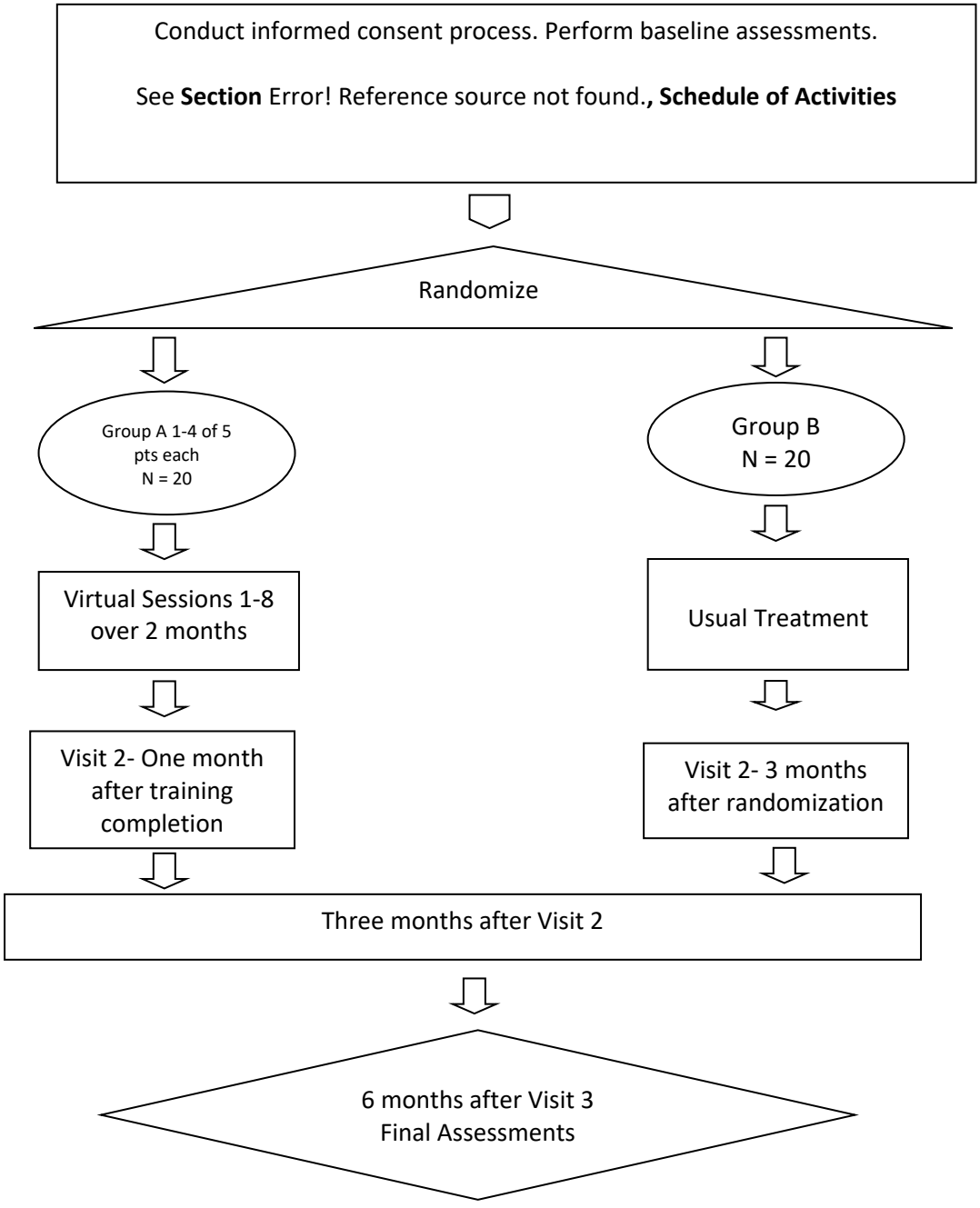
- Secondary Endpoints: HDI, HIT-6 for impact, MIDAS for disability, PCS, FFMQ and HADS at baseline, 3 months, 6 months and 12 months.

Schedule of Activities

	Pre-screening (Pre-consent)	Telephone Contact to set up screening visit	Baseline Visit 1 Day 1 - Screening/Enrol	8 virtual training visits for those randomized to ACT – see sched	Visit 2 About 3 mos after Visit 1	Visit 3 3 mos after Visit2	Visit 4 6 mos after V 3 Completion
EMR Review Eligibility	X						
Informed Consent			X				
Demographics			X				
Clinical history			X				
Randomization			X				
Outcome Evaluation							
HDI			X		X	X	X
HIT 6			X		X	X	X
MIDAS			X		X	X	X
PCS			X		X	X	X
FFMQ			X		X	X	X
Abortive medication use			X		X	X	X
HADS			X		X	X	X
Adverse Events Reporting					X	X	X

Schema

Total N: 40
Pre-screen potential participants by inclusion and exclusion criteria; schedule Visit



4. Subject Selection

We anticipate screening 100 active headache center participants, through referral of clinic providers, in order to reach the target enrollment size of 40 participants over two months.

Subject selection will be from those patients referred to us by providers in the headache center. Providers will be made aware that the study is recruiting and provided details of the study in written form. Under the prep to research provision, the referring provider will do the following in this process:

- discuss with the patient that there is a study for which they may qualify or be interested;
- communicate the name of the study and the PI;
- get verbal permission to provide their contact information to our study team;
- once permission is obtained, the referring provider will share the contact information with our research team securely.

Prior to calling those from whom permission was obtained, we will verify preliminary eligibility in the medical records (e.g., chronic migraine diagnosis) under a partial waiver of HIPAA. If we determine they are eligible, potential participants will then be contacted by phone or other preferred method of contact discuss the project.

Information collected under the HIPAA waivers, for recruitment purposes, of patients who either are not eligible or elect not to join the study will be destroyed as soon as possible.

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

1. Stated willingness and ability to engage in the consent process
2. Stated willingness to participate in the study, despite randomization outcome
3. Availability for the duration of the study
4. Males and females; Age 18-65
5. Diagnosis of chronic migraine, with or without medication overuse, and followed in the Graham Headache Center.
6. Access to necessary resources for participating in a technology-based intervention (i.e., virtual training visits)

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

1. Known major depression or other psychiatric condition as reported in the clinical documentation
2. Non-English speaking since meetings are interactive, in English, and translation is not possible.
3. Secondary headache diagnosis as reported in the clinical documentation
4. Any psychotherapy in the prior 18 months
5. Any reason which the treating provider feels would limit the participant's ability to learn or practice ACT
6. Previous experience with mindfulness or meditation approaches (lifetime)

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the

criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include the successful treatment of a previous affective disorder, and the lifting of physical activity restrictions previously in place.

5. Subject Enrollment

Subject screening and enrollment will take place after pre-screening. The screening visit will take about 30 minutes. It can be completed by phone or in person. Institutional email, or Patient Gateway, may be used only to schedule visits. During the visit, we will discuss the purpose of the study, review the consent form and address any questions and review and sign the consent form in person or by phone using econsent in REDCap. Screening and enrollment may be followed by a waiting period of up to several weeks, to allow enough participants to be enrolled to create a training group (this will be explained during the consent process).

6. STUDY PROCEDURES

After the consent process is completed, the participant will be randomized to group A or B and questionnaries will be administered.

We anticipate 3-4 training groups of 5 participants each. Intervention attendance will be monitored and recorded (e.g., via role call). Failure to attend more than 2 sessions in 8 weeks will result in removal from the study. Makeup sessions may be offered when possible. Training is conducted by a physician experienced in the procedure and is based on a prior published protocol (3).

The intervention will be completed virtually through use of an MGB instance of Zoom. No in-person offerings are anticipated. The intervention will be done by a study team psychologist trained in the use of ACT. Each session has a theme as noted in the included training documents. Intervention sessions will not be recorded. Subjects may interact during the training meetings. Subjects will be addresses through use of first names only. No other identifiers will be provided. Before each session the study team will ask participants to ensure they are in a private location.

No regular email communication is anticipated apart from scheduling information provided to the subjects.

Initial randomization is as per the study description. This is an open-label trial.Patients will be randomized to receive either ACT or usual treatment. Randomization will use a permuted block method (7). The randomization ratio will be 1:1. A biostatistician will generate the randomization codes and upload the randomization list in the Redcap system.

In addition, participants will maintain daily diaries on paper and this data will be collected periodically. These will be used to measure abortive medication intake and practice times.

Regular, daily or near-daily, practice of mindfulness both during and after the intervention sessions will be encouraged. Practice may be recorded in the daily diaries that participants are encouraged to maintain.

In addition, participants are provided two audio practice guidance recordings, one of 3 minutes in length and one of 12 minutes in length to help guide practice.

For this protocol, participants may use non-opioid analgesics for pain control, including over-the-counter medications and dietary supplements, and prescribed medications as per the recommendations of their provider, i.e. usual treatment. Abortive medication usage will be assessed at each study visit and documented in the relevant Case Report Form (CRF).

When a subject discontinues from ACT but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance
- Lost-to-follow up; unable to contact subject (see **Section** Error! Reference source not found.**, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study will not be replaced.

A participant will be considered lost to follow-up if he or she fails to return for one scheduled visit and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit within 2 weeks, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

Study procedures as per the Schedule of Activities, include questionnaires as below and the recording of diary information, along with assessment of any adverse events:
Data will be maintained in a secure fashion as described elsewhere in the protocol.
No specific provision is allowed for transmittal of specific questionnaire results to participants since individual scores are not likely to be of value to the participant.

Compensation in the amount of $50.00 will be provided to each participant after the completion of each study timepoint (BL, 3m, 6m, 12m). If the participant completes the entire study the compensation will total $200.00.

7. Risks and Discomforts

There are no known risks to therapy with ACT.
ACT is evidence-based and effective, and generally considered to be free of side effects. Nevertheless not all participants are good candidates for ACT. For participants with rooted trauma, for example, ACT may be not enough to meet their needs; moreover, as ACT sessions include many reflections, exercises and abstract concepts, participants with psychiatric problems may not be good candidates for this approach. ACT is also not suitable for participants who have difficulty linking discussions and insights for the different sessions since often such participants are not able to perform the exercises on their own. The training is fairly extensive, 8 hours over 2 months, and this could stress participants' schedules. We will remind participants of the voluntary nature of the research.

Loss of confidentiality is a risk related to the collection of protected health information and study data for this project. We will miminize these risks by using MGB REDCap and implementing other confidentiatily procedrues outlined in the confidentiality section below.
Loss of privacy is a risk related to study participation, including the virtual intervention. To mimimize this risk, the intervention will be conducted through the use of a secure MGB Zoom program. All participants will be reminded to minimize the disclosure of personal information while in the session; sessions will not be recorded; and participants will be asked to ensure they are in a private location where they feel comfortable participating and others cannot hear them (or the meeting in general); the use of headphones may be appropriate for some participants to protect the privacy of other participants.

Email communication will be conducted using send secure or permission will be obtained if unencrypted email is preferred, before emailing, and will be limited to meeting scheduling information.

8. Benefits

ACT theorizes that our thoughts and perspectives are shaped by language, past experiences and our environment. ACT encourages patients to separate themselves from their framework of negative thoughts and beliefs. In ACT, psychological flexibility is the ability to live a full and meaningful life despite ongoing adversity. Research has shown that ACT is an effective form of treatment for medical and psychological conditions. The goal of ACT is not to reduce or eliminate symptoms. Instead, ACT helps patients reframe their thinking about their condition and life events, and live their life in the most fulfilling way possible
The literature confirms links between stress and pain, and shows chronic pain to be a biopsychosocial condition, unlikely to be managed fully by medications alone. The increase of medication intake to face up to a chronic pain condition can increase the risk of medication overuse and addiction. ACT can help patients to tolerate and manage symptoms by reducing medication intake, promoting and encouraging a more holistic definition of wellness including acceptance of negative experiences, integrating negative emotions and learning to manage them. Metaphors and paradoxes are applied in ACT to support patients' understanding of the related concepts. Benefits have been demonstrated but in the short and long term in patients suffering from anxiety disorders, chronic pain conditions and migraine. The integration of ACT into standard care merits continued study and replication to more fully identify both the strengths and limitations of this particular integrative approach, which might be useful for reducing the risk of long-term development of CM associated with medication overuse headache.

9. Statistical Analysis

We expect that mean reduction in HDI scores from baseline to 3 months will be larger in the ACT treatment group compared to the usual treatment group among the subject with chronic migraine.

Based on the published study (4), we expect the participants will have an average baseline HDI of 51.4 ± 19.0. Seng et al.'s study observed a larger decrease in mean HDI score of 14.3 points from baseline to 4 months in the Mindfulness-Based Cognitive Therapy group compared to the usual care group (0.2 points reduction). Our proposed sample size of 40 participants (20 participants each group) will allow us to observe an 18.1 ± 19.0-point reduction in the ACT group from baseline to month 3 and a 0.2 ± 19.0-point reduction in the usual treatment group, with 80% power and a two-sided alpha of 5%. An 18.1-point reduction (35% from the baseline) is larger than the reported study. However, Jacobson et al.'s study suggested that a change in the HDI score of 29 points or more could be used to assess the efficacy of headache management strategies (8). Considering those two studies, we chose our effect estimate of 18.1 reduction for our ACT group. There is no reported standard deviation of change in HDI. For the purpose of the calculation, the standard deviation of 19.0 from the baseline value was utilized. Our proposed sample size of 40 participants will include a loss of follow-up of 10%.

All randomized subjects will be included in the Intention to Treat (ITT) analysis.

All numerical primary and secondary outcomes will be summarized using descriptive statistics (N, Mean, Standard Deviation, Minimum, and Maximum) at baseline, month 3, month 6, month 12, a difference

from baseline to month 3, a difference from baseline to month 6, and a difference from baseline to month 12, stratified by treatment group.

The change in HDI from baseline to 3 months will be calculated by subtracting the HDI at baseline from the HDI at 3 months. We will use a Student's test to assess the change from baseline to 3 months in HDI. We will check distributions of the change in HDI before we apply Student's t-test. If the data has non-normal distribution, we will apply Wilcoxon Rank Sum test. Treatment group will be tested at a 2-sided 5% significance level. All efforts will be made to collect the participants' HDI data at each visit. If we have missing baseline or 3 months HDI data, the subjects will be list wise deleted from the primary analysis.

The longitudinal secondary endpoints (HDI, HIT-6, MIDAS, HADS, PCS and FFMQ) will be presented graphically and numerically. The analysis will use a restricted maximum likelihood-based repeated measures approach with a random slope and intercept model. Visit will be analyzed as days since randomization. The analysis will include the fixed, categorical effect of treatment group, fixed continuous effect of visit, and the treatment group-by-visit interaction. The baseline value will be included as a fixed covariate. Random effects will be included for participant response and for both visit and intercept. An unstructured covariance structure will be used to model the within-participant errors. If this analysis fails to converge, the other structures that will be tested will include spatial power because visits are unevenly spaced, and compound symmetry. The covariance structure converging to the best fit, as determined by Akaike's information criterion, will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. The analysis will use all measurements obtained over the 12-month study period, including those from patients who had discontinued study. The model allows for missing data assuming missing at random. Significance tests will be based on least squares means using a two-sided $\alpha = 0.05$ with two-sided 95% confidence interval. The primary treatment comparison of slopes will be assessed through the treatment-by-visit interaction coefficient. Assumptions for models will be assessed by examining plots of the residual values.

We will examine all adverse events (AEs) and serious adverse events (SAE) by the type of event, as well as by body system class. We will report number of AEs and SAEs stratified by treatment group.

Baseline demographic or clinical characteristics will be summarized using descriptive statistics (N, Mean, Standard Deviation, Minimum, and Maximum for numerical characteristics and N and percentage for categorical characteristics). The summary will be stratified by treatment group.

There are no planned interim analyses. There is no planned sub-group analyses. There are no planned exploratory analyses.

10. Monitoring and Quality Assurance

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

For adverse events (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. Of note, the term "severe" does not necessarily equate to "serious".

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

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

A clinician with appropriate expertise in Headache Medicine will be responsible for determining whether an adverse event (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 procedures.
The occurrence of an adverse event (AE) or serious adverse event (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, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (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 will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric 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.

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. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The clinical research coordinator will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. 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.
In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

11. Data and Research Material Sharing

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

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <specify name of data capture system>, a 21 CFR Part 11-compliant data capture system provided by the <specify Data Coordinating Center>. 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.

Sending Data/Materials to Research Collaborators outside Mass General Brigham

NA

Receiving Data/Materials from Research Collaborators outside Mass General Brigham

NA

12. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting.
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected.
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☐ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol.
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies.
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research.
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens.
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research.
- ☐ Additional privacy and/or confidentiality protections

13. References

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