NYU Langone Health

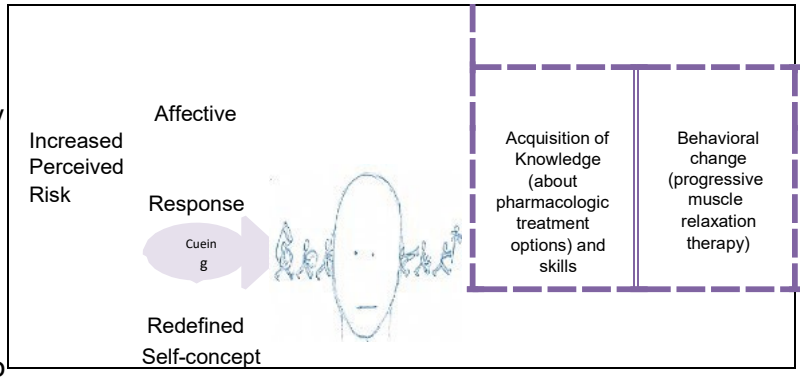
Official Title:	RELAXaHEAD for Headache Patients (Phase II): RELAXaHEAD for Migraine and Sleep
NCT Number:	NCT05466682
Study Number:	17-00525-2
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	• July 14, 2022

Purpose of the Study

Headaches are extremely common; migraine is the 6th most disabling condition per the World Health Organization (WHO). Post traumatic headache is one of the most common symptoms after a concussion. Prior research has shown that Progressive Muscle Relaxation Therapy (PMR) is an effective treatment for headache patients [1,2]. PMR is a simple, easily taught,[3,4], fairly safe .[1] but under-utilized behavioral treatment. [5,6] Prior research demonstrates that pain self-management training increases self-efficacy and self-management behaviors while improving pain and depression outcomes.[7]

Traditionally, psychologists have introduced PMR to patients. However, physicians have difficulty finding providers and patients have difficulty accessing and paying for behavioral treatments for chronic pain conditions such as for migraine.[8-10]

To address these limitations smart-phone based implementations of PMR have been developed by our group and others. **The long-term goal of this research is to assess the utility of smartphone-based PMR for the treatment of headaches.** While there are many commercially available electronic diary and MBI apps for headache, there is little data showing their efficacy.[11,12] Our RELAXaHEAD app incorporates the electronic PMR that was successfully used in an earlier epilepsy study[13] and beta tested with headache specialist and migraine patient input. It also has functionality to track medications. We plan to conduct a 2-arm randomized controlled study to evaluate the feasibility and acceptability of RELAX for use with headache patients. One arm will be the RELAX group (the RELAXaHEAD app) and the other arm will be a monitored usual care (MUC) group (this group receives standard of care and uses the electronic daily symptom reporting diary). The goals are to assess the feasibility and adherence of the RELAX intervention in persons with headache (Aim 1) and to gather data on the effects of the RELAX intervention on headache disability (Aim 2).



Aim 1: Conduct a feasibility and acceptability study of the RELAX approach in migraine and post-traumatic headache (PTH) patients who visit the NYU Department of Neurology General Practice and/or subspecialty groups or the NYU Concussion Center. We will recruit and randomize subjects (N=400) in the FGP Neurology Group including the MS Center and Headache Center and the NYU Concussion Center to receive the RELAX intervention or monitored usual care (MUC). Both groups will be asked to complete daily diaries, and data will also be collected on measures of recruitment, retention, adherence, and satisfaction with the PMR, the clinically important endpoint. With the PMR, we hypothesize that at least 70% of participants will be adherers (e.g., use RELAXaHEAD at least 4 days/week for 12 weeks). We will assess if the daily diary is acceptable by examining whether there is differential attrition with daily diary completion. We hypothesize no difference between the two groups for acceptability of the diary. We will define acceptability as an average score of ≥4 (0-5 Likert scale) on the 9-item acceptability questionnaire.[14] The outcomes for Aim 1 are the feasibility/acceptability outcomes; number of days of diary entered, number of days of pmr, time spent/day on pmr (Please refer to Table 2)

Aim 2: Conduct within group analyses of the RELAX approach vs MUC.

In the migraine patient population, the primary outcome will be migraine quality of life and migraine disability measured by Migraine Quality of Life (MSQ) and the MIDAS. In the migraine-MS population, a primary outcome will also be MS pain related disability as measured by the MOS Pain Effects Scale (PES). [15] Secondary outcomes include headache frequency and intensity, stress levels, sleep and psychiatric screens (NIH PROMIS depression and anxiety screens). We hypothesize that at 3 months compared with baseline there will be trends in the RELAX arm towards decreased disability (as measured by the Migraine Disability Assessment Scale (MIDAS)) and improvements in MS pain related quality of life in the MS-migraine patient population.

In the PTH patient population, we will examine the secondary outcomes noted above.

B a c k g r o u n d

Research indicates that behavioral therapies e.g., progressive muscle relaxation (PMR), cognitive behavioral therapy (CBT), and biofeedback are effective treatments for a wide range of conditions and are effectively free of adverse effects.[1] They have have enduring benefits [16] and may be less costly than pharmacologic interventions.[17] However, these behavioral treatments have not traditionally been implemented in outpatient neurology settings or medical settings such as primary care or obgyn where patients often present for care. Smartphone-based, electronically delivered behavioral interventions might be ideal interventions for testing in the neurology outpatient setting (and perhaps other outpatient settings where migraine patients present for care) because they are portable and do not require specialist intervention.

PMR has Grade A evidence for migraine prevention and has also been show to be effective in other headache disorders. [1] Research has already shown that prudent limited office treatment (PLOT), not just traditional clinic-based behavioral treatment programs, can reduce the frequency and intensity of migraine for up to 6 months. [18,19] Long-term, PLOT is more cost effective than traditional clinically based treatments and many preventive pharmacologic treatments.[20,21] In this proposal, we study the feasibility and acceptability of providing headache patients in the outpatient setting with electronically delivered PMR, a standardized, evidence-based behavioral treatment used for migraine since the 1980s.[22,23] We selected PMR as the behavioral intervention because of its success as a technique that patients can do independently.[3,4] For example, in the Stress Management in Living with Epilepsy (SMILE) study, [13] in a written communication with Dr. Sheryl Haut (December 2016), PMR was successfully delivered using a smartphone app. Preliminary daily diary adherence was around 85%. We have modelled our RELAXaHEAD app after the app used in the SMILE study. The RELAXaHEAD app has the same PMR as in the SMILE study but also includes a daily pain diary. Our RELAXaHEAD app has backend analytics built-in to record the amount of time spent playing the PMR. Pain intensity, duration, stress levels, mood, sleep, and medications taken can be recorded using the app. In addition, the RELAXaHEAD app allows the use of reminders and timely follow-up of non-compliant participants via real time investigator data monitoring capabilities. The RELAXaHEAD application was developed by IRODY and NYUMC MCIT previously approved its development. It is the previously unnamed app in the IRB study s16-00548.

Most migraineurs who present for care are between ages 18 and 50 years, and >80% of Americans in this age group have smartphones.[24] Migraine patients can successfully use smartphone applications. **Both patients and researchers prefer smartphone apps with electronic headache diaries**— a reliable method for data collection and more discreet than paper diaries,[25] with fewer secondary data errors,[26] less administrative burden,[27,28] high participant acceptance,[28] and potential cost savings.[29] Additionally, researchers prefer this format because it allows the use of reminders and timely follow-up of non- adherent participants via real time investigator data monitoring capabilities. Currently, Over 100 commercial headache applications are currently available, and many of these apps claim various purposes, including the ability to treat headaches with behavioral therapies. However, limited data exist on whether the smartphone applications with behavioral therapies for chronic pain conditions, like migraine, are feasible and acceptable. [12]

Study Design

From this point forward, patients are referred to as "subjects" if they agreed to enroll in the study.

Subjects will be recruited from the New York University Medical Center (NYUMC) FGP neurology practice*, urgent care practices and from the FGP primary care practices in addition to the private practice of Dr. Audrey Halpern (who is a private practice neurologist who is affiliated with NYU). Screening will be done as follows:

All methods will be done as below except for the following exceptions outlined below:
Main method: With help from the EPIC research data team, we will generate an appropriate report to identify potential subjects that may be contacted. These are people who are age 18-80 with a diagnosis of "headache" who were seen at NYU within the past 6 months. The report will flag those who have opted out of being contacting about research at NYU and the epic research team will delete such patients before sending us the report. Within the Department of Neurology, all locations will be notified by the department's leadership that recruitment of their patients may take place unless there is objection on the provider's part.

Exceptions:
Dr. Audrey Halpern's Office: Dr. Halpern does not use EPIC. She will approach her own patients to inquire about participation in the study.

Neurology Urgent Care Practice: At this time, there is no epic code listed as part of the Neurology Urgent Care visits so an epic report cannot be generated as in the cases above. However, the Neurology FGP maintains a list of the patients seen through the Neurology Urgent Care Practice. On a weekly basis, this list will be sent by a FGP administrator to the epic research team and the patients will be screened based on the study eligibility as described in the irb (diagnosis of "headache" and age 18-80). If these patients meet study eligibility and have not opted out of being contacted for research purposes, then they will be forwarded to Dr. Minen's research team. The Epic data lists will be generated weekly and potential subjects will be screened and contacted on a near daily basis. A record will be made in RedCap, a HIPAA compliant database, using de-identified info for all those who screen in and those who screen out. For those who screen in and decide to enroll in the study, an identified record will be created in RedCap.

We had recruited participants who had called the NYU Concussion Center. However, recruitment for this arm of the study is closed at this time. We had also recruited patients with Multiple Sclerosis and headache and recruitment has closed at this time.

Screening will be done by IRB approved members of the study team. This includes both paid staff and NYU nontraditional volunteers.

The NYU Headache Research Program has been recognized for its solid training of pre-health students in research methods. In fact, it received the first ever City College of New York S Jay Levy Fellowship for Future Leaders Distinguished Internship Site Host Award (2017-2018).

We carefully select from a group of specially selected group of CUNY students who are part of the highly coveted S Jay Levy Fellowship. These students are pre-selected by CUNY for their professionalism and top grades and then the students undergo a very selective interview process by Dr. Minen. We also take high achieving Barnard students who are pre-health who have high grades and many of whom are part of the Barnard Summer Research Institute. Dr. Minen has been a mentor as part of this program for several years, and the students in this program are supposed to learn research methods from start to finish, culminating in a poster presentation at a minimum. We have attached a copy of the training curriculum to this protocol based on the training that was done last year. In brief, the students take the online CITI training and pre-read selected articles prior to the on-site training. Then, there are four full days of one-site training led by Dr. Minen the first week

followed by an additional week of shadowing the already trained research team. Dr. Minen then observes each student the second week with a participant to ensure treatment fidelity.

All study team members will have undergone a one week training intensive to understand the screening process , recruitment process, informed consent process and enrollment process (as described throughout this IRB). In brief, research volunteers will be trained during an intense one week training on study procedures including an emphasis on how to screen, recruit, consent, and enroll the participants. This is a no risk/very low risk study unlike other interventional studies. It is similar to many of the hundreds of commercial apps available on the market that people use every day. Thus, it is appropriate for trained research volunteers to consent these participants just as they would be able to do so for survey type studies. They study team members will be carefully observed during the initial consent process to ensure that they are doing it correctly.
We have IRB approved scripts/messages that will be used for contacting potential participants. An additional one was created for the FGP urgent care participants. We also have IRB approved scripts for communicating with providers.

We will use either use a phone script to recruit potential subjects for the study or email script via NYU HIPAA compliant email, HeadacheResearch@nyumc.org or REDCap.

The total N will be 490. We had an initial approval for N=402. Going forward, we are hoping to recruit an additional 90 subjects from the FGP Urgent Care Center and from the Neurology Urgent Care Center.

The initial stats were calculated as follows:
Sample size: Phase 1: 432 subjects, Phase 2: 90 subjects

Phase 1: The NCCIH uses the Kramer reference for power calculation. As indicated by Kraemer and colleagues, our pilot sample size (402) is based on the pragmatics of recruitment and the requisites for examining feasibility. We anticipate an adherence rate of at least 70%. If the adherence rate is below 50%, we will consider the approach in need of further refinement. Thirty patients per arm will allow estimation of an exact 95% confidence interval whose lower bound exceeds 50%. Therefore, insufficient adherence would be ruled out, assuming the true adherence rate is 70% or greater. This approach obviates the need to handle missing data, because subjects who drop out will be assumed non-compliant.

Thus, we plan to try to enroll migraine patients from the general neurology group, the NYU Headache specialists within the main academic center (650 First Avenue/ACC), the NYU Headache Center in the Men's Health Center and from Dr. Halpern's office. We would also like to recruit at MS Society events and other neurology events.

Research assistants will evaluate which patients are eligible to participate based on the inclusion and exclusion criteria stated below.

Phase 2: We arrived at the 90 urgent care subjects based on our initial power analysis and then the NIH's request in the Just in Time to increase the N up to 85.

Our initial sample size was justified based on the feasibility outcome of compliance with PMR among patients in the RELAX group. We anticipated an initial compliance rate of at least 75%. The planned sample size also provided adequate power for the primary exploratory outcome (□MIDAS from baseline to 3 months) and the secondary outcome (number of headaches/30 days). Considering □MIDAS as the primary outcome can reduce data skewedness and improve study power. Based on the study, the standard deviation (SD) of □MIDAS ranges from 5 to 7. Using the conservative estimate of SD=7, group sample sizes of 30, with anticipated 25% dropout leading to approximately 23 patients per group, achieve 80% power to detect a clinically significant difference of 5.75 between the groups, assuming a significance level of 0.05 using a two-sided two-sample t-test.

Subsequently, based on later data, we found that only about half of the participants have full follow-through so the 90 (similar to the NIH request) is more adequate for this.

Gender of Subjects
Both genders will be included.

Age of Subjects
18-80 (18 – 65 in urgent care)

Racial and Ethnic Origin No enrollment restrictions.

Inclusion Criteria [Box 1] age 18–80;(18-65 in urgent care)

Meets migraine criteria based on International Classification of Headache Disorders (ICHD) 3 beta (based on questions in REDCap), Migraine Disability Assessment (MIDAS) score >5. 4+ headache days a month.

OR

Meets Chronic PTH criteria based on International Classificationof Headache Disorders (ICHD) 3 beta (based on questions in REDCap) and had 4+ headache days a month, is 3-12 months post initial injury.

OR

Meets Insomnia criteria based on the Insomnia Severity Index (score > or = 15)

Box 1: Inclusion Criteria: Age 18–80 years (age 18-65 in urgent care); Meets migraine criteria based on the International Classification of Headache Disorders (ICHD) criteria; Migraine Disability Assessment (MIDAS) score >5. 4+ headache days a month.OR Meets Chronic PTH criteria based on International Classification of Headache Disorders (ICHD) criteria, is 3-12 months post-injury, and there are 4+ headache days a month. Scoring > or = 15 on the ISI. Exclusion Criteria: Patients who have had Cognitive
Behavioral Therapy, Biofeedback, or other Relaxation Therapy in the past year; Cognitive deficit or other physical problem with the potential to interfere with behavioral therapy; Alcohol or other substance abuse as determined by self-report or prior documentation in the medical record; Opioid or barbiturate use 10+ days a month; Unable or unwilling to follow a treatment program that relies on written and audio file materials; Not having a smartphone.

Exclusion Criteria [Box 1]
Patients who have had Cognitive Behavioral Therapy,
Biofeedback or other Relaxation Therapy in the past year; Cognitive deficit or other physical problem with the potential to interfere with behavioral therapy; Alcohol or other substance abuse as determined by self-report or prior documentation in the medical record; Opioid or barbiturate use 10+ days a month; Unable or unwilling to follow a treatment program that relies on written and audio recorded materials; Not having a smartphone

Vulnerable Subjects
N/A

Methods & Procedures
[Please note that Phase 1 is now complete-we are now in Phase 2 of the study]
For phase 1 of the study, a single arm study was done to assess the feasibility and acceptability of the recruitment process and the app. The duration of this Phase was 6 months. The subjects were asked to use the application for at least 3 months. Compliance was checked during this time and compliance calls were done to remind the subject to use the application. In the latter 3 months we studied if the subjects continued to use the application on their own.

July 2020: We are reopening the Phase 1 single arm study to assess the feasibility of virtual subject enrollment prior to expansion to a larger study. Phase 1 will be conducted as above with a N=30 subjects. The steps will

be the same as before but instead of coming for an in-person appointment, subjects will enroll via virtual sessions. Like before, the data is stored and can be viewed by the PI and study team online. In this iteration, subjects may contact the physician/the physician may contact the subject to discuss app data if s/he wants to discuss headache management as part of clinical care. This is intended to take the place of paper diaries which were used during in-office visits.

Phase 2 of the study will be a two-arm randomized controlled trial (RCT) in the outpatient setting at NYULMC to assess feasibility and acceptability of the RELAX approach. The duration of Phase 2 is 3 months. We are beginning the urgent care RCT in May 2019. All patients will complete a migraine disability and migraine quality of life assessment and track their headache frequency and intensity using our RELAXaHEAD app. Data will be collected from the app and adherence will be reinforced with blinded telephone calls. Data collection on these outcomes are important to determine the user burden of data collection. The subjects will only use the application for an initial 60days based on the data we have to date (from Phase 1), and we will see if subjects continue to use the application during the third month.

The physician / NTV will provide the open-enrollment card to potential subjects when they approach them about the study.

Designated study team members will pre-screen patients in Epic as indicated elsewhere in the procedure using the Epic Research Report. They will obtain patient consent for the study. Once consented, patients will be randomized to RELAX or MUC. The study team member will then collect patients' health histories and baseline data in REDCap on an iPad, download the app onto patients' smartphones, and conduct the sessions (see below). Physicians listed as study staff on this protocol may also consent and enroll eligible patients if they note that one of the patients under his/her care is appropriate for the study. There is currently an Android version and an IOS version. In addition, we will use Data Core to locate potentially eligible patients with migraine within the NYU health system at NYU Langone and NYU Brooklyn sites from primary care and the various neurology divisions. These potential patients will be sent a message via MyChart.

The designated study team members will be trained to use the scripted protocol and treatment manual. The first four sessions of each member will be audio-recorded to assess treatment fidelity. Afterwards, one out of every ten will be audio-recorded to assess treatment fidelity.

<u>If the study subject is in the RELAXaHEAD (Intervention) Group</u>: The study team member will explain the rationale for PMR and load the RELAXaHEAD app onto the patients' smartphones.

Rationale (quoted from Smitherman T. and Penzien D. Headache: Advances in Psychotherapy 2014):

"As we discussed earlier, physical changes in our bodies associated with stress and arousal can produce headaches. Oftentimes, people say they are relaxed but their body still has a lot of tension that they do not recognize. It is important for you to learn how to 1) prevent your body from becoming tense;
2) recognize when your body becomes tense; and 3) truly relax your body and get rid of that tension.

Relaxation will help you learn to control physical arousal and thus help prevent headaches. Research has shown that learning relaxation leads to fewer and less intense headaches for most migraineand tension- type headache patients so long as they regularly use and practice their skills. This relaxation training program is going to teach you a specific set of procedures—not just 'trying to relax' on your own. You will learn to tense and then release various muscle groups throughout your body, step-by- step. By tensing your muscles first you can notice how different it feels to be truly relaxed. Over time you will be able to relax very quickly in almost any situation. Becoming skilled at relaxation will give you increased control over stress-related biological changes that cause headaches, and relaxation often produces many other positive changes."

PMR: The RA or RV will explain the rationale for PMR and download the application onto the subject's smartphones. The subject will perform PMR in the ED and discuss the optimal time and place to practice PMR at home.

Subjects will also enter their headache log daily on the app. The APP will track the amount of time playing the PMR. Subjects will be asked to do the following:

Intervention:
Week 1: 5 min deep breathing at least 5/7 days of the week
Week 2: 5 min PMR session at least 5/7 days of the week
Week 3: 15 min pmr preferred at least 5/7 days of the week
Week 4: pmr at least 4 days a week (optional body scan)
Week 5: pmr at least 3 days a week (optional body scan)
Weeks 6-8: use when it is most helpful (falling asleep, HA coming on, stress)

The study intervention will be 8 weeks in duration but the full study length will be 6 months. There will be a baseline assessment (T0), a f/u call or email at one week (T1), a 30 day phone call or email assessment (T2), a 60 day phone call/email (T3), and a 90 day phone call/email (T4) (to examine persistence of effect after a month). The last follow up will be at 6 months to examine persistence of effect 4 months after the intervention ends. As we learned previously, we are adding the option for email as some subjects prefer email.

The MUC session is where the subjects are explained that in migraine treatment, they may be given medications to take to stop a migraine and medications to prevent a migraine. The mainstay of migraine management is a headache diary where people can track their headache days, headache intensity, medications taken, and any other details they think might be pertinent to share with their medical provider. No written material is provided during this session.

MUC: To match the time spent with the designated study team member, subjects will be given a general education session consisting of basic migraine information, such as evidence-based ways to treat headaches: treat early, limit acute medications < 2–3 days/week, and call the primary care physician (PCP) if abortive medications are used more frequently. They will be shown a website: https://miachen26.wixsite.com/relaxahead (to be renamed). The study team member will load the app onto the subject's smartphone but the PMR component will be blocked on the version of the app that the MUC subject receives.

All subjects will be asked to track headache frequency, intensity, and acute medication use on app. All subjects will get the post enrollment card after they have been enrolled so that they have some instructions on what to do when they go home.

All subjects will receive written educational material about migraine.[30] All subjects will receive follow-up phone calls, texts, and/or SendSafe emails at 1 week of enrollment and 1, 2, 3, and 6 months after study enrollment. (The choice of calls, texts or emails came from prior subjects who participated in IRB approved study focus groups.) The study team has permission from MCIT to send the following text messages (and an emailing indicating such approval is part of the submission process):

1. Please remember to use the app.
2. Hi, The RELAXaHEAD team is trying to reach you. Please call xxx-yyy-zzz [study phone number]?
3. You are due for your follow-up call/email. Please be sure to call us at xx-yyy-zzzz or respond to the email. - The RELAXaHEAD team.

4. Remember-relaxation is beneficial for your health.
5. The best way to add relaxation into your routine is to pair it with an activity you do each day. Let us know if you want to discuss how to improve your adherence with the RELAXaHEAD app.
6. Research has suggested that the more one is able to practice relaxation, the better one's health. Log into the RELAXaHEAD app when able.
7. We will text participants once a week from our NYU MCIT study phone confirming that we have recorded that they have spent x amount of time practicing PMR within the application, and asking if they have practiced PMR independently without the application that week.

Follow-up will be assured by testing the subject's phone number in front of the subject and asking for alternative contact information. Subjects will also be called/emailed.texted after 3 days of no daily diary entry. If they are not reached, an email via HeadacheResearch@nyumc.org will also be sent as a reminder to input the data. During the calls, a designated study team member will reiterate the importance of adherence with the app. At 1,2 and 3 months, subjects will be asked to complete the MSQv2 and the MIDAS via phone or email to assess the treatment benefits. A designated study member will call the patient if they do not complete the assessment electronically. Throughout the study, subjects will be asked to record electronically any new and/or discontinued medications and interactions with the medical community. The study team also wants to collect additional patient information such as medications used before and after the research study (especially opioids), healthcare utilization, and comorbid diagnoses via i2b2, a member-driven non-profit foundation developing an open-source / open-data informatics community.

In addition, if any subject contacts us and want to withdraw from the study, we will ask them to complete the MSQv2 and MIDAS before they withdraw.Subjects who withdrew will be contacted via telephone or email at the end of the 6 months study period in order to verify their email address to be used to send the reimbursement gift card for their study participation. An IRB approved telephone voicemail and email script will be used. An attempt will be made to reach the subject via telephone and a voicemail will be left if unanswered. Following this, an email will be sent.

In addition, we will be conducting focus groups of patients who consented for the study to obtain additional feedback regarding the study procedures. Focus groups will range from 3-7 people with a goal of 5 participants per group. Participants will receive invitations to participate in the focus groups over telephone or over email. If they agree to do so, they will sign an informed consent form at the focus group meeting. Participants will be given a $50 dollars for participating in the group. The focus group duration will be one hour.

Symptoms Diary

On the smartphone application platform developed by IRODY [end user agreement was already signed as part of prior study-see attached] (used by the NYUMC epilepsy group for ongoing IRB approved studies and in another IRB approved headache study), subjects will be trained to keep records of headache occurrence, side effects, compliance and medicine changes on their mobile device. If a subject fails to consistently record their data, they will receive a call from the RV at NYU to ensure compliance with data maintenance. Information prompted by the device will include:

1. Headaches (number, intensity, duration, time)

2. Abortive and preventive migraine drug treatment

3. Concomitant medications

4. Episodes of non-compliance

5. Changes made to migraine medication treatment plan, if any, and reasons for the change

6. Adverse effects, including severity, seriousness, unexpectedness as part of pharmacovigilance

7. Mood and anxiety and stress levels, sleep quality and duration

8. Healthcare utilization

The symptoms diary may be accessed via the mobile application only.

The study team will not share the symptoms diary information with the subject's treating physician. However, subjects can elect to share their data with their treating physician independently.

The following questionnaires: PROMIS depression and anxiety screens, Insomnia Sleep Index (ISI) and the Perceived Stress Scale will be administered via REDCap.

In addition to the application, REDCap, a HIPAA Compliant research database system will be used. The study identifier and the PHI of the subjects will be stored in REDCap. In addition, we will use REDCap to send out the MIDAS to the subjects.

We will use the REDCap randomization feature to randomize our subjects.

Data Analysis and Data Monitoring Analysis Plan

Table 2 describes the outcome measures that will be used. We considered the feasibility outcome measures recommended by Kraemer and colleagues for pilot studies.[31] For this study, feasibility will be operationally defined as study recruitment, retention, and adherence measures for doing the PMR. Acceptability will be operationally defined as attrition, satisfaction, and willingness to participate in a similar intervention in the future. Satisfaction questions are as follows:

Responses will be 0–5 on the Likert Scale:

Daily Diary Satisfaction Questions

1. The app was easy to use
2. The information was easy to understand
3. The daily diary was relevant to me to help track my headaches
4. The app kept my interest and attention
5. I would be happy to use the app again

PMR *Satisfaction Questions*

1. The relaxation kept my interest and attention
2. The relaxation helped to improve my stress and low mood
3. The relaxation taught me skills that will help me handle future problems
4. I would be happy to do the relaxation again

Our primary outcome will be the change in the MSQv2 -a validated migraine quality of life measure (https://eprovide.mapi-trust.org/instruments/migraine-specific-quality-of-life-questionnaire). We will also usethe Migraine Disability Assessment Scale (MIDAS), measures disability over the past 3 months.[32-35] MIDAS scores have been shown to have excellent test-retest reliability, high internal consistency, and high external validity using a variety of measures—including diary-based measures.[32,34] MIDAS scores are also positively associated with physician judgements about the severity of headache and the need for treatment.[33] In the MS- migraine patient population, we will also assess the MOS Pain Effects Scale (PES).
Disability is a commonly used outcome in migraine trials evaluating outcomes of acute and preventative interventions,[36,37] because it is easy to understand and is meaningful to patients.

TABLE 2: OUTCOME MEASURES: DEFINITIONS AND SCALES
Aim 1: FEASIBILITY AND ACCEPTABILITY OUTCOMES
Feasibility: a) Proportion of patients who enrolled in the study/were recruited for the study, b) Percentage of patients who did PMR ≥4/7 days of the week, c) Number of days spent doing PMR ≥5 minutes/day as determined with the backend analytics in the RELAXaHEAD app, d) Minutes/day spent doing PMR, e) Reasons for non-adherence
Acceptability: a) Satisfaction using Likert scale questions on RELAXaHEAD usability, content, and functionality b) Willingness to repeat a similar treatment intervention in the future (Definitely No/Probably No/Unsure/Probably Yes/ Definitely Yes) c) Attrition
Aim 2: MIGRAINE QUALITY OF LIFE AND MIGRAINE DISABILITY OUTCOMES
Primary Outcome = Functionality: □□MIDAS: difference between scores of MIDAS [32,38] at 3 months and baseline. MOS Pain Effects Scale (PES).
Pain: 50% decrease in frequency and/or intensity of HAs (measured by electronic HA diary data).[39] Will control for adherence with PMR. (*Frequency*: # of HA days/30 days starting and ending at midnight; *Intensity*:0 (no HA), 1 (mild HA), 2 (moderate HA), 3 (severe HA) recommended by IHS.[39]
Acute medications used*: As recommended by IHS:# of days/week treated with medications, # of drug administrations/week for medications. Medications included: NSAIDs, acetaminophen, caffeine, aspirin, triptans, barbiturates, opioids, antipsychotics.
Psychiatric Comorbidity, Stress Levels, and Sleep: PROMIS depression and anxiety screens, the Perceived Stress Scale,[42-44] and Sleep Duration and Quality using Likert Scale questions (How would you rate the quality of your sleep/How rested or refreshed did you feel when you woke-up for the day).[45]
Adverse Events: *PMR*: Paradoxical anxiety, time burden/inconvenience, and any other adverse events experienced. Recorded in real time in the study diary.[39] As recommended by the IHS: Adverse events will be recorded as follows: Event Severity: Mild, Moderate, Severe; Event Seriousness: Serious, Non-Serious, Start and End Time.[39]

Quality Control: The designated study team member will download the data from the Diary Cloud Server. From this download, standard reports including missing days or entries as well as identification of any safety concerns will be created from the downloaded database and examined and reviewed by the PI (Dr. Minen) and the study team members.

Measurements: D a t a S t o r a g e a n d C o n f i d e n t i a l i t y

All patient health information will be entered into the REDCap database. Each subject will be assigned a unique alphanumeric identifier. The alphanumeric identifiers will be unrelated to the identity of the study subjects. Thus, we will use REDCap to store the confidential list linking subjects and their alphanumeric identifiers. Only the PI and study team members will have access to the linking database.

The consent forms (including the audio recording consent forms) will be kept in a separate locked file cabinet at 222 East 41st Street 14th floor . If someone were to gain illegal access to the locked filing cabinet with study data, they would have no way to link this data to any identifying information. There is no protected health information on the recordings as the study team members will be instructed to start the recordings after the patients have been identified.

The research team will perform all data analyses. The data collected and stored by IRODY is stored in a manner approved by the NYU MCIT. The data will then be transferred back to the PI and data will be stored electronically in a secure research database and will be available for the research team.

Research subjects will be assured that participation or non-participation in this investigation will not influence in any way the patient's treatment by his or her healthcare providers, and will not influence any future interactions he or she may have with NYU Langone.

The application produced by the company IRODY has been used by other researchers in the department of neurology at NYUMC. The symptoms diary on the mobile device used by subjects will be secured to comply with data privacy and other regulatory requirements. Data security is maintained by having a secure data protocol, which encrypts the information being sent from the mobile device to the cloud server and vice versa. The server is protected by a firewall. Daily backups will be performed. The app will not hold any personally identifying details and will be linked only to the Subject ID. The app does not collect any personal information from the mobile device. As stated above, the RVs and PI will have access to the symptoms diary data, as well as all subjects' names and phone numbers, in order to contact any participants who forget or are unable to enter their information in a timely manner. The RVs and PI will access the symptoms diary data only for the purpose of ensuring data completion and will not disclose any subjects' PHI.

Risk/Benefit Assessment

Risk

Risks from PMR: There is minimal harm in doing PMR therapy. PMR may cause some pain in previously injured sites. It may also cause some flooding of memories. If this occurs, subjects will be directed to turn their thoughts elsewhere. If this method is ineffective, subjects will be told that they can stop performing the relaxation.

Potential Breaches of Confidentiality: There is a small risk of breach of confidentiality. Protections against this are described.

Protection Against Risks

As stated above, subjects will be warned of the side effects.

Potential Benefits to the Subjects

Subjects may benefit by having decreased migraine disability and by having their migraine pain decrease in severity and/or frequency with the PMR.

Investigator's Qualifications & Experience

Please see attached.

Subject Identification, Recruitment and Consent/Assent

Method of Subject Identification and Recruitment

Virtual enrollment Phase 1:

Recruitment will be done via both direct and indirect contact.

Direct Contact: Neurologists may discuss the study with their patient/prospective subject (in person/via telemedicine or by telephone) and provide the study physicians contact information, to interested individuals. They may also obtain the patient's permission to be contacted by study staff. Any contact between study staff will take place with NYU HIPAA compliant email or telephone. Screening procedures have been identified earlier in the protocol.

Physicians will not be contacted if their patients choose to participate because a) they will all have been informed about the study before the study begins and b)it is a minimal risk study which should not interfere with the treatment plan.

Indirect Contact: Through the Epic research team, we will generate a list of people who were seen with headache or migraine in the past 6 months in the practices named above (Neurology, Primary Care and Urgent care) who are between ages 18-80 and who have not opted out of being conducted for research at NYU.18–80 years; Study team members will then pre-screen those to determine whether they might meet migraine criteria based on the International Classification of Headache Disorders (ICHD) criteria; Migraine Disability Assessment (MIDAS) score >5. 4+ headache days a month In addition, the following PHI will also be captured in the EPIC data pull: subject name, date of birth, MRN, telephone number, email address, medical records such as admission/discharge dates.

The following team members will have access to the EPIC search results: Principal investigator, biostatistician, research volunteers, research coordinators, and data analysts. The study team will search EPIC daily over the course of the study (12 months). As discussed above, the research team (pain and volunteers) will undergo rigorous training in study procedures.

For focus group: study team members will use the focus group recruitment announcement email or telephone script to find out if enrolled subjects would be willing to participate in a focus group on what they thought of the study.

As stated above, once contact is made, approved recruitment language will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study via telephone or email. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation. Any contact between study staff and potential participants will take place with NYU HIPAA compliant email, HeadacheResearch@nyumc.org or through REDCap. Any recruitment information sent by email will utilize Send Safe email.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact study coordinator or have subjects contact research-contact-optout@nyumc.org or 1-855-777-7858.

Initial Screening Questions for Chronic Post-traumatic headache:
When did you have your injury that led to concussion symptoms? Did you develop headaches

afterwards from the injury? If so, when did you first develop the headaches?
(Eligible would be 3-12 months post initial injury)

On a scale of 0-10, what is your average headache intensity? Maximum headache intensity?

Do you own a smartphone? Yes/no

Would you be interested in doing daily exercises to treat your headaches? Yes/no

If they meet criteria, when they come for the NYU Concussion Center appointment, they will be scheduled for a session with the RA to discuss the study, obtain informed consent in interested subjects, complete the REDCap survey, and download the app.

Process of Consent
Research volunteers or physicians who are study members will obtain consent. As indicated above, research volunteers will be trained during an intense one week training on study procedures including an emphasis on how to consent the participants. This is a no risk/very low risk study unlike other interventional studies. Thus, it is appropriate for trained research volunteers to consent these participants just as they would be able to do so for survey type studies. They will be carefully observed during the initial consent process to ensure that they

are doing it correctly. They will explain the rationale for the study (see above) and review the form with potential subjects. We will file an IRB addendum later on to add them to the protocol.

For focus group: subjects will sign an informed consent form in-person at the focus group meeting.

SubjectCapacity
Only subjects with capacity will be asked to participate in the study.

Subject/RepresentativeComprehension
Subjects will be asked to explain that they understand that they may or may not be offered this additional intervention and that the determination of whether they are offered it is random.

Subjects will be asked to explain that they understand that they will be asked to do a daily relaxation exercise and that they will be asked to record their headache characteristics, mood, anxiety and stress levels on the smartphone app as well as the number of hours that they slept/sleep quality.

DebriefingProcedures
N/A

Data Safety Monitoring Plan
The PI will be responsible for data safety monitoring. This is a minimal risk device. Minimal to no risk is expected for participants in the study. Only the PI, RVs and any future co-investigators will have access to the data. Co-Is would be added to the IRB at a later date. No personal/identifying information will be kept on an insecure site. No personal or identifiable information will be stored within the app. The PHI will be stored in REDCap. We will report all unanticipated events within a 24- to 48-hour time window or as soon as possible. There are no predetermined criteria for action.

ConsentForms
A consent form for each subject will be obtained. Please see attached.

DocumentationofConsent
The documentation will be kept in a locked storage unit in Dr. Minen's office on the 14th floor of the Department of Neurology, 222 East 41st street, New York, NY 10017.

PaymentforParticipation
There is payment for participation for all subjects. They will receive $25 for the initial survey and then $1/day for up to 60 days (the initial 60 day period) for data entered. If they complete 80% or more of the initial 60 day period, then the daily amount paid will be doubled. In addition, they will receive $15 for the one month and two month followup email or call and $25 for the 3 month and 6 month followup email or phone assessments. The maximum amount they can be paid is $225. The subject reimbursement amount is commensurate with other headache related smartphone application studies throughout the country.

July 2020: Phase 1 subjects: The subjects will receive $25 for the initial survey and then $1/day for up to 90 days if they complete at least 80% of the days data entry. In addition, they will receive $15 for the one month and two month followup email or call and $25 for the 3 month and 6 month followup email or phone assessments. The maximum amount they can be paid is $195. They will be paid at the end of 6 month study period.

Cost to Subjects:

Subjects can connect to wifi if they do not want to incur data usage costs.

Clinical trial registration will take place after IRB approval has been obtained.

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