Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

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The MOTS Trial
(Medication Overuse Treatment Strategy)

Study Protocol
Version 4
August 2020

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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Date: _____

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The MOTS Trial

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3. Supporting/ Collaborating Organizations

- American Headache and Migraine Association (AHMA)
- American Headache Society (AHS)
- National Headache Foundation (NHF)
- Migraine Research Foundation (MRF)
- American Migraine Foundation (AMF)
- American Academy of Neurology (AAN) Headache and Facial Pain Section
- Alliance for Headache Disorders Advocacy (AHDA)
- International Headache Society (IHS)
- One Mind for Research
- Mayo Clinic Health Solutions
- Migraine Again
- The Daily Migraine
- Migraine.com

4. **Funding**

This study is funded by a contract from the Patient Centered Outcomes Research Institute (PCORI); Application ID: PCS-1504-30133.

5. Study Background and Overview

Migraine has a one-year prevalence of 12% in the general population, including 18% of women and 6% of men. [Lipton 2007; Rasmussen 1995; Lipton 2001] The lifetime prevalence of migraine is 33% in women and 13% in men. [Launer 1999] One in four households in the United States has at least one member with migraine. [Lipton 2001] Thus, a large proportion of the general population is personally impacted by migraine at some point in their life, either due to having migraine themselves or supporting family members or friends who are suffering with migraine. The World Health Organization ranks migraine as the 3rd most prevalent medical disorder in the world. [Vos 2012] Migraine results in substantial suffering for individuals with migraine and their families. The World Health Organization considers migraine to be the 4th most disabling medical condition in women and the 8th most disabling medical condition overall. [Vos 2012] Migraine is associated with disabling pain, hypersensitivities to sensory stimuli, and reduced quality of life within several domains. [Lipton 2000; Lipton 2007; Terwindt 2000] Annual costs from migraine are estimated at $20 billion in the United States and €27 billion in Europe. [Stovner 2008; Stewart 2003]

Two percent of the United States population (approximately 7 million people) and 8% of the migraine population has chronic migraine, meaning that they have at least 15 days with headache per month including at least 8 days per month on which they have full-blown migraine attacks (Box - International Classification of Headache Disorders 3 beta diagnostic criteria for chronic migraine). [Natoli 2010; Buse 2012; ICHD 2013] Compared to patients with episodic migraine, patients with chronic migraine have more severe pain, more frequent pain, higher rates of comorbid disorders,

more migraine-related disability, lower income, and poorer quality of life. [Buse 2010; Bigal 2008; Buse 2012; Blumenfeld 2011] Compared to people with episodic migraine, people with chronic migraine also have greater healthcare utilization, including more frequent visits to their primary care physician, to specialists, to emergency departments, and are more frequently hospitalized and undergo more diagnostic tests. [Stokes 2011;Blumenfeld 2011] Annual total medical expenses are 4.4 times greater for patients with chronic migraine compared to patients with episodic migraine. [Munakata 2009] Each year, about 1 million people with episodic migraine transform to chronic migraine. Several factors associated with an increased risk for transforming to chronic migraine have been identified, including overuse of medications used to abort migraine attacks (i.e. "medication overuse"), female sex, obesity, presence of cutaneous allodynia, excessive caffeine intake, snoring, sleep disorders, major life changes, head or neck injury, lower socioeconomic status, and presence of comorbid pain disorders. [Schwedt 2014] [Bigal 2006] [Scher 2008a] [Louter 2013] [Scher 2008b]

The excessive use of medications intended to abort a migraine attack, "medication overuse", is a common, strong, and modifiable risk factor for transforming to chronic migraine. The one-year prevalence of medication overuse headache is approximately 2%-3% in the general population. [Westergaard 2014; Steiner 2014] Patients with chronic daily headache (i.e. at least 15 headache days/month) account for 70% of patients seen in headache specialty centers and the vast majority of these patients have chronic migraine. [Bigal 2004] Approximately 50% of patients seen in headache specialty medical centers have medication overuse and at least 50% of people with chronic migraine in the general population have medication overuse. [Natoli 2010; Davies 2012; Westergaard 2014] Overused medications include opioids, butalbital-containing medications (e.g. aspirin-butalbital-caffeine; acetaminophen-butalbital-caffeine), triptans, ergots, caffeine-containing medications (e.g. aspirin-acetaminophen-caffeine) and non-steroidal anti-inflammatory medications. The risk of transforming from episodic to chronic migraine is mediated by the specific medication that is being overused and the frequency with which that medication is used. Opioids and butalbital-containing medications are thought to be associated with the highest risk for transformation (odds ratios 1.4 and 1.7, respectively). [Bigal 2008] People who have chronic migraine and medication overuse have even poorer quality of life, greater disability, and greater losses in productivity compared to people who have chronic migraine without medication overuse. [Lanteri-Minet 2011; Steiner 2014] One-half of people who have chronic migraine with medication overuse have greater than 20 lost days from work, household work, and social activities each 3 months. [Steiner 2014] Amongst people who have chronic migraine with medication overuse, the mean number of days per 90 lost to headache is 14.2 workdays, 21.4 housework days, and 9 days of social activity. [Steiner 2014] Compared to people who have chronic headaches without medication overuse, people who have medication overuse have lower educational attainment, lower incomes, and are less likely to maintain full employment. [Westergaard 2014] The definition for medication overuse according the International Classification of Headache Disorders 3 beta is found in the Box.

The main treatment goals for patients who have chronic migraine with medication overuse are to reduce the frequency and severity of migraine attacks and to reduce the burden that the condition places on the daily lives of its sufferers. However, despite the high prevalence of medication overuse in the migraine population and the undeniable importance of treating medication overuse, the best treatment strategy for patients who have chronic migraine with medication overuse is

uncertain and is passionately debated in academic and clinical communities. Since medication overuse is a common condition that is associated with more frequent headaches, more severe pain, greater comorbidity, and toxicities related to taking too much of the overused medication, there is great need for determining the best treatment approach. While there is general agreement that patients who have chronic migraine with medication overuse should substantially reduce and limit the consumption of the overused medication to avoid systemic, renal, gastrointestinal and cardiovascular toxicities, accomplishing this objective in patients with frequent severe headache presents a major challenge for the patient and for the clinician. There is also agreement that a non-pharmacologic approach that includes adjustments in lifestyle factors are indicated for the treatment of chronic migraine with medication overuse. However, there is disagreement and clinical equipoise regarding the timing for discontinuing the overused medication in relation to using migraine prophylactic medications. [Hagen 2009] [Smith 2014] [Tassorelli 2014] [Zeeberg 2006] There are arguments for two commonly used treatment strategies: 1) early discontinuation of the overused medication plus migraine prophylactic therapy; and 2) migraine prophylactic therapy without early discontinuation of the overused medication. The argument for early discontinuation of the overused medication with initiation/optimization of migraine prophylactic therapy (e.g. beta-blockers, antidepressants, anticonvulsants) is based upon the following points: 1) migraine prophylactic medication is necessary to reduce migraine frequency and severity in patients who have very frequent headaches; 2) migraine prophylactic medications are ineffective when medication overuse persists; 3) medication overuse is partially a behavioral condition that has a component of medication dependence and thus patients will not necessarily reduce their usage of headache abortive medications on their own, even if the long-term outcome would be a reduction in headache frequency with concomitant prophylactic medications; 4) the reductions in headache frequency, severity, and duration that result from migraine prophylactic therapy will minimize the suffering associated with early discontinuation of the overused medication strategy, in which patients are unable to treat all of their withdrawal headaches and/or acute migraine attacks. However, other experts argue that early discontinuation of the overused medication is not necessary as long as migraine prophylactic therapy is initiated or optimized. Reasons for this argument include: 1) early discontinuation of the overused medication results in a period of more severe headaches and greater migraine-related functional impairment and this period of suffering is unnecessary if the prophylactic therapy is effective despite continued use of the overused medication; 2) prophylactic therapy works even in the presence of medication overuse and patients will naturally reduce their use of migraine abortive medications once their headache frequency declines; 3) medication overuse is the consequence of having high frequency headaches and not the cause of the increased headache frequency. If early discontinuation of the overused medication is not a necessary treatment component for patients who have chronic migraine with medication overuse, then patients could continue their abortive medications while optimizing migraine prophylactic therapy. This strategy would likely enhance rates of adherence to the treatment plan, optimize treatment outcomes, and avoid the period of unnecessary pain and suffering from inadequately treated headaches. To date, there are inadequate data and opposing expert opinions on this critical and pragmatic treatment issue that arises very frequently in clinical practice.

This study takes on even more importance given the widespread current undertreatment of chronic migraine, with or without medication overuse, in the population. In a recent epidemiologic web-based study of persons with migraine, only 40.8% reported currently consulting with a

healthcare professional. [Dodick 2014] Among those consulting a healthcare professional, 24.6% received an accurate diagnosis of CM and only 44.4% of this group received both acute and prophylactic pharmacologic treatments. Thus, among the sample of chronic migraine sufferers, only 4.5% (n=1254) successfully traversed all 3 barriers to migraine care (i.e., consulted a healthcare professional for migraine, received an accurate diagnosis, and were prescribed acute and prophylactic pharmacologic treatments). This study demonstrated that there is a large unmet need for improved treatment of patients with chronic migraine.

During the development of this research, patient stakeholders were engaged from the inception. The research question was confirmed to be of exceptional interest to the patient community and patient experts have actively participated in grant development and study design. We also administered a survey to 92 clinician members of the American Headache Society and results further demonstrate the importance of the clinical question at hand and the clinical equipoise that currently exists. Results showed: 1) 96% felt that migraine exerts a substantial burden on their patients; 2) 98% felt that medication overuse is an important issue for many people with migraine; 3) 93% answered that treating chronic migraine with medication overuse is often difficult; 4) 88% believed that there are different strategies for treating patients who have chronic migraine with medication overuse and that the most effective strategy is not known; and 5) 97% thought that a well-designed clinical trial that compares different treatment strategies for patients who have chronic migraine with medication overuse is needed. Determining the best treatment strategy for patients who have chronic migraine with medication overuse will directly impact the clinical approach to such patients and optimize patient outcomes.

6. Study Objective

The objective of this study is to compare two real-world methods of treating patients who have chronic migraine with medication overuse:

- migraine prophylactic therapy with immediate discontinuation of the overused medication
- migraine prophylactic therapy without immediate discontinuation of the overused medication.

7. Study Design

This is a prospective, parallel group, simple randomized trial during which patients will be randomized 1:1 to one of two treatment strategies:

- migraine prophylactic therapy with immediate discontinuation of the overused medication
- migraine prophylactic therapy without early discontinuation of the overused medication.

8. Subject Eligibility

Inclusion Criteria

- Adults, at least 21 years of age
- Chronic Migraine – diagnosed according to ICHD3beta criteria
- Medication Overuse – diagnosed according to ICHD3beta criteria
- Willingness to be randomized to either of the two treatment arms
- Willingness to maintain a headache diary
- Plan for follow-up care with the clinician
- No changes to migraine prophylactic therapy within the 4 weeks prior to randomization

Exclusion Criteria

- Younger than 21 years of age
- Headache diagnoses other than chronic migraine with medication overuse; episodic tension-type headache on 3 or fewer days per month is allowed
- Not willing to be randomized to either of the treatment arms
- Not willing to maintain a daily headache diary
- Not planning on follow-up care with the clinician
- In the opinion of the clinician, randomization to either treatment arm would be considered unsafe (Ex pregnancy, immediate discontinuation).
- Prisoners
- Diminished decision-making capacity which in the investigator's opinion would interfere with the person's ability to provide informed consent and complete study procedures.

ICHD3beta Diagnostic Criteria for Chronic Migraine

Chronic Migraine Diagnostic Criteria

A. Headache (tension-type-like and/or migraine-like) on ≥15 days/ month for >3 months and fulfilling criteria B and C
B. Occurring in a patient who has had ≥5 attacks of migraine with or without aura
C. On ≥8 days/month for >3 months, fulfilling any of the following:
   a) migraine without aura diagnostic criteria
   b) migraine with aura diagnostic criteria
   c) believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another headache diagnosis

ICHD3beta Diagnostic Criteria for Medication Overuse

Medication Overuse Diagnostic Criteria

A. Regular intake of ergotamine, triptans, opioids, combination analgesics, or a combination of drugs from different classes on ≥10 days per month for >3 months

or

B. Regular intake of simple analgesics (e.g. acetaminophen, NSAIDs) on ≥15 days per month for >3 months

9. Study Procedures

Consecutive patients presenting to the investigator's clinic, whether in-person or via telehealth methods, who meet inclusion/exclusion criteria should be offered enrollment. As a pragmatic study, potential participants will not be excluded based upon measures of clinical severity or based upon preconceived notions of their likelihood to respond to the study interventions. Chronic migraine patients with medication overuse will be identified just as they are in daily clinical practice – according to the patient's report of headache frequency, headache symptoms, acute medications used and their frequency of use. Patients with excessive use of opioids and butalbital containing medications such that immediate discontinuation, in the opinion of the investigator, will pose an unacceptable risk of withdrawal syndrome and a serious risk to patient safety will be excluded (this is expected to be a very small proportion of patients who have chronic migraine with medication overuse). We anticipate that about 90% of patients who are screened for this study will be eligible and 40% of eligible patients will agree to participate in this study. Thus, in order to meet enrollment targets we estimate that headache specialty centers will have to screen approximately 5-6 patients per month, while general neurology and primary care clinics will have to screen about 2 patients per month. In total, each headache specialty clinic is expected to enroll 24 patients per year, while general neurology and primary care clinics are expected to enroll 8 patients per year.

Recruitment Plan

	# patients screened each month	# patients enrolled each year
Headache Specialty Clinic	6	24
General Neurology Clinic	2	8
Primary Care Clinic	2	8

Study Visits

Each subject **must** have a research visit at baseline/randomization and at 12 weeks post-randomization. These research visits can occur in-person or using IRB-approved telehealth methods, such as, but not limited to telephone, video, e-mail, and regular mail. Other follow-up visits will occur according to the clinician's usual follow-up patterns (these are clinical visits, not study specified visits).

Baseline/Randomization Visit

a. Case Report Forms: The following case report forms and questionnaires are to be completed at the baseline visit:

- Inclusion/Exclusion Criteria
- Subject Contact Information
- Subject Demographics
- Headache Characteristics

- Medication Use
- Headache Impact Test 6 (HIT-6)
- PROMIS Pain Interference questionnaire
- Generalized Anxiety Disorder 7 (GAD-7)
- Patient Health Questionnaire 9 (PHQ-9)
- EuroQol 5D (EQ-5D-3L)
- Change in Migraine Therapy
- Migraine Functional Impact Questionnaire (MFIQ)

b. Randomization: Participants are to be randomized within the Medidata Rave online system. (see Appendix for instructions on how to use Medidata Rave) Randomization will be 1:1 to one of the two treatment strategies using a simple randomization technique. Randomization is to occur at the time when migraine prophylactic therapy is to be initiated or optimized. For example, if a patient is to receive a new prophylactic migraine medication, randomization would occur on the same day that the prescription is provided and the patient will start the medication. If it is known that there will be a delay between providing the patient with a preventive prescription and that patient receiving/starting the preventive medication, then randomization should occur at the time the patient will start the preventive. If a patient is going to be started on onabotulinumtoxinA, randomization is to occur on the day of the injections.

c. Migraine Prophylactic Therapy: Prophylactic therapy will be initiated or optimized for all participants. Participants who are not taking a migraine prophylactic medication at the time of study enrollment will be initiated on prophylactic medication. Participants who are already taking a migraine prophylactic medication will either have their dose optimized (if the dose was suboptimal at baseline), will be switched to a different prophylactic medication, or will be started on an additional prophylactic medication. Clinicians will be provided with guidance regarding their recommendations for migraine prophylactic therapy. Prophylactic medications have been divided into three tiers based upon the American Headache Society, American Academy of Neurology, and Canadian Headache Guidelines, safety profiles, and side effect profiles. (Silberstein 2012; Pringsheim 2012) The total number of medications in each tier has been reduced by not including more than one medication with the same presumed mechanism of action within each tier (e.g. not listing more than one beta-blocker within a tier). Clinicians will be instructed to first consider tier I medications, followed by tier II medications, followed by tier III medications. As is the case in typical clinical practice, clinicians will choose amongst the available medications within a tier based upon whether or not the patient has already tried and failed the medication, contraindications to taking the medication, drug-to-drug interactions, patient co-morbidities, likelihood of tolerating potential side effects, and cost. Target therapeutic doses and recommended titration schedules, assuming that the therapy is new for the patient, are provided. If a patient is already taking a prophylactic medication, the clinician may determine that a dosage increase for that medication is the preferred treatment recommendation. Patients can be included in the MOTS trial even when the clinician decides to use a preventive therapy that is not included in the "tiered" list below.

Tier 1:

- amitriptyline; target dose 30-150 mg; 10 mg qhs x 1 week, then increase by 10 mg each week

- propranolol; target dose 80-240mg; 80 mg daily x 1 week, then 120 mg daily; if using short acting form then dose twice daily (e.g. 40 mg bid; 60 mg bid); use long acting form once daily
- topiramate; target dose 50-200 mg; 15-25 mg qhs x 1 week, then increase by 15-25 mg each week
- onabotulinumtoxinA; 150-200 units
- any medication that receives FDA approval for the prevention of migraine (the approval must include the treatment of individuals with chronic migraine) during the conduction of the MOTS trial (e.g. CGRP monoclonal antibodies)

Tier 2:

- venlafaxine; target dose 75-225 mg; 37.5 mg qd x 1 week, then increase by 37.5 mg each week. Use short acting form twice daily; use long-acting form once daily
- valproic acid and derivatives; target dose 500-2000 mg; 250 mg bid x 1 week, then 500 mg bid. Use both short-acting and long-acting forms twice daily. Maximum dosage is 60mg/kg/day
- candesartan; target dose 16-32 mg; 4 mg bid x 1 week, then 8 mg bid. Increase by 4-8mg per week
- gabapentin; target dose 600-3600 mg; 200mg tid x 1 week; 300 mg tid x week 2, increase by 300-900 per day weekly.

Tier 3:

- lisinopril; target dose 10-40 mg; 10 mg qd x 1 week, increase by 10mg per week
- verapamil; target dose 120-480 mg; 40 mg tid x 1 week, then 80 mg tid; then 120mg tid week 3; then 160mg tid. If using regular form, continue tid dosing; if sustained release form, then use once daily
- nortriptyline; target dose 30-150 mg; 10 mg qhs x 1 week, then increase each week by 10 mg

Adjunctive non-pharmacologic interventions will be documented and limited during the first 12 weeks to those with levels of evidence sufficient to be recommended in prophylactic treatment guidelines. These include cognitive-behavioral therapy and biofeedback-assisted relaxation therapy. While two devices have recently been approved by the Food and Drug Administration for the acute treatment of migraine with aura (single pulse transcranial magnetic stimulation) or prevention of episodic migraine (supraorbital transcutaneous nerve stimulation [Cefaly®]), neither has been evaluated for the treatment of chronic migraine or medication overuse and they cannot be initiated during the randomization phase (12 weeks) of this study. Initiation of physical therapy, nerve blocks, acupuncture, chiropractic, and other non-pharmacological techniques sometimes employed by patients and/or clinicians in practice, have not been evaluated in this patient population and will not be permitted during the first 12 weeks of this study.

d. Discontinuation of Overused Medication: For participants who are randomized to the group in which early discontinuation of the overused medication is indicated, discontinuation of the overused medication will be performed in the outpatient setting, will not involve the use of

"bridging therapy", and will be immediate. Several studies have shown that outpatient discontinuation is effective and is similarly effective when compared to inpatient strategies for discontinuation. [Creac'h 2011] [Munksgaard 2012] [Rossi 2006] Since several studies have demonstrated a lack of benefit from prescribing transitional or "bridging" therapy, such as steroid tapers or occipital nerve blocks, during the discontinuation period, this protocol will not call for patients to be prescribed transitional therapy. [Dilli 2014] [Halker 2013] [Rabe 2013] [Boe 2007] If a patient requires inpatient detoxification (according to the opinion of the treating clinician) due to excessive use of opioids or butalbital-containing analgesics or if immediate discontinuation of the overused medication is not possible due to safety concerns, that potential participant will be excluded from this study. Otherwise, there will not be eligibility restrictions based on the medications that patients overuse.

Discontinuing the Overused Abortive Medication(s) (RQ-2) (RQ-5)

- Discontinuation is to be achieved in the outpatient setting
- No "bridging therapy" is to be prescribed (e.g. corticosteroids, extracranial nerve injections, daily NSAID use, ambulatory infusion therapy)
- The overused abortive medication(s) is/are to be immediately stopped and restricted use ($\leq$ 2 days per week) of an alternative abortive medication will be recommended

e. Symptomatic Therapy for Patients Randomized to Discontinuation of the Overused Medication: Clinicians will also be provided with instructions regarding the methods of prescribing alternative abortive medications to patients randomized to prophylactic therapy plus discontinuation of medication overuse. The specific medications from which the clinician can choose are detailed below and are based upon the American Headache Society, American Academy of Neurology, and Canadian Headache Society guidelines for abortive therapy of migraine. (Marmura 2015; Silberstein 2000; Worthington 2013) Although these patients will not continue to overuse abortive medications, they will be allowed to treat their most severe migraines within the limits imposed by this study protocol. We have chosen not to recommend complete cessation of all abortive therapies since that strategy would not be patient-centered, would likely result in many patients seeking emergency therapy (e.g. emergency department visits), and would increase the rates of patient non-adherence and study dropout.

- Avoid use of medications from the same class as the overused medication
- Up to 2 days per week:
    - Metoclopramide 10-20 mg or
    - Prochlorperazine 10 mg or 25 mg suppository
    - Odansetron 4mg-8mg (For patients with a history of extrapyramidal side effects or sensitivity to dopamine antagonists, or a personal or family history of a bradykinetic or hyperkinetic movement disorder)
- Up to 2 days per week
    - Triptans
        - almotriptan 12.5 mg
        - eletriptan 40 mg
        - frovatriptan 2.5 mg
        - naratriptan 2.5 mg

        - rizatriptan 5-10 mg
        - sumatriptan
            - oral 50-100 mg
            - nasal spray 10-20 mg
            - patch 6.5 mg
            - subcutaneous 4-6 mg
        - zolmitriptan
            - oral 2.5-5 mg
            - nasal spray 5 mg

      OR

    - Dihydroergotamine
        - nasal spray 2 mg
        - intravenous, intramuscular, or subcutaneous 1 mg

      OR

    - Ketorolac intramuscular 30 mg

      OR

    - Diphenhydramine intramuscular 25-50 mg

      OR

    - Non-steroidal anti-inflammatory drugs
        - aspirin 500 mg
        - diclofenac 50-100 mg
        - ibuprofen 400-600 mg
        - naproxen 400-550 mg

      OR

    - Combination analgesics
        - acetaminophen/aspirin/caffeine 500/500/130 mg
        - sumatriptan/naproxen 85/500 mg

      OR

    - Ergotamine tartrate 2 mg

      OR

    - Gepants
        - rimegepant 75 mg
        - ubrogepant 50-100 mg

      OR

    - Lasmiditan 50-200 mg

f. Symptomatic Therapy for Patients Randomized to Prophylactic Therapy Without Discontinuation:

- New abortive medications are not to be recommended
- Clinicians will be instructed to discuss the following with the patient: 1) prophylactic medication is being initiated or current prophylactic medication(s) is/are being adjusted; and 2) as a result, it is expected that migraine frequency will reduce and thus abortive medications will be required less frequently.

g. Headache Diary: Patients will maintain a daily headache diary during the following post-randomization weeks:

- 1-12 (days 1-84)
- 21-24 (days 141-168)
- 45-48 (days 309-336)

At the baseline visit, patients will need to receive instructions on the use of the electronic/internet based headache diary that is within the Medidata Rave system. Patients may choose to use either the online or app version of the diary (or a combination of both). Sign-in information needs to be obtained. A paper headache diary is also to be given to patients along with instructions for use.

This migraine and medication diary will require participants to record whether or not they had a headache on a given day, the maximum severity of headache pain during that day, whether the headache caused no, mild, moderate or severe functional impairment, whether or not they took migraine abortive medications that day (and which medication), whether or not they took migraine prophylactic medication that day, and any changes to their treatment regimen.

Twelve Week Follow-Up Visit

All subjects are to be seen for follow-up at 12 weeks post-randomization (+/- 1 week). This 12-week visit can be accomplished in-person (i.e. in the office) or using IRB-approved telehealth methods, such as, but not limited to telephone, video, e-mail, regular mail, and by completing internet-based questionnaires.

Subjects are to remain in the treatment group to which they were randomized through this 12-week visit. Subjects will remain in this study through week 48, but treatment recommendations starting with week 13 will be according to the clinician's usual clinical practice.

h. Case Report Forms: The following case report forms and questionnaires are to be completed at the 12-week visit:

- Follow-up Visit Headache Characteristics
- Medication Use
- Headache Impact Test 6 (HIT-6)
- PROMIS Pain Interference questionnaire
- Generalized Anxiety Disorder 7 (GAD-7)
- Patient Health Questionnaire 9 (PHQ-9)
- EuroQol 5D (EQ-5D-3L)
- Change in Migraine Therapy
- Migraine Functional Impact Questionnaire (MFIQ)

Other Follow-Up Visits and Telephone Contacts

The timing of these follow-up visits is left to the discretion of the clinician. However, consistent with good clinical care of patients who have chronic migraine with medication overuse, follow-up visits

are expected to occur approximately each 2-3 months. These visits can be accomplished in-person (i.e. in the office) or using IRB-approved telehealth methods, such as, but not limited to telephone, video, e-mail, regular mail, and by completing internet-based questionnaires.

i. Case Report Forms: At each follow-up visit, the following case report forms are to be completed:

- Follow-up Visit Headache Characteristics
- Medication Use
- Headache Impact Test 6 (HIT-6)
- PROMIS Pain Interference questionnaire
- Generalized Anxiety Disorder 7 (GAD-7)
- Patient Health Questionnaire 9 (PHQ-9)
- EuroQol 5D (EQ-5D-3L)
- Change in Migraine Therapy
- Migraine Functional Impact Questionnaire (MFIQ)

j. Headache Diary Adherence Monitoring:
Monitoring patient adherence to diary keeping and sending reminders to each participant will be necessary for improving adherence to daily diary keeping. The research team should monitor each patient's completion of the headache diary on a weekly basis. If non-adherence is noted, the study team should contact the patient via telephone, e-mail, text messages, and/or regular mail. In these communications, participants should be reminded to keep their daily headache diary and provided with further instructions if the participant is having any difficulty with the diary. No clinical recommendations should be made during these research communications. In addition, telephone calls, e-mails, text messages, or regular mail will be necessary at the beginning of the 21-24 week period and 45-48 week period to remind the patient to once again start maintaining the headache diary.

- 1-4 weeks post randomization
    - Day 1 after the baseline visit
    - Day 7-9 after the baseline visit
    - Day 14-16 after the baseline visit
    - Day 21-23 after the baseline visit

- 5-8 weeks post randomization
    - Day 28-30 after the baseline visit
    - Day 35-37 after the baseline visit
    - Day 42-44 after the baseline visit
    - Day 49-51 after the baseline visit

- 9-12 weeks post randomization
    - Day 56-58 after the baseline visit
    - Day 62-64 after the baseline visit

  - Day 69-71 after the baseline visit
  - Day 76-78 after the baseline visit

- 21-24 weeks post randomization
  - Day 139-141 after the baseline visit
  - Day 146-148 after the baseline visit
  - Day 153-155 after the baseline visit
  - Day 160-162 after the baseline visit

- 45-48 weeks post randomization:
  - Day 307-309 after the baseline visit
  - Day 314-326 after the baseline visit
  - Day 321-333 after the baseline visit
  - Day 328-340 after the baseline visit

k. Changes in Therapy: Changes in the subject's migraine treatment that might occur outside of the follow-up visits (e.g. via a telephone call with the patient) should be documented in the "Medications and Treatments" case report form within Medidata Rave. **10. Study Outcomes**

a. Primary Outcome: The primary outcome measure for this study will be frequency of moderate to severe headache days (i.e. days on which a headache lasts for at least 2 hours and at any time peaks at moderate or severe intensity) per 4 weeks measured during 9-12 weeks post-randomization. If non-inferiority is demonstrated for the primary outcome, then a test of superiority will be performed for the frequency of moderate to severe headache days during the first 2 weeks post-randomization.

b. Secondary Outcomes frequency of headaches associated with moderate to severe functional impairment, frequency of days taking abortive medications, headache frequency, treatment adherence rates, and rates of subject dropout. (RQ-2) (RQ-6) (PC-3) In addition, relapse rates (i.e. the proportion of subjects who stopped overusing the abortive medication but then returned to the overuse pattern) will be measured using the 21-24 week and 45-48 week data.
- Frequency of headaches associated with moderate to severe functional impairment
- Frequency of days taking symptomatic medications
- Headache Frequency
- Treatment Adherence Rates
- Subject Study Dropout Rates
- Relapse Rates (i.e. the proportion of subjects who stopped overusing the abortive medication but then returned to the overuse pattern)
- Quality of Life
- Disability

c. Heterogeneity of Treatment Effects Analyses
- Class of overused medication
- Baseline frequency of taking the overused medication
- Duration of medication overuse

- Years with migraine
- Years with chronic migraine
- Type of provider managing the patient (i.e. headache specialist, general neurologist, primary care physician)
- Frequency of follow-up visits
- Class of prophylactic therapy(s) used
- Baseline headache frequency
- Baseline anxiety and depression scores
- Patient age
- Patient sex
- Type of visit (in person vs. virtual)
- Calendar period (before or after initiation of virtual visits)

11. Sample Size and Data Analyses Plans

a. Sample Size

The sample size was calculated based upon showing non-inferiority of prophylactic therapy alone compared to prophylactic therapy with early discontinuation of overused medication. An effective sample of 288 per group (80% of 360) has 80% power (two-sided α .05) to determine that the mean difference is less than 1.5 moderate to severe headache days per four weeks, assuming a population difference of 0.0 moderate to severe headache days per four weeks (pooled SD 6.4 from Silberstein 2013).

b. Data Analyses Plans

Patients will be included in the primary analysis on the basis of intention-to-treat. The frequency of moderate to severe headache days during the 9-12 week post-randomization period will be compared among the two treatment groups by using a two-sample t test. The primary test will be a test of noninferiority. The noninferiority margin will be defined as a mean difference of 1.5 moderate to severe headache day per four weeks. A second primary measure will be assessed by using a fixed sequence gatekeeper strategy. If noninferiority is demonstrated for the frequency of moderate to severe headache days during the 9-12 week period, then a test of superiority will be performed for the frequency of moderate to severe headache days during the first 2 weeks post-randomization. Missing values will be handled by multiple imputation. Pattern mixture modeling will be used if the pattern of missing data differs between groups. In addition, baseline characteristics for subjects with missing primary outcome data will be compared to those without missing data. An interim analysis will be performed using data from 12 weeks after the 360th subject has been randomized. Interim analyses will be performed by using the alpha spending function method with a Haybittle-Peto boundary function. Results will be considered statistically significant if the nominal significance level is less than 0.001 at the interim analyses, or less than 0.049 at the final analysis. Per-protocol analyses will be performed in addition to the intention-to-treat analyses because the primary hypothesis is based on noninferiority. The intention-to-treat and per-protocol analyses would both have to demonstrate non-inferiority to consider the trial positive.

A confirmatory heterogeneity of treatment effect analysis for type of overused medication will be performed if the primary analysis demonstrates noninferiority. (HT-3) Patients will be classified into whether or not the overused medication was an opioid or barbiturate vs. another abortive medication. The frequency of moderate to severe headache days during the 9-12 week period will be compared among the two treatment groups by using a general linear model with terms for group, overused medication category (opioid or barbiturate versus other), and group by category interaction. Descriptive heterogeneity of treatment effect analyses will be performed for duration of overuse, baseline headache frequency, number of years with migraine, number of years with chronic migraine, the type of provider managing the patient (e.g. headache specialist vs. neurologist vs. primary care provider), patient sex, patient age, baseline anxiety and depression scores, the class of prophylactic therapy used, the frequency of follow-up visits with the clinician, type of visit, and calendar period. Analyses concerning prophylactic medications will focus on the therapy that was the change in treatment at the baseline visit. For example, if a participant is

taking medication A at baseline and the clinician adds medication B, it is medication B that would be considered the treatment of interest.

12. Potential Risks and Protection of Human Subjects

The study will be conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki, U.S. 21 Code of Federal Regulations for Protection of Human Subjects, and Institutional Review Boards, and pursuant to state and federal HIPAA regulations. Institutional Review Boards for each participating center must provide unconditional approval prior to that centers participation in this study. Documents proving IRB-approvals will be submitted to the Principal Investigators prior to each center's participation. All protocol amendments will require IRB approvals and documents confirming approval of such amendments will be submitted to the Principal Investigators. Each participating center's IRB and the IRB at the principal investigators' center (Mayo Clinic) will be informed of all serious or unexpected adverse events that occur during the study. Adverse events will also be reported to PCORI, if such reporting of adverse events is consistent with PCORI policy.

Written informed consent will be obtained from all potential subjects prior to their participation in this research. The informed consent process will be based upon principles discussed in the Declaration of Helsinki and in accordance with US 21CFR. Applicable HIPAA privacy notifications will be included. Participants will be given ample time and opportunities to ask questions about this study prior and following consent. All consent forms will require IRB approval prior to their use.

Patients will always have the right and will be informed of their right to withdraw from the study at any time. Enrolling clinicians will be made aware that the needs of their patients come first and thus the safety and wellbeing of study participants is of primary concern.

A Data and Safety Monitoring Board (DSMB) will review safety data on a quarterly basis through the first year of enrollment and then twice per year. A detailed data and safety monitoring plan will be submitted and approved by the Mayo IRB and by the funding entity (PCORI) prior to accrual of human subjects. Based upon the results of this review, the DSMB will make recommendations regarding study methods and continuation of the research.

The benefits of this proposed research study far outweigh the risks. As discussed in detail in the main body of this grant application, chronic migraine with medication overuse is a very common problem and one that exerts substantial negative impacts on the lives of people suffering with this condition. Despite its high prevalence, the significant burden that it causes, and the undeniable need for treating patients who have chronic migraine with medication overuse, the best treatment strategy is currently unknown. For the benefit of patients who have chronic migraine with medication overuse and their family members, it is essential that we move past this clinical equipoise and clarify the best treatment strategy. Given the design of this proposed study, the risks associated with participation are similar to those that a patient is exposed to during routine clinical care. Both treatment strategies used in this proposed research are commonly used in routine clinical practice. Each patient participant's enrolling clinician is also his or her treating clinician. Within the confines of the treatment strategy that an individual participant is randomized to, the clinician will utilize their best clinical skills for making treatment decisions, as would be done in

typical clinical practice. Adverse events will be managed just as they would be in typical clinical practice.

In all research involving human subjects, the loss of confidentiality is a principal concern. Therefore, steps will be taken to minimize this risk. All information collected from study participants will be locked in a secure location. Identifying information will be removed from the data forms and replaced by unidentifiable codes. Electronic databases/spreadsheets will be password protected and only accessible to those with access rights. (DN-1) Only de-identified data will be made widely available to other researchers. Data will be entered into Medidata Rave. Medidata Rave is the information technology system endorsed by Mayo Clinic's Clinical Trial Management System. The Medidata Rave system is compliant with 21 Code of Federal Regulations (CFR) Part 11 Food and Drug Administration (FDA) requirements. Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection and security. The Medidata Rave database access model is role based and fully auditable at the study, form, and field levels. Access is managed by the Mayo Clinic's Clinical Trial Management System Service and Solution Center, under a controlled and monitored access request system. Data will be transmitted via the Internet from investigational sites to the Mayo Clinic via state-of-the-art encryption mechanisms, thus ensuring security and confidentiality.

Women and minorities will be included in this study in proportions that represent the populations from which they are enrolled. Based upon the propensity of chronic migraine with medication overuse to impact women disproportionately more than men, we expect that 3.5 to 4 women will be enrolled into this study for every one man enrolled into this study. We anticipate that minorities will be enrolled in proportions that reflect the U.S. population, with approximately 35.6% of participants being of a race/ethnicity other than non-Hispanic white or European American. According to the 2010 U.S. Census of the total population (Hispanic and Non-Hispanic), 78.4% of the population is White, 13% of the population is Black or African American, 1.2% is American Indian or Alaska Native, 4.9% is Asian, 0.2% is Native Hawaiian and Other Pacific Islander, and 2.3% is two or more races. Hispanics accounted for 16.3% of the total U.S. population according to the 2010 Census. Thus, we anticipate that of the 720 enrolled patient participants, 576 will be women, 117 will be Hispanic, 564 will be White, 94 will be Black or African American, 9 will be American Indian or Alaska Native, 35 will be Asian, 1 will be Native Hawaiian or Other Pacific Islander, and 17 will be two or more races.

Children and adolescents under the age of 21 will not be included in this study. Although we considered including children and adolescents, their exclusion from this proposed study is based upon the facts that: 1) although little is known about the prevalence of medication overuse in the pediatric chronic migraine population, medication overuse is thought to be much less frequent among children and adolescents compared to adults; 2) the medications overused amongst children with medication overuse differ compared to the medications overused in adults; 3) the treatment strategies for treating children and adolescents who have chronic migraine with medication overuse differ from the strategies used when treating adults (e.g. onabotulinumtoxinA is approved for adult patients with chronic migraine but not for children or adolescents). Although additional investigations into chronic migraine with medication overuse in children and adolescents are needed, such investigations will be better performed in studies separate from this proposed PCORI study.

This study will not enroll participants from "vulnerable populations" (i.e. prisoners, pregnant women, children).

All investigators who participate in this trial will have to complete or demonstrate prior completion of education on the protection of human research participants. (DN-1) The principal investigators will require documentation that such training has been completed prior to investigators enrolling subjects into this study.

13. Informed Consent

Informed consent procedures will be performed according to the requirements and recommendations of each participating centers Institutional Review Board.

Written consent will be obtained from all subjects. Written consent can be obtained from the patient in the office, by using internet-based document software (e.g. DocuSign), by scanning paper documents and submitting them by e-mail, and by sending signed documents through regular mail. Only those methods that are IRB-approved will be used.Copies of consent forms will be submitted to the Mayo Clinic.

a. Informed Consent Personnel

Any member of the research team who obtains informed consent from a subject will need to be approved by their local IRB to do so.

b. Location and Privacy

The informed consent process will occur in a location that is approved by the local IRB.

c. Storage of Consent Documents

Consent documents will be stored at each participating center for a minimum of 3 years after conclusion of the study. The subject will be provided with a copy of the consent document. Copies of the consent documents will also be sent to the Mayo Clinic.

d. Withdrawal of Consent

Subjects will have the right to withdraw their consent at any time. After a participant withdraws from the study, they will not be contacted and their data will not be used moving forward.

14. Subject Retention

Telephone calls, e-mails, and other telehealth methods of communication with patients will help retain subjects and improve adherence rates. Only those methods that are IRB-approved will be used. The contact schedule can be seen above in section 9j.

Subjects will receive compensation of $30 per research visit, including the baseline visit and 12-week follow-up visit. Including these two mandatory research visits, subjects can receive compensation for up to 6 research visits maximum during their 48 weeks of participation with this study.

After two days of not entering diary data, subjects will receive e-mails and/or text messages reminding them to record their data in the internet-based or mobile app headache diary. Subjects will receive $50 compensation per 4-week period during which they are at least 80% compliant with providing headache diary data (i.e. provide diary data on at least 80% of days). Since subjects are asked to maintain the diary for five 4-week periods during the study (weeks 1-4, 5-8, 9-12, 21-24, and 45-48), the maximum compensation for diary compliance is $250 per subject.

15. Data Management

Data will be entered into a Medidata Rave electronic database capture system. Medidata Rave is the information technology system endorsed by Mayo Clinic's Clinical Trial Management System. Study sites will enter data into electronic case report forms using Medidata Rave. Case report forms are automatically presented to site investigators based on a predetermined, visit based schedule in order to improve study staff workflow and data quality. The Medidata Rave system is compliant with 21 Code of Federal Regulations (CFR) Part 11 Food and Drug Administration (FDA) requirements. Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection and security. During the course of the data entry into Medidata Rave, the system provides real-time within case report form and inter-case report form data consistency verification. Medidata Rave is flexible in nature so that all data can be entered even if "required" fields and other consistency checks requirements are not satisfied. The system uses an internal "flagging" or "query" system to distinguish the valid from the invalid data thereby ensuring compliance with the Food and Drug Administration guidance document "Computerized Systems Used in Clinical Trials". The Medidata Rave database access model is role-based and fully auditable at the study, form, and field levels. Access is managed by the Mayo Clinic's Clinical Trial Management System Service and Solution Center, under a controlled and monitored access request system. Data will be transmitted via the Internet from investigational sites to the Mayo Clinic via state-of-the-art encryption mechanisms, thus ensuring security and confidentiality.

16. Adverse Events Reporting

The adverse event process flow from the National Institutes of Health National Institute on Aging will be used for this study. (see appendix) Investigators will immediately report all serious adverse events to their local Institutional Review Board and to the Principal Investigators. The Principal Investigators will immediately report all serious adverse events to the Data and Safety Monitoring Board and to the Mayo Clinic Institutional Review Board. All serious and non-serious adverse events will be recorded and submitted to the Data and Safety Monitoring Board. Adverse events will be recorded using the Adverse Event forms created by the National Institutes of Health National Institute on Aging (see appendix).

17. Protocol Maintenance

All protocol changes will be tracked within a Protocol Change Log and the revised protocol will receive a new version number and date. A description of the revision and the most recent protocol will be sent to each of the investigative sites. Investigators will be required to confirm receipt and review of the revised protocol.

18. Study Website

The study website is available at: www.motstrial.org

The website hosts the study protocol, updates on study progress, participating centers and links to presentations and publications that relate to this study.

19. Study Registration

The study has been registered with clinicaltrials.gov (NCT02764320; 5/4/16) and results will be reported to clinicaltrials.gov.

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21. Appendices

a) Case Report Forms

- Inclusion/Exclusion Criteria
- Subject Contact Information
- Subject Demographics
- Headache Characteristics
- Medication Use
- Headache Impact Test 6 (HIT-6)
- PROMIS Pain Interference questionnaire
- Generalized Anxiety Disorder 7 (GAD-7)
- Patient Health Questionnaire 9 (PHQ-9)
- EuroQol 5D (EQ-5D-3L)
- Change in Migraine Therapy
- Migraine Functional Impact Questionnaire (MFIQ)

Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

Inclusion and Exclusion Criteria

Instructions: Place a mark in each bubble as you confirm the subject meets enrollment criteria.

Inclusion Criteria:

- ○ At least 21 years of age at the time of enrollment
- ○ Chronic Migraine diagnosed according to ICHD3 beta criteria (see criteria)
- ○ Medication Overuse diagnosed according to ICHD 3 beta criteria (see criteria)
- ○ Willing to be randomized to either of the two treatment arms
- ○ Willing to maintain a headache diary
- ○ Plans for follow-up care with the enrolling clinician
- ○ No changes to migraine prophylactic therapy within the last 4 weeks prior to randomization

Exclusion Criteria:

- ○ Younger than 21 years of age
- ○ Headache diagnosis other than migraine (with or without aura), probable migraine, chronic migraine with medication overuse; episodic tension type headaches on 3 or fewer days per month are allowed.
- ○ Not willing to be randomized to either of the treatment arms
- ○ Not willing to maintain a daily headache diary
- ○ Not planning on follow-up care with the clinician
- ○ In the opinion of the clinician, randomization to either treatment arm would be considered unsafe (Example: Pregnancy, immediate discontinuation, etc.)
- ○ Prisoner
- ○ Diminished decision-making capacity that in the investigator's opinion interferes with the ability to provide informed consent and complete study procedures

Chronic Migraine Diagnostic Criteria

A. Headache (tension-type-like and/or migraine-like) on ≥15 days/ month for >3 months and fulfilling criteria B and C
B. Occurring in a patient who has had ≥5 attacks of migraine with or without aura
C. On ≥8 days/month for >3 months, fulfilling any of the following:
   a) migraine without aura diagnostic criteria
   b) migraine with aura diagnostic criteria
   c) believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another headache diagnosis

Medication Overuse Diagnostic Criteria

A. Regular intake of ergotamine, triptans, opioids, combination analgesics, or a combination of drugs from different classes on ≥10 days per month for >3 months

or

B. Regular intake of simple analgesics (e.g. acetaminophen, NSAIDs) on ≥15 days per month for >3 months

Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

Contact Information

Name: _____ _____
(First) (Last)

Home: (_____) _____-_____ Work: (_____) _____-_____

Mobile: (_____) _____-_____ Email: _____

Address:

_____ Unit/Apt#_____

(Street)

City_____ State_____ Zip_____

Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

Subject Demographics

DOB: ___ ___ / ___ ___ / ___ ___ ___ ___
Month Day Year

Current age (years): _____

Sex at birth (circle one): 1 = Male 2 = Female

Race (circle all that apply):

1 = American Indian/Alaska Native 2 = Asian

3 = Black/African American 4 = Native Hawaiian/Other Pacific Islander

5 = White/Caucasian 6 = Other _____

Ethnicity: 1 = Hispanic 2 = Non-Hispanic

Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

Headache Characteristics

On average over the last 3 months, how many **days per month** (30 days) with headache of **any kind/severity**: days

On average over the last 3 months, how many **days per month** (30 days) with complete **headache freedom**: days

How many **days over the last 30** days with headache that at any time during the day became **moderate or severe** intensity: days

On those days when headache intensity became moderate or severe, on average **how many hours** did the pain remain **moderate or severe**? hours

How many **days in the last 30** days did the headache remain **mild** intensity all day long? days

How many **days in the last 30** days have **acute (as needed) medications** (e.g. triptans, analgesic) been taken for headache? days

How many **days in the last 30** days have analgesic (pain) medications been taken for conditions other than headache (e.g. other pain, fever)? days

How many **days in the last 30** days have **no** analgesic or acute medications been taken? days

How many **days in the last 30** days did the patient take a daily migraine **preventive** therapy(ies)? days

On average, how **long** do headaches last if **successfully treated**: hours

On average, how **long** do headaches last if **untreated or inadequately treated**: hours

Where is headache pain usually **located** (circle all that apply):

Right Left Front Back Side

Is headache typically **unilateral** (circle one):

Yes No

Headache **quality** (circle all that apply):

Pulsating/Throbbing Pressure/Aching Stabbing Burning

Headache **intensity**:

Average on 0 (no pain) to 10 (most severe pain) scale: /10

Maximum on 0 (no pain) to 10 (most severe pain) scale: /10

With headaches/migraine attacks is there ever:

Worsening of headache with physical activity:	Yes	No
Nausea:	Yes	No
Vomiting:	Yes	No
Sensitivity to light:	Yes	No
Sensitivity to sound:	Yes	No
Conjunctival injection on same side of headache:	Yes	No
Tearing on same side of headache:	Yes	No
Nasal congestion/rhinorrhea on same side of headache	Yes	No
Eyelid drooping on same side of headache	Yes	No

Are there ever **auras** with migraine attacks: Yes No

If yes, then what aura types are experienced:

Visual:	Yes	No
Sensory:	Yes	No
Motor:	Yes	No

Language: Yes No

Other: Yes No

What percentage of headaches are accompanied by auras: _____%

When was the patient's **first migraine** (month and year): __ __ / __ __ __ __

When was the **onset** of the **chronic migraine** pattern (month, year): __ __ / __ __ __ __

Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

Follow-Up Visit: Headache Characteristics

How many days over the last 30 days with headache of **any kind/severity**: days

How many **days over the last 30** days with complete **headache freedom**: days

How many days over the last 30 days with headache that at any time during the day became **moderate or severe** intensity: days

On those days when headache intensity became moderate or severe, on average **how many hours** did the pain remain **moderate or severe**? hours

How many **days in the last 30** days did the headache remain **mild** intensity all day long? days

On average, how **long** do headaches last if **successfully treated**: hours

On average, how **long** do headaches last if **untreated or inadequately treated**: hours
Headache **intensity** over the last 30 days:

Average on 0 (no pain) to 10 (most severe pain) scale: /10

Maximum on 0 (no pain) to 10 (most severe pain) scale: /10

How many **days in the last 30** days have **acute (as needed) medications** (e.g. triptans, analgesic) been taken for headache? days

How many **days in the last 30** days have **analgesic (pain) medications** been taken for conditions other than headache (e.g. other pain, fever)? days

How many **days in the last 30** days have **no** analgesic or acute medications been taken? days

How many **days in the last 30** days did the patient take a daily migraine **preventive** therapy(ies)? Days

Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

Current Treatments – Baseline Visit

On average over the last 3 months, how many days/month is the patient taking **abortive/analgesic medications**? (Include prescription and non-prescription medications; include all medications, regardless of the indication (e.g. count days taking an analgesic for pain other than migraine)?

____ ____ days per month

Medication Name (generic)	**Dose** (include units)	**Dosing Schedule** (e.g. once daily, twice daily)	**Days per Month Taking Medication**	**Duration that patient has been taking medication** (include units; e.g. weeks, months)	**Indication for medication (e.g. headache, back pain, etc)**

How long has the patient been in a **medication overuse pattern:** _____ months

Is the patient **currently** taking **medications to prevent headaches/migraines** (include medications that are considered migraine preventives regardless of the reason the patient is taking the medication; e.g. patient takes a beta-blocker for hypertension):

Yes No

If yes, complete the following table.

Medication Name (generic)	**Dose** (include units)	**Dosing Schedule** (e.g. once daily, twice daily)	**Duration that patient has been taking medication** (include units; e.g. weeks, months)	**Indication for medication (e.g. migraine, depression, hypertension)**

Is the patient **currently** using **non-medicinal treatments** (e.g. acupuncture, nerve stimulation, cognitive behavioral therapy) for headaches/migraine?

Yes No

If yes, complete the following table.

Treatment Name/ Description	**Dosing Schedule** (e.g. once daily, twice daily, once weekly)	**Duration that patient has been using this treatment** (include units; e.g. weeks, months)	**Indication for treatment (e.g. migraine, back pain, etc)**

Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

Headache Impact Test -6 (HIT-6)

Instructions: Choose one answer for each question.

1. When you have headaches, how often is the pain severe?

   Never Rarely Sometimes Very Often Always

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

   Never Rarely Sometimes Very Often Always

3. When you have a headache, how often do you wish you could lie down?

   Never Rarely Sometimes Very Often Always

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

   Never Rarely Sometimes Very Often Always

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

   Never Rarely Sometimes Very Often Always

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

   Never Rarely Sometimes Very Often Always

Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

PROMIS Pain Interference

Instructions: Mark one box per row.

In the past 7 days…

	Not at all	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
How much did pain interfere with your enjoyment of life?					
How much did pain interfere with your ability to concentrate?					
How much did pain interfere with your day to day activities?					
How much did pain interfere with your enjoyment of recreational activities?					
How much did pain interfere with doing your tasks away from home (e.g. getting groceries, running errands)?					
	Never	**Rarely**	**Sometimes**	**Often**	**Always**
How often did pain keep you from socializing with others?					

Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

Generalized Anxiety Disorder 7 (GAD-7)

Instructions: choose one answer for each question.

Over the last 2 weeks, how often have you been bothered by the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Feeling nervous, anxious or on edge	**0**	**1**	**2**	**3**
Not being able to stop or control worrying	**0**	**1**	**2**	**3**
Worrying too much about different things	**0**	**1**	**2**	**3**
Trouble relaxing	**0**	**1**	**2**	**3**
Being so restless that it is hard to sit still	**0**	**1**	**2**	**3**
Becoming easily annoyed or irritable	**0**	**1**	**2**	**3**
Feeling afraid as if something awful might happen	**0**	**1**	**2**	**3**

Add the score for each column + +
Total Score (add your column scores) =

Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

Patient Health Questionnaire 9 (PHQ-9)

Instructions: choose one answer for each question.

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	**0**	**1**	**2**	**3**
Feeling down, depressed, or hopeless	**0**	**1**	**2**	**3**
Trouble falling or staying asleep, or sleeping too much	**0**	**1**	**2**	**3**
Feeling tired or having little energy	**0**	**1**	**2**	**3**
Poor appetite or overeating	**0**	**1**	**2**	**3**
Feeling bad about yourself – or that you are a failure or have let yourself or your family down	**0**	**1**	**2**	**3**
Trouble concentrating on things, such as reading the newspaper or watching television	**0**	**1**	**2**	**3**
Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	**0**	**1**	**2**	**3**
Thoughts that you would be better off dead or hurting yourself in some way	**0**	**1**	**2**	**3**

Column totals _____ + ___
+_____Add totals together: _____

The Migraine Functional Impact Questionnaire (MFIQ)
(Version 2.0)

- The following questions are about your ability to function in the **past 7 days**.
- We would like to understand how a **migraine** affects your **day-to-day activities**.
- Symptoms of migraine can include headache pain, nausea, vomiting, or sensitivity to light or noise.
- We want you to think about the symptoms that **you** experience and how they impact **your** day-to-day activities.
- Please answer all questions by selecting the one option that best describes your experience.

1. In the past 7 days, how often did a migraine limit your ability **to move your head**?
   - ☐ Never
   - ☐ Rarely
   - ☐ Sometimes
   - ☐ Often
   - ☐ Always

2. In the past 7 days, how often did a migraine limit your ability to **move your body**? (For example, standing up, walking, bending)
   - ☐ Never
   - ☐ Rarely
   - ☐ Sometimes
   - ☐ Often
   - ☐ Always

3. In the past 7 days, how often did a migraine **limit your usual activities that required physical effort?**
   - ☐ Does not apply; do not usually do activities that require physical effort
   - ☐ Never
   - ☐ Rarely
   - ☐ Sometimes
   - ☐ Often
   - ☐ Always

4. In the past 7 days, how often did you **feel that you needed to rest or lie down** during the day because of your migraine?
   - □ Never

□ Rarely
□ Sometimes
□ Often
□ Always

5. In the past 7 days, how often did you **feel too tired to do things** because of your migraine?
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always

6. In the past 7 days, how difficult was it **to get yourself ready for the day**?
□ Not difficult
□ A little difficult
□ Moderately difficult
□ Very difficult
□ Extremely difficult

7, In the past 7 days, how often did you have difficulty completing specific personal grooming activities? (For example, brushing hair, shaving, applying make-up)
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always

8. In the past 7 days, how often did a migraine **affect your daily routine or schedule**?
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always

9. In the past 7 days, how often did you have to **change your plans** because of a migraine?
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always

10. In the past 7 days, how difficult was it **to do your usual chores at home**?
(For example, tidying up, cleaning up, preparing a meal, doing minor repairs)
□ Not difficult
□ A little difficult
□ Moderately difficult
□ Very difficult
□ Extremely difficult

11. In the past 7 days, how much did a migraine limit your ability **to do your usual chores outside the home**? (For example, shopping or running errands)
□ Not at all
□ Slightly

□ Moderately
□ Very much
□ Extremely

12. In the past 7 days, how much did a migraine affect **your ability to do your usual work or study-related activities**?
□ Does not apply; I have not worked* or studied at all during the past week for reasons unrelated to the disorder. *Work includes paid or unpaid work.

□ Not at all
□ Slightly
□ Moderately
□ Very much
□ Extremely

13. In the past 7 days, how much did a migraine affect your **ability to take care of your family?**
□ Does not apply; I do not live with family.
□ Not at all
□ Slightly
□ Moderately
□ Very much
□ Extremely

14. In the past 7 days, how difficult was it for you **to do activities that required you to concentrate**?
□ Not difficult
□ A little difficult
□ Moderately difficult
□ Very difficult
□ Extremely difficult

15. In the past 7 days, how difficult was it **to do activities in the presence of loud noises, strong smells, or bright lights?**
□ Does not apply; I do not need to do activities in the presence of loud noises, strong smells, or bright lights.
□ Not difficult
□ A little difficult
□ Moderately difficult
□ Very difficult
□ Extremely difficult

16. In the past 7 days, overall, how much did a migraine **affect your usual activities?**
□ Not at all
□ Slightly
□ Moderately
□ Very much
□ Extremely

17. In the past 7 days, how much did a migraine affect your usual social interactions? (For example, with family, friends or coworkers)
□ Not at all

□ Slightly
□ Moderately
□ Very much
□ Extremely

18. In the past 7 days, how often did you **avoid being around other people** because of a migraine?
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always
19. In the past, 7 days how much did you have to **limit your social activities** because of a migraine?
□ Not at all
□ Slightly
□ Moderately
□ Very much
□ Extremely
20. In the past 7 days, how often did a migraine **interfere with your relationship** with your partner or spouse?
□ Does not apply; do not have a partner or spouse
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always
21. In the past 7 days, how often did a migraine **limit your usual leisure activities**?
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always
22. In the past 7 days, how frustrated did you fell about being unable to do what you needed to do because of a migraine?
□ Not at all
□ Slightly
□ Moderately
□ Very much
□ Extremely
23. In the past 7 days, how often did you **worry about your migraines**?
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always
24. In the past 7 days, how often did you **feel like a burden on others** because of a

migraine?
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always

25. In the past 7 days, how often did you feel you **lacked control of your life** because of a migraine?
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always

26. In the past 7 days, how **disappointed** did you feel about having a migraine?
□ Not at all
□ Slightly
□ Moderately
□ Very much
□ Extremely

Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse
EuroQol 5D (EQ-5D-3L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

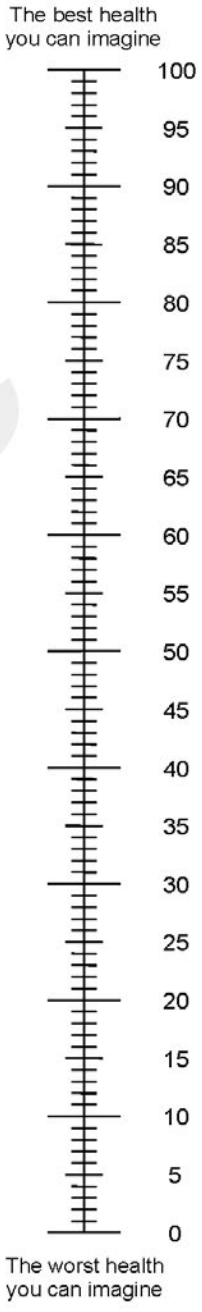
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Determining the Optimal Treatment Strategy for Patients who have Chronic Migraine with Medication Overuse

Headache Diary

Did you have a headache/migraine today?

Yes No

How long did the headache last (choose one)?

1-30 mins
31-60 mins
61 – 120 mins
2-4 hours
4-6 hours
6-12 hours
12-24 hours

What was the peak headache pain intensity (choose one)?

Mild Moderate Severe

If pain reached moderate or severe intensity, how long did it remain at that intensity (choose one)?

1-30 mins
31-60 mins
61 – 120 mins
2-4 hours
4-6 hours
6-12 hours
12-24 hours

How disabling was the headache/migraine (choose one)?

Able to function normally
Function somewhat reduced
Function severely reduced
Not able to function at all (e.g. bedbound)

Did you take your migraine PREVENTIVE medication today? (i.e. Prescription or over-the-counter medication/treatment that is used daily with the intent of reducing your migraine/headache frequency; these treatments are used regardless of whether or not a headache/migraine is present on that day)

Yes No

Did you take migraine ABORTIVE treatments today? (i.e. prescription or over-the-counter medication/treatment that is used to lessen or get rid of headache/migraine pain)?

Yes No

(If answered Yes the system will present a table for patients to enter their medications from a drop down list and how many times that day they took it. There will also be an option for the patient to write in other meds.

Did you take any PAIN medications today for reasons other than to treat a headache/migraine (prescription or over-the-counter)?

Yes No

(If answered Yes the system will present a table for patients to enter their medications from a drop down list and how many times that day they took it. There will also be an option for the patient to write in other meds.)

In the past 24 hours, overall, how difficult was it to do your usual activities?

□ Not difficult
□ A little difficult
□ Moderately difficult
□ Very difficult
□ Extremely difficult

In the past 24 hours how much of the time did you have difficulty moving your head?
□ None of the time
□ A little of the time
□ Some of the time
□ Most of the time
□ All of the time

In the past 24 hours how much of the time did you have difficulty moving your body?
□ None of the time
□ A little of the time
□ Some of the time

□ Most of the time
□ All of the time

In the past 24 hours were you able to get out of bed?
□ Without any difficulty
□ With a little difficulty
□ With some difficulty
□ With much difficulty
□ Unable to do

In the past 24 hours were you able to bend over?
□ Without any difficulty
□ With a little difficulty
□ With some difficulty
□ With much difficulty
□ Unable to do

In the past 24 hours were you able to do your usual activities that required physical effort?
□ Without any difficulty
□ With a little difficulty
□ With some difficulty
□ With much difficulty
□ Unable to do

b) Adverse Event Form

Adverse Event Flowsheet

Subject ID:
Protocol:
IRB #:

Adverse Event	Date of Onset	Date of Resolution	Intensity	Outcome	Action Taken	Investigator Initial and Date	Relationship to Study	Caused Study Withdrawal	SAE
			1. Mild 2. Moderate 3. Severe 4. N/A	1. Resolved 2. Resolved with sequalae 3. Unresolved 4. Death	1. None 2. Dose held 3. Dose reduced 4. Dose Increased 5. Dose incomplete 6. Dose delayed 7. Drug or dose discontinued permanently 8. Con Meds Given 9. Con Procedure 10. Hospitalized 11. Discontinued from study		1. Unrelated 2. Unlikely 3. Possibly 4. Probably 5. Definitely	Yes No	Yes No

Investigator Signature and Date: _____

Page # _____

c) Headache Treatment Form

Headache Treatment Form
(Preventative, Abortive, and Non-Pharmacological)

Subject ID:
Protocol:
IRB #:

Medication	Dose	Frequency	Route	Start Date	Stop Date	Indication

Page # ____