STUDY PROTOCOL

MICOAS QUANTITATIVE STUDY

Study title: A MiCOAS quantitative study to collect data on the de novo migraine-related patient-reported outcome measures using an observational and longitudinal study

Short title: MiCOAS Quant1

Study purpose: To provide data for the initial psychometric examination and validation of the MiCOAS daily diary and recall-based measures in a sample of people living with migraine with a self-reported medical diagnosis.

Study phase:	NA	**Protocol:**	2023-001
Version Date:	8/16/2023	**Version #:**	1.0

CONFIDENTIAL

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VERSION HISTORY

Version	Date	By	Description of Changes
1.0	05DEC23	RJW	Initial Protocol

ABBREVIATIONS

Abbreviation	Definition
COA	Clinical outcome assessment
DA	Daily assessment
eCOA	Electronic clinical outcome assessment
EDC	Electronic data capture
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
HIT-6	Six-item Headache Impact Test
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IHS	International Headache Society
IRB	Institutional review board
IRT	Item response theory
MFIQ	Migraine Functional Impact Questionnaire
MiCOAS	Migraine Clinical Outcome Assessment System
MiCOAS 7d	MiCOAS 7-day recall-based assessment
MiCOAS 14d	MiCOAS 14-day recall-based assessment
MiCOAS DA	MiCOAS daily assessment
MMD	Monthly migraine day
MMT	Modern measurement theory
MOS-Cog-R	Medical Outcomes Study-Cognitive Function measure-Revised
MSQ v2.1	Migraine-specific Quality of Life Questionnaire version 2.1
PAP	Psychometric analysis plan
PGIC	Patient global impression of change
PGIS	Patient global impression of status
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
SoA	Schedule of activities
VPG	Vector Psychometric Group, LLC

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2 PROTOCOL SUMMARY

2.1 SYNOPSIS

Protocol Title: A MiCOAS quantitative study to collect data on the de novo migraine-related patient-reported outcome measures using an observational longitudinal study

Protocol Number: 2023-001

Brief Title: MiCOAS Quant1

Study Rationale: MiCOAS Quant1 is an observational, short-term (maximum 8 weeks) longitudinal survey study of people living with migraine in which all data will be collected electronically. Enrolled participants will be randomized to 1 of 3 cohorts, with cohort 1 having a study duration of 8 weeks and the other 2 cohorts having study durations of 4 weeks. Once enrolled, participants will receive electronic notifications when assessment opportunities are available and when assessment windows will close. Participants will be asked to complete one or more electronic patient-reported outcome (ePRO) measures within each assessment window.

The purpose of this study is to collect data appropriate for a comprehensive examination of the psychometric properties of the developing Migraine Clinical Outcome Assessment System (MiCOAS) migraine daily assessment (MiCOAS-DA), as well as the developing 7-day and 14-day recall based measures (MiCOAS-7 and MiCOAS-14, respectively).

Research Objectives: The overall aim is to conduct a comprehensive, psychometric evaluation of the core item sets developed during the qualitative stages of the Migraine Clinical Outcome Assessment System (MiCOAS) project. The item sets will be completed daily (MiCOAS-DA) or using 7-day and 14-day recall periods (MiCOAS-7 and MiCOAS-14, respectively). The primary focus will be on evaluating the psychometric properties of items measuring hypothesized domains of Physical Function, Social Role Function, Emotional Function, and Cognitive Function using data from the MiCOAS-7 and MiCOAS-14 collected at the Baseline (Week 0), Week 4, and Week 8 visits. A key secondary objective is to evaluate the psychometric properties of items measuring hypothesized domains of Symptom, Physical Function, and Subjective Mental Acuity using data from the MiCOAS-DA collected over Month 1 (Weeks 1-4) and Month 2 (Weeks 5-8).

Study Design: This is an observational, short-term (maximum 8 weeks) longitudinal survey study of people living with migraine in which all data will be collected via Vector Psychometric Group, LLC (VPG)'s proprietary electronic clinical outcome assessment (eCOA) system, flexCOA. Enrolled participants will be randomized to one of three cohorts:

- Cohort 1: Total study duration of 8 weeks (2 months) and participants will complete MiCOAS-DA daily for the entire study length. Participants will also complete the MiCOAS-14 and key reference patient reported outcome measures (PROMs) throughout the 8-week study duration (e.g., weekly, biweekly, or monthly depending on the recall period of the PROM).

- Cohort 2: Total study duration of 4 weeks (1 month) and participants will complete MiCOAS-DA daily for the entirety of Month 1 (Weeks 1-4). Participants will also complete the MiCOAS-14 and key reference PROMs throughout the 4-week study duration (e.g., weekly, biweekly, or monthly depending on the recall period of the PROM).

- Cohort 3: Total study duration of 4 weeks (1 month) and participants will complete MiCOAS-DA daily for the entirety of Month 1 (Weeks 1-4). Participants will also complete the MiCOAS-7 and relevant reference PROMs throughout the 4-week study duration (e.g., weekly or monthly depending on the recall period of the PROM).

Cohorts were included in the design to allow for the collection of all necessary data for psychometric and validation analyses while limiting the burden to respondents.

Population: Adult patients with a self-reported medical diagnosis of migraine confirmed by a positive diagnosis on the 3-item ID Migraine screen (Lipton et al., 2003).

Variables: A range of variables will be collected. The primary focus will be on variables relating to the MiCOAS item sets (MiCOAS-DA, -7, and -14) and the reference PROMs used for validation, but data collection also includes:

- Demographics
- Clinical background characteristics (e.g., medications, brief medical history, comorbidities)
- Migraine-related characteristics (e.g., migraine history, headache days)
- Preventive and acute migraine/headache medication use
- Reference general headache-related PROMs

Data Source/Data Collection: Data will be collected electronically via the flexCOA eCOA system.

Study Size: Enrollment of approximately 1200 eligible participants is planned to achieve as many complete records as possible, with a target of 1000 participants who complete assessments throughout the full duration of their assigned study duration.

Study Duration: Minimum of 4 weeks, maximum of 8 weeks

Data Analysis: A range of analyses will be performed to evaluate the psychometric properties of the MiCOAS-DA, MiCOAS-7, and MiCOAS-14 including approaches falling within the classical test theory (e.g., reliability and validity assessments) and modern psychometric (e.g., factor analysis and item response theory) frameworks. Analyses involving the MiCOAS-7 and MiCOAS-14 will focus primarily on external validator data from the Baseline, Week 4, and Week 8 visits whereas analyses focused on the MiCOAS-DA will use daily reports from Months 1 and 2.

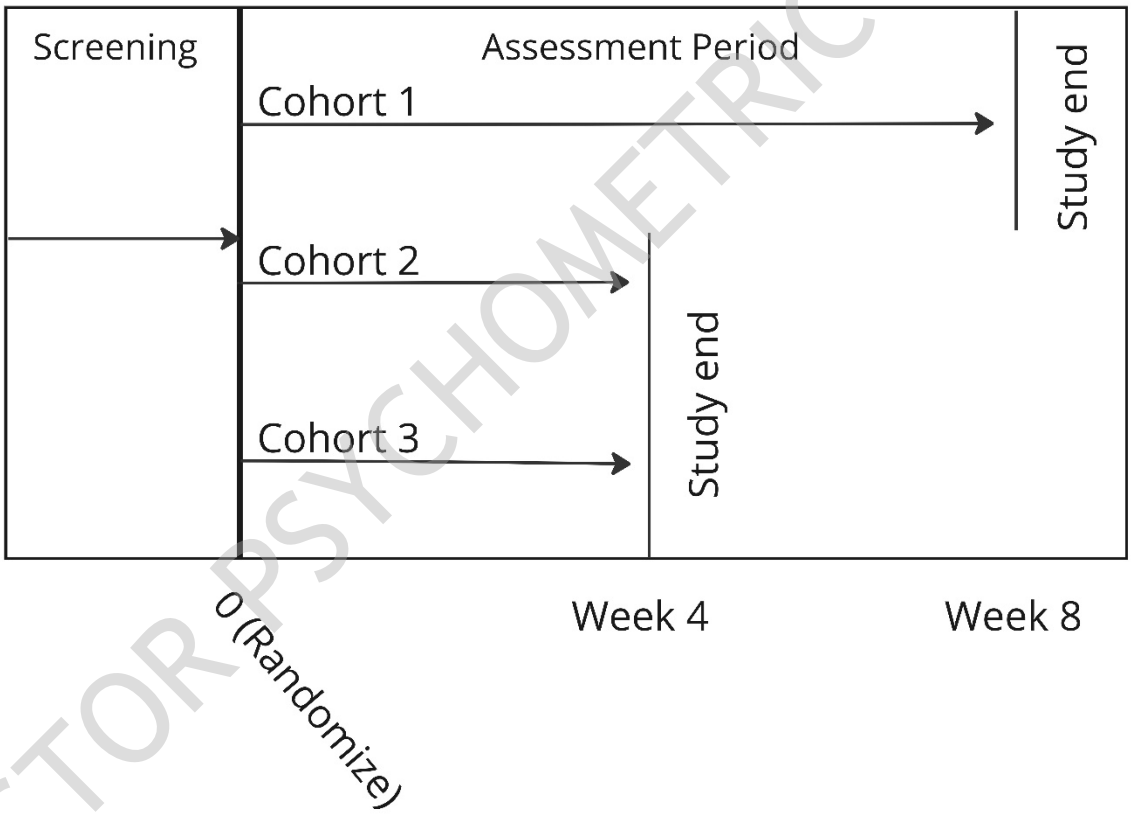
Milestones (anticipated): Study start: 1/5/2024. Observational Period: 4 to 8 weeks. Study Report: aimed to be provided within 4 months from the end of data collection.

Data Monitoring Committee: No

2.2 SCHEMA

This study is an observational, longitudinal cohort study of people with migraine aimed at evaluating the psychometric properties of 3 unique item sets derived from prior qualitative work done in an early phase of the MiCOAS project (Figure 1). Cohort 1 will be followed for 8 weeks (2 months) and Cohorts 2 and 3 will be followed for 4 weeks (1 month).

Figure 1. MiCOAS Quant1 study schema



2.3 SCHEDULE OF ACTIVITIES (SOA)

Cohort 1 (8-week study duration) will complete the MiCOAS-DA daily and, starting at Baseline, will complete the MiCOAS-14 biweekly through the duration of the study (Baseline, Week 2, Week 4, Week 6, Week 8). Cohort 2 (4-week study duration) will complete the MiCOAS-DA daily through Month 1 (Weeks 1-4) and will complete the MiCOAS-14 biweekly through the duration of the study (Baseline, Week 2, and Week 4). Cohort 3 (4-week study duration) will complete the MiCOAS-DA daily through Month 1 (Weeks 1-4), and will complete the MiCOAS-7 weekly through the duration of the study (Baseline, Week 1, Week 2, Week 3, and Week 4). For all cohorts, a variety of headache-related and general PROMs will be completed across the duration of the study (timing of PROM administration depending on the PROM recall timeframe and the focal MICOAS measure's recall timeframe [7d or 14d]). Figure 2 provides complete details on the SoA.

Figure 2. MiCOAS Quant1 SoA

Measure	Baseline Day 0	Month 1 Week 1 Day 7	Month 1 Week 2 Day 14	Month 1 Week 3 Day 21	Month 1 Week 4 Day 28	Month 2 Week 5 Day 35	Month 2 Week 6 Day 42	Month 2 Week 7 Day 49	Month 2 Week 8 Day 56
Cohort 1 – DA Emphasis (n=150)									
MiCOAS									
MiCOAS DA		■	■	■	■	■	■	■	■
MiCOAS 7d									
MiCOAS 14d	■		■		■		■		■
Cognition									
MOS-Cog-R 7d	■	■	■	■	■	■	■	■	■
Headache PROM									
HIT-6 (4-week recall)	■				■				■
MFIQ v2 (7-day recall)	■		■		■		■		■
MSQ v2.1 (4-week recall)	■				■				■
General PROM									
PGIS (14-day recall)	■		■		■		■		■
PGIC			■		■		■		■
Cohort 2 – 14-day PROM Emphasis (n=350)									
MiCOAS						■	■	■	■
MiCOAS DA		■	■	■	■	■	■	■	■
MiCOAS 7d						■	■	■	■
MiCOAS 14d	■		■		■	■	■	■	■
Cognition						■	■	■	■
MOS-Cog-R 7d	■	■	■	■	■	■	■	■	■
Headache PROM						■	■	■	■
HIT-6 (4-week recall)	■				■	■	■	■	■
MFIQ v2 (7-day recall)	■		■		■	■	■	■	■
MSQ v2.1 (4-week recall)	■				■	■	■	■	■
General PROM						■	■	■	■
PGIS (14-day recall)	■		■		■	■	■	■	■
PGIC			■		■	■	■	■	■
Cohort 3 – 7-day PROM Emphasis (n=500)									
MiCOAS						■	■	■	■
MiCOAS DA		■	■	■	■	■	■	■	■
MiCOAS 7d	■	■	■	■	■	■	■	■	■
MiCOAS 14d						■	■	■	■
Cognition						■	■	■	■
MOS-Cog-R 7d	■	■	■	■	■	■	■	■	■
Headache PROM						■	■	■	■
HIT-6 (4-week recall)	■				■	■	■	■	■
MFIQ v2 (7-day recall)	■	■	■	■	■	■	■	■	■
MSQ v2.1 (4-week recall)	■				■	■	■	■	■
General PROM						■	■	■	■
PGIS (7-day recall)	■	■	■	■	■	■	■	■	■
PGIC		■	■	■	■	■	■	■	■

Note. MiCOAS DD = MiCOAS Daily Diary. MiCOAS 7d = MiCOAS 7-day recall based questionnaire. MiCOAS 14d = MiCOAS 14-day recall-based questionnaire. MOS-Cog-R-7d = Medical Outcome Study- Cognition measure revised with 7-day recall. HIT-6 = 6-item HEadache Impact Test short form. MFIQ v2 = Migraine Functional Impact Questionnaire version 2.0. MSQ v2.1 = Migraine-specific Quality of Life Questionnaire version 2.1. PGIS = Patient global impression of status. PGIC = Patient global impression of change.

3 INTRODUCTION

The MiCOAS project is a joint partnership between Vector Psychometric Group, LLC (VPG) and Albert Einstein Medical School (co-primary investigators: RJ Wirth, PhD and Richard B. Lipton, MD FACS) that has received a U.S. Food and Drug Administration (FDA) grant to develop a core set of outcomes for use in migraine clinical trials. Over the last 4 years, the MiCOAS research group has completed 2 systematic literature reviews and several rounds of concept elicitation interviews with people living with migraine to understand what is important to them in terms of symptomology, impact, function and outcomes and identify gaps in the existing PROMs. More recently, draft instruments have been developed based on information provided by people living with migraine via the qualitative interviews.

The MiCOAS research group developed this document to delineate an observational, short-term longitudinal study that will allow for the initial investigation into the psychometric properties of the developing MiCOAS measures, which currently include a 23-item daily assessment (DA) that is intended to create 3 measures (symptoms [10 items], mental acuity [5 items], and physical function [7 items]) with one additional general item and recall-based measures intended to create 4 measures (physical function [9 items], social role function [7 items], emotional function [6 items], and cognitive function [10 items]), along with 4 additional general items. The recall-based measures will be implemented with both a 7-day recall period and a 14-day recall period.

The purpose of the current document is to detail the design and planned implementation of an electronically collected, observational, non-interventional, short-term longitudinal study of people living with migraine that includes the newly developed MiCOAS measures as well as relevant reference measures that will allow for the psychometric examination of the MiCOAS-DA and recall-based measures.

3.1 STUDY RATIONALE

MiCOAS Quant1 is an observational, short-term (maximum 8 weeks) longitudinal survey study of people living with migraine in which all data will be collected via VPG's proprietary eCOA system, flexCOA. Enrolled participants will be randomized to 1 of 3 cohorts, with cohort 1 having a study duration of 8 weeks and the other 2 cohorts having a study duration of 4 weeks. Once enrolled, participants will receive electronic notifications when assessment opportunities are available and when assessment windows will close. After logging into the flexCOA system, participants will be asked to complete several ePRO measures within each assessment window. No devices will be provided to participants – that is, collection will be based on the "Bring Your Own Device" model of eCOA measure administration.

The purpose of this study is to collect data appropriate for a comprehensive examination of the psychometric properties of the developing MiCOAS-DA, as well as the developing 7-day and 14-day recall based measures (MiCOAS-7 and MiCOAS-14, respectively).

3.2 BACKGROUND

As noted previously, the MiCOAS project team has completed 2 systematic reviews of COAs used in migraine research, one focused on preventive migraine research and the other focused on acute. An overarching finding in these publications (Houts et al., 2021; McGinley et al. 2021) was the inconsistent use of multi-item PROMs that rigorously assess topics and content areas patients have indicated are important to them, such as cognitive impacts and other functional impairments due to migraine.

After numerous rounds of concept elicitation and cognitive debriefing interviews of people living with migraine, both chronic and episodic, the MiCOAS project team has initial drafts of several multi-item patient centered PRO measures. One of the questionnaires that contain these measures is intended for daily assessments (the MiCOAS-DA) while 2 other questionnaires are recall-based. The overarching purpose of this study is to collect data appropriate for a comprehensive examination of the psychometric properties of the patient-centered measures the MiCOAS project team is developing. Specifically, the developing MiCOAS-DA measures, as well as the developing MiCOAS-7 and MiCOAS-14 versions. Such analysis results will allow for further refinement of the questionnaires and provide initial information on the reliability and validity of the developing measures.

4 OBJECTIVES AND TARGET OUTCOMES/TIMEPOINTS

This study will enroll people with a self-reported diagnosis of migraine. The broader goal of this study is to evaluate the psychometric properties of the qualitative-supported item sets within the MiCOAS-DA, MiCOAS-7, and MICOAS-14 questionnaires. For the MiCOAS DA, it is hypothesized that 3 unique domains/measures will underlay the items and, for the MiCOAS recall-based tool variations, it is hypothesized that there will be 4 unique domains/measures and 3-4 general items that do not fall within the hypothesized domains. The primary objective is to evaluate the psychometric properties of 7 and 14-day recall item sets (MiCOAS-7 and MiCOAS-14), but a secondary objective is to assess the psychometric properties of the MiCOAS-DA.

4.1 PRIMARY OBJECTIVE

The primary objective of this longitudinal, observational study is to evaluate the psychometric properties of the MiCOAS-14 (Cohorts 1 & 2) and MiCOAS-7 (Cohort 3). Both the MiCOAS-7 and MiCOAS-14 have a total of 36 items, of which 4 are general items and 32 items are hypothesized to contribute to 4 unique measures: 1) Physical Function (9 items), Social Role Function (7 items), Emotional Function (6 items), and Cognitive Function (10 items). Psychometric analyses will largely focus on data collected at target visits of Baseline and Week 4 (Month 1). Below is a list of specific goals for the primary objective

- Describe the properties of the items
- Evaluate the dimensionality of the latent constructs underlying item sets
- Assess reliability of the measures
- Assess the validity of inferences made using scores from the measures

4.2 SECONDARY OBJECTIVE

The secondary objective is to evaluate the psychometric properties of the MiCOAS-DA using data from all 3 cohorts and specifically using cohort 1 data for test-retest reliability analyses. The MiCOAS-DA has 23 total items, of which 1 is a general item and 22 items are hypothesized to contribute to 3 unique measures: 1) Symptoms (10 items), Physical Function (7 items), Mental Acuity (5 items). Psychometric analyses will largely focus on data collected at Baseline and Week 4 (Month 1) visits. Below is a list of specific goals for the primary objective:

- Describe the properties of the items
- Evaluate the dimensionality of the latent constructs underlying item sets
- Assess reliability of the measures
- Assess the validity of inferences made using scores from the measures

5 STUDY DESIGN

5.1 OVERALL DESIGN

The QUANT1 study will be observational/non-investigational in nature and will collect data longitudinally over the course of 8 weeks. In total, the MiCOAS research team seeks to have a sample size of approximately 1000 respondents who completed assessments through the full length of their study duration. Given the developing MiCOAS measures under investigation, as well as the need to include reference measures that will allow for validation analyses of the scores coming from the MiCOAS-DA and recall-based measures, a cohort design was selected in an effort to reduce respondent burden within any given assessment time.

Three cohorts will be used, in which Cohort 1 (approximate n = 150) will have a focus on collecting information used to examine the MiCOAS-DA and the MiCOAS-14 measures, Cohort 2 (approximate n = 350) will have a focus on the MiCOAS-DA and the MiCOAS14 measures, and Cohort 3 (approximate n = 500) will be focused on collecting data to examine the MiCOAS-DA and the MiCOAS-7 measures.

5.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Given the lack of intervention, the scientific rationale for the study design is quite straightforward. As seen in the SoA, there are numerous assessments where the MiCOAS measures and reference measures will both be collected. These cross-sectional aspects of the study design will allow the planned analyses to provide evidence regarding the reliability and validity of the MiCOAS measure scores and inferences based on those scores, such as dimensionality assessments, convergent and discriminant correlations, and known-groups validity.

The longitudinal aspect of the study will be used to assess test-retest reliability of the new MiCOAS measure items and scores and, if sufficient within person change is observed on conventional measures, the MiCOAS team will assess sensitivity to change and establish preliminary thresholds for clinically meaningful within person change. The duration of the study (8 weeks in Cohort 1, 4 weeks in Cohorts 2 and 3) was selected based on the desire to ensure monthly migraine day (MMD), often the primary outcome in preventive migraine clinical trials, can be calculated and used as a reference variable in the planned analyses, with the two months of daily assessment data in Cohort 1 providing two consecutive months of MMD data for examination.

Finally, the cohort aspect of the design was selected to reduce respondent burden and in hopes of increasing compliance and study completion. The length of the daily assessment is considered appropriate based on qualitative work the MiCOAS project team has completed and the selection of reference measures and number of assessments per cohort were informed by concerns regarding the number of items per assessment and ensuring that (outside of the DAs) assessments were not so frequent as to be burdensome to participants.

5.3 END OF STUDY DEFINITION

The end of the study is defined as the date of the last assessment of the last participant in the SoA shown in the Section 3.3.

The Exit assessment is defined as the last scheduled assessment shown in the SoA (Section 3.3) for the study. A participant is considered to have completed the study if he/she has completed all study assessments including the Exit assessment. If the participant is discontinued or withdraws from the study before the Exit assessment, the last assessment before the discontinuation or withdrawal will be considered an Early Termination assessment and assessment data going forward will be considered missing for that participant.

6 STUDY POPULATION

The study population consists of people living with migraine who have a self-reported medical diagnosis of such.

An individual will be initially eligible for the study if all inclusion criteria are met and none of the exclusion criteria are met. Final determination of eligibility will be based on a person's self-report in responding to a set of screening questions, including the 7-item American Migraine Prevalence and Prevention/American Migraine Study (AMPP/AMS) diagnostic module for migraine which has been previously validated (e.g., Lipton et al., 2001).

6.1 INCLUSION CRITERIA

To be eligible for inclusion in the study, at the time of screening, a person must:

- Be currently living in the US
- Be between 18 and 75 years of age
    - Note, age of consent is over 18 in some U.S. states. Age of eligibility within each state will be modified, as needed, to be consistent with state laws ensuring all subjects may legally consent.
- Report being diagnosed with migraine by a healthcare professional
- Report experiencing 4-26 headache days per month over the last 3 months covering the typical range of eligibility in clinical trials.
- Report being able to distinguish between a day with migraine and other types of headache days
- Meet the criteria for migraine on the AMPP/AMS diagnostic module (Lipton et al., 2001; see item 7 of Appendix A):
    - Respondent meets criteria for migraine if:
        - 2/4 pain features (items 1-4) with score of ≥3
        - AND nausea (item 5) score ≥3 OR BOTH photophobia (item 6) AND phonophobia (item 7) score ≥3.
- Be comfortable reading and speaking in English (i.e., ability to read, write, speak, and understand English well enough to complete informed consent process and take part in the interview).
- Be able to provide informed consent to participate in the study and complete the informed consent documentation

6.2 EXCLUSION CRITERIA

An individual reporting any of the following at the time of screening will be excluded from this study:

- Self-reported of any other clinically significant health condition that might interfere with the person's ability to provide non-confounded descriptions of their experience with migraine-related cognitive, psychosocial, or physical impacts. These include:
    - Multiple sclerosis
    - Traumatic brain injury or spinal cord injury
    - Schizophrenia
    - Bi-polar disorder
    - Alzheimer's disease or dementia
    - Epilepsy
    - Stroke
    - Cognitive impairment
- Self-reported use of opioids or barbiturates more than 4 days during the past 30 days
- Self-reported alcohol or drug abuse over the past 3 months
- Is currently participating in a clinical trial related to migraine
- Is an employee or family member of an employee of FDA, Vector Psychometric Group, LLC, or the Albert Einstein College of Medicine.
- Is unwilling to complete a daily assessment, taking about 5 minutes per day, every day of the study.
- Is unwilling to complete other assessments, taking about 45 minutes per assessment, multiple times throughout the study.

A copy of the Inclusion/Exclusion criteria items can be found in Appendix A.

6.3 LIFESTYLE CONSIDERATIONS

No additional restrictions are required.

6.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the study but are not subsequently entered in the study (e.g., randomized/stratified/enrolled) either because they are not otherwise eligible or because consent is withdrawn before an assessment is completed. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal

information typically includes demography, screen failure details, eligibility criteria, and any serious adverse event. Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened.

6.5 EFFORTS TO MINIMIZE BIAS

Prior to initiation of study participation, each participant who provides informed consent will be assigned a participant number that will serve as the participant identification number on all study documents.

7 PARTICIPANT DISCONTINUATION/WITHDRAWAL

A premature discontinuation will occur if a participant who signs informed consent form (ICF) and ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

7.1 PARTICIPANT DISCONTINUATION

Given the nature and design of this study, the reasons for discontinuation are limited.

The investigator should consider withdrawing a participant from the study early if any of the following criteria are met:

- Participant is unwilling or unable to continue to comply with study procedures
- Participant is unwilling or unable to continue in the study

Whenever possible, the decision to withdraw a participant from the study should be discussed with the PIs prior to withdrawal.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.2 PARTICIPANT WITHDRAWAL

A participant may withdraw from the study:

- at any time at the participant's own request
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit, if applicable, as shown in the SoA.

7.3 PARTICIPANT LOST TO FOLLOW UP

A participant will be considered lost to follow up if he or she repeatedly fails to complete scheduled assessments and is unable to be contacted by the research team.

8 STUDY ASSESSMENTS

Study procedures and their timing are summarized in the SoA. Immediate safety concerns should be discussed with the PIs immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention. Given this is a non-investigational, observational study, the likelihood of safety concerns is exceptionally low.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed to confirm that potential participants meet all eligibility criteria.

8.1 PATIENT-REPORTED OUTCOMES

8.1.1 Health & Demographics

The Health & Demographics questionnaire is a 20-item assessment that asks participants about their health history and their migraine related medication use. It also asks about participants' gender, race, ethnicity, education, as well as other demographic variables.

A copy of the Health & Demographics items can be found in Appendix B.

8.1.2 MiCOAS Daily Assessment (MiCOAS DA)

The MiCOAS-DA is a *de novo* assessment intended to be completed by participants on a daily (calendar day) basis. The content of the items is spread across 2 general item and 3 individual measures:

- Symptoms (10 items)
- Subjective Mental Acuity (5 items; includes 1 symptom item)
- Physical Function (7 items)

The MiCOAS-DA also includes two general items asking about the participants day with respect to their experience. These two items ("Did you have a migraine day?" and "Did you have a good day?") of the MiCOAS DA use a Yes/No response scale. Nine of the symptom items use a 4-category ordinal response scale, with verbal labels (0 = Did not have to 3 = Severe verbal labels). One symptom item asks which symptom experienced was most bothersome. The remaining 11 non-symptom items use 5-category ordinal response scales, with verbal labels varying depending on item content. Most symptom items use a severity response scale (0 = Did not have to 4 = Severe verbal labels) while the non-symptom mental acuity and function items use a difficulty response scale (verbal labels ranging from 0= Not at all difficult to 4 = Unable to do).

Additionally, MMDs is a common outcome in preventive migraine trials, several other symptom and symptom-related items not included in the MiCOAS-DA based on relevance/importance to patients, such as duration of

head pain, medication use, and unilaterality of pain, are also included in the DA to allow for the identification of a migraine day and, when summarized, the calculation of MMDs.

A copy of the MiCOAS DA items can be found in Appendix C.

8.1.3 MiCOAS Recall-based Measures

The MiCOAS recall-based measures are *de novo* instruments. There are four MiCOAS recall-based measures totaling 32 items:

- Physical function (9 items)
- Subjective Cognition (10 items)
- Social role function (7 items)
- Emotional function (6 items)

Additionally, 4 general function items ("On how many days did you have migraine symptoms?", "How often did you feel good?", "How often were you able to enjoy all or part of the day?", and "How often did you want to spend time alone in a comfortable environment?") are also included. Two versions of the recall-based measures have been created, one with a 7-day recall period and the other with a 14-day recall period (MiCOAS-7 and MiCOAS-14, respectively). The physical function, social role function, and emotional function scale items generally use a 5-category ordinal response scale with frequency labels (i.e., 0 = Never to 4 = Always), while the cognitive function scale items tend to use 5-category ordinal responses with verbal labels on a difficulty scale (i.e., 0 = Not difficult at all to 4 = Unable to do). All MiCOAS scores are calculated such that higher values are associated with more negative outcomes (e.g., worse physical function).

A copy of the MiCOAS Recall-based items can be found in Appendix D. The same set of items are used for the 7-day and 14-day recall.

8.1.4 The Migraine Functional Impact Questionnaire (MFIQ)

The Migraine Functional Impact Questionnaire (MFIQ v2; Hareendran et al., 2018; Kawata et al., 2019) is a 26-item questionnaire with a 7-day recall period intended to create measures of:

- Physical function (5 items)
- Usual activities (11 items)
- Social function (5 items)
- Emotional function (5 items)

All items use an ordinal, 5-category response scale, with verbal labels varying based on item content. Higher scores on each of the MFIQ domains are associated with worse outcomes (e.g., poorer physical function).

A list of the MFIQ items can be found in Appendix E.

8.1.5 The Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1)

The Migraine-specific Quality of Life Questionnaire (MSQ v2.1; e.g., Martin et al., 2000) is a 14-item measure with a 4-week recall period intended to assess 3 domains:

- Role function - restrictive (7 items)
- Role function – preventive (4 items)
- Emotional function (3 items)

All items use a 6-category ordered response scale with verbal labels ranging from 1 = None of the time to 6 = All of the time. For all three domains of the MSQ v2.1, summed scores from the items contributing to each domain are calculated and then rescaled to a 0 to 100 metric. For all domains, higher scores are associated with better quality of life/outcomes (e.g., fewer role restrictions due to migraine).

A copy of the MSQ v2.1 items can be found in Appendix F.

8.1.6 The 6-item Headache Impact Test (HIT-6)

The 6-item Headache Impact Test (HIT-6; Bayliss & Batenhorst, 2002) is designed to measure the adverse impacts that migraine and headaches have on respondents' lives over the last 4 weeks. All 6 items use a 5-category ordinal response scale with verbal labels ranging from Never to Always. The HIT-6 total score is found as a summed score. The weighting of response options as they contribute to this sum score is as follows: Never (6 points), Rarely (8 points), Sometimes (10 points), Very Often (11 points), and Always (13 points). Rather than using more typical 1 to 5 response-category values, this weighting scheme was empirically determined in the initial publication of the HIT-6 (Kosinski et al., 2003) to maximize the degree to which the HIT-6 summed score mirrored scores derived using IRT estimation and more items from the adaptive administration of the HIT item bank; scores range from 36 to 79 with higher scores indicating greater impact due to migraine/headaches. Thresholds for severity categories have been suggested for the HIT-6 scores (Bayliss & Batenhorst, 2002) which are: 49 or less = Little to no impact; 50-55 = Moderate impact; 56-59 = Substantial impact; and 60 or greater = Severe impact.

A copy of the HIT-6 items can be found in Appendix G.

8.1.7 Revised MOS Cognitive Function (MOS-Cog-R) measure

The revised Medical Outcomes Study (MOS) Cognitive Function measure (MOS-Cog-R; Yarlas, White, & Bjorner, 2013) is a 6-item assessment intended to assess cognitive function in adults. The recall period for the MOS-Cog-R is 7 days. The item content of the measure covers such topics as concentration and thinking, confusion, attention, and subjective reaction time. All items of the MOS-Cog-R use a 5-category response scale, with verbal labels ranging from "No time" to "All of the time." A total score is calculated by summing the 6 individual item responses and higher total score values are associated with better cognitive functioning.

A copy of the MOS-Cog-R items can be found in Appendix H.

8.1.8 Patient Global Impression of Severity (PGIS)

A patient global impression of status (PGIS) item, asking participants their impression of their migraine severity over the last 7 or 14 days depending on Cohort.

This item can be found in Appendix I.

8.1.9 Patient Global Impression of (PGIC)

A patient global impression of change (PGIC) item, asking participants their impression of their migraine severity has changed "since the start of the study."

This item can be found in Appendix J.

8.1.10 Monthly Migraine Days

MMD is the number of "migraine days" over the selected 28-day periods. It will be calculated when at least 15 days of the diary are completed out of each 28-day period (through Week 4, Week 5, Day 1 through Week 8). If the number of missing days in the respective 28-day period is > 15 days, MMD will be coded as missing. When the number of missing days in the respective 28-day period is between 1 and 14, a normalization procedure will be applied by multiplying the proportion of migraine days (number of migraine days divided by total number of non-missing days) by 28. For example, if a subject reports 5 migraine days over a total of 20 non-missing diary days, the normalized MMD value would be 7 (i.e., (5/20)*28 = 7).

The definition of a migraine day will be adapted from the International Headache Society International Classification of Headache Disorders-3 criteria of migraine and current FDA draft guidance (FDA, 2023). Specifically, a qualified migraine day is defined as any calendar day with a headache (head pain of mild, moderate, or severe intensity), with or without aura, lasting for ≥ 30 minutes and meeting either of the following criteria (A or B):

A. ≥ 2 of the following headache characteristics:
    a. Unilateral location
    b. Pulsating quality (throbbing),
    c. Moderate or severe pain intensity,
    d. Aggravation by or causing avoidance of routine physical activity (e.g., walking to climbing stairs)
B. ≥ 1 of the following:
    a. Nausea and/or vomiting,
    b. Photophobia
    c. Phonophobia

Additionally, the use of acute migraine medications to treat head pain of any duration will also be considered a qualified migraine day.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

There are no statistical hypotheses regarding efficacy for this study.

9.1.1 Multiplicity Adjustment

No adjustments for multiplicity will be included in the analysis.

9.2 SAMPLE SIZE DETERMINATION

The primary analyses of concern from this study are the psychometric analyses related to dimensionality, which will be based on modern measurement theory (MMT) analysis techniques such as item factor analysis and analyses from the item response theory (IRT) framework. There are no formal statistical tests that are routinely relied upon in MMT; as such, power analysis or similar to justify the proposed sample size is unavailable. Indeed, MacCallum, Widaman, Zhang, and Hon (1999), after an extensive review of existing recommendations and a large simulation study, stated "that common rules of thumb regarding sample size in factor analysis are not valid or useful. The minimum level of N, or the minimum N:p ratio, needed to assure good recovery of population factors is not constant across studies, but rather is dependent on some aspects of the variables and design in a given study." (P. 96) Based on their simulation results and making a recommendation for a worst-case scenario factor analysis, MacCallum and colleagues stated samples well over 500 will be necessary. The proposed completion sample of approximately 1000 participants is well over this minimum and should be of appropriate size for the planned analyses. Further, given that item factor analysis and IRT have been demonstrated to be equivalent models (e.g., Takane & De Leeuw, 1987; Wirth & Edwards, 2007), any sample size requirements sufficient for factor analysis will also be appropriate for the application of IRT analysis methods.

9.3 ANALYSES SETS

The analysis sets will consist of experimental units as defined below:

- Full Analysis Set (FAS): All participants who completed at least one recall-based assessment (that is, at least one non-daily assessment) will contribute to the FAS. Upon review of the data, additional observations may be excluded from the FAS, based on data cleaning rules specified in the psychometric analysis plan (PAP).

9.4 STATISTICAL ANALYSES

In general, continuous variables will be summarized by number of participants, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants responding to each discrete category.

9.5 PSYCHOMETRIC ANALYSES

A PAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing or unused data. The main features of the planned psychometric analyses of the target outcomes/endpoints are, for each measure of both the MiCOAS-DA and recall-based measures:

- Descriptive Statistics of sample
- Item-Level Descriptive Statistics
- Psychometric Analyses
    - Dimensionality/Item Factor Analytic Modeling
    - Item Response Theory Analyses
- Reliability
    - Internal Consistency Reliability
    - Test-retest Reliability
- Validation Analyses
    - Convergent/Discriminant Validity
    - Known Groups Analyses
    - Ability to Detect Change
    - Meaningful Within-person Change Threshold Estimates

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH)/International Organization for Standardization good clinical practice guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an institutional review board (IRB)/Independent ethics committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures. Given the observational nature of this study, however, such SAEs or safety findings are unlikely.
- Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.2 FINANCIAL DISCLOSURES

Investigators and sub-investigators will provide sufficient, accurate financial information as necessary to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study. All disseminations of results will include the required FDA language regarding grant funding and the current amount of the award based on the most recent notice of award at the time of publication/presentation.

10.3 INFORMED CONSENT PROCESS

If contacted at the email addresses/phone numbers provided on the electronic ICF , the investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act of 1996 requirements, where applicable, and the IRB/IEC or study center.

The study record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the electronically signed consent was obtained.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.4 DATA PROTECTION

Participants will be assigned a unique identifier. Any participant records or datasets that are provided to sponsor staff for analysis will contain the identifier only; participant names or any information which would make the participant identifiable will not be provided to study personnel unless required.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

10.5 DATA QUALITY ASSURANCE

The Sponsor will permit study-related monitoring (if needed), audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Records and documents, including electronically signed ICFs, pertaining to the conduct of this study must be retained by the Sponsor on secure, encrypted servers. Record retention and destruction will be consistent with Sponsor standard operating procedures.

10.5.1 Data Capture System

An electronic data capture (EDC) system will be used in this study for the collection of study data. All study data will be directly recorded by the participant, into the EDC system. The electronic data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

Data collected via the sponsor-provided data capture system(s) will be stored by the sponsor. The investigator will have continuous access to the data during the study and until decommissioning of the study within the data capture system(s).

10.6 SOURCE DOCUMENTS

Definition of what constitutes source data can be found in Section 4.0 of ICH E6, Good Clinical Practice: Consolidated Guidance and must follow ALCOA, i.e., records must be attributable, legible, contemporaneous, original, and accurate.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. All source material is provided by the subjects directly into the EDC system.

10.7 PUBLICATION POLICY

VPG as the sponsor has proprietary interest in this study. Authorship will be established prior to the writing of the manuscript.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.8 COMPLIANCE WITH PROTOCOL

The investigator is responsible for compliance with the protocol. Protocol deviations will be discussed with the PIs upon identification. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

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12 APPENDIX A – MICOAS QUANT1 I/E SCREENER

The following questions ask about you. Your answers will be used to see whether you are eligible to participate in a study about people's experience with migraine.

Please read each question carefully.

Check the box next to your answer for each question.

1. Are you an employee of the Food and Drug Administration, Albert Einstein College of Medicine, or Vector Psychometric Group?
   - ☐ Yes
   - ☐ No

2. Has a doctor or other health care professional ever told you that you have migraine?
   - ☐ Yes
   - ☐ No

3. How old are you?
   - ☐ Less than 18 years old
   - ☐ 18 to 75 years old
   - ☐ 76 years old or more

4. Do you currently live in the United States?
   - ☐ Yes
   - ☐ No

5. Are you able to tell the difference between a day with migraine and days with other types of headaches?
   - ☐ Yes
   - ☐ No

6. Over the last 3 months, how many migraine headache days have you typically had per month?
   - ☐ 0-3 headache days per month
   - ☐ 4-8 headache days per month
   - ☐ 9-14 headache days per month
   - ☐ 15-20 headache days per month
   - ☐ 21-26 headache days per month
   - ☐ More than 26 headache days per month

7. Please rate how frequently you experience the following symptoms when you have a headache:

	Never	Rarely	Less than Half the Time	Half the Time or More
The pain is worse on one side				
The pain is pounding, pulsating, or throbbing				
The pain has moderate or severe intensity				
The pain is made worse by routine activities such as walking or climbing stairs				
You feel nauseated or sick to your stomach or vomit (throw up)				
Light bothers you (more than when you do not have a headache)				
Sound bothers you (more than when you do not have a headache)				
Your skin is sensitive to things that are usually not painful such as taking a shower, laying your head on a pillow, brushing your hair or wearing an earring.				

8. Has a doctor or other health care professional ever told you that you have any of the following? (Please check all that apply)
   - ☐ Multiple sclerosis
   - ☐ Traumatic brain injury or spinal cord injury
   - ☐ Schizophrenia
   - ☐ Bi-polar disorder
   - ☐ Alzheimer's disease or dementia
   - ☐ Epilepsy
   - ☐ Stroke
   - ☐ Cognitive impairment
   - ☐ None of the above

9. In the last 30 days, how often have you used an opioid (e.g., Percocet or OxyContin) or barbiturate (e.g., Fioricet or Seconal) medication, either for your migraine or for something else?
   - ☐ 0 -2 days
   - ☐ 3-4 days
   - ☐ 5-7 days
   - ☐ 8-10 days
   - ☐ More than 10 days

10. Are you comfortable reading English, such as to read a newspaper or fill out a medical form on your own?
    - ☐ Yes
    - ☐ No

11. Over the <u>past 3 months:</u>

	YES	NO
Have you felt that you should cut down on your drinking or recreational drug use?	1	0
Have people annoyed you by criticizing your drinking or recreational drug use?	1	0
Have you felt guilty about your drinking or recreational drug use?	1	0
Have you had a drink or taken recreational drugs first thing in the morning?	1	0

12. Are you currently enrolled in a clinical trial for migraine?
    - ☐ Yes
    - ☐ No

13. This study involves a daily diary that is to be completed every day and takes about 5 minutes to complete. Are you willing to complete a daily diary?
    - ☐ Yes
    - ☐ No

14. This study also includes days when other questionnaires will be asked, and it may take up to 45 minutes to complete. Are you willing to continue with participation?
    - ☐ Yes
    - ☐ No

13 APPENDIX B – HEALTH AND DEMOGRAPHIC QUESTIONNAIRE

We will use your answers to these questions to describe the sample of people living with migraine who participated in this study. This information will also allow us to better understand how this study relates to the broader population of people living with migraine.

There are 22 questions, but some questions have multiple parts. This survey should take about 10 minutes to fill out.

Please read each question carefully. Check the box next to your answer or fill in the requested information for each question.

The following questions are about you.

1. What is your current age?

   _____ years old [DROP DOWN]

2. How old were you when you were first told by a doctor or other health care provider that you have migraine?

   _____ years old [DROP DOWN] plus an option "I don't remember"

3. In the last 4 weeks, how many days did you have headache of any kind (including migraine)?
   _____ days with headache (including migraine) [DROP DOWN]

4. In the last 4 weeks, how many days were you completely free of headache of any kind (including migraine)?
   _____ days free of headache (including migraine) [DROP DOWN]

5. Over the past year, have you taken medication(s) to treat your migraine headaches when they happen? (These may be over-the-counter or prescription).
   - ☐ Yes [Continue to Question 6]
   - ☐ No [Continue to Question 7]

6. What medication(s) have you taken within the past year to treat your migraine headaches when they happen? *(select **all** that apply)*
   - ☐ Acetaminophen (generic)
   - ☐ Acetaminophen, aspirin, caffeine (generic)
   - ☐ Acetaminophen with codeine (generic)
   - ☐ Advil (ibuprofen)
   - ☐ Aleve (naproxen sodium)
   - ☐ Almotriptan (generic)
   - ☐ Amerge (naratriptan)
   - ☐ Anaprox (naproxen)
   - ☐ Ansaid (flurbiprofen)

☐ Aspirin
☐ Axert (almotriptan)
☐ Butorphanol tartrate (generic)
☐ Cambia (diclofenac)
☐ Cataflam (diclofenac)
☐ Celebrex (celecoxib)
☐ Celecoxib (generic)
☐ Compazine (prochlorperazine)
☐ Darvocet (acetaminophen and propoxyphene)
☐ Darvon (propoxyphene+ aspirin+ caffeine)
☐ Demerol (meperidine)
☐ DHE-45 injection (dihydroergotamine)
☐ Diclofenac (generic)
☐ Dihydroergotamine (generic)
☐ Duradrin (Isometheptene+ dichloralphenazone+ acetaminophen)
☐ Eletriptan (generic)
☐ Esgic (butalbital+ caffeine+ acetaminophen) with or without codeine
☐ Etodolac (generic)
☐ Excedrin (acetaminophen+ aspirin+ caffeine)
☐ Excedrin "Generic" (acetaminophen+ aspirin+ caffeine)
☐ Excedrin Migraine (acetaminophen+ aspirin+ caffeine)
☐ Fioricet (butalbital+ caffeine+ acetaminophen) with or without codeine
☐ Fiorinal (butalbital+ caffeine+ aspirin) with or without codeine
☐ Flurbiprofen (generic)
☐ Frova (frovatriptan)
☐ Frovatriptan (generic)
☐ Hydrocodone with or without acetaminophen (generic)
☐ Ibuprofen (generic)
☐ Imitrex (sumatriptan) nasal spray
☐ Imitrex (sumatriptan) pills or tablets/capsules
☐ Indocin (indomethacin)
☐ Indomethacin (generic)
☐ Ketoprofen (generic)
☐ Ketorolac (generic)
☐ Lasmiditan (generic)
☐ Lidocaine nasal spray
☐ Lodine (etodolac)
☐ Maxalt (rizatriptan)
☐ Meclofenamate (generic)
☐ Meclomen (meclofenamate)
☐ Meloxicam (generic)
☐ Meperidine (generic)
☐ Metoclopramide (generic)
☐ Midrin (Isometheptene+ dichloralphenazone+ acetaminophen)
☐ Migranal nasal spray (dihydorergotamine)

☐ Mobic (meloxicam)
☐ Motrin (including prescription Motrin) (ibuprofen)
☐ Nabumetone (generic)
☐ Naprosyn (naproxen)
☐ Naproxen (generic)
☐ Naproxen sodium (generic)
☐ Naratriptan (generic)
☐ Nasal spray (non-prescription) Please specify: _____
☐ Nurtec (rimegepant)
☐ Orudis/ Oruvail (ketoprofen)
☐ Oxycodone (generic)
☐ Percocet, Percodan (oxycodone)
☐ Phenergan (promethazine)
☐ Phrenilin or Phrenilin Forte (butalbital+ acetaminophen)
☐ Prochlorperazine (generic)
☐ Promethazine (generic)
☐ Reglan (metoclopramide)
☐ Relafen (nabumetone)
☐ Relpax (eletriptan)
☐ Reyvow (lasmiditan)
☐ Rimegepant (Nurtec)
☐ Rizatriptan (generic)
☐ Roxicodone (oxycodone)
☐ Sinus or allergy medications (e.g., Tylenol Sinus)
☐ Stadol (butorphanol tartrate)
☐ Sumatriptan (generic)
☐ Toradol (ketorolac)
☐ Tramadol compound (generic)
☐ Treximet (sumatriptan + naproxen sodium)
☐ Tylenol (acetaminophen)
☐ Tylenol with codeine
☐ Ubrelvy (ubrogepant)
☐ Ultram, Ultracet (tramadol compound)
☐ Vanquish (acetaminophen+ aspirin+ caffeine medication)
☐ Vicodin (acetaminophen and hydrocodone or other hydrocodone compound)
☐ Voltaren (diclofenac) pills or tablets/capsules
☐ Voltaren (diclofenac) topical gel
☐ Zolmitriptan (generic)
☐ Zomig (zolmitriptan) pills or tablets/capsules
☐ Zomig (zolmitriptan) nasal spray
☐ Other prescription injection Please specify_____
☐ Other prescription medication (pills or tablets/capsules) Please specify _____
☐ Other prescription nasal spray Please specify _____
☐ Other prescription topical Please specify _____

7. Do you currently take any medication(s) or receive any treatment(s) to prevent or reduce the frequency or severity of migraine (i.e., preventive medication)?
   - ☐ Yes [Continue to Question 8]
   - ☐ No [Continue to Question 9]

8. What medication(s) do you take or what treatment(s) do you receive to prevent or reduce the frequency or severity of migraine (i.e., preventive medication)? *(select **all** that apply)*
   - ☐ AbotulinumtoxinA (generic)
   - ☐ Acetazolamide (generic)
   - ☐ Aimovig (erenumab)
   - ☐ Ajovy (fremanezumab)
   - ☐ Amitriptyline (generic)
   - ☐ Aspirin
   - ☐ Atacand (candesartan)
   - ☐ Atenolol (generic)
   - ☐ Blocadren (timolol)
   - ☐ Botox (onabotulinumtoxin A)
   - ☐ Calan/Covera-HS/Isoptin, Verelan (verapamil)
   - ☐ Candesartan (generic)
   - ☐ Clopidogrel (generic)
   - ☐ Coenyzme Q10
   - ☐ Corgard (nadolol)
   - ☐ Cymbalta (duloxetine)
   - ☐ Cyproheptadine (generic)
   - ☐ Depakote (divalproex sodium)
   - ☐ Desvenlafaxine (generic)
   - ☐ Diamox (acetazolamide)
   - ☐ Divalproex sodium (generic)
   - ☐ Duloxetine (generic)
   - ☐ Dysport (abotulinumtoxinA)
   - ☐ Effexor (venlafaxine)
   - ☐ Elavil (amitriptylline)
   - ☐ Emgality (galcanezumab)
   - ☐ Escitalopram oxalate (generic)
   - ☐ Fluoxetine (generic)
   - ☐ Gabapentin (generic)
   - ☐ Inderal (propranolol)
   - ☐ Lacosamide (generic)
   - ☐ Lexapro (escitalopram oxalate)
   - ☐ Lisinopril (generic)
   - ☐ Lopressor (metoprolol)
   - ☐ Lyrica (pregabalin)
   - ☐ Magnesium
   - ☐ Memantine (generic)
   - ☐ Metoprolol (generic)
   - ☐ Nadolol (generic)

☐ Namenda (memantine)
☐ Neurontin (gabapentin)
☐ Nifedipine (generic)
☐ Nortriptyline (generic)
☐ Nurtec (rimegepant)
☐ Onabotulinumtoxin A (generic)
☐ Pamelor (nortriptylline)
☐ Paroxetine (generic)
☐ Paxil (paroxetine)
☐ Periactin (cyproheptadine)
☐ Plavix (clopidogrel)
☐ Pregabalin (generic)
☐ Prinivil (lisinopril)
☐ Pristiq (desvenlafaxine)
☐ Procardia (nifedipine)
☐ Propranolol (generic)
☐ Prozac (fluoxetine)
☐ Qudexy (topiramate)
☐ Riboflavin (vitamin B2)
☐ Rimegepant (Nurtec)
☐ Sertraline (generic)
☐ Tenormin (atenolol)
☐ Timolol (generic)
☐ Tizanidine (generic)
☐ Topamax (topiramate)
☐ Topiramate (generic)
☐ Toprol XL (metoprolol)
☐ Trokendi (topiramate)
☐ Venlafaxine (generic)
☐ Verapamil (generic)
☐ Vimpat (lacosamide)
☐ Vitamin B2
☐ Vyepti (eptinezumab)
☐ Zanaflex (tizanidine)
☐ Zestril (lisinopril)
☐ Zoloft (sertraline)
☐ Other Please specify _____

9. Do you currently use any of the following medications for any reason, including for your migraine? (Select any that apply)
    - ☐ No, I don't currently use any of these medications
    - ☐ Amitriptyline (Elavil, Vanatrip)
    - ☐ Amoxapine (Asendin)
    - ☐ Clomipramine (Anafranil)
    - ☐ Desipramine (Normpramin)
    - ☐ Divalproex sodium (Depakote)
    - ☐ Doxepin (Sinequan)
    - ☐ Eletriptan (Relpax)
    - ☐ Imipramine (Tofranil)
    - ☐ Lasmiditan (Reyvow)
    - ☐ Nortriptyline (Pamelor, Aventyl Hydrochloride)
    - ☐ Protriptyline (Vivactil)
    - ☐ Topiramate (Topamax, Trokendi XR, Qudexy XR, Topiragen)
    - ☐ Trimipramine (Surmontil)

10. What sex were you assigned at birth? *(select one only)*
    - ☐ Male
    - ☐ Female
    - ☐ Other (please share if you would like): _____
    - ☐ Prefer not to answer

11. What is your gender? *(select one only)*
    - ☐ Woman
    - ☐ Man
    - ☐ Trans Woman
    - ☐ Trans Man
    - ☐ Genderqueer/ Gender Non-Binary
    - ☐ Other (please share if you would like):_____
    - ☐ Prefer not to answer

12. Are you of Hispanic, Latino, or Spanish origin? *(select one only)*[1]
    - ☐ Yes (Optional: How would you describe yourself? _____)
    - ☐ No
    - ☐ Prefer not to answer

13. What race best describes you? *(select all that apply)*[1]
    - ☐ American Indian or Alaska Native
    - ☐ Asian
    - ☐ Black or African American
    - ☐ Native Hawaiian or Other Pacific Islander
    - ☐ White
    - ☐ Other (please specify): _____
    - ☐ Prefer not to answer

14. What language do you speak most of the time at home? *(select one only)*
    - ☐ English
    - ☐ Another language
      Please specify _____

15. Are you currently married or living with a domestic partner or significant other?
    - ☐ Yes
    - ☐ No

16. Other than yourself, how many adults live in your household? _____ [DROP DOWN]

[1] Categories have been selected to conform with federal requirements for the collection and reporting of race and ethnicity data in clinical research, as described in the NIH policy guidelines at: https://grants.nih.gov/grants/funding/women_min/guidelines.htm

17. How many children live (part-time or full-time) in your household? _____ [DROP DOWN]

18. How would describe how much education you have completed? _____ [DROP DOWN]

19. How would you describe your current employment status? *(select **all** that apply)*
    - ☐ Student
    - ☐ Employed for wages or self-employed (full time or part time)
      Approximate number of hours worked per week: _____ [DROP DOWN]
    - ☐ Not currently employed and looking for work
    - ☐ Not currently employed and not looking for work
    - ☐ Homemaker
    - ☐ Retired
    - ☐ Disabled (or on disability or leave of absence)
    - ☐ Other, please specify_____
    - ☐ Prefer not to answer

20. Which of these income categories comes closest to the total yearly income for your household, from all sources? *(select one only)*
    - ☐ Under $30,000
    - ☐ $30,000 to $59,999
    - ☐ $60,000 to $90,000
    - ☐ More than $90,000
    - ☐ Prefer not to answer

14 APPENDIX C – MICOAS DAILY ASSESSMENT (MICOAS DA)

NOTE: For ease of review, items seen at every administration are presented in **bold.** Items seen based on participant responses/conditional logic are presented in *italics*.

In the past 24 hours….

1. Did you have a good day?
   ☐ Yes ☐ No

2. Did you have a migraine day?
   ☐ Yes ☐ No

3. Did you have a headache or head pain?
   ☐ Did not have ☐ Mild ☐ Moderate ☐ Severe

   3.1 *How long did the headache last? [if #3 >= Mild]*
   30 minutes or less
   More than 30 minutes but 2 hours or less
   More than 2 hours but less than 4 hours
   4 hours or more

   3.2 Did your head pain get worse with activity [if #3 >= Mild]
   ☐ Yes ☐ No

   3.3 Did you have throbbing/pounding head pain? [if #3 >= Mild]
   ☐ Yes ☐ No

   3.4 Did you have pain only or worse on one side of your head? [if #3 >= Mild]
   ☐ Yes ☐ No

   3.5 Did you take any medication to alleviate your head pain? [if #3 >= Mild]
   ☐ Yes ☐ No

   3.6 Did you seek care from a health care provider today because of your headache or head pain? [if #3 >= Mild]
   ☐ Yes ☐ No

4 Did you experience any of the following? (check all that apply)
   Aura (e.g., visual spots or flashes of light, skin tingling or numbness) [if yes, present 4.1]
   Dizziness or vertigo [if yes, present 4.2]
   Mental Slowness or Fogginess [if yes, present 4.3]
   Nausea [if yes, present 4.4]
   Neck Pain [if yes, present 4.5]
   Sensitivity to Light [if yes, present 4.6]
   Sensitivity to Sound [if yes, present 4.7]
   Tired [if yes, present 4.8]
   Vomiting [if yes, present 4.9]
   None of the above [unavailable to select if any other response is selected; if selected go to #5]

[If YES to corresponding response to #4 present 1 item per screen]

4.1 Aura was
☐ Mild ☐ Moderate ☐ Severe

4.2 Dizziness or vertigo was
☐ Mild ☐ Moderate ☐ Severe

4.3 Mental Slowness or Fogginess was
☐ Mild ☐ Moderate ☐ Severe

4.4 Nausea was
☐ Mild ☐ Moderate ☐ Severe

4.5 Neck Pain was
☐ Mild ☐ Moderate ☐ Severe

4.6 Sensitivity to Light was
☐ Mild ☐ Moderate ☐ Severe

4.7 Sensitivity to Sound was
☐ Mild ☐ Moderate ☐ Severe

4.8 Tiredness was
☐ Mild ☐ Moderate ☐ Severe

4.9 Vomiting was
☐ Mild ☐ Moderate ☐ Severe

4.10 Which one of the following symptoms other than pain was most bothersome to you? (Select one) [Only if at least 1 "Yes" to 4]
[Present those with "YES" response to #4]
Aura [if selected for #4]
Dizziness or vertigo [if selected for #4]
Mental Slowness or Fogginess [if selected for #4]
Nausea [if selected for #4]
Neck Pain [if selected for #4]
Sensitivity to Light [if selected for #4]
Sensitivity to Sound [if selected for #4]
Tiredness [if selected for #4]
Vomiting [if selected for #4]
Another symptom was most bothersome [if at least one symptom was selected for #4]

5 Were any of the following difficult? (check all that apply)
Bending Forward [if yes, present 5.1]
Concentrating [if yes, present 5.2]
Getting Ready for the Day (e.g., get showered and dressed) [if yes, present 5.3]
Keeping Your Plans for the Day [if yes, present 5.4]
Moving Your Body [if yes, present 5.5]
Moving Your Head [if yes, present 5.6]
Remembering the correct words for things [if yes, present 5.7]
Speaking Clearly [if yes, present 5.8]
Strenuous Physical Activity [if yes, present 5.9]
Thinking Clearly [if yes, present 5.10]
Walking [if yes, present 5.11]
None of the above [unavailable to select if any other option is selected; if selected END]

[If YES to corresponding response to #6 present 1 item per screen]

5.1 Bending forward was
☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

5.2 Concentrating was
☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

5.3 Getting ready for the day (e.g., get showered and dressed) was
☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

5.4 Keeping your plans for the day was
☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

5.5 Moving your body was
☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

5.6 Moving your head was
☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

5.7 Remembering the correct words for things was
☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

5.8 Speaking clearly was
☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

5.9 Strenuous physical activity was
☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

5.10 Thinking clearly was
☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

5.11 Walking was
☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

15 APPENDIX D – MICOAS RECALL-BASED MEASURES

The following questions are about your experiences over the past 7/14 days.

In the past [7 days | 14 days] …

1. On how many days did you have migraine symptoms?

   Drop down/check box choice of 0-7 or 0-14

2. How often did you feel good?

   ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

3. How often were you able to enjoy all or part of a day?

   ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

4. How often did you want to spend time alone in a comfortable environment?

   ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

5. Was it difficult for you to do your usual day-to-day activities?

   ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

6. Was it difficult for you to take care of people or pets that you usually take care of?

   ☐ Does not apply to me ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

7. Was it difficult for you to manage your usual tasks and responsibilities at school or at work?

   ☐ Does not apply to me ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

8. How often were you too tired to do your regular daily activities?

   ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

9. How often did you have to miss your regular daily activities? Include times that you stopped early or started late.

   ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

10. Was it difficult for you to do usual activities that require physical exertion, like going up stairs?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

11. Was it difficult for you to do your regular household chores?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

12. Was it difficult for you to do activities because you were sensitive to light?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

13. Was it difficult for you to do activities because you were sensitive to smells?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

14. Was it difficult for you to do activities because you were sensitive to sound?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

15. Was it difficult for you to do errands?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

16. Was it difficult for you to keep plans you made?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

17. How often were you reluctant to make plans with other people?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

18. How often did you have to cancel or change your plans for social or recreation activities?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

19. Was it difficult for you to enjoy social activity with other people?

☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

20. Was it difficult for you to take part in activities you do for fun?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

21. How often did you feel you did not have control over your life?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

22. How often did you feel worried about having a migraine attack?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

23. How often were you concerned that your migraine attacks would affect other people's lives?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

24. How often did you feel sad or depressed?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

25. How often did you feel frustrated?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

26. How often did you feel irritable?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

27. Was it difficult for you to concentrate?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

28. Was it difficult for you to speak clearly?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

29. Was it difficult for you to remember the right word for something?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

30. Was it difficult for you to have a conversation?

☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

31. Was it difficult for you to understand what was said to you?

☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

32. Was it difficult for you to understand what you were reading?

☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

33. Was it difficult for you to make day-to-day decisions?

☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

34. Was it difficult for you to carry out tasks that required many steps?

☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do

35. Was it difficult for you to remember things that were important to you?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

36. Was it difficult for you to do tasks that required you to concentrate?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

16 APPENDIX E – 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, 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 feel 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

17 APPENDIX F – MIGRAINE-SPECIFIC QUALITY OF LIFE QUESTIONNAIRE (MSQ) (VERSION 2.1)

PATIENT INSTRUCTIONS:

Please fill out this questionnaire. It will help us understand the effects of migraine headache on your daily activities.

The questionnaire has been designed so that it can be completed quickly and easily. Please check only one answer for each question. You should answer every question.

Thank you for your time.

While answering the following questions, please think about ***all migraine attacks*** you may have had ***in the past 4 weeks***.

1. In the past 4 weeks, how often have migraines **interfered** with how well you dealt with family, friends and others who are close to you? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

2. In the past 4 weeks, how often have migraines **interfered** with your leisure time activities, such as reading or exercising? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

3. In the past 4 weeks, how often have you had **difficulty** in performing work or daily activities because of migraine symptoms? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

4. In the past 4 weeks, how often did migraines **keep you** from getting as much done at work or at home? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

5. In the past 4 weeks, how often did migraines **limit** your ability to concentrate on work or daily activities? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

6. In the past 4 weeks, how often have migraines **left you too tired** to do work or daily activities? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

7. In the past 4 weeks, how often have migraines **limited** the number of days you have felt energetic? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

8. In the past 4 weeks, how often have you had to **cancel** work or daily activities because you had a migraine? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

9. In the past 4 weeks, how often did you **need help** in handling routine tasks such as every day household chores, doing necessary business, shopping, or caring for others, when you had a migraine? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

10. In the past 4 weeks, how often did you have to **stop** work or daily activities to deal with migraine symptoms? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

11. In the past 4 weeks, how often were you **not able to go** to social activities such as parties, dinner with friends, because you had a migraine? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

12. In the past 4 weeks, how often have you **felt** fed up or frustrated because of your migraines? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

13. In the past 4 weeks, how often have you **felt** like you were a burden on others because of your migraines? (Select only **one** response.)
   - ❑ None of the time
   - ❑ A little bit of the time
   - ❑ Some of the time
   - ❑ A good bit of the time
   - ❑ Most of the time
   - ❑ All of the time

14. In the past 4 weeks, how often have you been **afraid** of letting others down because of your migraines? (Select only **one** response.)
    - ❑ None of the time
    - ❑ A little bit of the time
    - ❑ Some of the time
    - ❑ A good bit of the time
    - ❑ Most of the time
    - ❑ All of the time

18 APPENDIX G – 6-ITEM HEADACHE IMPACT TEST (HIT-6) MEASURE

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please select one answer for each question:

	Never	Rarely	Sometimes	Very Often	Always
When you have headaches, how often is the pain severe?					
How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?					
When you have a headache, how often do you wish you could lie down?					
In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?					
In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?					
In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?					

19 APPENDIX H – REVISED MOS COGNITIVE FUNCTION (MOS-COG-R) MEASURE

For each of the following questions, please select the one response that best describes your answer.

	All of the time	Most of the time	Less than Half the Time	Half the Time or More
How much of the time during the past 4 weeks:				
How much of the time during the past 4 weeks:				
How much of the time during the past 4 weeks:				
How much of the time during the past 4 weeks:				
How much of the time during the past 4 weeks:				
How much of the time during the past 4 weeks:				

20 APPENDIX I - PATIENT GLOBAL IMPRESSION OF SEVERITY (PGIS)

Please choose the response below that best describes the severity of your migraines over the past week.

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

Please choose the response below that best describes the severity of your migraines over the past two weeks.

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

21 APPENDIX J - PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the study, my overall migraine status is:

- ☐ Very Much Improved
- ☐ Much Improved
- ☐ Minimally Improved
- ☐ No Change
- ☐ Minimally Worse
- ☐ Much Worse
- ☐ Very Much Worse