MiCOAS UH3

QUALITATIVE STUDY PROTOCOL : CONCEPT ELICITATION

VECTOR PSYCHOMETRIC GROUP, LLC

CHAPEL HILL, NORTH CAROLINA U.S.A.

REVISION HISTORY

Version	Date	By	Description of Changes
1.0	06/15/2021	R. Mangrum	Incorporates feedback from External Technical Advisory Committee

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PROTOCOL SYNOPSIS

STUDY TITLE: Qualitative Concept Elicitation to Support Development of the Migraine Clinical Outcome Assessment System (MiCOAS)

STUDY DESIGN: Observational, non-interventional, cross-sectional, qualitative study of people with episodic or chronic migraine. The study will recruit study participants through a web-based screening survey for participation in a one-time individual semi-structured interview conducted via telephone or web-conferencing system.

STUDY OBJECTIVES: This study aims to develop knowledge and evidence about the experience of people living with migraine disease to support the development and refinement of clinical outcome assessment measures for future use in clinical trials of migraine treatments.

STUDY POPULATION SAMPLE: This study will include approximately 48 participants, stratified by average monthly headache day frequency, that are representative of the population of patients with migraine who are generally included in clinical trials. As is typical with qualitative research of this kind, the final sample size for this study will remain flexible as the interview data collection progresses and concept saturation is assessed.

The study will include adults diagnosed with migraine in the US and meeting the following inclusion and exclusion criteria, based on their self-report on the initial screening questionnaire:

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

- Be a resident of the US.
- Be between 18 and 75 years of age.
- Report being diagnosed with migraine by a healthcare professional.
- Be able to distinguish between a day with migraine and other types of headache days.
- Report experiencing 4-26 headache days per month over the last 3 months.
- Report experiencing limitations on physical or cognitive activities on at least 1 day over the last 3 months because of migraine.
- Be comfortable reading and speaking in English.
- Provide informed consent to participate in the study.
- Be willing to have their interview audio recorded and transcribed.

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

- Self-reported diagnosis of any other clinically significant health condition that might interfere with the person's ability to provide non-confounded descriptions of their experience, such as multiple sclerosis or dementia.
- 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.
- Have participated in an interview or focus group related to migraine experience in the past 12 months.

- Is an employee or family member of an employee of FDA, Vector Psychometric Group, or the Albert Einstein College of Medicine.

Finally, data gathered through a health and demographic survey will be used to ensure that a) the sample includes individuals representing a variety of demographic characteristics (e.g., age, sex, race) and b) does not oversample from individuals whose perspectives may skew or confound results (e.g., people with advanced degrees, people using medications with known cognitive side effects).

DATA COLLECTION: Data for study analyses will be collected using the following instruments:

- Appendix B: Participant Eligibility Screener (delivered via web-based questionnaire platform)
- Appendix D: Health and Demographic Information Form (delivered via web-based questionnaire)
- Appendix F: Interview Guide

ANALYTIC APPROACH: Audio-recordings will be transcribed verbatim and deidentified by removing any information that identifies, or could be used to identify, participants. Deidentified transcripts will be uploaded to NVivo Windows, a qualitative data analysis system. Transcripts will be classified by case characteristics and coded to identify relevant concepts. Codes for similar or related concepts will be grouped hierarchically. The research team will develop a preliminary codebook which will be further expanded and refined as appropriate during coding using a consensus-based team approach.

Concept saturation will be monitored for the appearance of novel concepts across chronologically ordered interviews to determine the point at which additional interviews are unlikely to result in the identification of further relevant concepts.

Coded data will then be summarized both quantitatively (e.g., assessment of the number of interviews endorsing each coded concept) and qualitatively (e.g., summary of code scope and content illustrated by example quotes, assessment of disconfirming examples).

TIMELINE: The estimated length of this qualitative study from the time of Institutional Review Board (IRB) review to completion of the draft study report is expected to be approximately 6-9 months. However, study length is highly dependent upon recruitment rate and participant availability.

ABBREVIATIONS

CHAMP	The Coalition for Headache and Migraine Patients
COA	Clinical Outcome Assessment
Einstein	Albert Einstein College of Medicine
ETAC	External Technical Advisory Committee
FDA	U.S. Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
MiCOAS	Migraine Clinical Outcome Assessment System
QDAS	Qualitative Data Analysis System
VPG	Vector Psychometric Group, LLC

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F	Initial Qualitative Interview Guide**

* Screen shots of the online platform version of this form will also be provided to the IRB for review.

**Initial version will be provided; given the dynamic interviewing process, the interview guide may be modified/refined throughout participant interviews.

INTRODUCTION

Migraine is a highly prevalent neurological disease that is associated with significant economic, social, and individual burden, including disability.[1-3] Migraine impacts people's ability to function across multiple roles and settings ranging from occupational or academic to social, familial, and personal.[2-8] Although there are many subtypes of migraine, one important distinction is between episodic migraine, defined as ≤14 headache days per month over a 3-month period, and chronic migraine, defined ≥15 headache days per month over a 3-month period, of which at least 8 are linked to migraine.[9] Episodic and chronic migraine are associated with different levels of impact on well-being, with studies demonstrating that chronic migraine conveys significantly higher burdens compared with episodic migraine.[10]

Migraine impacts or limits functioning across an array of cognitive, physical, and psychosocial domains. This places burden on both people who live with the condition, their families, and their communities.[5] The 2016 Global Burden of Disease analysis listed migraine as the second most disabling condition worldwide, second only to low back pain, and reported that migraine caused 45.1 million years lived with disability per year.[11] The economic consequences of migraine are substantial. Migraine results in almost 112 million total days of bedrest per year, costing American employers $8 billion per year due solely to missed workdays.[3] Studies also show that migraine is comorbid with a wide range of other health conditions (e.g., cardiovascular disease, depression, anxiety, asthma, fibromyalgia) thus contributing to increased burden and direct and indirect costs.[12-15]

Treatments for migraine, which include both pharmacologic and non-pharmacologic therapies, are categorized as either acute or preventive.[4,6] Acute treatments aim to resolve migraine symptoms when an attack occurs and return individuals to a normal level of functioning as quickly as possible.[16] Preventive migraine treatments aim "to reduce the frequency, duration, or severity of attacks."[17] Both acute and preventive migraine treatments also aim to preserve or enhance individuals' health-related quality of life, and to reduce burden associated with migraine.

In recent years, FDA has approved many new acute and preventive migraine treatments and a significant level of interest in developing new treatments persists in headache medicine. However, there are significant limitations to the evidence regarding the meaningfulness and validity of current clinical outcome assessments (COA) used in migraine treatment trials. Most notably, several of these assessments were developed with limited or no qualitative study to collect direct and systematic input from people living with migraine.

In acute migraine trials, coprimary endpoints are typically freedom from pain and freedom from the individual's designated most bothersome symptom at 2 hours post-dose. For preventive treatment trials, the standard primary endpoint is reduction in mean migraine (or headache) days per month. While these endpoints are important and capture what patients with migraine value, further empirical evidence can help identify supplemental measures that assess other impacts of migraine. Further, it is unclear if migraine-specific instruments that assess broader quality of life, functioning, and disability are comprehensive in addressing outcomes that are important to people with migraine. Taken together, this demonstrates a clear

need for better integration of people with migraine in determining how to define and measure clinical endpoints for assessing treatment efficacy.

1. STUDY BACKGROUND AND AIMS

To assess and address current limitations in patient-reported outcome metrics for evaluation of therapies in migraine, Vector Psychometric Group, LLC (VPG) in collaboration with Albert Einstein College of Medicine (Einstein) was awarded a U.S. Food and Drug Administration (FDA) grant to support the development of a patient-informed and publicly available standard core set of COAs for migraine. This project to develop the Migraine Clinical Outcome Assessment System (MiCOAS) focuses on incorporating data about the lived experience of people living with migraine and feedback regarding impacts and outcomes most meaningful to them.

To support this work, VPG assembled key stakeholders (i.e., patient advocates, healthcare professionals, COA development experts, psychometricians, regulators, industry, and payers) in an External Technical Advisory Committee (ETAC) that provides ongoing guidance in the implementation of the project (AIM 1) and conducted a comprehensive systematic review of the migraine literature to fully understand existing outcomes and COAs used in both acute and preventive migraine trials (AIM 2). The research team then partnered with Pharmerit to conduct a qualitative study (AIM 3) to capture the perceived symptom, disability and impact experiences of persons living with migraine, with a specific focus on understanding the treatment benefits that people with this disease value most.

Execution of these initial three AIMS provided substantial evidence of widespread physical, psychological, social, and cognitive burden associated with migraine. Participants in the qualitative study, for example, reported a broad array of factors associated with migraine-related functioning and disability. However, work to date also showed that no existing patient-reported outcome measure (PROM) appears suitable for assessing functional impairment or disability over all the domains identified as important by people with migraine. For example, existing measures vary widely in which functions are included, as well as how functions are conceptualized and measured with respect to timeframe or response scale. As a result, a major concern has emerged regarding how to assess these functional outcomes reliably in a manner that is meaningful to patients with migraine and can be used to support valid claims regarding a treatment's impact on migraine-related functioning and disability.

1.1. QUALITATIVE STUDY OBJECTIVES

The overall goal of the qualitative study described in this protocol is to support the development of person-centered COAs for the measurement of migraine outcomes and endpoints in therapeutic treatment trials by collecting data regarding people's experience of physical, cognitive, and psychosocial function impacts that result from migraine. Building on the previous round of qualitative work, concept elicitation interviews will provide data to support understanding of the underlying concepts, content, structure, and scope of the functional impact or disability outcomes relevant for studies of both acute and preventive treatments. Secondarily, most bothersome symptom, severity of symptoms and impacts, and ability to recall migraine experience over a period of time will also be qualitatively examined. Across all study objectives, differences in symptoms and outcomes by ictal and interictal phases will be examined.

Data collection will consist of interviews with people with migraine focused on the following objectives:

1. **Develop knowledge of function concepts in migraine**. To assess and improve the previously developed list of concepts related to cognitive, psychosocial, and physical functioning that are reported by people with migraine.

2. **Develop knowledge of relevant timeframes for experience and for recall**. To understand how interview participants conceptualize symptoms and function relative to ictal and interictal periods, and how they perceive their capacity to recall or judge their experiences over different periods of time.

3. **Develop knowledge of the relevance of different outcomes to patients.** To understand which impacts on functioning are the most bothersome, the most consequential in reducing overall quality of life, or the most desirable to address through treatment, as well as how much change in experience with treatment is meaningful, desirable, or acceptable. To understand how patient perspectives on the importance of different outcomes align with standard definitions of most bothersome symptom used in trials of migraine treatment.

4. **Develop knowledge of severity, frequency**. To explore variation in the severity of symptoms, limitations on functioning, or disability as experienced by people living with migraine, and to build knowledge of how people describe and judge severity (e.g., as more intense, more frequent, more disabling) and how they perceive and make decisions about treatment based on absolute or comparative aspects of severity or limitations on functioning.

5. **Develop knowledge of language.** To identify the specific language people living with migraine use to express concepts relevant to symptoms and functioning.

2. METHOD

2.1. Study Design Overview

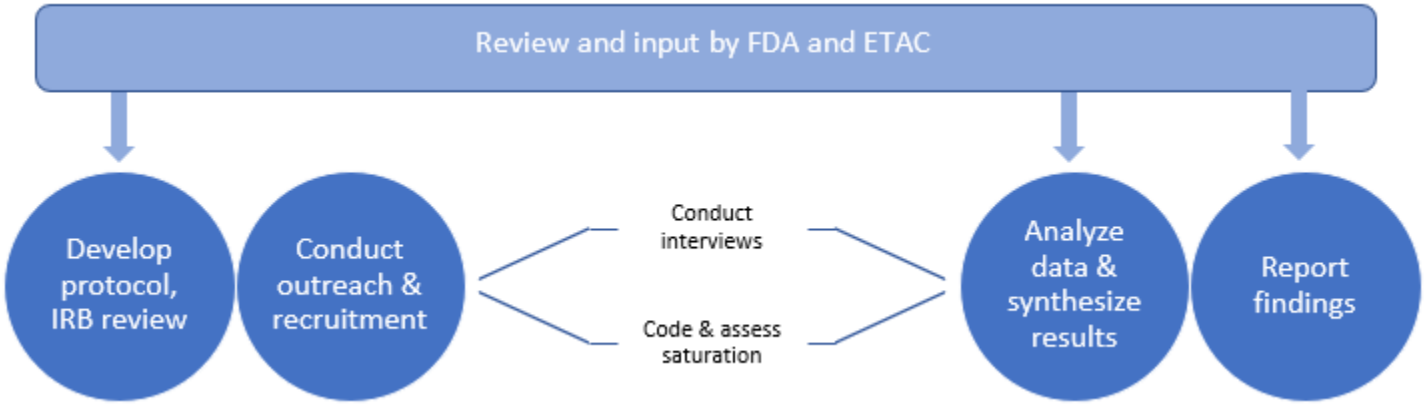
This is an observational, cross-sectional, qualitative study of people with migraine. As a non-interventional observational study, participants will not be assigned to any treatment based on the study protocol, nor will participation in the study impact the normal care they receive from their current health care provider.

The study involves conducting one-time individual qualitative interviews via telephone or web-conferencing with approximately 48 US-based people who self-report that they have been diagnosed with migraine by a physician. The interviews will focus on understanding individual's experience of the cognitive, psychosocial, and physical impacts that result from migraine. Data will consist of information from a health and demographic survey and transcripts of interviews.

Figure 1 depicts the overall flow for this study. The estimated length of this qualitative study from the time of Institutional Review Board (IRB) response to completion of the draft study report is approximately 6-9 months.

Individual interviews were selected instead of focus groups to permit a detailed, comprehensive study of individual experiences of functioning and disability and provide clarity about complex, interrelated factors within illness experience.[18, 19] Conducting one-on-one interviews provides the interviewer with more control over the conversation, allowing for greater personalization to each person, and eliminates group dynamics, such as a social desirability response bias, that may constrain individuals from sharing their genuine perspectives. Individual interviews offer participants a private, unhurried environment which makes it easier to share detailed experiences and address questions that may be sensitive or embarrassing.[20] Telephone/web-conference interviews will be conducted in lieu of in-person interviews to minimize the logistical burden for study participants (i.e., not required to travel for the interview) and to allow maximum flexibility in accommodating participant availability and personal comfort.

Figure 1. Overall Study Flow



2.2. Stakeholder Engagement in the Study

The study team will engage with two stakeholder groups in designing and executing this study. These engagements provide opportunities for stakeholders to provide input into data collection and analysis procedures, which improves the likelihood that study results will be relevant and meaningful to patients and clinicians.[21] The ETAC will provide input on the interview guide and codebook and will advise on the interpretation of results. The Coalition for Headache and Migraine Patients (CHAMP) will provide input on the interview guide and participate in mock interviews to test and refine the interview guide. CHAMP may also advise on the codebook and interpretation of results.

2.3. Study Population Sample

2.3.1. Sample Size and Description

This study will employ stratified purposive sampling (a type of non-probability sampling) to recruit approximately 48 people diagnosed with migraine who exhibit variation in self-reported headache frequency. In this approach, desired characteristics based on the population of interest and relevant to the research objectives are used to select potential study participants and to capture variations across key cohorts among the common core of concepts that emerge.[22-25] Headache frequency stratifications and approximate target sample sizes are summarized in Table 1 below. This sampling and stratification approach mirrors the approach used in many clinical trials. It also seeks to balance participation by people with episodic and chronic migraine and provides a robust opportunity to explore variation in experience as well as assess conceptual saturation within each stratum. However, these are estimates that may change in response to participant availability and iterative analyses of early interview data. As saturation is assessed, the number of participants in strata may shift and the overall number of participants may change as well.

Table 1. Targeted Sampling Stratification by Headache Frequency

Self-Reported Number of Headache Days/Month	Proposed No. Participants	Migraine Type
4-8 days	12	Episodic
9-14 days	12	Episodic
15-20 days	12	Chronic
21-26 days	12	Chronic
TOTAL	**48**	

In this study, stratified purposive sampling will be used to optimize information-rich data capture and to ensure that findings reflect the varied range of perspectives and experiences among people with migraine. The purposive sampling strategy will be used to minimize potential bias associated with large imbalances or clustering in key demographic variables (such as age, sex, or race). For example, the study team will aim to

ensure no more than a 70/30 percent female to male gender imbalance. Variety in enrolled participant characteristics will be monitored by the research team during recruitment to ensure the sample includes a mix of demographic and health characteristics. Given the targeted sample size, it is not feasible to institute quotas for specific characteristics; however, the study team will align the sample with the epidemiological profile of migraine disease and avoid oversampling from populations who may skew results, such as college-educated persons or individuals who are using medications with known cognitive side effects.

In a concept elicitation study, sample size is justified based on achieving evidence of concept saturation. Saturation refers to the point during data collection when no new relevant information is being identified and additional interviews are unlikely to contribute to knowledge (see Section 2.5.4, Assessment of Saturation).[23, 26-29] Methodological research on data saturation has consistently demonstrated that between 12-25 interviews is sufficient to exhaustively collect all concepts and themes,[23, 28] thus the research team believes that a sample of the proposed size carries a strong likelihood of achieving concept saturation within strata. As is typical with concept elicitation studies using content analysis methods, the final sample size for this study will remain flexible as the interview data collection progresses and concept saturation is assessed. For this reason, if the research team finds that fewer interviews are required, based on the emerging analysis of interview data, then recruitment will be stopped short of the initial target. Conversely, if saturation is not reached within the originally planned interview sample, then additional participant interviews will be conducted to the point of concept saturation.

2.3.2. Inclusion and Exclusion Criteria

An individual will be eligible for the study if all inclusion criteria are met and none of the exclusion criteria are met. Determination of eligibility will be based on a person's self-report in responding to a set of screening questions (Appendix B).

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
- Report being diagnosed with migraine by a healthcare professional
- Report experiencing 4-26 headache days per month over the last 3 months
- Report being able to distinguish between a day with migraine and other types of headache days
- Report experiencing limitations on physical or cognitive activities on at least 1 day over the last 3 months because of migraine
- 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.
- Be willing to have their interview audio recorded for the purpose of transcription and data analysis

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

- Self-reported diagnosis or 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
    - Stroke or traumatic brain injury
    - Fibromyalgia or chronic fatigue
    - Epilepsy
    - Serious mental illness, such as schizophrenia or bipolar disorder
    - Alzheimer's disease or dementia, or other conditions that create 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.
- Have participated in an interview or focus group related to migraine experience in the past 12 months or participated in the MiCOAS UG3 study.
- Is an employee or family member of an employee of FDA, Vector Psychometric Group, or the Albert Einstein College of Medicine.

2.3.3. Participant Recruitment and Compensation

Participants for this study will be recruited through a collaboration between VPG and CHAMP, an advocacy organization for people with headache, migraine, and cluster diseases. CHAMP focuses on identifying the unmet needs of those with headache, migraine, and cluster diseases, and continuously works to better support people with migraine and their caregivers.

Outreach procedures. CHAMP will distribute study announcements through their website, social media, and other distribution channels to reach potentially eligible individuals. All announcements will direct individuals to a designated study webpage to access detailed study information and, if interested, complete an electronic screening questionnaire.

The following channels will be used throughout the study until the target sample size is reached:

- Electronic newsletter – CHAMP will post information about the study in an electronic newsletter on their website and email the newsletter directly to individuals who have previously agreed to receive content from CHAMP electronically. The newsletter will include a link to the study web-based platform.

- Social media – CHAMP will post announcements on the coalition's social media platforms (e.g., Facebook, Instagram, and Twitter) linking to the study web-based platform.

The study announcement will also list a primary contact and telephone number for a member of the study research team for individuals who have further questions. The content across all study announcement channels will include consistent and concise introductory information highlighting key details of this study (Appendix A).

VPG and CHAMP will communicate frequently throughout the study recruitment period to assess the status of participant recruitment, answer any study-related questions, address issues as they arise, and determine if and/or when to initiate additional recruitment channels. As possible, CHAMP will provide regular updates to VPG regarding the number of individuals reached through various channels to track study outreach and assess the efficacy of different recruitment strategies.

Eligibility screening procedures. On the study's web-based platform, an electronic participant eligibility screener will be used to determine whether individuals meet the study eligibility criteria. The participant eligibility screener (Appendix B) will present questions based on the inclusion and exclusion criteria (shown in Section 2.3.2).

Individuals who do not meet all eligibility criteria will be immediately notified through the study web-based platform and thanked for their interest. Individuals who meet all eligibility criteria in the screener will be prompted to proceed to informed consent for study participation.

Informed consent procedures. Eligible individuals will read and review the informed consent form (Appendix C) and, if they choose to participate, will provide their consent through the study's web-based platform. If an eligible person has questions regarding the study or the informed consent form or would like to discuss the study further before choosing to accept or decline participation, the individual may contact the research team directly (via phone or email).

Completing informed consent will constitute enrollment as a study participant but does not guarantee that the individual will be contacted for an interview. Enrolled participants will be asked to complete the electronic Health and Demographic Information Form (Appendix D) and a short electronic form to provide limited contact information (Appendix E) and preferred contact timeframe to the research team. Contact information will only be used for contacting those individuals selected to participate in an interview.

A member of the research team will contact each participant directly to schedule the telephone/web-conference interview. Interviews will be scheduled at times that accommodate participants' availability,

time zones, and preferences for time of day. After an interview has been scheduled, the research team will contact each participant once by their preferred method (email or phone), approximately 1 to 3 days prior to their scheduled interview, to remind the participant about the interview and reconfirm their availability.

Participant compensation. Participants who complete an interview will be offered a $125 cash e-gift card (e.g., Mastercard) as compensation for their time and expertise. Participants will receive the gift card by email.

2.4. Data Collection and Study Procedures

Guidance from the ETAC (AIM 1), results from the migraine literature review (AIM 2), and results of the qualitative study of migraine symptoms and meaningful treatment outcomes (AIM 3) informed the development of data collection forms and the interview guide for this study.

The study data collection period will begin when the first participant has provided informed consent and end after the last participant has completed their interview.

2.4.1. Data Collection Instruments and Sources

Study participants will continue to receive their usual medical care during their participation in this study. No interventions, medical assessments, or tests will be required for this study. Data sources for the study are described below (Table 2).

Table 2. Data Collection Instruments and Data Files

Document/Form	Purpose
Participant Eligibility Screener (Appendix B)	To determine participant's study eligibility based on self-reported responses to questions
Health and Demographic Information Form (Appendix D)	To obtain participant's health and demographic information
Participant Contact Information (Appendix E)	To obtain participant's contact information for reconfirming eligibility, scheduling interview, conducting the telephone interview
Qualitative Interview Guide (Appendix F)	To guide semi-structured interview on migraine symptoms, impacts and outcomes, and to obtain participant address information needed for issuing incentive payment
Interview audio recordings and transcripts from this study and from the UG3 study	To capture participant interview responses verbatim for analysis

2.4.2. INTERVIEWS

The overarching purpose of the interviews is to gather evidence that will inform answers to study goals and objectives (as described in Section 1). Interviews will be designed and executed to invite participants to share their experiences with and perspectives on migraine in a manner that will

1) Elicit a full understanding of concepts that capture the effects of migraine on physical, cognitive, and psychosocial functioning. Interviews will also include an exploration of:

    a. Relationship between effects and migraine symptoms or phases: How these effects relate to specific symptoms, ictal and interictal periods, or to overall migraine severity or frequency.

    b. Timeframes: How people perceive variation or change in symptoms and functioning over time.

    c. Importance: How people perceive the importance of different aspects of functioning, including perceptions of relationships or sequences among symptoms or functions that may affect judgments of importance (e.g., migraine causes fatigue and fatigue affects ability to work after an attack); and

    d. Recall and judgment: How people perceive their ability (or preference) to recall or judge symptoms and functioning over different time frames or scoring schemes.

2) Elicit a fuller understanding about what symptoms or functioning outcomes are burdensome to people with migraine, including

    a. Perceived level of burden: How bothersome symptoms or functioning outcomes are and how bothersome-ness varies over ictal/interictal period(s).

    b. Dependencies among burdens: What interrelationships people perceive among bothersome symptoms or functions (e.g., does relief of one symptom consistently imply relief of another).

    c. Recall and judgment: Whether people generally view most bothersome symptoms in binary terms (e.g., is/is not present, is/is not most bothersome) or if they believe they can rate the severity of symptom.

3) Identify the specific language people with migraine commonly use to express these concepts.

The interviews will be conducted in English using a semi-structured key informant interview guide (**Appendix F**). The interviewer will begin with broad questions intended to elicit spontaneous responses describing individual experiences with migraine and its impact on function. The interviewer will then seek in-depth responses through open-ended questions focused on specific aspects of migraine and function as well as targeted probes to ensure consistent data collection on key symptoms, impacts, or functions. Topics for the interview will include:

- Migraine attack frequency, duration, and symptoms experienced, including attention to how attacks cluster and to the severity of symptoms to understand how these variations affect function. This data will be collected in limited detail primarily to provide context for the information on other topics.
- Effects of migraine on functioning domains including:
    - Effects on physical and cognitive functioning, including basic and instrumental activities of daily living.
    - Effects on work/school, social, familial, recreational, spiritual, and leisure activities.
    - Effects on other quality of life domains, such as mental and emotional well-being, or satisfaction with ability to fulfill social roles.
- Forms of treatment currently used and perceived impacts of treatments on function, what patients want that is not being delivered, and what factors people take into account when choosing treatment (either in general or in the moment).
- Perspectives on how bothersome different symptoms or functional impairments are, including how participants perceive the standard options (photophobia, phonophobia, and nausea) used in clinical studies; how participants view these symptoms relative to each other and to function; and whether participants would identify different or additional symptoms as most bothersome.

Interviews will be conducted one-on-one by phone or web-conferencing system by trained interviewers (see Section 2.4.3) and will last approximately 60 to 90 minutes each. Interviews will be audio-recorded with participant's permission confirmed before recording begins.

Participants who complete interviews will be compensated for their time in the form of an electronic cash gift card. Compensation will be e-mailed by VPG directly using the email address provided by the participant; interviewers will confirm that address at the end of the interview prior to sending the e-card.

The interviews will be conducted in an iterative fashion, with continuous rounds of data analysis to identify emerging themes and concepts and thus, inform areas for additional probing. As interviewing is a dynamic process, the interview guide is intended to be flexible and will be modified and refined as needed throughout the participant interview process. For example, the interview guide may be modified to emphasize different aspects of experience or ask new questions as a way to make sure that needed evidence is collected.

2.4.3. Interviewer Training and Quality Assurance

All participant interviews will be conducted by members of the VPG research team who have experience conducting interviews with patients and who have been trained in qualitative data collection techniques for patient-centered concept elicitation and COA development. Prior to conducting interviews, all interviewers will study the protocol and interview guide (**Appendix F**) until they are thoroughly familiar with the content. Interviewers will participate in mock interview sessions as part of training. The mock sessions serve

to test question flow, identify problematic or awkward phrasing, and to test the general timing of the interview.

Completed interviews will be analyzed promptly, providing an opportunity to see if the interview guide is working as intended and to review each interviewer's skills in eliciting frank discussions. The interviewers will also debrief regularly to discuss challenges and successful strategies, as well as reflect on whether collected data appears to be suitable for study aims.

2.5. Data Analysis

Data analysis will include both descriptive and interpretive methods. Descriptive methods will consist of a quantitative summary of participant characteristics and quantified and stratified summary tables of content codes for symptoms and impacts. Interpretive methods will include examining content themes and summarizing information about how interview participants make judgments about severity or weigh tradeoffs when thinking about preferences or outcomes.

2.5.1. Participant Sample Description

Data obtained from the Participant Eligibility Screener (**Appendix B**) and the Health and Demographic Information Form (**Appendix D**) will be aggregated and presented in a table format to characterize the study sample.

2.5.2. Secondary Analysis of UG3 Interview Data

Interviews conducted for the MiCOAS UG3 study include participants' spontaneously-offered perspectives on severity of symptoms, degree of burden from functional limitations, timeframes, and interrelationships between symptoms and functional outcomes. These perspectives were most often mentioned in the context of the outcome prioritization exercise. Transcripts from the UG3 study will be reviewed and coded for relevant content as a way to further enrich the findings that will be used to develop migraine measure items.

2.5.3. Analysis of Concept Elicitation Data

Audio-recordings will be transcribed verbatim and uploaded to NVivo Windows, a qualitative data analysis system (QDAS) that supports both keyword-based and manual hierarchical coding of text data. The following data reduction and analysis procedures will be used.

Coding. Analysts will code transcripts to identify relevant concepts and terminology used by study participants and organize codes into hierarchical groups based on similarity of domain or concept content. An initial hierarchy of codes to guide coding will be defined by the research team based on

- Findings from the UG3 study.
- Standard frameworks for functioning and disability, such as the International Classification of Functioning, Disability and Health.

- Input from clinical experts including a United Council for Neurologic Subspecialties headache expert neurologist, a headache psychologist, and ETAC members.

The codebook and analytic procedures will reflect phenomenological bracketing that distinguishes between absolute aspects of individual participant's experience (e.g., specific functional limitations, such as disruption of sleep) and their consciousness of that experience (e.g., perceptions of how bothersome it is or how it is connected to other absolute concepts).

Analysts will conduct a line-by-line review of each transcript to identify portions of text expressing relevant concepts for coding. Analysts will create new codes and sub-codes as needed to reflect participants' perspectives and terminology accurately and comprehensively. As new codes are created, the research team will review and refine them as needed by reaching agreement on how codes are defined and placed within the codebook. Throughout coding, analysts will also consider whether codes should be grouped differently, merged, or subdivided. An audit trail of decisions to create, reorganize, merge, or divide codes will be maintained.

Case classification. Case classifications will be used to support understanding of patterns in participant experience of symptoms and function or disability. Case classifications are used to stratify coded data, examine differences, and test assumptions or hypotheses. Analysts will classify each transcript with case variables reflecting

- Selected migraine experience characteristics, such as headache days/month and whether the participant does or does not experience aura, clustering of headache days, or menstrual headaches. These case classifications will support, for example, a richer understanding of how number and severity of functional impairments is related to these illness characteristics.

- Selected demographic characteristics, such as sex, age, employment status, and number of years with migraine, that may affect reports of function outcomes. These case classifications will support a nuanced understanding of how functional outcomes may be related to differences in background characteristics.

- Selected individual characteristics that may affect reports of function outcomes, such as presence of co-morbid conditions (e.g., depression) or use of medications that are known to impair cognitive or physical function (e.g., topiramate, divalproex sodium, eletriptan, lasmiditan, or tricyclic antidepressants).

Assessment of inter-coder agreement. Consistency of coding and case classification will be assured through assessment of inter-coder agreement and resolution of inconsistencies. The first 3 transcripts will be independently coded by 2 researchers. After the coding is complete, they will meet and compare coding and the identification of new concepts for the codebook. They will resolve any differences through consensus, update code definitions as needed, and record decisions in the audit trail. Coders will then separately code 3 transcripts following the agreed coding scheme, meeting regularly to discuss new codes and address questions that arise. Coders will then independently code the 10th transcript and compare their coding

again. To maintain consistency and agreement for the rest of the coding phase, coders will review together the coding of every 10th transcript until interviewing is completed.

Code reporting. After coding is finalized, summary reports will be generated showing, for example, how many interviews endorsed the concepts categorized by each code, both with and without case classification stratification. Code reports will also be generated listing the coded text from all interviews.

Thematic analysis. Code reports will be used to conduct thematic analysis of interview data coded for each concept. Thematic analysis will confirm that concepts represented by codes have been properly and clearly distinguished and appropriately placed in the conceptual hierarchy, and that variations in individual experiences have been accounted for. Any changes to the conceptual arrangement of codes will be recorded in the audit trail.

Analysts will verify findings through negative case analysis, theoretical triangulation, and reflexive analysis.[30] Negative case analysis will consist of deliberately seeking disconfirming examples in transcripts. Theoretical triangulation will entail comparing results with existing conceptual frameworks for migraine and disability to systematically interrogate any divergences and similarities. Reflexive analysis will involve review of the audit trail to ensure consistent, well-reasoned decision making was applied throughout coding and thematic analysis.

Analysts will develop descriptive summaries of the content and scope of concepts. These summaries may also include tables of concept frequencies or distributions across interviews, discussion of where code content overlaps, and discussion of any disconfirming examples found in the data. Summaries will be illustrated with exemplary verbatim quotes that reflect both the typical content and the range of variation in content found for each concept.

Analysts will also develop summaries that discuss the relationships that participants perceived between symptoms and functional outcomes, how judgments of bothersome-ness or severity are made, and how participants express preferences or view tradeoffs among symptoms and outcomes.

2.5.4. Assessment of Saturation

Saturation is assessed by documenting which interview constituted the first instance of each concept. Saturation is reached when interviews no longer produce novel data. The saturation assessment will follow current best practices and the FDA's Guidance to Industry regarding evidence of saturation in qualitative research carried out to support PRO instrument development.[21,27] Saturation assessment in this study will ensure that participant interviews yield a *comprehensive* set of concepts based on direct report from people with migraine.

The standard approach to saturation analysis involves comparing each interview to those that preceded it and, when several interviews have passed with no new content, data collection often ceases. However, given the breadth and variation in possible impacts and experiences of disability that may be found in this study, interviews will first be classified by whether the participant reported physical, cognitive, or psychosocial impacts. Saturation of concepts within each of these three broad domains will then be tracked

alongside overall concept saturation. For example, if subsequent interview participants do not experience cognitive impacts at all, their experience cannot contribute data regarding conceptualization of cognitive effects. Similarly, saturation analysis will take into account whether participants are experiencing episodic or chronic migraine.

3. REPORTING AND DISSEMINATION OF STUDY RESULTS

3.1. Qualitative Study Report

A comprehensive research report will be developed to summarize the following study components: background and objectives, study design and methods, results and interview findings, limitations, discussion, and conclusions. Methods will be presented in sufficient detail to permit replication. Supporting documents, such as the final codebook, will be included as appendices.

The findings outlined in this report will be used by the study team to assess concordance between the constructs/outcomes identified through other study AIMS, including the prior qualitative study, and those identified to be important to people with migraine via one-on-one interviews. This comparative assessment will be used to confirm and/or augment, as necessary, the migraine treatment outcomes and endpoints that require additional development/refinement.

3.2. Potential Publications and Publication Policy

The results of this study, with prior review from the FDA, may be submitted for publication in a scientific journal and/or for presentation at a medical or scientific conference. If published or presented, the results of this study will be described in such a way that confidential or proprietary information is not disclosed.

Selection of authors for any scientific publication(s) developed from this study will comply with the International Committee of Medical Journal Editors guidelines.[31] Accordingly, authorship should be based on achieving all of the following 4 criteria:[31]

1. Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data.
2. Drafting the article or revising it critically for important intellectual content.
3. Final approval of the version to be published.
4. Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a publication should meet all four criteria. Each author must agree to their inclusion in the list of authors. Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate.

Individuals who may have contributed to this study but not sufficiently to qualify for authorship may be listed in the acknowledgements.

4. DATA MANAGEMENT

4.1. Data Storage and Handling

The data for all electronic forms completed by participants will be collected using the flexCOA® survey platform. flexCOA® is a proprietary electronic data collection platform owned by VPG that facilitates in the distribution of surveys, measures, and questionnaires. flexCOA® is compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and individual data collected within the system are encrypted and protected. Throughout the study, the VPG research team will regularly export study data from flexCOA® to the designated secure MiCOAS study folder.

The MiCOAS study folder will reside in secure, encrypted servers within VPG's information technology systems. Access to this folder will be restricted to the members of the VPG research team who are involved in this study. No participant-identifiable study data will be printed in hard copy. After study completion, VPG will securely archive all study participant-identifiable data for a period of 5 years, and then securely destroy the data consistent with current VPG standard operating procedures.

Audio files from participant telephone interviews will be labeled with the participant's unique identification number and uploaded to the designated, secure MiCOAS study folder immediately after completion of each interview. Once the audio file is confirmed as successfully stored in SharePoint, the audio file will be deleted from the recording device. The audio file for each study participant will be securely transferred for transcription. When transcripts are completed by the transcriber, an analyst will review the transcript and redact any potentially identifying information, such as references to places, occupations, or events. Once the final de-identified transcript has been created, the recording will be securely destroyed. The de-identified interview transcripts will be uploaded to NVivo Windows for analysis. The NVivo Windows QDAS platform complies with HIPAA data security requirements.

4.2. Data Monitoring and Quality Assurance

Prior to initiation of participant recruitment, quality checks will be performed on the electronically-collected data via user acceptance testing as performed by the research team. Any issues will be identified and resolved. The research team will actively monitor the web-based screening data collection and review information entered by study participants when data is exported. In an effort to avoid missing data, key fields within each electronic data collection form will be marked as required before a study participant (or potential participant) can proceed to the next form or step in the data collection process. Certain questions will also be limited by pre-specified response options.

In addition, when contacting study participants, the research team will confim the information completed by the participant during the web-based screening process to finalize eligibility determination. Reconfirmation provides greater certainty that the study participant is in fact eligible based on the specified study inclusion and exclusion criteria.

5. ETHICAL AND REGULATORY OBLIGATIONS

This study will be conducted in compliance with FDA and federal regulations for the protection of human subjects, the American Psychological Association code of ethics, and all local regulatory requirements applicable to non-interventional studies.

4.1. Institutional Review Board

This study will be submitted to an IRB for review before initiation of any study activities. This is expected to be submitted to a centralized IRB. Study advertising and recruitment of potential participants will not begin until after written confirmation of IRB approval or determination of exemption is received.

4.1. Informed Consent

This study will be performed in accordance with the ethical principles that are consistent with local and national applicable regulatory requirements. This study will use a remote consent process and form. The consent form will describe the purpose of the study, data collection procedures, benefits and risks of participation, confidentiality measures to be taken, and participant rights. It will include study contact information, and a description of and contact for the IRB. Individuals will be encouraged to email or call the study contact with any questions they may have prior to consenting to participate in the study. Individuals will be able to take as much time as they need to consider their decision until enrollment in the study closes.

Prior to enrollment in this study, each person will be required to provide informed consent during the web-based screening process to confirm that they have agreed to participate in this study. The web-based screening questionnaire will require active acknowledgement of consent to complete screening prior to the administration of screening questions. If eligible, a second, more detailed consent interaction will be provided for eligible participants (i.e., the Informed Consent Form, Appendix C) prior to proceeding to the electronic Health and Demographic Information Form (Appendix D), Participant Contact Information (Appendix E) and the interview process. If important new information becomes available during the study, the consent form will be revised. Key informed consent elements, such as the right to withdraw at any time, decline to answer questions, or decline to be audio-recorded, will be reconfirmed at the beginning of scheduled interviews.

Study participants will not receive any direct clinical benefits from their participation in this study. However, the information obtained from study participants is expected to provide a better understanding of people’s experience with migraine and migraine treatment. Improving our understanding of their view on their condition and its treatment may help other people with migraine in the future. No physical or medical risks or burdens are expected to occur due to participants’ involvement in this study. However, it is possible that participants may feel uncomfortable answering some of the interview questions, and during or after the interviews, participants may become more aware of the symptoms, impacts, or other factors related to migraine. Participants may also find the interview mentally tiring. Interviewers will be trained regarding potential sensitivities of those with migraine and participants will be encouraged to talk with their healthcare professional about any medical questions or concerns.

4.2. CONFIDENTIALITY

VPG and Einstein will comply with regulatory requirements regarding the conduct of qualitative research, that does not involve the testing of a treatment or procedure. The study will be conducted in accordance with applicable data privacy requirements, such as HIPAA. All participant data collected and processed for the purposes of this study will be managed by the research team with adequate precautions to ensure the confidentiality of the data, in accordance with applicable national and/or local laws and regulations governing personal data protection.

Participants' names and contact information will be provided directly by the participant to VPG and will be used only for the purposes of this study (i.e., to answer questions regarding the study, reconfirm eligibility, schedule the interview, conduct the interview, and send compensation for study participation). The study report and any publication or presentation of this study data will not contain any participant identifiable information and participant identity will remain confidential.

Personnel from the following organizations may examine the research study records: VPG, Einstein, regulatory agencies (e.g., FDA), and IRBs. Only research study staff directly involved in participant recruitment and data collection will know the identity of the participants, and all other study data retained for study analyses (descriptive quantitative data from questionnaire responses and interview transcripts) will be coded with a unique study ID and/or fully de-identified.

REFERENCES

1. Blumenfeld AM, Varon SF, Wilcox TK, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). *Cephalalgia*. Feb 2011;31(3):301-15. doi:10.1177/0333102410381145
2. Buse DC, Lipton RB. Global perspectives on the burden of episodic and chronic migraine. *Cephalalgia*. 2013:885-90. vol. 11.
3. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. *Arch Intern Med*. Apr 1999;159(8):813-8. doi:10.1001/archinte.159.8.813
4. Society AH. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. *Headache*. 01 2019;59(1):1-18. doi:10.1111/head.13456
5. Buse DC, Scher AI, Dodick DW, et al. Impact of Migraine on the Family: Perspectives of People With Migraine and Their Spouse/Domestic Partner in the CaMEO Study. *Mayo Clin Proc*. Apr 2016;doi:10.1016/j.mayocp.2016.02.013
6. Haut SR, Bigal ME, Lipton RB. Chronic disorders with episodic manifestations: focus on epilepsy and migraine. *Lancet Neurol*. Feb 2006;5(2):148-157. doi:10.1016/s1474-4422(06)70348-9
7. Lipton RB, Buse DC, Adams AM, Varon SF, Fanning KM, Reed ML. Family Impact of Migraine: Development of the Impact of Migraine on Partners and Adolescent Children (IMPAC) Scale. *Headache*. Apr 2017;57(4):570-585. doi:10.1111/head.13028
8. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. Jul-Aug 2001;41(7):646-57. doi:10.1046/j.1526-4610.2001.041007646.x
9. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. Jan 2018;38(1):1-211. doi:10.1177/0333102417738202
10. Lanteri-Minet M. Economic burden and costs of chronic migraine. *Curr Pain Headache Rep*. Jan 2014;18(1):385. doi:10.1007/s11916-013-0385-0
11. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. Nov 2018;17(11):954-976. doi:10.1016/s1474-4422(18)30322-3
12. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *J Neurol Neurosurg Psychiatry*. Apr 2010;81(4):428-32. doi:10.1136/jnnp.2009.192492
13. Buse DC, Silberstein SD, Manack AN, Papapetropoulos S, Lipton RB. Psychiatric comorbidities of episodic and chronic migraine. *J Neurol*. Aug 2013;260(8):1960-9. doi:10.1007/s00415-012-6725-x
14. Ford JH, Ye W, Nichols RM, Foster SA, Nelson DR. Treatment patterns and predictors of costs among patients with migraine: evidence from the United States medical expenditure panel survey. *J Med Econ*. Sep 2019;22(9):849-858. doi:10.1080/13696998.2019.1607358
15. Lipton RB, Fanning KM, Buse DC, et al. Identifying Natural Subgroups of Migraine Based on Comorbidity and Concomitant Condition Profiles: Results of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. *Headache*. Jul 2018;58(7):933-947. doi:10.1111/head.13342
16. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies. *Headache*. Jan 2015;55(1):3-20. doi:10.1111/head.12499
17. Silberstein SD. Preventive Migraine Treatment. *Continuum (Minneap Minn)*. Aug 2015;21(4 Headache):973-89. doi:10.1212/con.0000000000000199
18. Brédart A, Marrel A, Abetz-Webb L, Lasch K, Acquadro C. Interviewing to develop Patient-Reported Outcome (PRO) measures for clinical research: eliciting patients' experience. *Health Qual Life Outcomes*. Feb 5 2014;12:15. doi:10.1186/1477-7525-12-15
19. Britten N. Qualitative research on health communication: What can it contribute? *Patient Education and Counseling*. 2011;82(3):384-388.

20. Carter S, Henderson L. Approaches to qualitative data collection is social science. In: Bowling A, Ebrahim S, eds. *Handbook of Health Research Methods: Investigation, Measurement, and Analysis*. Open University Press; 2005
21. Forsythe LP, Carman KL, Szydlowski V, et al. Patient Engagement In Research: Early Findings From The Patient-Centered Outcomes Research Institute. *Health Aff (Millwood)*. Mar 2019;38(3):359-367. doi:10.1377/hlthaff.2018.05067
22. Lasch KE, Marquis P, Vigneux M, et al. PRO development: rigorous qualitative research as the crucial foundation. *Qual Life Res*. Oct 2010;19(8):1087-96. doi:10.1007/s11136-010-9677-6
23. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field methods*. 2006;18(1):59-82.
24. Patton MQ, Patton MQ. *Qualitative research and evaluation methods*. 3 ed. Sage Publications; 2002:xxiv, 598, 65 p.
25. Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1--eliciting concepts for a new PRO instrument. *Value Health*. Dec 2011;14(8):967-77. doi:10.1016/j.jval.2011.06.014
26. Rothman M, Burke L, Erickson P, Leidy NK, Patrick DL, Petrie CD. Use of existing patient-reported outcome (PRO) instruments and their modification: the ISPOR Good Research Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PRO Task Force Report. *Value Health*. Nov-Dec 2009;12(8):1075-83. doi:10.1111/j.1524-4733.2009.00603.x
27. United States Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. *Fed Regist*. 2009 Dec;74(235):65132-3.
28. Turner-Bowker DM, Lamoureux RE, Stokes J, et al. Informing a priori Sample Size Estimation in Qualitative Concept Elicitation Interview Studies for Clinical Outcome Assessment (COA) Instrument Development. *Value in Health*. 2018;
29. Robinson OC. Sampling in interview-based qualitative research: A theoretical and practical guide. *Qualitative research in psychology*. 2014;11(1):25-41.
30. Roller MR, Lavrakas PJ. *Applied Qualitative Research Design*. Guilford Press; 2015.
31. International Committee of Medical Journal Editors. Defining the Role of Authors and Contributors. Web. International Committee of Medical journal Editors. Accessed April 10, 2019, http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html