# Qualitative Concept Elicitation Study Protocol

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| **Protocol title** | **Migraine Clinical Outcome Assessment System: Understanding the Experience of People with Migraine** |
| **Pharmerit Protocol #** | 19192 |
| **Date and Version** | May 20, 2020; Version 3.0 |
| **Research Organization** | **Pharmerit International**<br>4350 East-West Hwy, Suite 1110<br>Bethesda, MD 20814 |
| **Sponsor** | **Vector Psychometric Group, LLC as funded by FDA Grant #1UG3FD006795-01**<br>847 Emily Lane<br>Chapel Hill, NC 27516-0807<br>Phone: 1.919.768.7142 |
| **Principal Investigator(s) of Subcontract** | Kelly McCarrier, PhD, MPH<br>kmccarrier@pharmerit.com<br><br>Maya T. Gerstein, DrPH, MPH<br>mgerstein@pharmerit.com |
| **Sponsor Primary Contact/Principal Investigator of FDA Grant** | R.J. Wirth, PhD<br>RJWirth@VPGcentral.com |

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
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| MiCOAS | Migraine Clinical Outcome Assessment System |
| GBD | Global burden of disease |
| YLDs | Years lived with disability |
| EM | Episodic migraine |
| CM | Chronic migraine |
| COAs | Clinical outcome assessments |
| MBS | Most bothersome symptom |
| FDA | U.S. Food and Drug Administration |
| ETAC | External technical advisory committee |
| IRB | Institutional review board |
| ICF | Informed consent form |
| DHIF | Demographic and health information form |
| ICMJE | International committee of medical journal editors |
| HIPAA | Health insurance portability and accountability act |
| CIOMS | Council for international organizations of medical sciences |

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# 1 Protocol Synopsis

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| **Study Title:** | Migraine Clinical Outcome Assessment System:<br>Understanding the Experience of People with Migraine |
| **Study Objectives:** | 1. To identify the most common and most bothersome symptoms experienced by people with migraine.<br>2. To explore variation of severity and frequency of symptoms among people with migraine.<br>3. To describe the key impacts of migraine symptoms on people's' lives.<br>4. To describe the treatment outcomes that are most valued by people with migraine when they use acute or preventive treatments.<br>5. To identify the specific language people with migraine use to express symptoms, impacts, and outcomes. |
| **Rationale** | Migraine is a highly prevalent and potentially severely disabling neurological disease that is associated with significant economic, social, and personal burden. Treatments for migraine fall under 2 broad categories, acute and preventive. Both acute and preventive migraine treatments have broader aims to increase individuals' health related quality of life by decreasing disability, impact, and burden associated with migraine.<br><br>In recent years, the FDA has approved several new acute and preventive migraine treatments and the field of migraine is currently experiencing an explosion in new treatment developments. However, there are significant qualitative limitations to the current clinical outcome assessments (COAs) used in acute and preventive migraine treatment trials. Most notably, several of these assessments were developed with limited explicit input from people with migraine.<br><br>To 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 U.S. Food and drug Administration (FDA) Grant # 1UG3FD006795-01 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 the patient experience and feedback regarding outcomes most meaningful to them. A key component of this work is the conduct of qualitative research interviews to capture the experiences of persons living with migraine, with a specific focus on understanding the treatment benefits that persons with this disease value most.<br><br>This protocol describes in detail the qualitative methodology and tasks associated with AIM 3 of the above referenced grant award, which builds off prior workstreams to provide qualitative insights on the patient-experience and ensure that migraine treatment endpoints identified during AIM 1 and AIM 2 as targets for development/refinement for MiCOAS are meaningful to people with migraine. |
| **Study Timelines** | 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 |

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| | be approximately 6-9 months. However, study length is highly dependent upon recruitment rate and participant availability. |
| **Study Design:** | This is an observational, non-interventional, cross-sectional, qualitative study of people with migraine. The study involves recruitment of study participants through a web-based screening survey for participation in a one-time individual qualitative interview conducted via telephone or web-conferencing. |
| **Study Population:** | The study will include adults diagnosed with migraine in the US meeting the following self-report inclusion and exclusion criteria:<br><br>To be eligible for inclusion in the study, at the time of screening, a person must:<br>• Be a resident of the US<br>• Be between 18 and 75 years of age<br>• Report being diagnosed with migraine by a healthcare professional.<br>• Report experiencing any two out of the three below clinical criteria for migraine:<br>  ○ Limited activities on at least 1 day over the last 3 months because of their headaches<br>  ○ Bothered by lights when having a headache<br>  ○ Gets sick to their stomach or nauseated with their headache<br>• Be able to distinguish between a day with migraine and other types of headache days<br>• Be proficient in the English language (i.e. ability to read, write, speak, and understand English well enough to complete informed consent process and take part in the interview).<br>• Provide informed consent to participate in the study and complete the web-based informed consent documentation.<br>• Be willing to have their interview audio recorded for the purpose of transcription and data analysis<br><br>An individual reporting any of the following at the time of screening will be excluded from this study:<br>• Self-reported diagnosis of a pain disorder, or any other clinically significant disease(s) that might interfere with the person's ability to provide non-confounded descriptions of their experience with migraine symptoms and impacts. These include:<br>  ○ Multiple Sclerosis<br>  ○ Epilepsy<br>• Self-reported diagnosis of severe mental illness, cognitive impairment, or any other disorder that compromises the ability to give informed consent. These include:<br>  ○ Schizophrenia<br>  ○ Bi-polar disorder<br>  ○ Cognitive impairment |

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| | ○ Alzheimer's disease or dementia<br>• Self-reported alcohol or drug abuse over the past 3 months.<br>• Self-reported symptoms or hospitalization related to COVID-19 infection<br>• Is an employee or family member of an employee of Vector Psychometric Group, Pharmerit International, Montefiore Medical Center or the Albert Einstein College of Medicine. |
| **Study Treatment:** | No treatment will be administered as part of this study. 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. |
| **Variables and Data:** | Data for study analyses will collected using the following study documents:<br>• Appendix B: Participant Eligibility Screener (delivered via web-based questionnaire platform)<br>• Appendix D: Demographic and Health Information Form (DHIF; delivered via web-based questionnaire)<br>• Appendix F: Qualitative Interview Guide<br>• Appendix G: Screenshots of web-based screening, consent and data collection platform. |
| **Sample Size and Data Analysis:** | This study will include approximately 40 participants, stratified by headache frequency. 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.<br><br>Audio-recordings will be transcribed verbatim and entered in ATLAS.ti v8.0, a software package used for qualitative data analysis. A coding process will be used to identify relevant concepts and to organize these within groupings or related concepts. The Pharmerit research team will develop a preliminary coding framework which will be further refined using a consensus-based team approach. Codes will be developed from the verbatim words of interview participants and conceptually equivalent codes grouped and merged as appropriate.<br><br>After coding is finalized, outputs from ATLAS.ti will be used to summarize findings from the coding process, such as the number of cases (i.e. participant interviews) expressing each coded symptom or impact concept. These types of outputs will help inform more in-depth analysis of the content and context of coded interview data, which will be reflected in summary tables, accompanying narratives, and exemplary verbatim quotes that reflect the key concepts documented through this inquiry.<br><br>Evidence of concept saturation will be assessed through a process that examines the appearance of novel concepts across sets of chronologically ordered interviews to determine the point at which additional interviews are unlikely to result in the identification of further symptom or impact concepts. |

# 2 Introduction and Background

Migraine is a highly prevalent and potentially severely disabling neurological disease that is associated with significant economic, social, and personal burden.[1-3] It is a chronic disorder characterized by episodic attacks, which can impact the functioning of the individual in multiple roles and settings including occupational, academic, social, familial, and personal. [2-8] The 2016 Global Burden of Disease (GBD) analysis reported that migraine is the second most disabling disease worldwide, second only to low back pain, and that migraine caused 45.1 million years lived with disability (YLDs) in 2016 alone.[9]

From an economic standpoint, it was estimated that 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] There is also strong evidence that migraine is comorbid with many other medical, neurologic, and psychiatric conditions (e.g., cardiovascular disease, depression, anxiety, asthma, fibromyalgia) causing increased burden and direct and indirect costs [10-13] More broadly, migraine has been shown to negatively impact an array of social, emotional, and physical domains extending beyond the individual with migraine to family members as well.[5]

There are many subtypes of migraine. One important distinction is between episodic migraine (EM) and chronic migraine (CM).[14] These groups are largely distinguished by the number of headache days that occur each month; CM requires 15 or more headache days per month or more than 3 months with at least 8 days/month having features of migraine headache. Treatments for migraine fall under 2 broad categories, acute and preventive.[4,6] Acute migraine treatments aim to resolve migraine symptoms when an attack occurs and return individuals to a “normal” level of functioning as quickly as possible.[15] Preventive migraine treatments aim “to reduce the frequency, duration, or severity of attacks”.[16] Both acute and preventive migraine treatments have broader aims to increase individuals’ health-related quality of life (HRQoL) by decreasing disability, impact, and burden associated with migraine.

In recent years, the FDA has approved several new acute and preventive migraine treatments and the field of migraine is currently experiencing an explosion in new treatment developments. However, there are significant qualitative limitations to the current clinical outcome assessments (COAs) used in acute and preventive migraine treatment trials. Most notably, several of these assessments were developed with limited explicit input from people with migraine.

In acute migraine trials, common coprimary endpoints are pain freedom and absence of the individual’s designated most bothersome symptom (MBS) at 2 hours post-dose. In evaluation of preventive treatment efficacy, the standard primary endpoint has been reduction in mean migraine (or headache) days per month. In both contexts, there is no empirical evidence to support that these endpoints fully capture what people with migraine value most in terms of treatment efficacy. Further, it is unclear if instruments that assess broader quality of life, functional impact, and disability in a manner that is specific to individuals with migraine are comprehensive. Taken together, these trends demonstrate a clear need for better integration of people with migraine in migraine therapy endpoint development.

To 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 U.S. Food and drug Administration (FDA) Grant # 1UG3FD006795-01 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 the experience of people living with mgiraine and feedback regarding outcomes most meaningful to them. A key component of this work is the conduct of qualitative research interviews to capture the experiences of persons living with migraine, with a specific focus on understanding the treatment benefits that persons with this disease value most.

In the first two aims of the awarded study, VPG will assemble key stakeholders (i.e., advocates, clinicians, COA development experts, psychometricians, regulators, and payers) in an External Technical Advisory Committee (ETAC) to provide ongoing guidance in the implementation of the project (AIM 1) and conduct a comprehensive systematic review of the migraine literature to fully understand currently utilized outcomes in both acute and preventive migraine trials (AIM 2).

This protocol describes in detail the qualitative methodology and tasks associated with AIM 3 of the MiCOAS project, which builds on these prior aims (i.e. ETAC discussions and the findings of the literature review) to provide qualitative insights on the people's experience and ensure that endpoints identified during AIM 1 and AIM 2 as targets for development/refinement are meaningful to people with migraine.

# 3 Study Goals and Objectives

The overall goal of this study is to support the development of a core COA set for the measurement of migraine endpoints by exploring and documenting the experiences of people with migraine through qualitative research.

Qualitative interviews with people with migraine will be conducted with the following specific objectives:

1. To understand the experience of living with migraine
2. To capture the symptoms and impacts experienced by people with migraine during all phases of a migraine attack and in-between attacks.
3. To capture within and across person variation in symptoms, impacts, and disease burden
4. To explore participants priorities for acute and preventive migraine treatment
5. To identify the specific language people with migraine use to express symptoms, impacts, and outcomes

# 4 Method

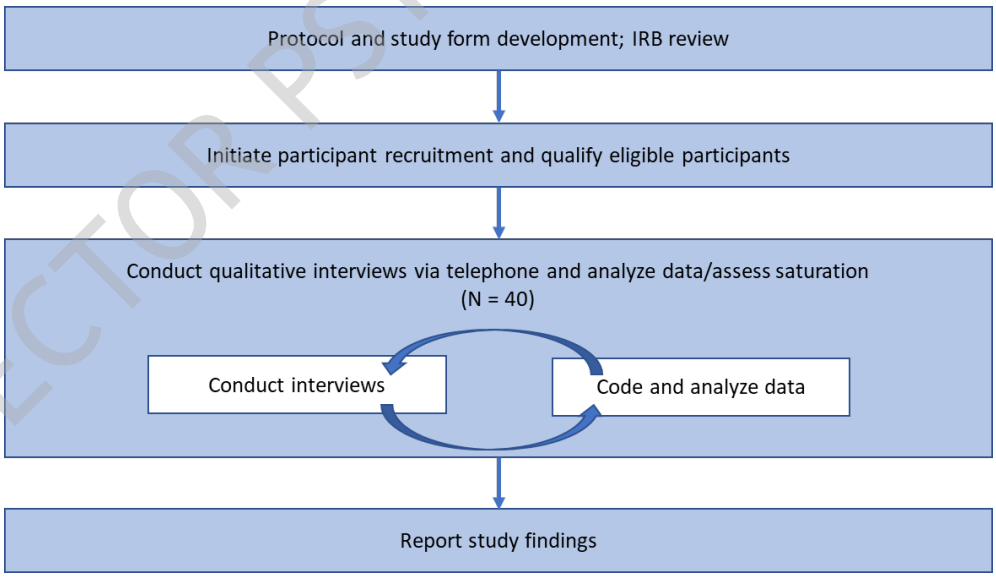
## 4.1 Study Design Overview

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 a one-time individual qualitative interview via telephone or web-conferencing with approximately 40 US-based people diagnosed with migraine (based on self-report). The interviews will focus on understanding individual's experience with migraine in terms of symptoms, impacts, and outcomes. The resulting interview transcripts will be used to conduct qualitative data analysis. 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.

The approach of individual interviews was selected as opposed to focus groups due to the desire to explore depth rather than breadth of understanding related to individual experiences and decision-making.[17] Conducting individual interviews also removes the influence of group social desirability and allows for further individual probing. Telephone/web-conference interviews will be conducted in lieu of in-person interviews to reduce the logistical burden for study participants (i.e. not required to travel for the interview), and to allow for greater flexibility in interview scheduling to accommodate participant availability.

**Figure 1. Overall Study Flow**




Abbreviations: IRB, institutional review board

## 4.2 Study Sample

### 4.2.1 Sample Size and Description

This study will employ stratified purposive sampling (a type of non-probability sampling) to recruit approximately 40 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. [18-20] Headache frequency stratifications and approximate targeted sample sizes are summarized in Table 1 below. Stratified sample sizes are estimates that may change in response to participant availability and iterative analyses of early interview data.

**Table 1. Targeted Sampling Stratification by Headache Frequency**

| Headache Frequency | Approximate Targeted Sample |
|---|---|
| 0-1 headache day a month | N= 2 |
| 2-3 headache days a month | N= 6 |
| 4-7 headache days a month | N= 6 |
| 8-14 headache days a month | N= 6 |
| 15-24 headache days a month | N= 18 |
| 24 or more headache days a month | N=2 |
| **TOTAL** | **N=40** |

In this study, stratified purposive sampling will be utilized to allow for information-rich data capture and to ensure that qualitative findings reflect the full-range of perspectives among people with migraine and any important differences in their symptoms, impacts, and prioritized outcomes. The purposive sampling strategy will also be used to prevent 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. Given the targeted sample size, it is not feasible to institute specific quotas around race/ethnicity and other demographic features, but the study team will make a concerted effort to align the sample with the epidemiological profile of migraine disease.

In qualitative research, adequacy of a study's sample size is largely justified based on achieving evidence of concept saturation. Saturation refers to the point during data collection when no new relevant information is identified and additional interviews are unlikely to yield novel concepts (see Section 4.4.3 for methods on saturation assessment).[21-24] Based on substantial experience conducting qualitative research and recent methodological research in this area,[25] the research team believes that a sample of this size carries a strong likelihood of achieving concept saturation. As is typical with qualitative research using grounded theory-based methods, the final sample size for this study will remain flexible as the interview data collection progresses and concept saturation is assessed.[26] For this reason, if the research team finds that all planned interviews are not necessary 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.

The study will include adults with migraine in the US, according to the inclusion and exclusion criteria described in Section 4.2.2.

### 4.2.2 Inclusion and Exclusion Criteria

An individual will be eligible for the study if all inclusion criteria are met (see Section 4.2.2.1) and none of the exclusion criteria are met (see Section 4.2.2.2). **Determination of eligibility will be based on a person's self-report** by responding to a set of screening questions (described further in Section 4.2.3).

#### 4.2.2.1 Inclusion Criteria

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.
- Report experiencing any two out of the three below clinical criteria for migraine:
    - Limited activities on at least 1 day over the last 3 months because of their headaches
    - Bothered by lights when having a headache
    - Gets sick to their stomach or nauseated with their headache
- Be able to distinguish between a day with migraine and other types of headache days
- Be proficient in the English language (i.e. ability to read, write, speak, and understand English well enough to complete informed consent process and take part in the interview).
- Provide informed consent to participate in the study and complete the web-based informed consent documentation.
- Be willing to have their interview audio recorded for the purpose of transcription and data analysis

#### 4.2.2.2 Exclusion Criteria

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

- Self-reported diagnosis of a pain disorder, or any other clinically significant disease(s) that might interfere with the person's ability to provide non-confounded descriptions of their experience with migraine symptoms and impacts. These include:
    - Multiple Sclerosis
    - Epilepsy

- Self-reported diagnosis of severe mental illness, cognitive impairment, or any other disorder that compromises the ability to give informed consent. These include:
    - Schizophrenia
    - Bi-polar disorder
    - Cognitive impairment
    - Alzheimer's disease or dementia
- Self-reported alcohol or drug abuse over the past 3 months.
- Self-reported symptoms or hospitalization related to COVID-19 infection
- Is an employee or family member of an employee of Vector Psychometric Group, Pharmerit International, Montefiore Medical Center or the Albert Einstein College of Medicine.

### 4.2.3 Participant Recruitment

Participants for this study will be recruited through a collaboration between Pharmerit and The Coalition for Headache and Migraine Patients (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. As such, collaboration with CHAMP provides a unique opportunity for people with migraine connected with the coalition to be informed about and participate in this patient-centered research effort.

CHAMP will distribute study announcements through their organization website, social media presence, and other distribution channels to reach potentially eligible individuals. All announcements will direct individuals interested in study participation to a designated study webpage where they will receive more detailed study information and complete an electronic screening questionnaire.

The following channels will be used throughout the study until the target sample size (as described in Section 4.2.1) 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 link to the study-specific website (for further information and screening).
- Social media – CHAMP will post announcements on the coalition's social media platforms (e.g., Facebook, Instagram, and Twitter) linking to the study website.

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).

The Pharmerit research team will remain in close contact with VPG and CHAMP throughout the study recruitment period to proactively 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 best as possible, CHAMP will provide regular updates to Pharmerit to communicate the number of individuals reached through various recruitment channels to track study outreach.

Once an individual reaches the study website, an electronic participant eligibility screener will be used to determine if the person meets the study eligibility criteria. The participant eligibility screener (Appendix B) will be comprised of a series of questions based on the inclusion and exclusion criteria (as stated in Section 4.2.2) and additional questions to meet study sampling parameters.

After the participant eligibility screener is completed and submitted, individuals who do not meet all eligibility criteria will be immediately notified through the study website platform that they are not eligible for participation in this study. Individuals who meet all eligibility criteria based on self-reported responses to the screener questionnaire will be prompted to proceed to informed consent for interview participation. Eligible individuals will read and review the informed consent form (ICF) (Appendix C) and, if they choose to participate, will provide their consent through the study website. If an eligible person has questions regarding the study and/or the ICF or would like to discuss the study further before choosing to accept or decline participation, the individual may contact the Pharmerit research team directly (via phone or email).

Once all questions are answered, if the eligible person remains interested in participating in this study, they will be directed to return to the study website and be routed back to the ICF to provide their consent to participate.

After providing their consent to participate, the eligible person will be considered a study participant, and will next be asked to complete the electronic Demographic and Health Information Form (DHIF; Appendix D) and a short electronic form to provide limited contact information (Appendix E) and preferred time of contact to the Pharmerit research team for purposes of scheduling the interview, coordinating additional interview logistics, and conducting the interview session.

A member of the Pharmerit research team will contact each participant directly to schedule the telephone/web-conference interview and will be as flexible as possible to accommodate participants' availability and timing preferences. After an interview has been scheduled, Pharmerit will contact each participant once, approximately 1 to 3 days prior to their scheduled interview, to remind the participant about the interview and reconfirm their availability.

## 4.3 Data Collection and Study Procedures

Guidance from the ETAC (AIM 1) and results from the migraine literature review (AIM 2) informed the development of data collection forms and the interview guide for this study.

The study data collection period will be considered to have started when the first participant has provided informed consent and ended after the last participant has completed their interview.

### 4.3.1 Data Collection Documents

Study participants will be treated in accordance with usual medical practice during their participation in this study. As such, no additional medical assessments or tests will be required for this study. Data collection for this qualitative study will be accomplished using the documents and files described below (Table 2).

**Table 2. Data Collection Documents and Files**

| Document/Form | Purpose |
|---|---|
| Participant Eligibility Screener [Appendix B] | • To determine participant's study eligibility based on self-reported responses to questions |
| Informed Consent Form (ICF) [Appendix C] | • To obtain participant's permission to be included in the study |
| Demographic and Health Information Form (DHIF) [Appendix D] | • To obtain participant's demographic and health information |
| Participant Contact Information [Appendix E] | • To obtain participant's contact information for reconfirming eligibility, scheduling interview, and conducting the telephone interview |
| Qualitative Interview Guide and Ranking Exercise [Appendix F] | • To guide semi-structured interview on migraine symptoms, impacts and outcomes |
| Participant interview audio file and transcript | • To capture participant interview responses verbatim |

### 4.3.2 Qualitative Interviews

The in-depth qualitative interviews will be conducted using a semi-structured interview guide (Appendix F). The interview will begin by asking broad exploratory questions on the individual's migraine history and experiences with migraine and its treatment. The interview will continue to build on this using a migraine attack reconstruction exercise and other focused but open-ended questions for more in-depth exploration of topics such as:

- Key migraine symptoms at all phases of a migraine attack and in-between attacks
- Impact of migraine on personal and family life including:
    - Limitations on daily functioning including work, school, and household
    - Limitations on leisure activities
    - Physical functioning
    - Emotional burden
    - Cognitive interference
    - Social and familial relationships
- Within-person variation of migraine symptoms, impacts and disease burden
- Experience with and priorities for migraine treatment, including:
    - Effect of treatment on symptoms and impacts
    - Treatment burden

- Valued treatment outcomes
  - During the interview, when feasible, participants will be asked to complete a virtual card ranking exercise to assist in determining priorities for acute and preventive treatment. Interviewers will share their screen with the participant using Microsoft Teams and ask the participant to talk through ranking shared lists of preventive and acute treatment outcomes in order of importance to them. This will be facilitated through QuestionPRO®, an encryption-secured survey platform (Appendix F).

- Changes in migraine experience due to COVID-19 and stay-at-home orders
  - Given the circumstances surrounding the COVID-19 pandemic and stay-at-home orders, the interview guide has been strcutured to capture participants' experience with migraine prior to disruptions brought about due to COVID-19 and to document, as appropriate, more recent changes in migraine symptoms or impacts due to the impacts of the pandemic.

- Note: Recent work in this space by Pharma (MPFID by Amgen and AIM-D by Allergan- though less is in the public domain on AIM-D) tends to identify four key domains after qualitative work and factor analysis; physical function, usual activities, social function , emotional function. Areas of additional interest include the effect of migraine on concentration and thinking which could be a fifth domain or could be thought to load on one of the other identified domains. Yet another area of importance that has not been sufficiently explored is the effect on driving.

Follow-up probes will be asked as needed to gain a deeper understanding of a participant's experience.

The general purpose of the interviews is to 1) provide a full understanding of the concepts that are relevant and important from the participant perspective, 2) conceptualize the symptoms, impacts (physical, mental, social, functioning in daily life), treatment experiences, treatment burden, and treatment outcomes most valued by people with migraine, 3) describe any differences in the experiences of people with migraine and the outcomes they value most, and 4) identify the specific language people with migraine commonly use to express symptoms, impacts, treatment experiences, treatment burden, and treatment outcomes.

Interviews will be conducted over the phone/web-conferencing, audio-recorded (with participant's permission) by trained interviewers (see Section 4.3.3) and will last approximately 60 to 90 minutes each. Upon completion of the interview, each participant will be compensated for their time in the form of a $125 cash gift card. Compensation will be mailed by Pharmerit directly using the mailing address provided by the participant at the end of their interview session. The participant's address will be requested by the interviewer after the interview recording has stopped and will only be used for the purpose of mailing compensation for study participation.

The interviews will be conducted in an iterative fashion, with 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, with modified versions implemented in subsequent interviews. In addition to the iterative process described above, a short pause in data collection to review performance of the interview guide is planned after a series of 3-5 pilot interviews have been conducted.

### 4.3.3 Interviewer Training and Quality Assurance

All participant interviews will be conducted by the Pharmerit research team who have experience conducting qualitative interviews and have been previously trained in qualitative data collection techniques for COA development and other health outcomes research approaches. Prior to conducting interviews, all interviewers will review the study protocol and interview guide (Appendix F) and will participate in mock interview sessions. The mock sessions serve to test question flow, identify problematic or awkward phrasing, and to test the general timing of the interview.

## 4.4 Data Analyses

### 4.4.1 Participant Sample Description

Information on the participant sample will be based on the descriptive data obtained from the Participant Eligibility Screener (Appendix B) and the DHIF (Appendix D), according to participants' self-report. This data will be tabulated and presented in a table format to characterize the study sample.

### 4.4.2 Analysis of Concept Elicitation Data

Audio-recordings will be transcribed verbatim and entered in ATLAS.ti v8.0, a software package which is designed to facilitate the storage, coding, and analysis of qualitative data. ATLAS.ti allows the researcher to code data at various levels of analysis and search for coded data using Boolean operators. The goal of the coding process is to identify relevant concepts and expressions of study participants and to organize these within similar groupings. Through careful review of each transcript, relevant portions of text expressing codable concepts will be identified and tagged with a code. The Pharmerit research team will develop a preliminary coding framework which will be further refined using a consensus-based team approach. Codes will be developed from the verbatim words of interview participants and conceptually equivalent codes grouped and merged as appropriate.

Consistency of coding will be assured through assessment of inter-coder agreement and resolution of inconsistencies. Four transcripts (10% of the overall sample) will each be dual coded independently by 2 researchers. After the coding is complete, they will meet and compare the concepts identified and codes assigned, resolving any differences through consensus. The coding will then proceed following the agreed coding scheme, with coders meeting regularly to discuss new codes and resolve discrepancies. After coding is finalized, outputs from ATLAS.ti will be generated listing, for example, the number of cases (i.e. participant interviews) that reflected the

concepts categorized by each code. These types of outputs will help inform more in-depth analysis of the content and context of coded interview data, which will be reflected in summary tables, accompanying narratives, and exemplary verbatim quotes that reflect the key concepts documented through this inquiry.

### 4.4.3 Assessment of Saturation

Saturation (as previously defined in Section 4.2.1), will be assessed in the interview data via a process that examines the appearance of novel concepts across chronologically-ordered groups of interview transcripts. Given the initial sample size of 40, transcripts will be organized chronologically and analyzed in 8 sets, with approximately 5 interviews in each set. Concept codes derived from the second group of interviews will be compared with codes from the first group to determine if any ***new*** concepts were identified as a result of analysis of the second group's interview data. If new concept codes are identified during second group interview data analysis, then saturation has not been achieved. This comparative exercise will be repeated across all interview groups to identify the point of saturation. In addition to assessing concept saturation within the entire interview sample, concept saturation will also be assessed in sub-samples of participants with episodic and chronic migraine following a similar process to the one detailed above.

The saturation assessment will follow current industry best practices and the FDA's Guidance to Industry regarding evidence of 'saturation' in qualitative research carried out to support PRO instrument development.[21, 24] Conducting the saturation assessment in this study will ensure that participant interviews yield a *comprehensive* set of concepts based on direct report from people with migraine.

# 5 Reporting and Communication of Study Results

## 5.1 Qualitative Study Report

A comprehensive research report will be developed to summarize the following for this qualitative study: background and objectives, study design and methods, results/interview findings, discussion and limitations, conclusions. All references associated with the report will be listed and supporting documents will be included as appendices.

The findings outlined in this report will be used by VPG and their collaborators to assess concordance between the constructs/outcomes identified through AIMS 1 and 2 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 endpoints that require additional development/refinement.

## 5.2 Potential Publications and Publication Policy

The results of this study, with prior written permission from MiCOAS PIs and FDA, may be submitted for publication in a scientific journal or for presentation at a medical or industry 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 (ICMJE) guidelines.[27] As such, individuals named as authors 'should have participated sufficiently in the work to take public responsibility for the content.' Authorship should be based on achieving all of the following 4 criteria:[27]

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. VPG will be promptly notified of any amendments subsequently requested by reviewers or journal editors.

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

# 6 Data Management

## 6.1 Data Storage and Handling

The data for all electronic forms (i.e., Participant Eligibility Screener [Appendix B], ICF [Appendix C], DHIF [Appendix D], Participant Contact Information [Appendix E]) 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 flexCOA system are encrypted and protected. Throughout the study, the VPG research team will regularly export study data from flexCOA® to a secure and designated VPG study folder. Data will be transferred to Pharmerit using encrypted email or encrypted VPG file share software.

The VPG study folder will be located 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 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 data for a period of 5 years, and then securely destroy consistent with current VPG standard operating procedures.

Audio files from participant telephone interviews will be labeled with the participants unique identification number and uploaded to a designated, secure Pharmerit SharePoint 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. The transcriber will then create de-identified transcripts and save the transcripts back to Pharmerit's secure SharePoint file storage system. The de-identified interview transcripts will be entered in ATLAS.ti for data analysis. The ATLAS.ti server is hosted at Pharmerit, protected by the local area network security, and data restricted to designated users using high complexity password security.

The Pharmerit SharePoint study folder will be located in secure servers within Pharmerit's information technology systems. Access to this folder will be restricted to the members of the Pharmerit research team involved in this study. If any participant-identifiable study data is printed in hard copy, the documentation will be stored in a locked filing cabinet at the Pharmerit offices in Bethesda, Maryland. After study completion, Pharmerit will securely archive all study participant data for a period of 5 years, and then securely destroy.

## 6.2 Data Monitoring and Quality Assurance

Prior to initiation of participant recruitment, quality checks with 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 Pharmerit and VPG research teams 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 Pharmerit 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.

# 7 Ethical and Regulatory Obligations

This study will be conducted under Pharmerit's Federal Wide Assurance (FWA) for the Protection of Human Subjects *[FWA #: 00029229; Institution: Pharmerit International LP; Expires: 01/27/2025]* and in compliance with the recommendations of the Declaration of Helsinki and the International Ethical Guidelines for Epidemiological Studies by the Council for International Organizations of Medical Sciences (CIOMS). In addition, this study will adhere to all local regulatory requirements applicable to non-interventional studies.

## 7.1 Institutional Review Board

This study will be submitted to an IRB for review and approval (or determination of exemption from IRB oversight) 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 exemption, if applicable) is received.

## 7.2 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 nature and purpose of this study and data collection will be explained to each person prior to their enrollment as a study participant. Enough time will be allowed to discuss any questions raised by the individual. The individual will be allowed as much time as they need to consider their decision for participating in this study.

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. 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.

Prior to participation in study activities, 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 research. The web-based screening questionnaire will be introduced first and administered only after the participant has confirmed that they would like to fill out the questionnaire by pressing "begin" on the online screening platform. If the participant is deemed eligible, they will then be

routed to a detailed informed consent form (i.e., the ICF [Appendix C]) prior to proceeding to the electronic DHIF (Appendix D), Participant Contact Information sheet (Appendix E) and considered for interview. If important new information becomes available during the study, the consent form will be revised.

## 7.3 Confidentiality

Pharmerit 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 international data privacy requirements, such as HIPAA and European General Data Privacy Requirements (GDPR). All participant data collected and processed for the purposes of this study will be managed by the Pharmerit research team with adequate precautions to ensure the confidentiality of the data, in accordance with applicable national and/or local laws and regulations on personal data protection.

Participants' names and contact information will be provided directly by the participant to Pharmerit 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: Pharmerit, 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.

# 8 List of Appendices

This protocol includes the following appendices (Table 3):

**Table 3. List of Appendices**

| Protocol Appendix | Document/Form |
|---|---|
| A | Study Announcement/Advertising Content |
| B | Participant Eligibility Screener |
| C | Informed Consent Form (ICF) |
| D | Demographic and Health Information Form (DHIF) |
| E | Participant Contact Information Form |
| F | Initial Qualitative Interview Guide* |
| G | Screen shots of online screening, informed consent, and data collection platform |
| *Initial version will be provided; given the dynamic interviewing process, the interview guide may be modified/refined throughout participant interviews. | |

# 9 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.* 2011;31(3):301-315.
2. Buse DC, Lipton RB. Global perspectives on the burden of episodic and chronic migraine. *Cephalalgia.* 2013;33(11):885-890.
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.* 1999;159(8):813-818.
4. American Headache S. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. *Headache.* 2019;59(1):1-18.
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.* 2016.
6. Haut SR, Bigal ME, Lipton RB. Chronic disorders with episodic manifestations: focus on epilepsy and migraine. *Lancet Neurol.* 2006;5(2):148-157.
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.* 2017;57(4):570-585.
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.* 2001;41(7):646-657.
9. Collaborators GBDH. 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.* 2018;17(11):954-976.
10. 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.* 2010;81(4):428-432.
11. Buse DC, Silberstein SD, Manack AN, Papapetropoulos S, Lipton RB. Psychiatric comorbidities of episodic and chronic migraine. *J Neurol.* 2013;260(8):1960-1969.
12. 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.* 2019;22(9):849-858.
13. 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.* 2018;58(7):933-947.
14. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia.* 2018;38(1):1-211.
15. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies. *Headache.* 2015;55(1):3-20.
16. Silberstein SD. Preventive Migraine Treatment. *Continuum (Minneap Minn).* 2015;21(4 Headache):973-989.
17. 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 and Quality of Life Outcomes.* 2014;12(1).
18. Lasch KE, Marquis P, Vigneux M, et al. PRO development: rigorous qualitative research as the crucial foundation. *Quality of Life Research.* 2010;19(8):1087-1096.
19. 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.

20. Patton MQ, Patton MQ. *Qualitative research and evaluation methods.* 3 ed. Thousand Oaks, Calif.: Sage Publications; 2002.
21. 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 in Health.* 2011;14(8):967-977.
22. Charmaz K. *Constructing grounded theory: A practical guide through qualitative analysis.* Sage; 2006.
23. 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 in Health.* 2009;12(8):1075-1083.
24. 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):65132-65133.
25. 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.
26. Robinson OC. Sampling in interview-based qualitative research: A theoretical and practical guide. *Qualitative research in psychology.* 2014;11(1):25-41.
27. International Committee of Medical Journal Editors. Defining the Role of Authors and Contributors. *Roles and Responsabilities* [Web]. 2019; http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html Accessed April 10, 2019.

# Appendix

## Appendix A

Study Announcement and

## Appendix B

Participant Eligibility Screener.p

## Appendix C

Informed Consent Form (ICF).pdf

## Appendix D

Demographic and Health Information

## Appendix E

Participant Contact Information Form.pd

## Appendix F

Initial Qualitative Interview Guide.pdf

Section 5 QuestionPro Screens

## Appendix G

Online screening, informed consent, a