MiCOAS UH3 Cognitive Debriefing Study Protocol

Protocol Title	Cognitive Debriefing Interviews to Support Development of the Migraine Clinical Outcome Assessment System (MiCOAS)
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Research Organization	**Vector Psychometric Group, LLC** 847 Emily Lane Chapel Hill, NC 27516-0807 Phone: 1.919.768.7142

VECTOR PSYCHOMETRIC GROUP, LLC

CHAPEL HILL, NORTH CAROLINA U.S.A

VERSION HISTORY

Version	Date	Author(s)	Summary of Changes/Comments
1.0	12/1/2021	Rikki Mangrum, MLS	
1.1	3/2/2022	Rikki Mangrum, MLS	Updated to describe recruiting sites and draft instruments to be tested

LIST OF ABBREVIATIONS

Abbreviation	Definition
Einstein	Albert Einstein College of Medicine
FDA	U.S. Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act of 1996
IRB	Institutional review board
MiCOAS	Migraine Clinical Outcome Assessment System
PROM	Patient reported outcome measure
VPG	Vector Psychometric Group, LLC

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1. PROTOCOL SYNOPSIS

STUDY TITLE: Cognitive Debriefing Interviews 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 involves recruitment of study participants through health clinics for participation in a one-time, individual, semi-structured interview conducted via video-conferencing.

STUDY OBJECTIVES: In this study, proposed migraine measure questionnaire components will undergo cognitive review by people living with migraine to establish whether there is evidence that respondents will understand and complete the questionnaire as intended. Questionnaire components to be reviewed by participants include the measure name, all accompanying instructions or information, and all item content and response options.

STUDY POPULATION SAMPLE: This study will include approximately 40 participants who are representative of the population of people with migraine generally included in clinical trials of acute or preventive migraine treatments. A limited sample is appropriate because the instrument does not include branching skip patterns and participants will see all items in each version of the instrument. However, 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 questionnaire validity evidence is accrued.

The study will include adults who meet the following inclusion and exclusion criteria:

Inclusion criteria:

- Be a resident of the US.
- Be between 18 and 75 years of age.
- Have been diagnosed by a healthcare professional (i.e., meets the ICHD-3 criteria for migraine with or without aura).
- Report being able to distinguish between a day with migraine and other types of headache days.
- Report experiencing 4-26 headache days per month.
- 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, which includes being willing to be on camera for the interview and to have their interview video recorded and transcribed.

Exclusion criteria:

- 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.

- Reported alcohol or drug abuse over the past 3 months (not inclusive of medication overuse to treat migraine).

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

- Appendix A: Case report form completed by clinical site coordinators who recruit patients
- Appendix C: Health and Demographic Information Survey (delivered via a web-based questionnaire platform)
- Appendix E: Interview Guide
- Appendix F: Draft PROM instruments

ANALYTIC APPROACH: Video-recordings of interviews will be transcribed verbatim and deidentified by removing any information that identifies, or could be used to identify, participants.

Disposition tables will be prepared for each element of the questionnaire included in each round of testing. Analysts will examine the transcripts for relevant data for each item in the table and record results in the disposition table.

Items or other components of the questionnaire that are not understood as intended, create challenges for respondents, or are judged to be poor quality or not relevant to participants will be flagged and referred for revision or removal. Revised components will be re-tested in a subsequent interview.

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 3 months. However, study length is highly dependent upon recruitment rate and participant availability, as well as the number of rounds of testing required.

2. STUDY PROTOCOL

2.1. Purpose

To establish and report evidence of the content validity of a patient-reported outcome measure (PROM), respondent understanding of all aspects of the instrument must be systematically assessed. Cognitive interviewing is used after questionnaire items are created or selected. Results from cognitive interviews determine whether

a) The instrument's content captures important aspects of the relevant concepts of interest, as assessed by patients.

b) Patient respondents understand and use the instrument as intended, such that they can follow instructions for completing it and understand aspects such as the recall period or response scales.

2.2. Draft Instruments

The study will examine draft PROM questions. These questions have been organized into two draft instruments for the initial wave of cognitive debriefing interviews:

- Instrument 1: Includes 13 questions capturing symptoms experiences over the past 24-hours and 58 questions asking about physical functioning and symptoms over the past 14 days

- Instrument 2: Includes 74 questions about cognitive and psychosocial functioning over the past 14 days

These initial draft instruments will include all alternative versions of items and will test items with all possible response options. After the initial wave of interviews, the number of items included in the draft instruments will sharply decrease as evidence is gathered about which items and response options are most suitable for the PROM (see section 2.5 Method).

2.3. Population and Sample

A sample of people with migraine will be selected that is representative of the population of migraine patients who participate in clinical trials of novel treatments. Because the instrument presented in each round of testing will not include branching skip patterns, a limited sample size is appropriate. However, 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 questionnaire validity evidence is accrued.

Each item in the evolving instrument will be reviewed by a minimum of 5 participants in each round of testing. To achieve review by an overall diverse population sample, the following participant attributes will be considered when selecting individuals for interviews:

- Migraine frequency type (episodic <15 days/month, chronic ≥15 days per month)
- Sex and gender identity
- Race
- Ethnicity
- Age
- Level of education
- Income
- Geographic location (to account for vernacular and cultural differences)

To ensure data collection balances input from individuals with episodic and chronic migraine, each round of testing will to gather data from people with these two broad types of migraine. Within the episodic and chronic groups, enrollment will also aim to include a mix of people with different average numbers of headaches per month. For all other participant characteristics, enrollment will seek an overall mix of characteristics across all selected participants over the course of the study.

2.4. Context of Use

To reflect the aim of validating the PROM as a clinical outcome assessment for drug development and clinical trials, cognitive debriefing will examine respondent understanding, including understanding specific to the use of the instrument to assess change in migraine symptoms and functioning. The interview protocol will include, for example, questions focused on determining how respondents interpret and apply the different response scales or recall timeframes. Determining whether respondents find these scales and timeframes understandable, applicable, and relevant to assessing change will be crucial to establishing content validity for the instrument for use in a clinical trial of treatment.

2.5. Method

Methods used in this study will adhere to guidance on best practices specific to the establishment of content validity for a PROM intended for medical product evaluation.[1-3]

Beause this study will test a large number of new and modified PROM items, data collection will be conducted in several waves. In the first wave, the focus of analysis will be to identify items that participants view as not relevant; determine which alternative items for relevant concepts are best understood and acceptable to people with migraine; ascertain which items participants view as repetitive or difficult to understand; and assess which response options are clear, useful, and appropriate for each item. As such, a primary goal of wave 1 analysis will be to assemble evidence that can be used to sharply reduce the number of items in the draft

instruments. Subsequent waves of interviews will then provide evidence to further refine the draft instrument and gather evidence of its content validity and comprehensibility.

2.5.1. Recruitment

Participants will be recruited by clinic site partners and all recruited participants will have an established migraine diagnosis by a clinician. Participants will be enrolled to represent a variety of demographic and health characteristics. The study will include adults who meet the following inclusion and exclusion criteria:

Inclusion criteria:

- Be a resident of the US.
- Be between 18 and 75 years of age.
- Have been diagnosed by a healthcare professional (i.e., meets the ICHD-3 criteria for migraine with or without aura).
- Report being able to distinguish between a day with migraine and other types of headache days.
- Report experiencing 4-26 migraine headache days per month.
- 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, which includes being willing to be on camera for the interview and to have the interview video recorded and transcribed.

Exclusion criteria:

- 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.
- Reported alcohol or drug abuse over the past 3 months (not inclusive of medication overuse to treat migraine).

When clinic site coordinators identify patients who are eligible for the study, they will complete the interview study case report form (CRF) documenting eligibility and key health and demographic characteristics. Sites will create a participant number for each individual to be included on the CRF. Site coordinators will also provide each prospective study participant with the informed consent form for their review. If an eligible subject wishes to participate, the site will receive the signed informed consent form and document the date it was signed on the CRF. Participants who consent will then be directed to the study website to complete the health and demographic survey and provide their contact information to VPG for interview scheduling.

Through a secure SharePoint, sites will upload (1) a copy of the CRF, (2) the signature page of the consent document, (3) a separate list of participant names and assigned participant IDs.

Once eligible individuals complete all the enrollment steps, they will be contacted for an interview by a member of VPG's staff. VPG will keep site coordinators updated on whether enrolled, consented participants complete the survey and/or interview steps, as this will determine whether recruitment should continue.

2.5.2. Data Collection

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.

2.5.2.1. 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 and forms for the study are described in Table 2. Enrolled participants who are scheduled for a wave 1 interview will be provided with a link to the study website where they may complete the draft PROM online in advance. Participants will receive a PDF version of their completed PROM via email. Enrolled participants who are scheduled for a wave 2 interview will complete the draft PROM during the interview itself.

Table 2. Data Collection Instruments and Data Files

Document/Form	Purpose
Case Report Form (Appendix A)	To determine participant's study eligibility
Health and Demographic Information Form (Appendix C)	To obtain participant's health and demographic information
Participant Contact Information (Appendix D)	To obtain participant's contact information for reconfirming eligibility, scheduling interview, and conducting the video interview
Cognitive Debriefing Interview Guide	To guide the semi-structured interview about the PROM instrument

(Appendix E)	
Draft PROMs (Appendix F)	To capture participant's answers to the PROM so that they can be discussed during the interview.
Interview video recordings and transcripts	To capture participant interview responses verbatim for analysis

2.5.3. Interviews

Due to the continuing COVID-19 pandemic, it is likely that most people will not be willing to participate in face-to-face interviews. Study methods have been adapted to reflect a virtual interview format. Adaptations are described in the following subsections.

Interview duration and design.

Interviews will take up to 60 minutes. In the first wave of interviews, participants will complete a draft PROM ahead of time and at their convenience. The first wave is expected to include 10 interviews, 5 for each version of the instrument. In subsequent waves of interviews, participants will complete the PROM during the interview and the instrument will include no more 50 items in a given interview.

To facilitate communication between interviewer and participant, all interviews will be conducted using an online conferencing system with both people on camera so that they can see each other. The interviewer will also display the PROM instrument on screen so that both people can see it.

"Think aloud" commentary process.

Think aloud procedures will be used starting in the second wave of interviews. Best practice entails closely observing participants as they complete the think aloud review step because body language and facial expressions often reveal a great deal about how the participant interacts with a measure.[4] In a virtual interview, several obstacles may interfere with this process.

1. Participants must be willing to be on camera for the interview. As a result, access to a webcam and willingness to be on camera are included as eligibility criteria. Some potential participants may decline to enroll in the study because of this requirement due to concerns about privacy. To mitigate these concerns, the informed consent document and interview scheduling communications will include information about privacy capabilities in Microsoft Teams and plain language explaining why the camera is needed.

2. The interviewer must display the instrument on the screen and support the participant in completing and reviewing it. Participants will vary in their ability to utilize conferencing applications that include interactive components. Participants who have experience with online conferencing may not be familiar with VPG's preferred platform. As a result, the interview protocol must allow time for orienting the participant to the program and for the interviewer to move content on screen. After the initial wave of interviews, the interviewer will also record the participant's answers for them. When the interviewer has to do this, however, it distracts from the observation of the participant and active listening to the think aloud commentary. To compensate for this, VPG will supply a supporting staff member for virtual interviews. The support staff will remain in the interview for the think aloud step and provide technical support, thus permitting the interviewer to maintain focus. Participants will be informed during the scheduling process if there will be two interviewers present for part of their interview.

2.5.3.1. Saturation and number of interviews per cycle.

Data saturation is the standard for cognitive review, but the number of interviews required to attain saturation varies depending on the number of items, the complexity of the instrument, and the characteristics of the patient population, as well as the desired level of evidence. A widely-used heuristic in cognitive interviewing is that a minimum of 5 reviewers are needed to assess whether an item should be revised or eliminated, but additional interviews may be needed to confirm an item's quality or to surface challenges.[5] In other words, 5 interviews may suffice to identify major problems with items but may provide insufficient evidence that an item needs no improvement. Because several rounds of review are anticipated in this study, VPG will interview a minimum of 5 participants about each item in each round. When interviews with 5 individuals indicate problems with components of the draft instrument, these findings will be referred to the research team for decision making. Revised components will then be tested in the next round of interviews. Components that pass initial testing with 5 individuals will also be included in later rounds of testing to acquire further evidence of their quality and acceptability. Items that have been reviewed by 10 participants without any problems being identified, may be excluded from additional rounds of testing to reduce participant burden, as appropriate.

2.5.3.2. Participant compensation

Participants who complete an interview will be compensated with a $75 electonic Mastercard delivered by email. Participants who participate in the first wave of interviews will complete a longer version of the PROM online ahead of time and will receive an additional $25.

2.5.3.3. Interview Training and monitoring.

Interviewers will prepare by reviewing study aims specific to content validation, reviewing relevant FDA and International Society for Pharamacoeconomics and Outcomes Research

guidance on cognitive interview procedures, closely studying the interview guide, and practicing with the virtual interview platform. New or inexperienced interviewers will observe at least 5 interviews conducted by a skilled interviewer; this may be achieved by watching recordings or by passively observing live interviews with the permission of the participant. New or inexperienced interviewers will be monitored during their first 2-3 interviews by an experienced interviewer. In both situations, participants will be informed in advance that there will be two interviewers present.

Interviewers will participate in mock interviews as part of their training. These interviews will also be used to refine the wording of interview questions and to test the virtual interview platform and logistics plan.

The qualitative study director will monitor the quality of interviews by reviewing several recordings or transcripts in each round. Monitoring will assess both interviewer adherence to best practices as well as the quality and comprehensiveness of data elicited during interviews. Quality issues with interviewers will be addressed through additional training. Issues with comprehensiveness of the data will be shared with the research team for decision making about whether and how to modify the interview guide.

2.5.4. Preparation of Transcripts

Audio from the interview recordings will be professionally transcribed. When transcripts are received, VPG will review the transcript for accuracy and remove any content that may serve to identify the interview participant, such as personal names. VPG will also add notes to the transcript describing any facial expressions or body language recorded in the video, and add timestamps indicating the time participants took to read and complete items. Line numbers will also be added to transcripts to improve the audit trail of data related to specific issues raised by participants. Line numbers will be included in all sample quotes included in analytic tables to support later verification, as needed.

2.6. Analysis

Rigorous analysis of cognitive debriefing data first requires that analysts operate from an accurate grasp of how each component of a PROM instrument is intended to be understood by measure respondents. Analysts will use both recordings and transcripts during analysis. Analysts then make and record judgments about the alignment between the interview participant's thoughts and the intent of the PROM. These judgments will be recorded in a structured manner in a disposition table including each component of the instrument, as shown in Table 3.

2.6.1. Intended Meaning

The research team will supply a written description of the intended domain and the intended and acceptable interpretations of each component of the instrument, beginning with the name.

2.6.2. Disposition Table

The disposition table will be used to record data extracted from interview transcripts. It will include an accounting of the percent of interviews in which participants' understanding aligned overall with the intended interpretation and will concisely summarize what participants said. The table will record any directive suggestions made by participants and will include quotes reflecting the nature of variances and any problems participants had with components of the instrument.

The table will also record the rationale and text of any revisions to the instrument and the results of subsequent cognitive review.

In the Analyst's Comments column, analysts will summarize interview content and include, as appropriate, comments characterizing

- Degree of alignment or variation among participants and between participants and the intended interpretation.
- Responses to items (e.g., participant comments related to ceiling, floor, missing options, or irrelevance of the response options for that specific item)
- Item problems, such as
    - Misreading or misinterpretation of a word or phrase (e.g., missing the word "need to" in "how often did you need to rest or lie down"), including notations indicating whether this could be related to the instrument layout.
    - Issues with clarity or ambiguity (e.g., item includes terms or phrases that are unclear or could be interpreted in more than one way)
    - Issues with wording (e.g., words and phrases are unknown)
    - Other problems

Table 3. Sample Disposition Table (fake data for illustration only)

Component	Item ID	Original Text	Response Scale	Testing Interviews	Overall % Agreement	Analyst's Comments	Participant Suggestions	Example Quotations	Flag for Revision	Change after Round 1	Rationale for Change After Round 1
PROM Name	00	MiCOAS	NA	CI_01, CI_02, CI_03, CI_04, CI_05	100%	Participants did not notice the name until asked. All were neutral about the name.	NA		N		
Timeframe	01	In the past 7 days…	NA	CI_01, CI_02, CI_03, CI_04, CI_05	60%	CI_02, CI_05 interpreted as "since the most recent weekend" and "what a typical week has been like recently." The other 3 participants correctly interpreted this to mean they should think back over the 7 days immediately past.	NA	I guess I read that as being within the current week, which I think of as starting on Monday, so yeah, I wouldn't necessarily think about the last 7 days in a row (002-line 154)	Y	None	Continue to test to evaluate prevalence of misinterpretation

2.6.3. Flagging items for revision

Items with lower overall agreement (60% or less, or 3 or fewer of 5 participants) or where individual participants encountered any difficulty in understanding the item or selecting a response will be flagged for discussion and possible elimination or revision by the research team. Items will also be flagged for dicussion if at least two participants identify the item as unimportant or not relevant, consider it repetitive of other items, or express a negative view of the match between the item and the associated time frame or response options. Finally, items will be flagged for discussion if individual participants identify insensitive or culturally inappropriate language.

2.6.4. Iterative re-testing

Items that are revised will undergo re-testing in a subsequent cognitive review interview. Items that have not been revised but require additional evidence to reach saturation may also be re-tested in subsequent interviews.

2.6.5. Assessing saturation

Saturation will be assessed by the proportion of participants demonstrating overall agreement with the intent of each component as well as research team assessment of how reported problems might affect measure function. For example, 2 out of 5 participants may say they are not familiar with the phrase “wiped out,” but if they correctly interpret it to mean “tired” on their own, then revision may not be warranted. However, if 3 of 7 participants interpret the term “weak” to mean “lacking character and fortitude” and never connect it to physical function, then the item should be reconsidered.

Assessments of saturation and decisions about item revision must also be made with reference to well-established principles of measure writing.[1] For example, participants may variously raise objections to timeframes or response scales for specific items. These objections must be weighed against evidence that consistency for these components can be critical for measurement accuracy.

3. Reporting and Dissemination of Study Results

VPG will prepare a summary report of the cognitive debriefing results. The report will comprise the following components: background and objectives, study design and methods, results, limitations, and discussion. The report will also include the final disposition table and the revised PROM instrument.

3.1. 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. Accordingly, authorship should be based on achieving all of the following 4 criteria:

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

Case report forms and informed consent forms handled by recruitment sites will be scanned and uploaded to a secure Sharepoint created for this piurpose. 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 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.

Recordings from participant 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 recording is confirmed as successfully stored in the study folder, the file will be deleted from the recording device. The recording for each study participant will be securely transferred for transcription through a credentialed file-sharing service restricted to interviewers and transcriptionists. 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.

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.

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.

5.1. Institutional Review Board

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

5.2. Informed Consent

This study will be performed in accordance with ethical principles that are consistent with local and national applicable regulatory requirements. Site coordinators will provide eligible participants with a copy of the consent form for their review. 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 a signed informed consent form to the site coordinator. When site coordinators receive a signed consent form, they will provide the participant with a link to the study website where they may complete their enrollment by filling out the electronic Health and Demographic Information Survey (Appendix C) and Participant Contact Information Form (Appendix D). Participants who complete all enrollment steps will then be contacted to schedule an interview. 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 or to decline to answer questions, 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.

5.3. Confidentiality

VPG, Einstein, and all clinic site partners 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' 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. Case report forms, copies of signed informed consent documents, and study IDs linked to participant names provided by recruiting sites will be uploaded by site coordinators directly to a secure Sharepoint accessible only to research team members involved in this qualitative study.

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.

6. REFERENCES

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3. 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.

4. Padilla J-L, Leighton JP. Cognitive interviewing and think aloud methods. *Understanding and investigating response processes in validation research*. Springer; 2017:211-228.

5. Beatty PC, Willis GB. Research Synthesis: The Practice of Cognitive Interviewing. *Public Opinion Quarterly*. 2007;71(2):287-311. doi:10.1093/poq/nfm006

APPENDIX A: CASE REPORT FORM

[placeholder]

APPENDIX B: INFORMED CONSENT

PARTICIPANT CONSENT FORM

TITLE:	Cognitive Debriefing to Support Development of the Migraine Clinical Outcome Assessment System (MiCOAS)
PROTOCOL NO.:	MiCOAS UH3 2022-02
SPONSOR:	Vector Psychometric Group, LLC Under a grant from the United States Food and Drug Administration (FDA) (#3UH3FD006795-02S1)
INVESTIGATOR:	R.J. Wirth, PhD 847 Emily Lane Chapel Hill, North Carolina 27516 United States
STUDY-RELATED PHONE NUMBER(S):	Lexy Bryant lexy.bryant@vpgcentral.com [301-392-7991] Rikki Mangrum rikki.mangrum@vpgcentral.com 919-893-9055

Why am I being contacted?

You are being invited to take part in a research study about people who have migraine headaches. If you participate, you will be one of about 40 participants in this study.

If you choose to participate, you:

- Will be asked to answer a 10-minute online survey about your background and health
- May be asked to complete a 30-minute online questionnaire about your migraine experiences before your interview
- May be invited to participate in one interview that will last about 60 minutes

The main **benefit** of this research is that your participation will help scientists develop measures of the impact migraine has on people's lives. These measures will be used to evaluate how well treatments for migraine work. But, there is no direct benefit to you for participating.

The main **risk** of the research is that you may find the interview tiring.

Your participation is **voluntary**. Your alternative is to not participate. The decision to participate is up to you. You always have the right not to answer questions. You may also stop your participation at any time. If you do not want to participate or decide to stop participating, there will be no penalty or loss of benefit to which you are otherwise entitled.

More information about all these topics is provided below.

Why is this study being done?

The purpose of this study is to test a draft survey that measures migraine experience. This measure includes questions about migraine symptoms and how migraine affects people's ability to do the things they want to do from day to day.

How will this study help people with migraine?

The information collected during this study will be used to improve the survey measure. The measure can then be used to understand whether treatments for migraine, such as medicines, are working as intended.

Who is paying for this study?

The United States Food and Drug Administration (FDA) is funding the study through grant number 3UH3FD006795-02S1.

Who is conducting this study?

Vector Psychometric Group, LLC, and Albert Einstein College of Medicine are conducting this study. In the rest of this document, Vector Psychometric Group will be called VPG.

What should I know about this research?

The study involves

- answering the measure survey questions before or during your interview
- talking with the interviewer about your thoughts about the measure survey

The study does not involve any medical treatments and will not affect your medical care in any way.

If you have any questions about the study after you read this form, please call or email the study contact listed at the top of this form. Ask all the questions you want before you decide about participating.

Taking part in this study is voluntary. It is your decision whether to participate at all times. No matter how you choose, there will be no penalty or loss of benefits to which you are otherwise entitled.

- You can choose not to take part at all.
- You can agree to take part and later change your mind at any time.

What are you asking me to do?

We are asking you to fill out a survey about your health and background. We may also ask you to take part in an interview to hear your thoughts on the draft measure. If you are selected for an interview, you will be asked to fill out a version of the measure survey either before or during your interview.

The health and background survey will take about 10 minutes to fill out.

If you are asked to fill out a version of the measure survey before your interview, it will take about 30 minutes to complete.

The interview will last about 60 minutes. The interview will take place through a video conferencing platform called Microsoft Teams. You will be required to be on camera so that you and the interviewer can see each other, so you need to have a working webcam. You will receive a unique, private link for your interview.

The interview will be video-recorded and transcribed. Microsoft Teams allows you to use a background image, which provides privacy by blocking out your surroundings. If you would like to use this feature, the interviewer will help you turn it on before the recording starts.

What do I do if I am interested in taking part in this research?

Taking part in the study requires a few steps.

1. **Consent to participate in the study**. The first step is completing this informed consent form.

Take your time to read the form and ask any questions before giving your consent. You can reach out to the study contact listed at the top to ask any questions that you have about this study.

If you want to participate, you should indicate your consent at the bottom of this form.

Indicating consent to participate in the study does not waive your legal rights in any way. Your consent does not release VPG or any other institution involved in this study or in the review of this study from their legal and professional responsibilities to protect your identity and your personal information to the extent required by any applicable laws and regulations.

2. **Complete enrollment in the study**. Enrolling in the study involves filling out a survey of questions about your health and your background. After you fill out the survey, you may be contacted to schedule an interview. We may not be able to interview everyone who enrolls in the study.

   The survey will ask about your health history and medications you use for migraine. It will also ask about your gender, race or ethnicity, education, and so on. We use this information to be sure that the people we interview are like all the different people who live with migraine.

   You will also be asked to provide contact information, such as your name and telephone number or email address. The research team will use your contact information only for scheduling an interview and providing payment. No one will share your contact information outside the research team.

3. **Give permission for your interview to be video-recorded and transcribed**. Your interview will be video-recorded so the interviewer can create a transcript of the interview. This written copy of your exact words helps the research team be accurate in describing the experiences of people living with migraine. The research team will also use the video recording to look at body language or how long it takes to read and answer questions, which helps the team understand how well the measure works.

   The interviewer will ask you to confirm your permission to record before starting the interview.

   If you do not want to give permission for your interview to be recorded and transcribed, you will not be able to participate in this study.

4. **Complete an interview**. If you are selected for an interview, VPG will contact you to schedule an interview appointment with a researcher from the study team. The interview will be scheduled at a time that works well for you. VPG will also

contact you once, about 1 to 3 days ahead of time, to remind you about the interview.

The interview will last about 60 minutes. If you did not fill out the measure survey ahead of time, you will be asked to answer the survey questions at the beginning of the interview. Then the interviewer will ask about your thoughts on each part of the measure survey.

How will you protect my privacy?

Your privacy is very important to us, and we make every effort to protect you and your health information to the furthest extent possible. But there is a risk of loss of confidentiality when you participate in a research study.

There are several things we do to protect your privacy and respect the confidentiality of information you may share with us.

- **We store information in secure locations and limit the people who can access it.** We store all our data in secure, electronic files that can only be accessed by certain members of the research team. We will never use your name or identify you as an individual in any way in any reports, presentations, or publications of this study.

- **We don't connect your name or contact information with your data**. To protect your identity, we use a study-specific identification number instead of your name or other personal information. This number protects your identity and is used to label all information collected from you.

  We keep your name and contact information separate from the interview transcript and survey responses. We only need this information to schedule your interview and provide payment, so we don't need to keep it with the study data.

- **Study staff with access to your personal data are bound by confidentiality rules**. If you participate in the study, the people who schedule or conduct your interview will know your name or personal details. The interview recording will be heard by the person who creates the transcript. These staff are bound by confidentiality rules and trained in how to maintain privacy and security of data.

- **We remove information that might help to identify you from your interview transcript**. We remove anything you or the interviewer may say during your interview that might be used to identify you. For example, you might say where you work or talk about how many children you have. When this happens, these details will be deleted from the transcript. Your transcript will then be combined with transcripts for all the other study participants for analysis.

- **We destroy video recordings of interviews as soon as we no longer need them.** Once the final transcript is ready, the video recording of your interview will be securely destroyed.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible for:

- Completing a survey about your background and your health.
- Completing an interview if you are selected, which includes filling out the measure survey either before or during the interview.

Could being in this research hurt me?

There are no anticipated physical risks to participating in this study. The study involves completing a survey and taking part in a video interview.

There is a chance that you may find the interview too tiring. If that is the case, you can tell the interviewer that you are too tired to continue. You have the choice to stop your participation or to continue the interview at another time.

Will it cost me money to take part in this research?

There are no costs to you for participating in this study.

Will being in this research benefit me?

You may not receive any direct health benefits from participating in this study. This research study is not designed to diagnose, treat, or prevent any disease.

However, your contribution will help researchers better understand how to measure people's experience of migraine. This could lead to better ways of measuring the burden of migraine and the benefits of treatment.

Will I be paid for taking part in this research?

If you complete an interview, you will receive $75 as a thank you for your time. You will receive this payment as an electronic gift card (e.g., MasterCard or Visa) after you

complete the interview. If you also complete the online questionnaire prior to your interview, you will receive an additional $25 as a thank you for this extra time.

Choosing to not answer some questions or to stop participating part way through the interview will not affect your payment.

What other choices do I have besides taking part in this research?

Your alternative is to not take part in this study.

What happens to the information collected for this research?

When this study is completed, we will write a report based on what we learn from all the study participants. This report will be shared with the FDA, who is the sponsor of this study, and with the public. The results may also be presented at scientific conferences or published in a research journal so that others can learn from this study. None of these reports or presentations will have any of your identifying data or report your results alone. They will report results that are combined among participants. Any quotes that are used will not include information that allows others to identify you.

The data from this study may be shared with other researchers directly involved in the conduct of this study, such as scientists from Albert Einstein College of Medicine. Study data may also be shared with authorities responsible for oversight of the study conduct such as the FDA, state regulatory agencies (if applicable), and Institutional Review Boards (IRBs), for the purposes of auditing this study to ensure data integrity and protection of study participants. We only share the data that does not include information that could identify you and information has been compiled from all study participants. However, not all parties who will have access to your information as part of this study are prohibited by federal law from further sharing it; therefore, the information once received by them, may no longer be protected by federal law.

There is a possibility that identifiers might be removed from the identifiable private information, and after such removal, the information may be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

Who can answer my questions about this research?

If you have any questions, concerns, complaints, or think this research has hurt you or made you sick after participating, please call or email the study contact listed at the top of this form. You may also contact the principal investigator.

This research study is being overseen by an IRB. An IRB is a group of people (scientists and non-scientists) who perform an independent review of research studies to ensure that they are ethical, fair, and safe. The goal of the IRB is to protect the rights and welfare of study participants. You may talk to WCG IRB at 855-818-2289 or researchquestions@wcgirb.com if:

- You have questions, concerns, or complaints that are not being answered by the study contact or principal investigator.
- You cannot reach the study contact.
- You want to talk to someone else about the research.
- You have questions about your rights as a study participant.

Can I be removed from this research without my approval?

The research team may remove you from this research without your approval. Possible reasons for removal include:

- If you are not able to keep your scheduled interview appointment.
- If you decline to have your interview video recorded or transcribed.
- If this study is cancelled by the sponsor, the FDA, or the IRB.

What happens if I agree to be in this research, but I change my mind later?

You may withdraw your consent to participate at any time during this study. Withdrawing at any time during this study will in no way influence the care that you are receiving from your doctor or other healthcare providers. There will be no penalty or loss of benefits to which you are otherwise entitled if you withdraw from this study.

To withdraw consent from this study, please notify the study contact listed at the top of this form that you want to withdraw.

If you withdraw consent prior to participating in the interview, you will receive no compensation.

If you withdraw consent, no new data about you will be collected and none of your data will be analyzed. All data you provided will be destroyed.

If you do not withdraw consent, but do not complete all parts of the study, any completed data may be used in analysis.

Agree or disagree to participate

Signing below indicates that you have read and understood the information provided, and that you voluntarily **agree** to participate in this research study. You will be provided with a link to a website where you can complete the next steps.

If you **do not agree** to participate in this research study, then do not sign below.

I agree to participate in the MiCOAS interview study.

Print name:_____

Signature: _____

Date signed: _____

APPENDIX C: HEALTH AND DEMOGRAPHIC SURVEY

APPENDIX D. PARTICIPANT CONTACT INFORMATION FORM

APPENDIX E: COGNITIVE DEBRIEFING INTERVIEW GUIDE

APPENDIX F. INITIAL DRAFT PROM INSTRUMENTS

These two instruments are the versions that will be tested in the first wave of interviews. Based on interview results, items will be removed from the instruments or modified prior to additional waves of interviews.