Migraine Clinical Outcome Assessment System (MiCOAS)

REPORT ON THE DEVELOPMENT OF THE DRAFT MICOAS MEASURES AND ASSESSMENT OF LEGACY MEASURES' ALIGNMENT WITH CORE CONCEPTS OF INTEREST

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ABBREVIATIONS

CHAMP	The Coalition for Headache and Migraine Patients
COA	clinical outcome assessment
COI	concept of interest
Einstein	Albert Einstein College of Medicine
ETAC	External Technical Advisory Committee
FDA	U.S. Food and Drug Administration
HRQoL	health related quality of life
MiCOAS	Migraine Clinical Outcome Assessment System
PRO	patient reported outcome
PROM	patient reported outcome measure
VPG	Vector Psychometric Group, LLC

1. INTRODUCTION

Migraine is a neurological condition that can lead to significant economic, social, and individual burden, including disability (Blumenfeld et al., 2011; Buse & Lipton, 2013; Hu et al., 1999). Migraine affects people's ability to function across a wide spectrum of roles and activities, including both short-term impairments associated with migraine attacks and long-term impairments associated with life with a chronic, variable health condition (Buse & Lipton, 2013; Buse et al., 2016; Haut et al., 2006; Hu et al., 1999; Lipton et al., 2017; Lipton et al., 2001; American Headache Society, 2019). For diagnostic purposes that guide both research and clinical care, a distinction is made between episodic migraine, defined as migraine with ≤14 headache days per month over a 3-month period, and chronic migraine, with ≥15 headache days per month over a 3-month period, of which at least 8 are linked to migraine (International Headache Society, 2018). Episodic and chronic migraine are linked to different levels of impact on well-being, with studies demonstrating that chronic migraine conveys significantly higher burdens compared with episodic migraine and that burdens increase as the number of monthly headache days increases (Buse et al., 2010; Lanteri-Minet, 2014). Research has shown that people living with migraine experience symptom-related impairments and disability, decrements in quality of life, higher rates of comorbidities, increased healthcare resource utilization, and higher direct and indirect costs compared to people without migraine; these rates increase with monthly headache day frequency (Buse, Reed, Fanning, Bostic, Dodick, et al., 2020; Buse, Reed, Fanning, Bostic, & Lipton, 2020; Ishii et al., 2021). This research on impairment of functioning historically has focused principally on headache, which can be overwhelmingly intense and long-lasting, leading people to discontinue all function until the pain fades. However, in recent years, researchers have increased attention to the impacts of symptoms other than headache, such as nausea and aura, as well as impairments that may occur before or after the headache phase of a migraine attack (Ashina et al., 2023; Vincent et al., 2022).

Treatments for migraine, which include both pharmacologic and non-pharmacologic therapies, are generally categorized as either acute or preventive (Haut et al., 2006; American Headache Society, 2019). Acute treatments aim to resolve migraine symptoms when an attack occurs and return individuals to a normal level of functioning as quickly as possible (Marmura et al., 2015). Preventive migraine treatments aim to reduce the frequency, duration, or severity of attacks (Silberstein, 2015). Both types of treatments also aim to preserve or enhance an individual's health-related quality of life (HRQoL). In recent years, the US Food and Drug Administration (FDA) has approved multiple novel migraine treatments, but opportunities for developing new treatments still remain in headache medicine. Among the goals of new therapeutic development is finding treatments that effectively address the spectrum of migraine symptoms and impacts and achieving a better understanding of which treatments are most effective for different types of symptoms or for different groups of patients. However, there are significant limitations to the evidence regarding the meaningfulness and validity of current clinical outcome assessments (COAs) for evaluating the full variety of symptoms and burdens of migraine during clinical trials (Houts et al., 2021; McGinley et al., 2021).

In acute migraine trials, co-primary endpoints are typically pain freedom and freedom from the individual's most bothersome symptom, both often at 2-hours post-dose (Houts et al., 2021). However, identification of

most bothersome symptom in treatment trials has been limited—study subjects typically must choose from a short list of symptoms (e.g., nausea, photophobia, and phonophobia) known to be associated principally with the headache phase. For preventive treatment trials, the standard primary endpoint is reduction in mean migraine (or headache) days per month (McGinley et al., 2021). Although these endpoints are clinically important and also capture central components of what people with migraine value, reliance on these few outcomes may result in missed opportunities to assess the full array of symptoms and burdens that disrupt the lives of people with migraine and to understand the efficacy of treatment in addressing them.

To assess and address limitations in patient-reported outcome (PRO) metrics for evaluation of therapies in migraine, Vector Psychometric Group, LLC (VPG), in collaboration with Albert Einstein College of Medicine (Einstein), was awarded an FDA grant to support the development of a patient-informed and publicly available standard core set of COAs for migraine. This project to develop the Migraine Clinical Outcome Assessment System (MiCOAS) focuses on incorporating data about the experience of people living with migraine into the questions included in the core COAs.

To support development of a set of core endpoints, the MiCOAS research team engaged in several foundational studies:

1. Systematic literature reviews of COAs and endpoints used for clinical research on both acute and preventive medication therapies for migraine

2. Concept elicitation studies to understand patient experiences with both symptoms and impairments of functioning across all phases of migraine, including interictal periods (i.e., periods between migraine attacks)

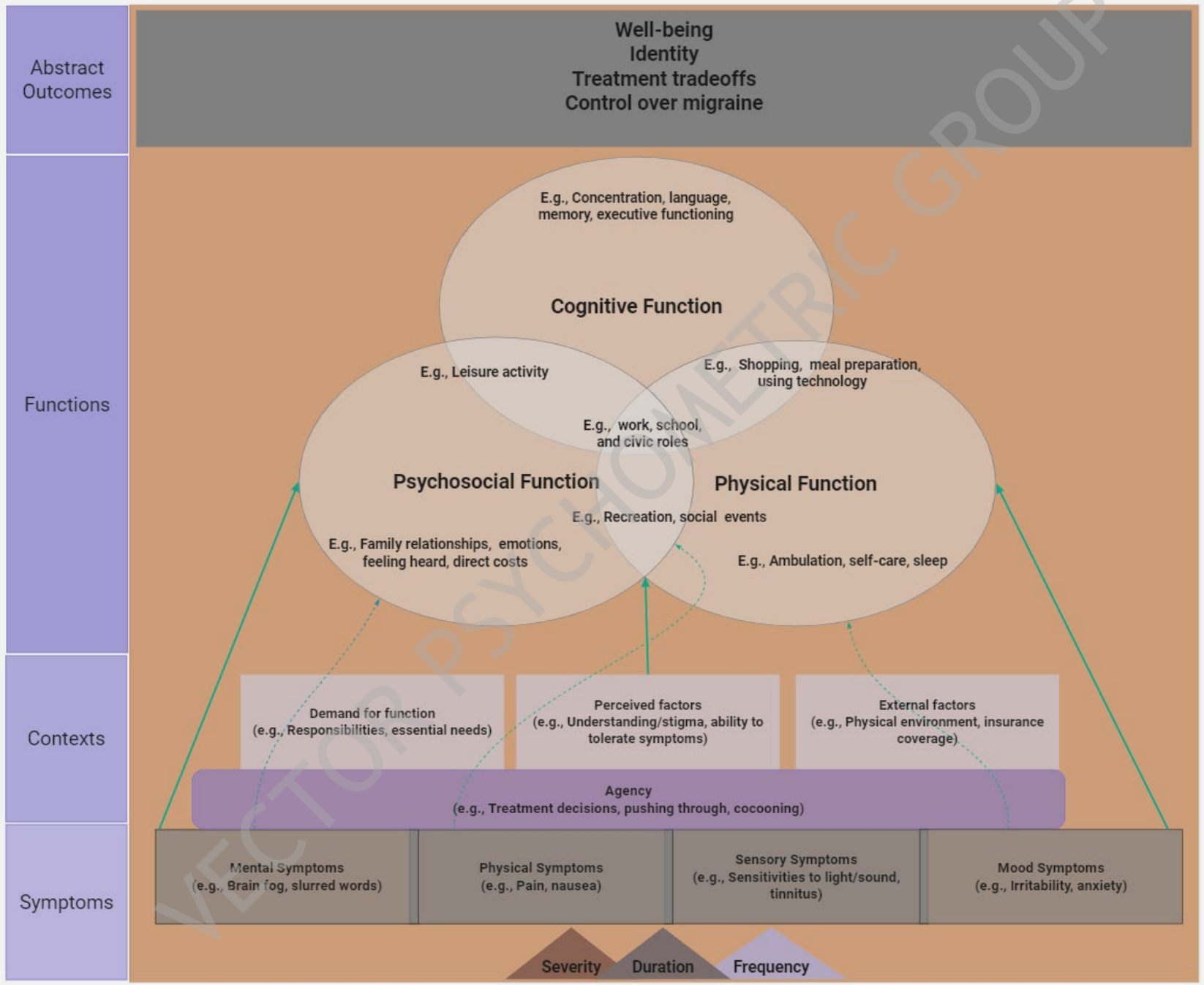
3. Review of the content and structure of existing patient-reported outcome measures (PROMs) developed for migraine or headache disorders

Information from these foundational activities was used to evaluate the scope of existing PROMs and to guide the MiCOAS team in selecting, modifying, or creating PROM items that could be used to assess the full range of important symptoms and impacts described by people who live with migraine. In this report, we describe the methods for developing a conceptual model and measurement framework for migraine, as well as methods for developing an initial set of items for core outcomes in migraine. These items were then evaluated through two cognitive debriefing studies (n = 55 interview participants), which are described in a separate report. Results of the cognitive debriefing studies were used to reduce and refine candidate items, support the selection of response options and recall reference periods, and to organize content into final draft instruments suitable for psychometric evaluation. The final draft instruments also include several modifications to the instruments implemented during the cognitive debriefing process; those modifications are described in this report.

2. PATIENT-CENTERED CONCEPTUAL MODEL OF MIGRAINE

To guide measure development activities, the MiCOAS team first created a holistic, patient-centered conceptual model of migraine experience (Figure 1) based on the full complement of concepts discussed by people with migraine during two concept elicitation studies (n = 71 interview participants) conducted by the MiCOAS team. Conceptual modeling was achieved by classifying discrete concepts and experiences described in interviews into groups based on thematic similarities (e.g., different impairments of concentration were grouped together, and then impairments of concentration were also grouped together with other impacts on cognitive functioning, such as memory or decision making) or theoretical principles (e.g., physical symptoms comprised symptoms that affect the body, such as pain and nausea, while symptoms that affected the senses, such as sensitivity to light or smell, were grouped together as sensory symptoms). The model was reviewed and discussed by FDA, the External Technical Advisory Committee (ETAC), and patient representatives of member organizations of The Coalition for Headache and Migraine Patients (CHAMP), a patient advocacy group. Iterative modifications to the model were implemented to reflect feedback on terminology and visual display. One consistent piece of feedback was that the model is complex and difficult to understand without a verbal explanation. Consequently, all stakeholders believed it would benefit from an explanatory video or recorded presentation to explain what each of the components are and how they are related to each other.

Figure 1. Holistic Patient-Centered Conceptual Model of Migraine



3. DOMAIN AND CONCEPT DEFINITIONS

The domains in the patient-centered conceptual model, the primary concepts corresponding to each domain, and their definitions are outlined in the Table 1.

Table 1. Domain and Concept Definitions for the Patient-Centered Conceptual Model

Domain	Concept	Definition
Symptoms		Symptoms of migraine that occur before, after, during or in between attacks
	Mental symptoms	Experiences of mental slowness or fogginess, changes in mental acuity or feeling as though one's cognition has been altered from normal
	Sensory symptoms	Sensitivities to sensory stimuli such as light, sound and smell, and perceptual symptoms associated with aura
	Physical symptoms	Experiences of pain in the head and neck, nausea, fatigue, dizziness
	Mood symptoms	Experiences of changes in mood such as irritability
	Severity	Severity of symptoms experienced during a migraine attack
	Duration	Duration of migraine attacks or specific symptoms
	Frequency	Number of attacks over a given period of time
Contextual factors		Factors that may affect how people experience illness or treatment
	Demand for function	Responsibilities and essential needs which one is not able to skip or delegate to someone else during a migraine attack
	Perceived factors	Perceived understanding or lack of understanding from others; stigma experienced in relationships, the

Domain	Concept	Definition
		workplace, and healthcare settings; internalized stigma; and perceptions of one's ability to manage migraine
	External factors	Factors in the environment that can exacerbate migraine or make it easier to manage; access to healthcare
	Agency	Making decisions about treatment in general or for a specific attack; making lifestyle adjustments; pushing through migraine (i.e., continuing with functioning during a migraine attack despite symptoms or impairments), or conversely, cocooning (i.e., withdrawing to a comfortable place during migraine attacks)
Physical function		Aspects of physical functioning that are relevant to understanding migraine burden
	Movement and ambulation	Ability to move around (e.g., bend over, stand up, move head, walk)
	Basic self-care	Ability to engage in normal daily care of oneself (e.g., grooming, dressing)
	Basic home care	Ability to engage in normal tasks around the house (e.g., chores, repairs, gardening)
	Shopping and running errands	Ability to go shopping and engage in other errands outside the home
	Exertion	Ability to do activities that require a physical effort (e.g., exercise, climbing stairs, lifting heavy items)
	Ability to carry out usual activities	Ability to complete one's usual tasks and activities for the day
Cognitive function		Aspects of cognitive functioning that are relevant to understanding migraine burden

Domain	Concept	Definition
	Concentration	Ability to concentrate for long or short periods of time, including completing tasks with many steps and multi-tasking
	Memory	Ability to recall from memory, either short term or long term
	Language	Ability to speak, converse, read and write, and understand numbers or do math
	Executive functioning	Ability to make decisions
Psychosocial function		Aspects of mental, emotional, and social functioning that are relevant to understanding migraine burden
	School, work, and civic roles	Ability to engage in paid or volunteer work or attend school, including university or other educational programs
	Family, social life, leisure, and recreation	Ability to carry out family responsibilities, and engage in social, leisure, or recreational activities of any kind
	Emotional states	Impacts on or changes in mood (e.g., irritability, frustration, depression)
	Feeling heard	The sense that others understand what one is going through and listens to one's priorities
	Direct costs	Medication costs, time spent seeking care, time spent to get insurance coverage
Abstract outcomes		Broad, abstract outcomes that may result from the aggregation of all other aspects of illness, treatment, lifestyle, and external factors
	Well-being	Broad ability to enjoy life and do the things one expects, wants, or needs to do

Domain	Concept	Definition
	Identity	Loss of or change in identity due to developing migraine or due to changes in migraine experiences
	Treatment tradeoffs	Balancing tradeoffs between treatment benefits and drawbacks (e.g., side effects, long term consequences of use, cost)
	Control over migraine	Consistency or limited variability in the frequency, severity, and duration of attacks; perceived consistent ability to control attacks or symptoms when they occur (e.g., medication efficacy); knowing when and why attacks occur (i.e., triggers and exacerbators); and ability to plan around migraine attacks or specific symptoms

4. INITIAL FRAMEWORK FOR MEASURE SELECTION OR DEVELOPMENT

Using the patient-centered conceptual model and the defined domains and concepts, the MiCOAS team selected a set of specific concepts of interest (COIs) and organized them into a proposed conceptual model for measurement that could be used to support item selection or development. COIs were selected according to several criteria and selections were discussed with both FDA and the ETAC. The selection criteria included:

1. **Selected concepts should reflect all types of experiences that matter to people with migraine.** This includes not only those concepts that reflect burdens which could be reduced through therapy, but also concepts that reflect beneficial outcomes people desire. For example, interview participants made clear that attack symptom reduction or achievement of fewer headache days were centrally important, but these outcomes did not necessarily equate to feeling good or being able to function fully.

2. **Selected concepts should capture symptoms and impacts of migraine that were commonly experienced or described as bothersome or disabling by interview participants.** "Commonly experienced" was defined as: three or more participants reported that they experienced the symptom or impact on a regular basis (i.e., it was a usual part of their migraine experiences) and/or more than three participants reported having experienced the symptom or impact at some points in time, even if they did not usually experience it. "Bothersome or disabling" was defined as: more than one participant described the symptom/impact as bothersome or distressing or indicated that it interfered with functioning that they wanted, needed, or expected to be able to do.

3. **Selected concepts should represent experiences that are amenable to measurement through a self-reported COA**. Concepts such as the sufficiency of health insurance or adequacy of prescribed amounts of medication, though important to patients, may not be best assessed through self-report and were excluded from the measurement model.

4. **Selected concepts for symptoms and impacts should be reasonably likely to respond directly to successful medical intervention (drug or device)**. Concepts such as stigma, for example, were excluded because they are not directly affected by treatment, though indirect effects may result from successful therapy in the long term.

5. **Selected concepts should represent experiences that could reasonably be expected to exhibit change over the limited duration of a clinical trial (3-6 months) as a function of treatment.** Long-term outcomes, such as identity or sense of self, were excluded because changes may take years to occur.

6. **Selected concepts should be concrete and specific**. Concepts should be ones for which people can consistently judge the frequency, severity, difficulty, duration, bothersomeness, level of change, or some other measurable attribute. Perceived level of social support was excluded, for example, because it is an abstract concept with both objective and subjective characteristics that were differentially

constructed by study participants. Individuals may experience objectively different social support contexts as well as perceive similar social support environments differently. For instance, people with the same intimate family structure may have markedly different feelings about that family and its role in their migraine experience. Likewise, some people will care deeply about and be strongly affected by social support in the workplace while others will not. These characteristics make perceived social support difficult to measure reliably and, when measured, it is also challenging to interpret results.

The hypothesized concept model for measurement is shown in Figure 2. This model depicts the concepts organized into domains representing potentially logical scales that distinguish between symptoms and fundamental aspects of functioning. Concepts that pertained to multiple domains in the patient-centered conceptual model (Figure 1) were assigned to a single measurement domain. For example, participants in the concept elicitation studies usually described irritability (a mood) as a symptom of migraine but described depression and anxiety as impacts of migraine. Additionally, participants noted that the chief consequences of irritability as a symptom lay in the psychosocial realm (e.g., impacts on personal relationships, subsequent feelings of guilt). To achieve clarity in the measurement model, all moods were placed together in the psychosocial domain. Definitions for each concept in the measurement model are provided in Table 2.

The concepts of frequency, severity, and duration, which constituted the foundation of the holistic model diagram, are not depicted in Figure 2, as these cut across all other concepts and thus are primarily relevant to the establishment of response options, the determination of recall periods, and design of clinical trials (e.g., the determination of when and how often respondents should be assessed). Severity and frequency were deemed important for use in rating scales for all concepts. Duration, by contrast, was regarded as important primarily for migraine attack symptoms as opposed to impacts on functioning, but assessing duration presented some significant obstacles for measure design. First, and perhaps most importantly, useful assessment of duration might require asking respondents to time their experiences, which would be burdensome and impractical for respondents. Second, participants in the MiCOAS concept elicitation studies described difficulties with noticing certain symptoms and the circumstances affecting ability to notice varied. For example, participants indicated that being deeply engaged in activity could make it harder to notice developing symptoms or reported being in so much pain during the headache phase that they could not tell if other symptoms were (still) occurring. Consequently, although measuring duration of migraine symptoms should remain an important goal for clinical trials, creating such assessments will require additional investigation of how this might feasibly be achieved.

Figure 2. Initial Concept Model for Measurement

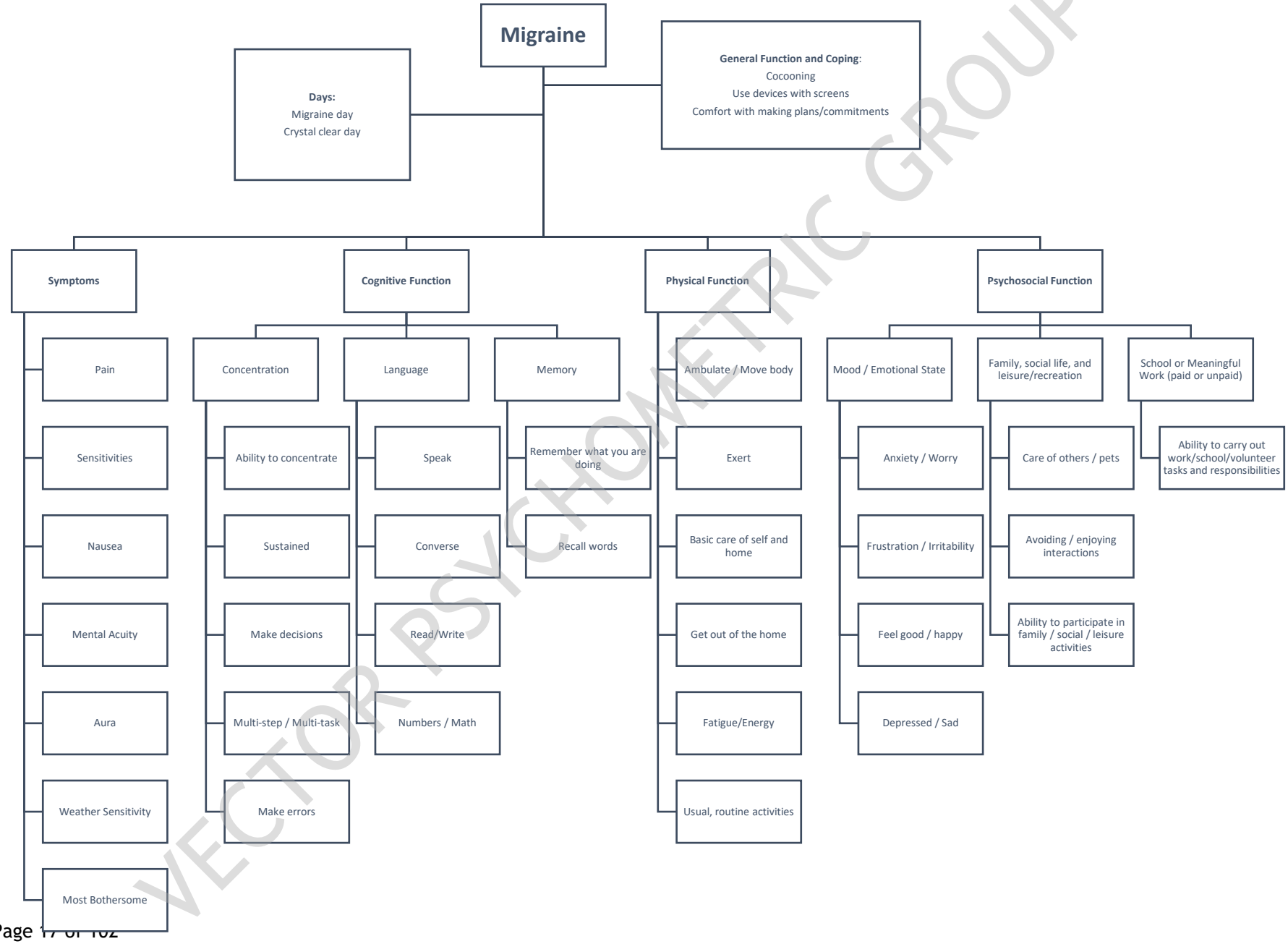


Table 2. Initial Concept Model for Measurement: Domain and Concept Definitions

Domain	Concept	Definition
Days		
	Migraine day	A 24-hour period in which migraine symptoms occurred
	Crystal clear day	A 24-hour period without migraine symptoms
Symptoms		
	Most bothersome symptom	Respondent-designated symptom (other than pain) that is most bothersome during migraine attacks
	Pain	Experiences of pain (e.g., headache, head pain, throbbing, neck pain)
	Sensitivities	Sensitivities to light, sound and smell
	Nausea	Experiences of nausea and vomiting
	Mental Acuity	Experiences of mental slowness or fogginess, or feeling as though one's cognition has been altered from normal
	Aura	Experiencing an aura (e.g., visual spots or flashes of light, skin tingling or numbness)
	Weather Sensitivity	Sensitivity to changes in the weather
General function and coping		
	Cocooning	Withdrawing to a comfortable environment (e.g., a dark room, a cool, tiled floor) to wait for an attack to pass

Domain	Concept	Definition
	Comfort with making plans	Experience of feeling confident or worried about making plans or commitments because of uncertainty about whether migraine will prevent fulfillment
	Use devices with screens	Difficulty using devices with screens, impacts can arise from sensitivities to light, sound, or movement or from cognitive challenges
Physical function		
	Movement and ambulation	Ability to move around (e.g., bend over, stand up, move head) and walk
	Basic self-care	Ability to engage in normal daily care of oneself (e.g., bathing and dressing)
	Basic home care	Ability to engage in normal tasks around the house (e.g., chores)
	Activities outside the home	Ability to engage in tasks outside the home (e.g., running errands)
	Exertion	Ability to do activities that require a physical effort (e.g., exercise, climbing stairs)
	Fatigue/energy	Having energy or being too tired to carry out activities
	Ability to carry out usual activities	Ability to complete one's usual tasks and activities for the day
Cognitive function		
	Ability to concentrate/ sustained	Ability to concentrate for a short or sustained period of time
	Ability to make decisions	Ability to make day to day decisions

Domain	Concept	Definition
	Muti-step/multi-task	Ability to multi-task and complete tasks with many steps
	Remember what you are doing	Ability to recall from short term (e.g., why you walked into a room)
	Recall words	Ability to remember the right word for something
	Ability to speak	Ability to speak clearly without slurring words
	Ability to converse	Ability to have a conversation
	Read/write	Ability to read and understand what one is reading, ability to write
	Numbers/math	Ability to complete simple tasks that require doing math or understanding numbers
Psychosocial function		
	Work/ school	Ability to engage in paid or volunteer work or attend school and carry out responsibilities at work/school
	Ability to participate in family, social, leisure activities	Ability to participate in activities with family and social and leisure activities
	Avoiding/ enjoying interactions	Avoidance of family, social or leisure activities, or ability to enjoy such activities when present
	Care of others/pets	Ability to take care of other people or pets that you need to take care of
	Worry/Anxiety	Feeling worried or anxious about having a migraine attack or about how migraine will affect others

Domain	Concept	Definition
	Irritability	Feeling irritable
	Frustration	Feeling frustrated
	Depressed/sad	Feeling sad or depressed
	Feel good	May be absence of migraine symptoms or feeling good for all or part of a day despite symptoms

5. LEGACY MEASURE ASSESSMENT

During the course of the MiCOAS project, the research team assembled information about 69 existing PROMs that have been used in migraine research. Of these PROMs, 20 were specifically designed for assessment of migraine or headache *and* accessible in full text (i.e., detailed item phrasing was available in a publication or other accessible resource, or the MiCOAS project was able to obtain permission to use a review copy of the instrument for the purpose of understanding its precise content).

Items for these 20 legacy migraine measures (see Table 2) were assembled in an Excel spreadsheet and then separately classified by two MiCOAS analysts and independently audited by a third analyst. The classification procedure endeavored to:

1. Identify alignment of each item's content with the overall domains or concepts identified from the MiCOAS concept elicitation studies (i.e., the patient-centered conceptual model in Figure 1)

2. Identify each item's alignment with concepts selected for the MiCOAS measurement framework

3. Identify any items that appeared to capture concepts not reflected in the MiCOAS measurement framework or qualitative study data

4. Identify items whose meaning was unclear

Because the original intended meaning of items was not explicitly documented for any of the instruments, analysts relied on matching terminology. When terminology did not match, analysts used their own interpretation of each item, with the triple review process intended to mitigate potential for individual bias. When analysts did not agree about item classification, final determination was made by majority vote. When analysts agreed that an item's meaning was unclear, it was labeled accordingly. Examples included an item asking about being "disappointed" about having a migraine and another asking about feeling "physically uncomfortable." In these cases, the item language alone was insufficient to understand its intent (e.g., disappointment might refer to feelings similar to sadness or frustration or disappointment might occur as a result of missing planned activities).

Only a small number (n = 6) of legacy items referenced concepts that were not found at all in MiCOAS data, including four from a single instrument. Some of these items appeared related to concepts in the MiCOAS framework (e.g., feeling 'helpless' seems similar to the MiCOAS concept of 'control over migraine,' although no MiCOAS study participants used the term 'helpless'). Others were sufficiently vague as to be potentially linked to multiple concepts (e.g., an item about 'doubting my ability to do a good job' could refer specifically to work performance or encompass other contexts in which this phrase might be used, such as doing a good job of being a parent). Finally, some instruments included many items that did not fit within the scope of the proposed MiCOAS concept model for measurement but were matched to concepts in the broader MiCOAS data. Examples include items asking about convenience of using medication, knowledge of migraine triggers, or self-efficacy.

Table 3. Legacy Migraine and Headache Measures

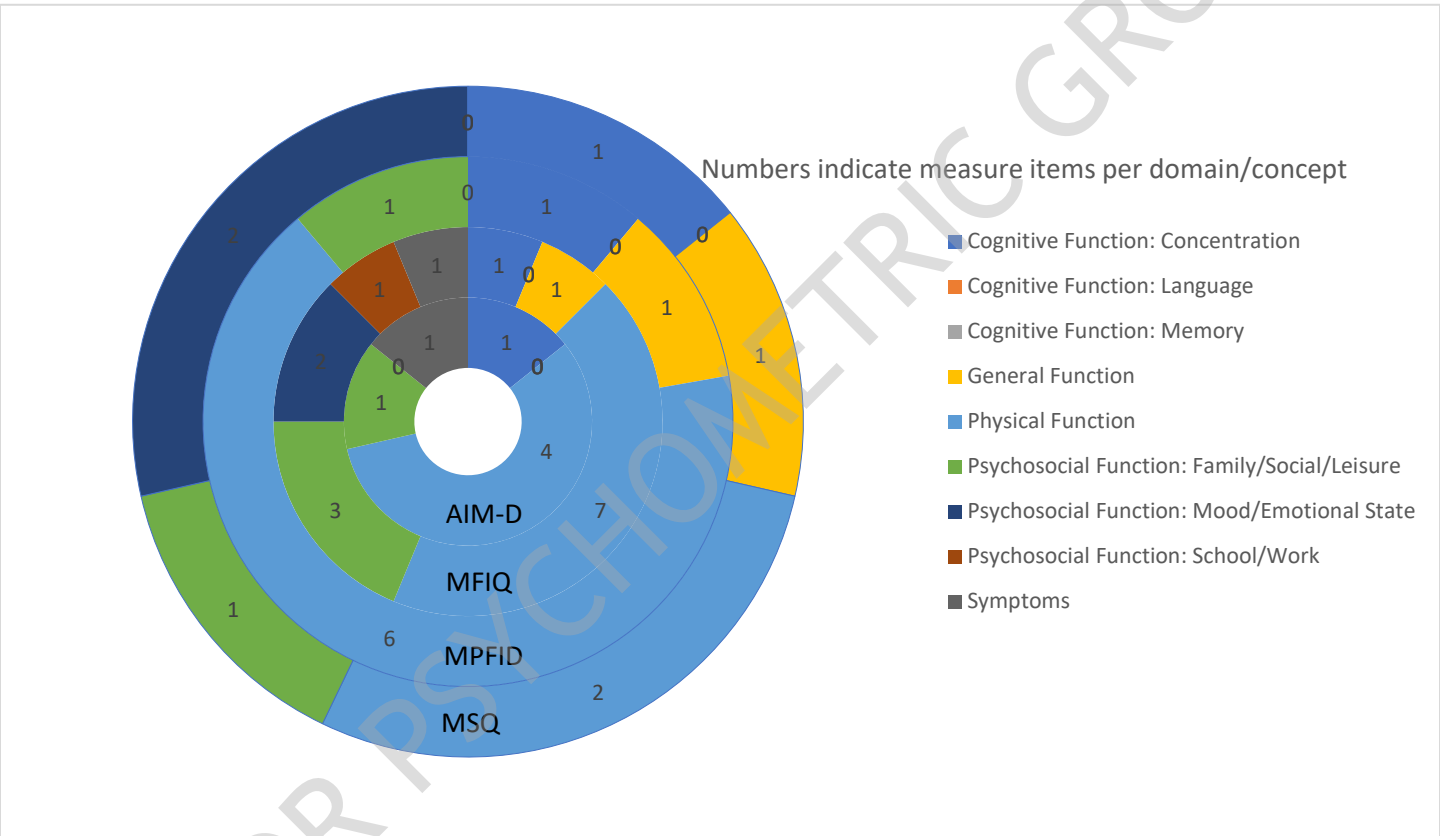
Acronym	Name	Measure Owner or Steward	Citation
24hr MSQOL	24 Hour Migraine-Specific Quality of Life	Merck	Hartmaier, S. L., Santanello, N. C., Epstein, R. S., & Silberstein, S. D. (1995). Development of a brief 24-hour migraine-specific quality of life questionnaire. *Headache*, *35*(6), 320-329.
AIM-D	Activity Impairment in Migraine-Diary	AbbVie	Lipton, R. B., Gandhi, P., Stokes, J., Cala, M. L., Evans, C. J., Knoble, N., Gelhorn, H. L., Revicki, D., Viswanathan, H. N., & Dodick, D. W. (2022). Development and validation of a novel patient-reported outcome measure in people with episodic migraine and chronic migraine: The Activity Impairment in Migraine Diary. *Headache*, *62*(1), 89–105.
FIMQ	Functional Impact of Migraine (previously Assessment of Chronic Migraine Impacts)	Authors	Blumenfeld, A., Rosa, K., Evans, C., Lai, H., Yang, M., Gillard, P., Aurora, S. (2014). Psychometric evaluation of the Assessment of Chronic Migraine Impacts (ACM-I) and Assessment of Chronic Migraine Symptoms (ACM-S). *Headache*, *54*(6), P15.
GAMS	Global Assessment of Migraine Severity	Authors	Sajobi, T. T., Amoozegar, F., Wang, M., Wiebe, N., Fiest, K. M., Patten, S. B., & Jette, N. (2019). Global assessment of migraine severity measure: preliminary evidence of construct validity. *BMC Neurology*, *19*(1), 53.
HANA	Headache Needs Assessment	Abbott Laboratories	Cramer, J. A., Silberstein, S. D., & Winner, P. (2001). Development and validation of the Headache Needs Assessment (HANA) survey. *Headache*, *41*(4), 402–409.
HDI	Headache Disability Index	American Academy of Neurology	Jacobson, G. P., Ramadan, N. M., Aggarwal, S. K., & Newman, C. W. (1994). The Henry Ford Hospital Headache Disability Inventory (HDI). *Neurology*, *44*(5), 837–842.
HImQ	Headache Impact Questionnaire	GlaxoSmithKline	Stewart, W. F., Lipton, R. B., Simon, D., Von Korff, M., & Liberman, J. (1998). Reliability of an illness severity measure for headache in a population sample of migraine sufferers. *Cephalalgia*, *18*(1), 44–51.
HIT-6	Headache Impact Test 6	QualityMetric, Inc. and GlaxoSmithKline	Kosinski, M., Bayliss, M. S., Bjorner, J. B., Ware, J. E., Jr, Garber, W. H., Batenhorst, A., Cady, R., Dahlöf, C. G., Dowson, A., & Tepper, S.

Acronym	Name	Measure Owner or Steward	Citation
			(2003). A six-item short-form survey for measuring headache impact: the HIT-6. *Quality of Life Research*, *12*(8), 963–974.
HMSE	Headache Management Self-Efficacy Scale	Authors	French, D. J., Holroyd, K. A., Pinell, C., Malinoski, P. T., O'Donnell, F., & Hill, K. R. (2000). Perceived self-efficacy and headache-related disability. *Headache*, *40*(8), 647–656.
HSLC	Headache-Specific Locus of Control Questionnaire	Authors	Martin, N. J., Holroyd, K. A., & Penzien, D. B. (1990). The headache-specific locus of control scale: adaptation to recurrent headaches. *Headache*, *30*(11), 729–734.
MFIQ (v.2)	Migraine Functional Impact Questionnaire	Evidera	Hareendran, A., Skalicky, A., Mannix, S., Lavoie, S., Desai, P., Bayliss, M., Thach, A. V., Mikol, D. D., & Buse, D. C. (2018). Development of a New Tool for Evaluating the Benefit of Preventive Treatments for Migraine on Functional Outcomes - The Migraine Functional Impact Questionnaire (MFIQ). *Headache*, *58*(10), 1612–1628.
MIBS-4	Migraine Interictal Burden Scale	Authors	Buse, D. C., Rupnow, M. F., & Lipton, R. B. (2009). Assessing and managing all aspects of migraine: migraine attacks, migraine-related functional impairment, common comorbidities, and quality of life. *Mayo Clinic Proceedings*, *84*(5), 422–435.
MIDAS	Migraine Disability Assessment	Caremark, Innovative Medical Research, AstraZeneca	Accessible via the MIDAS calculator at QxMD (https://qxmd.com/calculate/calculator_439/midas-migraine-disability-assessment)
MIG-SCOG	Cognitive Impairment Scale for Migraine Attacks	Authors	Gil-Gouveia, R., Oliveira, A. G., & Martins, I. P. (2011). A subjective cognitive impairment scale for migraine attacks. The MIG-SCOG: development and validation. *Cephalalgia*, *31*(9), 984–991.
MPFID	Migraine Physical Function Impact Diary	Amgen / Evidera	Hareendran, A., Mannix, S., Skalicky, A., Bayliss, M., Blumenfeld, A., Buse, D. C., Desai, P. R., Ortmeier, B. G., & Sapra, S. (2017). Development and exploration of the content validity of a patient-reported outcome measure to evaluate the impact of migraine-the migraine physical function impact diary (MPFID). *Health and Quality of Life Outcomes*, *15*(1), 1-10.

Acronym	Name	Measure Owner or Steward	Citation
MPQ / MPQ-5	Migraine Prevention Questionnaire	Authors	Lipton, R.B., Serrano, D., Buse, D.C., et al. (2007). The Migraine Prevention Questionnaire (MPQ): development and validation. *Headache*, *47*(5):770–1.
MSQ / MSQ v 2.1	Migraine-Specific Quality of Life Questionnaire	GlaxoSmithKline	v. 1: Jhingran, P., J. T. Osterhaus, D. W. Miller, J. T. Lee and L. Kirchdoerfer (1998). Development and validation of the migraine-specific quality of life questionnaire. *Headache*, *38*(4): 295-302. ; v 2.: Jhingran, P., S. M. Davis, L. M. LaVange, D. W. Miller and R. W. Helms (1998). MSQ: Migraine-specific quality-of-life questionnaire: Further investigation of the factor structure. *PharmacoEconomics.*, *13*(6): 707-717. ; v. 2.1: Martin, B. C., D. S. Pathak, M. I. Sharfman, J. U. Adelman, F. Taylor, W. J. Kwong and P. Jhingran (2000). Validity and reliability of the migraine-specific quality of life questionnaire (MSQ Version 2.1). *Headache*, *40*(3): 204-215.
MSQOL	Migraine Specific Quality of Life Questionnaire	Glaxo Wellcome	Wagner, T. H., Patrick, D. L., Galer, B. S., & Berzon, R. A. (1996). A new instrument to assess the long-term quality of life effects from migraine: development and psychometric testing of the MSQOL. *Headache*, *36*(8), 484–492.
M-TAQ	Migraine Therapy Assessment Questionnaire	Merck	Chatterton, M. L., Lofland, J. H., Shechter, A., Curtice, W. S., Hu, X. H., Lenow, J., Smullens, S. N., Nash, D. B., & Silberstein, S. D. (2002). Reliability and validity of the migraine therapy assessment questionnaire. *Headache*, *42*(10), 1006–1015.
PPMQr	Patient Perception of Migraine Questionnaire-revised	Authors	Davis, K. H., Black, L., & Sleath, B. (2002). Validation of the Patient Perception of Migraine Questionnaire. *Value in Health*, *5*(5), 422–430.

With classification complete, the MiCOAS team was able to compare the content of the legacy measures to each other and to the proposed measurement concept model in a concise and consistent way. This allowed the research team to assess which measure(s) might be most suited as core measures. It also permitted an assessment of gaps and weaknesses in the set of available measures. Detailed results of the measure content comparison are shown in Appendix A. To further support measure comparison, the research team also used visualizations that more concisely depicted the overall conceptual coverage of each measure. An example of such a visualization is shown in Figure 3, which shows the similarities and differences in coverage across four measures, as well as gaps (e.g., all four measures lack items addressing language and memory).

Figure 3. Example Visualization of Measure Content Comparison



AIM-D: Activity Impairment in Migraine-Diary; MFIQ: Migraine Functional Impact Questionnaire v. 2; MPFID: Migraine Physical Function Impact Diary; MSQ: Migraine-Specific Quality of Life Questionnaire v.2.1

The results of this analysis highlighted several central obstacles to selecting existing instruments wholesale to establish core measures for migraine. These obstacles included:

1. **Significant duplication across measures for selected concepts (e.g., basic physical functions) paired with varied inclusion of other concepts (e.g., cognition, irritability).** This meant that multiple measures would be needed to ensure assessment of all relevant concepts, but the burden of repetitive measurement would then be high. Further, the manner in which each instrument was scored ultimately might not permit an assessment of the desired domains or COIs.

2. **Variations in the ways existing measures appeared to define concepts undermined their apparent similarity to each other and to the MiCOAS framework.** Across measures, items were observed to define or combine concepts in ways that may affect measure results. For example, an item in one instrument defined 'leisure activities' only in terms of passive cognitive activities like reading or listening to music. This item may thus primarily capture cognitive impairment rather than impact on leisure activities in general. By contrast, an item in another instrument defining leisure activities as 'shopping, reading, exercising' demonstrated potential for overlapping assessments of certain functions because the MiCOAS framework construes shopping as part of 'getting out of the home' while exercising is construed as part of 'exertion' (i.e., ability to do strenuous activities).

3. **Significant gaps in the scope of each measure, a variety of structural differences (e.g., recall time periods and response options) between measures, and gaps in conceptual coverage across the entire set of measures.** These issues indicated that substantial modifications and additions to existing measures would be required to achieve a system for measuring all the concepts considered important by people with migraine. Given that all the measures were copyrighted and some were subject to proprietary licensing requirements, making needed modifications or additions might not be feasible or permitted.

Following the legacy measure assessment, the MiCOAS team determined that legacy measures would not provide a satisfactory core measure set that addressed all of the domains and concepts in the proposed measurement framework. Following discussion with FDA, the research team determined that composing new instruments grounded in the accumulated qualitative and measure review evidence was the optimal path forward.

6. DRAFT INSTRUMENT DEVELOPMENT

To develop the MiCOAS item library, the research team assigned sets of concepts and corresponding legacy items to teams consisting of one psychometrician and one clinician. Each team reviewed the data and developed draft items to capture concepts in alignment with the MiCOAS measurement framework while avoiding infringement of existing legacy items. The resulting item library was then iteratively reviewed by the MiCOAS team to refine items according to the following criteria:

1. **Clarity and simplicity**. Clarity of items was assessed on the basis of consistent phrasing in plain language, word length, grammatical structure, simplicity of content (e.g., avoiding double-barreled items, limiting use of directive examples), avoidance of idiomatic expressions, and translatability. Maintaining simplicity of content also entailed excluding items that captured concepts in ways that blended multiple functions. For example, although impairment of ability to drive a car is a common and serious issue for many people with migraine, it is also a highly complex human activity. Driving requires both physical and cognitive skills and is influenced by both subjective judgments about the relative risk or safety of driving at any given time or under given circumstances (e.g., weather conditions, presence of passengers) and the perceived necessity of driving or availability of other means of transportation at a given time.

    a. **Translatability.** Items were translated into Spanish, French, and Dutch by VPG staff with appropriate language skills to test translatability and identify idioms, grammatical structures or expressions that did not consistently work well in languages other than English. For example, the phrase “less sharp” could not be translated literally since sharpness is not used to refer to mental acuity in the other languages tested, while “mentally slow or foggy” was more universal.

    b. **Consistent grammar structure.** Whenever possible, items were designed to work with both frequency and difficulty response options. Thus, most items were written with the stem “was it difficult for you to” rather than “how often” or “how difficult”.

2. **Broad applicability to the population of people who live with migraine.** Maintaining broad applicability to the migraine population entailed limiting the number of items that would not be applicable to all people (e.g., work, caring for other people or pets) and providing ‘not applicable’ response options to increase measure precision. In place of a suite of items asking about ability to perform various routine functions, the MiCOAS team elected to create items that ask instead about a person’s ability to undertake their normal daily schedule, whatever that might be.

3. **Applicability to both acute and preventive treatments.** Outcomes for both types of treatments may be similar, but may be expressed differently both by clinicians and by people with migraine. For acute treatments, for example, symptom or impact resolution is typically the focus rather than symptom or impact prevention. Thus, acute treatment trials may require questions specific to times when people use the trial medication to treat an attack, and these questions would not be applicable in the

preventive treatment context. Consequently, the MiCOAS team sought to express items in a neutral manner that did not presuppose a particular indication. This approach provided a means to develop measures that reflect core concepts but may also mean that these core measures do not include additional content that may be of specific value in a trial of acute or preventive medications. For example, acute trials would likely benefit from asking questions about how quickly after symptom onset the medication was taken, how quickly it worked, and how long the effect was sustained. Preventive trials might benefit from asking questions about whether acute medication or other treatments were used when attacks occurred. Similarly, the treatment burdens of acute and preventive treatments are different and vary from treatment to treatment (e.g., quarterly infusions or injections impose different burdens than a pill taken every other day). Consequently, no items about treatment burden were included.

4. **Fit with a relatively short reference time frame of up to 14 days.** Findings from the concept elicitation studies suggested that a daily PROM could be desirable for clinical trials and that it should capture key symptoms and overall function and should be brief. Similarly, the findings suggested that any other recall period used should be fairly short, such as 7 or 14 days. For example, interviews indicated that people may find it harder to remember or rate their symptoms if they have multiple attacks over the course of a month, particularly if their attacks are largely similar and "*blur together*." Numerous interview participants noted that they found it useful to keep a daily log of symptoms and key impacts for a few weeks or months—for example, to understand how their migraine might be changing, to confirm suspicions about migraine triggers, or to gather data prior to meeting with a doctor.

5. **Directly ask about positive experiences or improvements.** Three questions to capture the notion of 'good days' were developed (i.e., a 'crystal clear' or 'good' day was intended to convey days with minimal/no symptoms or days on which people felt good and/or were able to do what they wanted to do/ enjoy themselves). These questions are: "Did you have a good day?" for the past 24 hours, and "How often were you able to enjoy all or part of a day" and "How often did you feel good" for the past 7/14 days. These questions were included for two reasons. First, the concept elicitation study findings suggested that the subjective burden of measure may be mitigated by including questions intended to capture positive experiences—a finding supported by subsequent cognitive debriefing interviews. Put simply, people appreciated being asked about when things were going well for them. Second, these questions could also provide contextualizing direct judgments by respondents that may affirm or contrast with inferred judgements based on data that primarily reflects illness symptoms and impacts on functioning. For example, PROM scoring rubrics typically include a claim like 'lower scores indicate lower quality of life,' but this reflects an assumption that ratings that primarily capture unpleasant symptoms and unwanted impacts provide a genuine and complete reflection of quality of life. This assumption that 'good' quality of life is the absence of 'bad' quality of life runs counter to some of the MiCOAS qualitative study findings. Those findings suggested that many people with migraine engage in adaptive behaviors, including the establishment of new frameworks for thinking

about quality of life, that may confound this conventional approach to interpreting PRO assessments. Individuals with migraine, for example, may report frequent symptoms and significant constraints on 'normal' functioning, yet describe their overall lives as rich, fulfilling, and of high quality. This apparent paradox is not only interesting, but also potentially valuable for a more nuanced understanding of people's experiences of illness and their perspectives on the benefits of treatment. For example, clinicians often observe that patients complain about symptoms and impacts of migraine but are unwilling to take treatments that might help them. One explanation may be that, for some patients, symptoms and impacts are bothersome and worth complaining about, but quality of life remains high on balance. These individuals may view the tradeoffs of undertaking new treatment, which invariably comes with burdens and side effects, quite differently than individuals who regard their overall quality of life as poor. Items about positive experiences should be retained in the final instruments even if they will not be used in scoring given their potential to create positive engagement with the study and reduce feelings of burden.

6. **Limit respondent burden.** Initial testing involved a large set of draft items to enable comparison of alternate phrasings for the same concept and comparison of different response options. However, limiting respondent burden was a key consideration in the development of the final 24-hour and 7/14-day measures. During waves 1 and 2 of testing, participants were asked how many questions they would be willing to answer and how much time they would be willing to spend on a daily measure and on a measure to be filled out every 14 days, during a clinical trial lasting approximately 3 months. Participants commonly were willing to answer at least 10 questions and spend 5-10 minutes for the 24-hour instrument and answer at least 20 questions and spend 10 minutes or more for a 14-day instrument. Generally, the acceptable time frames respondents gave were longer than would be necessary for the number of items cited. Item reductions following waves 1 and 2 were made with the goal of shortening both measures to ensure they can be completed within the desired time frames. During waves 3 and 4, two of the 18 participants noted that the number of questions on the 24-hour measure could be excessive if they had to complete all the items every day. However, in an eCOA implementation, participants need not be asked items about their symptoms at all unless they report experiencing migraine symptoms during the past 24-hours, thus completing the full questionnaire daily is unlikely. In a pencil-and-paper implementation, instructions could be added to tell respondents to skip questions about specific symptoms if they respond 'No' to the initial question about presence of migraine symptoms. Participants in waves 3 and 4 did not raise any concerns with the length of the 7/14-day measure.

6.1. DRAFT INSTRUMENT CONTENT

An initial draft set of 93 unique items was developed for cognitive testing. The draft set reflected the potential use of several response option sets (e.g., yes/no, ratings for severity, ratings of difficulty), which resulted in 144 draft items for testing. Appendix B provides a disposition table for each draft item indicating decisions to retain, drop, or revise items.

Most items were phrased so that they could be used in either a 24-hour recall instrument (i.e., a daily assessment), or an instrument with a longer recall period such as 7 or 14 days. Following cognitive debriefing and final input from all stakeholders, the item set was reduced to 57 unique items divided between a daily assessment of 22 items and a 7/14-day recall assessment of 36 items, with one item assessed in both measures. Each item is queried with a single response set; most items in the 7/14-day instrument have frequency responses but some have difficulty responses. The rationale for the use of two response options is explained in section 6.1.3.

Instructions were kept as simple as possible and focused on the key information respondents should bear in mind when answering. This approach supports convenient electronic implementation of COAs, where screen space may be limited and prohibit the lingering display of lengthy instructions, and also minimizes reading burden on respondents, who will complete the instruments repeatedly over the course of a single study.

As noted in Section 9 (Modifications for implementation of the 24-hour instrument), two additional items were duplicated between the two measures for the psychometric study (reported separately) to support statistical analysis of a hypothesized cognition scale based on daily assessments. Depending on the study findings, these two items may be permanently retained in the daily assessment to produce meaningful scores for cognition.

These draft instruments included several features that are described in sections 6.1.1 through 6.1.6.

6.1.1. DRAFT ITEMS INCLUDED ALTERNATES FOR THE SAME CONCEPT

Both concept elicitation data and the review of legacy measures showed that numerous concepts could be described in different ways. For example, respondents could be asked about difficulty with a specific activity, reluctance to engage in the activity, or avoidance of the activity. All three approaches were supported by the concept elicitation data (i.e., participants talked about all three types of experiences) and found in legacy measures, but there was no data to indicate whether one approach was preferable to the other or whether respondents would regard them as similar or significantly different. For novel concepts, such as some cognition concepts, alternate items were developed to reflect the different ways study participants had described their experiences. For example, participants had described having trouble remembering what they were doing, such as why they had walked into a room, as well as difficulty remembering what they were talking about while speaking. Both descriptions relate to challenges with concentration and working memory, but it was not clear whether one description was preferable to the other. Accordingly, the initial bank of 93 items included numerous alternate items and data from the cognitive debriefing study were used to support decisions to retain or drop items.

6.1.2. SELECTION OF RECALL TIME PERIODS

Daily assessment of migraine symptoms is commonplace in clinical trials, but the review of legacy measures revealed a broad range of longer-term reference periods (e.g., a week, a month, three months) as well as measures with mixed reference periods, no reference period specified, or some other recall instruction used

(e.g., during a headache, in between headaches). The MiCOAS team, ETAC members, and FDA all had concerns about recall periods of a month or longer given potential problems with remembering and rating the specifics of migraine attacks over this length of time, particularly for respondents with frequent migraine in a preventive treatment trial. Across many chronic conditions, a common practice is to ask about the most recent 7-day period, a practice that has been demonstrated to provide a representative picture of patient experience. However, a minority of chronic conditions are both episodic and highly variable in the way that migraine is. This raised questions about the tradeoffs between a 7-day vs. a 14-day time period. Specifically, a 7-day recall measure given periodically might result in measurement that failed to capture migraine attacks and impacts that respondents had during the unmeasured periods of time. The could be significant issue for people with lower-frequency episodic migraine. By contrast, a 7-day recall measure given every week increases measurement burden. A 14-day recall measure could minimize this burden and/or increase the likelihood of capturing migraine experiences, but the potential drawback might be reduction in respondent ability to recall or variability that results from differences in the ways that respondents rate aggregated experiences.

Cognitive debriefing interview data suggested that participants could easily recall both symptoms and proximal impairments of functioning (e.g., impacts on ability to move around or think clearly) over a 1–2-week period. However, the data also indicated that participants uniformly thought that symptoms and proximal impacts on functioning should be captured on a daily basis in the context of evaluating treatment. Data from the concept elicitation and cognitive debriefing studies indicated that the tradeoffs among 1–2-week recall periods do not conveniently align across PRO concepts. For example, some outcomes involve activities or functions that may not occur on a weekly basis (e.g., recreation or social activities, running errands), with participants often perceiving that a 14-day recall period was preferable. Other outcomes are related to having migraine as a disease but may have a weaker link to specific symptoms or attack severity (e.g., frustration, reluctance to make plans); these outcomes may also be more suited to a longer recall time frame, with some participants suggesting as much as a month.

The team considered three primary factors in selecting a 14-day reference period for the initial cognitive debriefing of the PROM items.

1. The number of potential items in the final instruments and the frequency with which they might be administered, which will establish the level of measurement burden for patients in clinical trials.

2. The need to create instruments that could support clinical trials for both acute and preventive indications for therapies in populations of patients with both episodic and chronic migraine. Trial designs could thus vary in inclusion of patients with low frequency (e.g., average 4 headache days per month over 3 months) and high frequency (e.g., average 25 headache days per month over 3 months) migraine.

3. Findings from prior research investigating the performance of measures of the same concepts covering different reference periods that suggest different strengths and weaknesses, but did not indicate

significant issues with patient recall across a variety of experiences until reference periods stretched considerably beyond 14 days (Clarke et al., 2008; Norquist et al., 2012; Stull et al., 2009). Findings from these studies indicated that apparent differences in rating were not solely due to decay of memory and that decay in memory does not occur in the same way for all experiences. Rather, the studies identify a variety of factors that contribute to observed differences in ratings over shorter and longer periods of time. These factors include the variability of the measured experience, whether it is acute or chronic, whether it is a simple or complex experiences (e.g., nausea vs. impairments of ability to work), and whether an overall assessment is preferable because variability in experience is unlikely to be predictive of burden (e.g., counting episodes of irritable bowel syndrome may not adequately reflect disruption of daily life (Norquist et al., 2012)). The MiCOAS team also noted the prevalence of development of 7-day measures in the context of chronic conditions that are *not* episodic in nature. For these conditions, a weekly recall may be expected to include relevant disease experience. Literature for other episodic conditions, such as epilepsy, are characterized by PROMs that use longer recall periods, including ones that mix reference periods, asking some questions for 2 weeks, some for 1-3 months, and some for 1 year (e.g., Schougaard et al. (2018)). This highlights specific challenges for PROM development in conditions that are chronic but also episodic or waxing/waning.

There is literature specifically comparing daily or momentary assessment to measures of pain with longer recall periods that similarly indicates that differences in scores may be influenced by the variability of pain experiences as well as its peak severity (Redelmeier & Kahneman, 1996; Stone et al., 2005). Finally, in examining the performance of MIDAS, Stewart et al. (2000) found that the offset to recalled estimates was higher for the three-month measure than for daily measures for pain and role function, family, social and leisure activities. To some degree, the correlations between MIDAS and the daily assessment overestimated agreement; however, the overall MIDAS score was not significantly different than the average daily diary metric and when the intended implementation is to examine change in scores, then the offset may not matter.

Study findings of this type supported assumptions made by the MiCOAS team that recall of some experiences could be affected by attack frequency, which had been derived from the concept elicitation study findings, as well as the relative strength of connections study participants made between HRQoL outcomes and attack symptoms. Participants did say they were better able to recall migraine attacks when they were less frequent or unusual, however they also tended to refer to very long periods of time (e.g., several months to several years) when making this observation. Similarly, participants described different links between migraine attacks and some aspects of HRQoL. For example, attack symptoms often differentially interfered with basic daily functioning, such as moving around, concentrating, or doing whatever activities had been planned for the day. Other aspects of functioning were linked more generally to having migraine and to the overall frequency of attacks, rather than to the specific symptoms and severity of each attack.

6.1.3. USE OF TWO DIFFERENT PRIMARY RESPONSE SCALES

Concept elicitation findings indicated that people with migraine primarily think about their experiences in terms of the frequency, level of severity or difficulty, and duration. Many participants also referenced the speed of onset for symptoms or impacts as well as how rapidly they resolve either naturally or with an acute treatment. These features also had consequences for how study participants thought about migraine burden. For example, mild symptoms that last several days were viewed differently than severe symptoms that last 4-6 hours, and these two experiences were associated with varying perspectives on impacts. For example, some people might regard long-lasting mild symptoms as a tolerable annoyance, while others found it draining and disruptive. Similarly, people reported being unable to function during severe attacks, while others were able to push through and continue functioning. Although a complete assessment of migraine experience might entail gathering data about all four features of migraine, the resulting measure would be long and would likely be regarded as both repetitive and tedious. Legacy measures reflected a long-standing practice of asking respondents to assess both frequency and severity of their experiences.

The MiCOAS team held several discussions about the desirability and feasibility of including assessments of duration and speed of onset/resolution of symptoms and impacts. Debate focused on the practical problems of clearly defining the parameters of these features. For example, how might respondents be instructed to assess when a migraine attack begins and ends? How might speed of onset or resolution be described in measure items or responses? Ultimately, including these two features of migraine was deemed infeasible for several key reasons, as follow:

- Qualitative study findings reflected a high degree of variation in how participants think about the beginning and end of a migraine attack, which has consequences for assessing duration and speed of symptoms. This variation was compounded by the fact that many participants indicated that they did not always notice when their symptoms were beginning or did not pay close attention to how long certain symptoms lingered

- Study findings also indicated that although these features appear conceptually distinct, they are in fact overlapping. For example, many study participants factored duration into judgments of frequency or severity

The initial draft items were therefore developed to use frequency and/or severity/difficulty response sets. Waves of cognitive debriefing interview results were examined to determine which response sets worked best with each item given each potential recall time frame (i.e., 24 hours or 7/14-days). A debriefing study specifically focused on reference time frames and response options was also conducted to develop findings to support final selection of these features. These studies showed that study participants regarded it as essential that MiCOAS use a 24-instrument that assessed symptom occurrence and severity, as well as the level of difficulty experienced with basic functions (e.g., walking, thinking). This approach was viewed as providing an optimal assessment of both the frequency (i.e., count of days on which these experiences occurred) and

level of severity or difficulty encountered. Key findings from these studies that supported the use of two different response scales in final 7/14-day measure included:

- Preference for and ease of using frequency response options for experiences that are periodic, such as running errands or engaging in social activity
- Preference for and ease of using difficulty response options for experiences that are pervasive, variable, and/or instinctive, such as concentrating, because assessing their frequency can be challenging

6.1.4. DELIBERATE INCLUSION OF 'POSITIVE' ITEMS

Interview participants in both the original concept elicitation studies and the cognitive debriefing often expressed annoyance with the narrow focus found in typical migraine assessments on unpleasant symptoms and negative impacts. They spontaneously expressed that it was nice to be asked about what was going well and whether they were able to enjoy life. During cognitive debriefing, numerous participants responded warmly to the inclusion of items asking about good days, ability to enjoy the day, and ability to keep to one's plans. Participants commented that these items made them "feel heard" and some even expressed that the inclusion of these items increased their confidence in the questionnaire overall. Ultimately, these few items may not work well in concert with the many items that do inquire about symptoms and impairment of specific functions, but it may nevertheless be worthwhile to keep them in the measure even if they are not included in the scoring rubric. If the presence of these questions reduces patients' sense of burden in completing the questionnaire and improves their perception that the assessment is patient-centered, these benefits may have independent value for the COA. If these items were slated for removal based on their psychometric performance, it could also be important in the future to investigate the ways in which respondents answer questions when the 'positive' questions are and are not present in the instrument (i.e., to ascertain whether the mere presence of these items influences respondent ratings of other concepts in the measure). If including these items does not alter measure performance, but can improve respondents' experience of completing the measure, retaining them as unscored items would be supported.

6.1.5. DELIBERATE INCLUSION OF A DUPLICATE ITEM

One item was duplicated between the 24-hour and 14-day instruments: "Was it difficult for you to concentrate?" This item addresses a concept that appears to play an important role in understanding changes in subjective mental acuity (i.e., 'brain fog') as a migraine attack symptom and as a proximal impact of other symptoms like pain that may interfere with concentration. The concept was also deemed important for understanding overall HRQoL and interictal impacts of migraine. For example, fatigue following an attack or anxiety about exposure to migraine triggers may contribute to difficulties with concentration during interictal periods.

6.1.6. DELIBERATE INCLUSION OF TWO DOUBLE-BARRELED ITEMS

The draft instruments were provided to the ETAC and FDA for review and comment during 2023, resulting in the following revisions and comments regarding double-barreled items.

1. **"Did you experience dizziness or vertigo?" in the 24-hour instrument**. Dizziness/vertigo had been identified during the two concept elicitation studies as a common symptom of migraine that could result in substantial impairment of function. However, it was observed that interview participants did not consistently differentiate between dizziness and vertigo, which are neurologically different. Instead, study results suggested that people with migraine might use the terms interchangeably. When the initial item library was developed, dizziness/vertigo was not included due to concerns that one or more items asking about this symptom might produce data that could not be accurately understood in a clinical context. For example, individuals who experienced dizziness might answer 'yes' to both questions about dizziness and about vertigo. Similarly, individuals who were actually experiencing vertigo might answer 'yes' to the dizziness question and 'no' to the vertigo question if they were unfamiliar with the distinction.

   During cognitive debriefing, the word vertigo was used by only one participant, who appeared to use it interchangeably with dizziness. Ten participants discussed dizziness as a symptom they experience, including one individual who identified it as important missing content. Independent of this finding, the ETAC also spontaneously raised dizziness as a missing concept when reviewing instrument content in June 2023. After a discussion of the earlier rationale for omitting the concept, the ETAC noted that the benefits of gathering data from patients about this important, disabling symptom outweighed their concerns over the clinical clarity of the data. They noted that including an item about dizziness/vertigo could contribute to understanding which sets of symptoms generate the greatest impairments of functioning. Because people with migraine may not correctly distinguish between dizziness and vertigo, a double-barreled item was deemed acceptable.

   The MiCOAS research team discussed the addition of the new item with the FDA in August 2023. FDA's clinical experts concurred that patients use the terms dizziness and vertigo interchangeably, and that making an accurate distinction between these two symptoms can be challenging even for neurologists. FDA's measurement experts noted that, although avoidance of double-barreled or ambiguous items is a crucial principle of PROM development, there were compelling reasons to make an exception in this specific case.

2. **"How often did you enjoy all or part of a day?" in the 7/14-day instrument.** This item was included as part of the strategy for including items that reflect positive experiences. The item was purposefully phrased this way for two reasons. First, the item was intended to reflect positive experience in general, rather than to make it measurable in detail, thus the distinction between enjoying all or only part of a day was considered less important than keeping the number of items to a minimum by not asking two questions about this concept. Second, the phrasing "how often did you enjoy at least part of day"

might appear to capture the concept without double-barreled grammar, but the MiCOAS team was concerned that the phrase “at least” might be interpreted to mean very small increments of time (e.g., 15 minutes) rather than a substantive portion of the day (e.g., several hours). During the ETAC meeting in 2023, discussion touched on the important differences between being able to enjoy all of a day or only part of a day. ETAC members noted that a more granular assessment could be important for preventive studies in particular because it would be valuable to assess whether people with frequent migraine were benefiting by being able to enjoy more full days. Cognitive debriefing study results indicated that participants understood the item and were not confused by its double-barreled structure. In addition, study participants described the item as redundant with the question about having a ‘good day,’ which was as intended. The MiCOAS team elected to keep the item as-is for the psychometric study and review its performance prior to considering any modification.

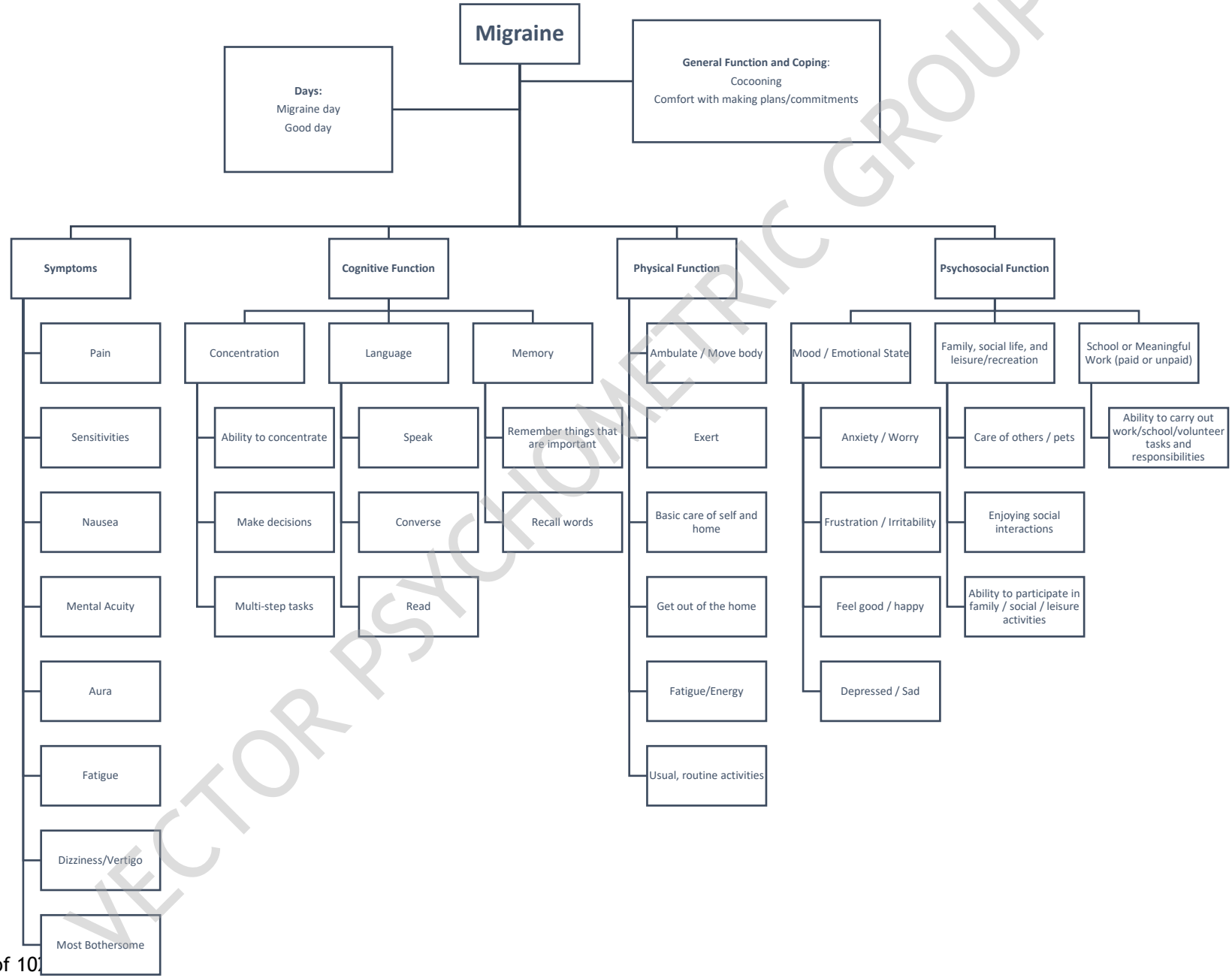
7. REVISED FRAMEWORK FOR MEASUREMENT

Based on findings from cognitive debriefing interviews, the initial concept model for measurement (see Figure 2) was modified to remove concepts that cognitive debriefing study participants indicated were inappropriate or not needed for evaluating treatment effect. This resulted in the removal of the following concepts:

- Use devices with screens
- Weather sensitivity
- Sustained concentration
- Multi-tasking
- Writing
- Numbers/math
- Making errors
- Avoidance of social interactions

The framework was also updated to revise terminology (e.g., 'crystal clear' day was rephrased as 'good day') and to add the dizziness/vertigo item. The revised concept model is depicted in Figure 3.

Figure 4. Revised Measurement Framework



8. DOMAIN FRAMEWORKS

Domain framework diagrams were developed to show the hypothesized domain structure and the draft items that apply to each domain. These diagrams are shown in Figures 5 through 9.

Figure 5. Domain Structures for Days and General Functioning

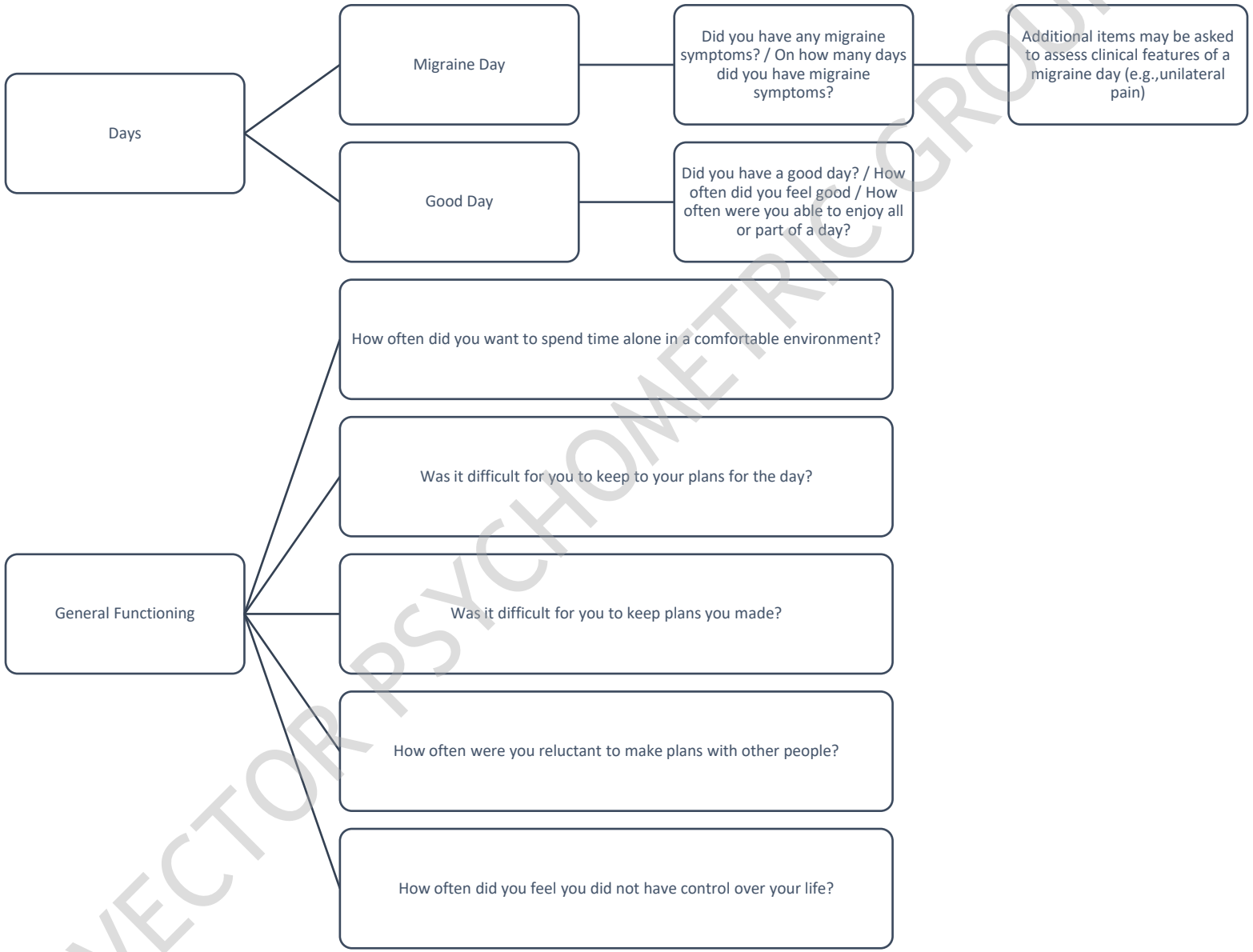


Figure 6. Domain Structure for Symptoms

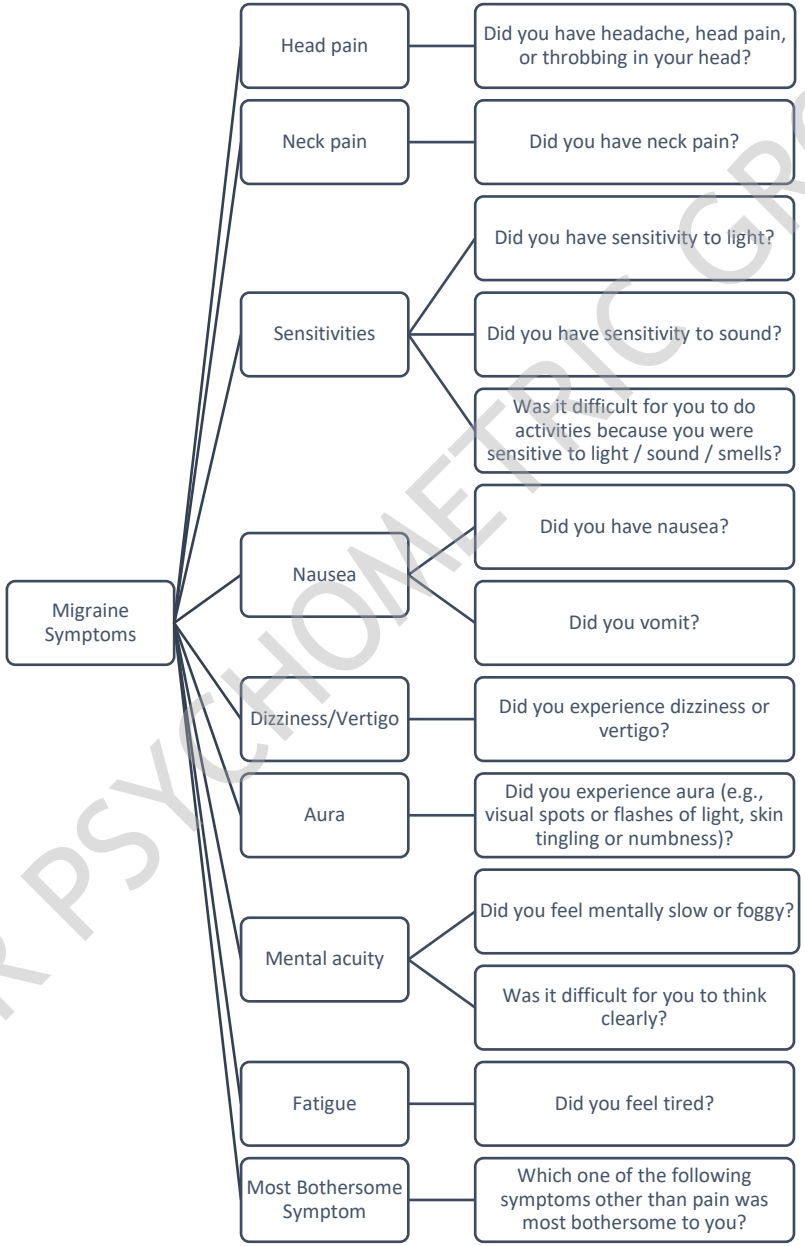


Figure 7. Domain Structure for Cognitive Functioning

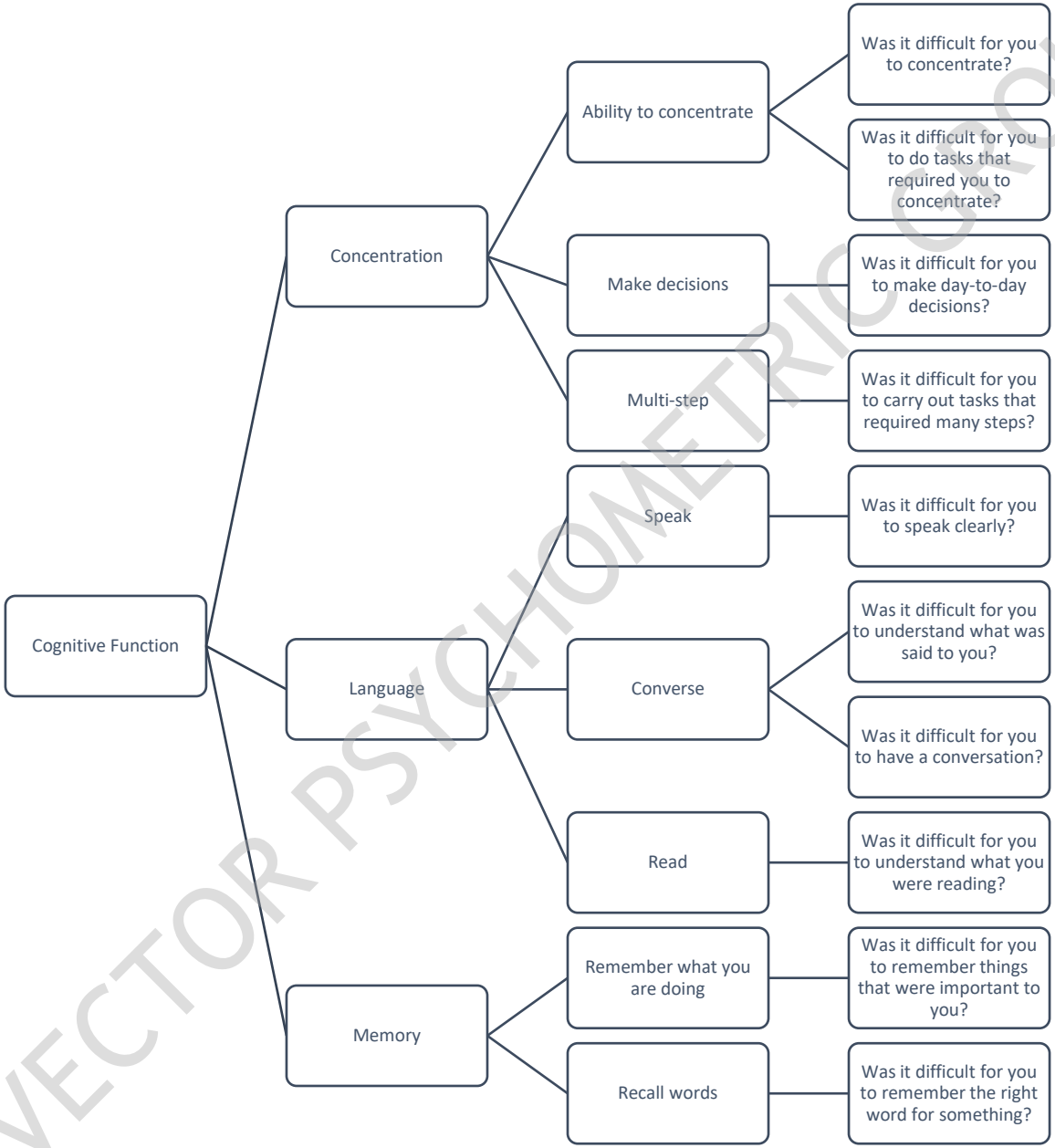


Figure 8. Domain Structure for Physical Functioning

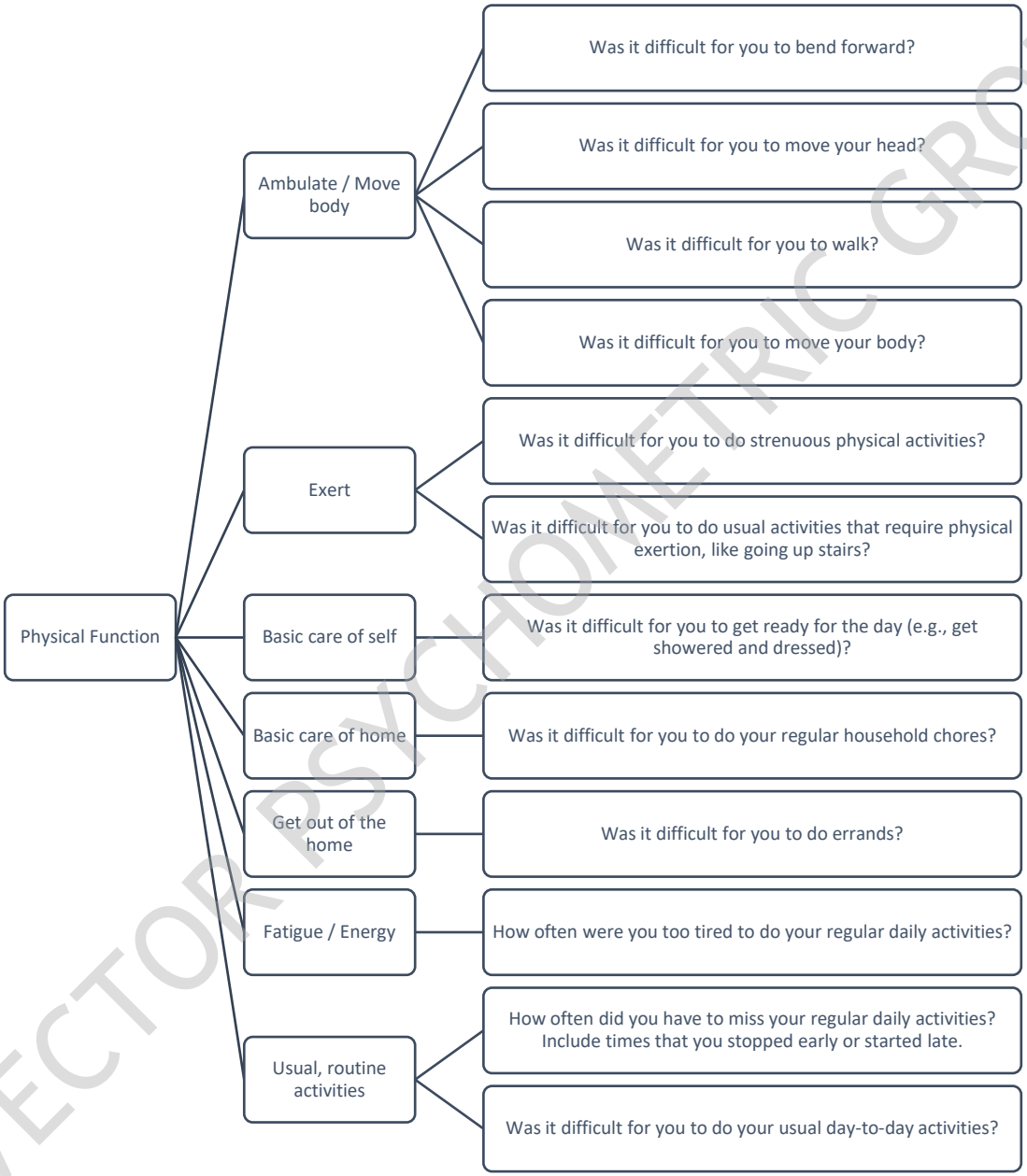
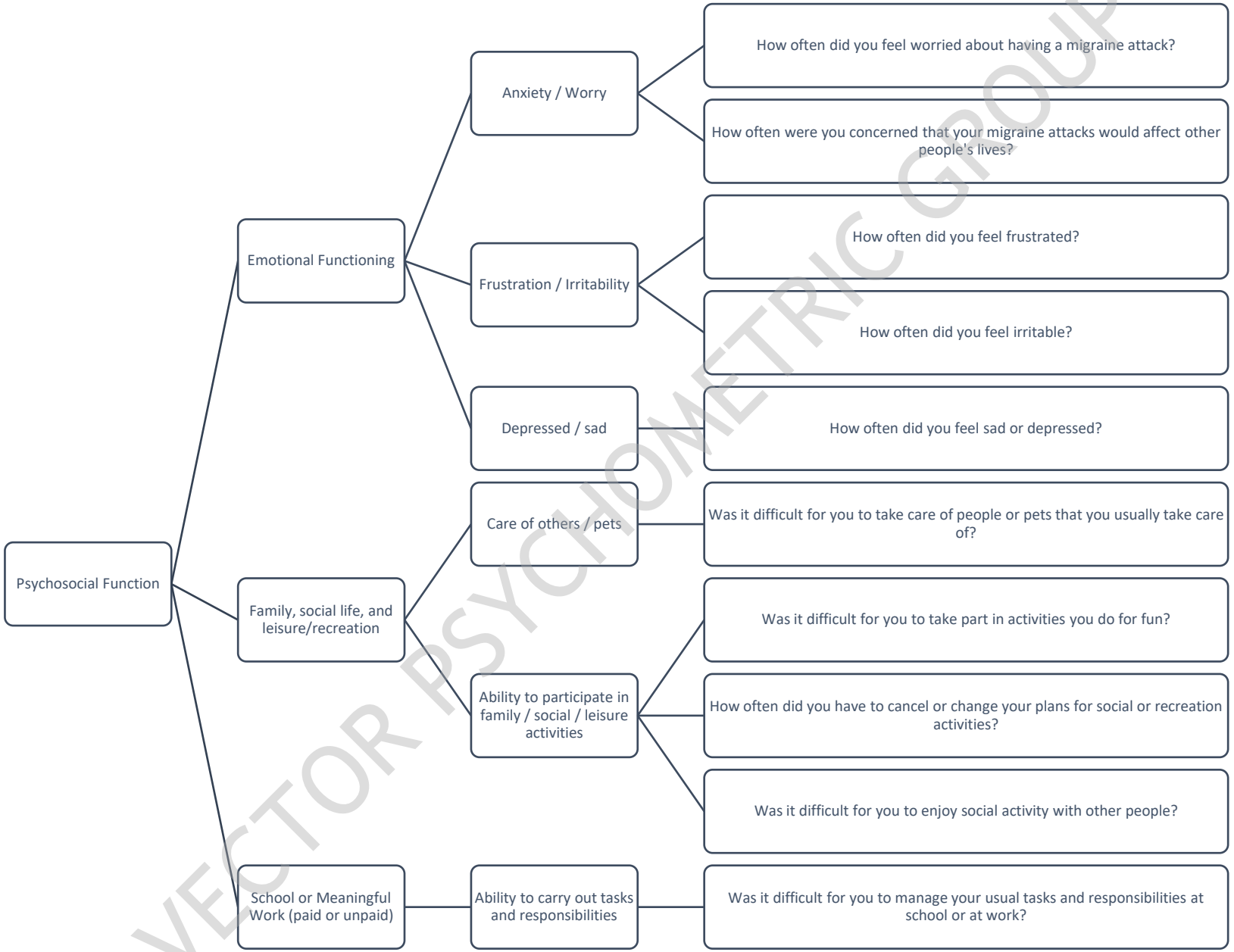


Figure 9. Domain Structure for Psychosocial Functioning



9. PROPOSED SCALES

24-HOUR INSTRUMENT

The MiCOAS team hypothesized that the 24-hour instrument includes two scales: a symptom scale and a functioning scale.

Instructions for the instrument are as follows:

- The following questions are about your experiences during the past 24 hours.
    - On each page or each screen, the phrase "During the past 24 hours…" is to appear above the question(s) as a reminder

The symptom scale consists of questions 1-13, which record experiences that people with migraine describe as symptoms. The functioning scale consists of questions 14-22, which record commonly experienced functioning impairments associated with migraine attacks. The conceptual basis for the hypothesized distinction between the two scales is that people may experience mild or isolated symptoms that do not result in any impairments of functioning on a given day, thus these two scales have the capacity to operate independently.

24-Hour Symptom Scale

Item and Response Options	Intended Meaning
1. Did you have any migraine symptoms? ☐ Yes ☐ No	To assess whether the respondent experienced any migraine symptoms on the relevant day
2. Did you have a good day? ☐ Yes ☐ No	To assess whether the respondent considered the day to be a good day irrespective of whether they report any symptoms or impacts for the day, with the aim of capturing times when people feel minimally- or unaffected by migraine
3. Did you have headache, head pain, or throbbing in your head? ☐ Did not have this symptom ☐ Mild ☐ Moderate ☐ Severe ☐ I never experience this symptom	To capture headache as a symptom; terms 'head pain' and 'throbbing' were included because MiCOAS study participants referred to head pain or throbbing that they did not consider a "full" headache (e.g., as a prodrome or postdrome symptom)
4. Did you have nausea? ☐ Did not have this symptom ☐ Mild ☐ Moderate ☐ Severe ☐ I never experience this symptom	To capture nausea as a symptom
5. Did you vomit? ☐ Did not have this symptom ☐ Mild ☐ Moderate ☐ Severe ☐ I never experience this symptom	To capture vomiting as a symptom
6. Did you have sensitivity to light? ☐ Did not have this symptom ☐ Mild ☐ Moderate ☐ Severe ☐ I never experience this symptom	To capture photophobia as a symptom
7. Did you have sensitivity to sound? ☐ Did not have this symptom ☐ Mild ☐ Moderate ☐ Severe ☐ I never experience this symptom	To capture phonophobia as a symptom
8. Did you have neck pain? ☐ Did not have this symptom ☐ Mild ☐ Moderate ☐ Severe ☐ I never experience this symptom	To capture neck pain as a symptom
9. Did you experience aura (e.g., visual spots or flashes of light, skin tingling or numbness)? ☐ Did not have this symptom ☐ Mild ☐ Moderate ☐ Severe ☐ I never experience this symptom	To capture aura as a symptom

Item and Response Options	Intended Meaning
10. Did you experience dizziness or vertigo? ☐ Did not have this symptom ☐ Mild ☐ Moderate ☐ Severe ☐ I never experience this symptom	To capture dizziness or vertigo as a symptom
11. Did you feel mentally slow or foggy? ☐ Did not have this symptom ☐ Mild ☐ Moderate ☐ Severe ☐ I never experience this symptom	To capture brain fog as a symptom; brain fog was described as a change in subjective mental acuity before, during, and after attacks, a sense of slowed mental function or 'thinking through a fog'
12. Did you feel tired? ☐ Did not have this symptom ☐ Mild ☐ Moderate ☐ Severe ☐ I never experience this symptom	To capture fatigue as a symptom or proximal impact of an attack
13. Which one of the following symptoms other than pain was most bothersome to you? (Select one) ☐ Nausea ☐ Sensitivity to light ☐ Sensitivity to sound ☐ Feeling mentally slow or foggy ☐ Another symptom was most bothersome	Currently a standard question for clinical trials of acute migraine treatment; depending on trial aims, all assessed symptoms could be listed as response options or the options could be restricted to cardinal symptoms only

Item and Response Options	Intended Meaning
14. Was it difficult for you to move your body? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture any difficulty with movement, including shifting body position in any way. Difficulty can include increased pain, nausea, dizziness, or other symptoms resulting from movement, or reluctance or avoidance of moving. This item purposefully reflects redundancy or overlap with items about walking, moving the head, bending forward, and getting ready for the day.
15. Was it difficult for you to walk? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture any difficulty with walking any distance, including the need to use any form of support to walk or avoidance of walking. Difficulty can include increased symptoms due to movement, or reluctance or avoidance of moving. This item purposefully reflects redundancy or overlap with items about moving the body, moving the head, bending forward, and getting ready for the day.
16. Was it difficult for you to move your head? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture any difficulty with moving the head, including turning the head while lying down. Difficulty can include increased symptoms due to movement, or reluctance or avoidance of moving. This item purposefully reflects redundancy or overlap with items about moving the body, walking, bending forward, and getting ready for the day.
17. Was it difficult for you to bend forward? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture any difficulty with bending forward, including any movement that results in the head moving past vertical. Difficulty can include increased symptoms due to movement, or reluctance or avoidance of moving. This item purposefully reflects redundancy or overlap with items about moving the body, walking, moving the head, and getting ready for the day.
18. Was it difficult for you to do strenuous physical activities? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture any difficulty with any strenuous activity of any duration that requires exertion and/or raises the heart rate, such as brisk walking, climbing stairs, exercising, or ordinary tasks that may require exertion. Difficulty can include increased symptoms, or reluctance or avoidance of moving. This item purposefully reflects redundancy or overlap with items about walking and getting ready for the day (i.e., because showering can require exertion).

Item and Response Options	Intended Meaning
19. Was it difficult for you to think clearly? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture difficulty with clear thinking. Difficulty can include distractions or impairments due to symptoms, as well as avoidance of activities that require thinking. This item purposefully reflects redundancy or overlap with items about concentrating and feeling mentally slow or foggy.
20. Was it difficult for you to concentrate? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture any impact on ability to concentrate. Difficulty can include challenges with concentrating on activities due to symptoms as well as avoidance of tasks that require concentration. This item purposefully reflects redundancy or overlap with items about thinking clearly and feeling mentally slow or foggy.
21. Was it difficult for you to get ready for the day (e.g., get showered and dressed)? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture any difficulty with routine grooming and dressing activities. Difficulty can include impairments due to symptoms, difficulty with or avoidance of movement, or fatigue.
22. Was it difficult for you to keep to your plans for the day? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture any interference with the day's planned activities resulting from migraine. Difficulty can include challenges experienced in carrying out plans, as well as having to cancel or miss out on planned activities, reschedule or delay planned activities or tasks.

7/14 DAY INSTRUMENT

The MiCOAS team hypothesized that the 7/14-day instrument includes one anchoring question and four scales.

Instructions for the instrument are as follows:

- For 7 days: The following questions are about your experiences over the <u>past 7 days</u>
    - On each page or each screen, the phrase "In the past 7 days…" is to appear above the question(s) as a reminder
- For 14 days: The following questions are about your experiences over the <u>past 14 days</u>
    - On each page or each screen, the phrase "In the past 14 days…" is to appear above the question(s) as a reminder

The anchoring question is question 1, which can be used with any scale if the entire instrument is not being used.

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

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

The four scales are:

- A physical and general functioning scale with 12 items (questions 2-13)
- A cognition scale with 10 items (questions 14-23)
- A social role functioning scale with 7 items (questions 24-30)
- An emotional functioning scale with 6 items (questions 31-36)

The conceptual basis for the hypothesized distinction between the four scales is that they capture distinct domains of impact from migraine and that MiCOAS study participants varied with reference to whether the specific domain was relevant to them as individuals. For example, some participants did not consider social functioning to be personally relevant and some participants did not report experiencing impacts on cognition or emotional states. As a result, these four scales appear to have the capacity to stand alone and operate separately from each other. In addition, participants who did experience outcomes within any given domain varied with respect to whether each item was personally relevant or considered redundant of other items. For example, some participants experienced irritability but not depression, and some participants made clear distinctions between 'regular daily activities' and concepts like 'errands' or 'chores', while others considered these questions repetitive. As a result, each scale appears to have the capacity to measure functioning outcomes across a range of participants without unnecessary redundancy.

Physical and General Functioning Scale (Experiences of Difficulty with Physical Activities and General Functioning)

Item and Response Options	Intended Meaning
2. How often did you feel good? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture times when people feel minimally- or unaffected by migraine
3. How often were you able to enjoy all or part of a day? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture times when people feel minimally- or unaffected by migraine, or are able to push through or ignore their symptoms
4. How often did you want to spend time alone in a comfortable environment? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture times when people wanted to retreat and 'cocoon' (e.g., to a dark room) because of migraine and/or times when they did so
5. Was it difficult for you to do your usual day-to-day activities? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture general ability to function before, during, after, or between attacks. Usual day-to-day activities encompass any physical, cognitive, or social activities that the person usually undertakes in the course of days in a 1-2 week period. Difficulty may include direct physical or cognitive impairments, slowed performance, pushing though, reluctance, or avoidance. This item purposefully reflects duplication or overlap with items asking about being too tired to do regular activities, having to miss regular activities, difficulty with chores or errands, and difficulties specifically due to photo- or phonophobia.
6. How often were you too tired to do your regular daily activities? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture fatigue that impedes general ability to function. This item specifically intends to capture interictal fatigue together with fatigue that coincides with an attack. Regular daily activities encompass any physical, cognitive, or social activities that the person usually undertakes in the course of days in a 1-2 week period.
7. How often did you have to miss your regular daily activities? Include times that you stopped early or started late. ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture 'missing out,' or absences or cessations from regular activities caused by migraine, including work or school. The phrasing (i.e., inclusion of "have to" and indications of stopping/starting) are intended to prompt respondents to focus on actual absence or cessation, in contrast to being physically present but not paying

	attention. However, some respondents may still include cognitive/mental absence depending on the nature of their regular daily activities.
8. Was it difficult for you to do usual activities that require physical exertion, like going up stairs? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture difficulty with any activity requiring exertion. Stairs is provided as an example and is meant to suggest that respondents should think of incidental activities of this kind, rather than focusing only on activities like exercise or sports. The example is also not intended to be restrictive (i.e., cause respondents to focus only on difficulty with stair climbing and exclude consideration of sports or exercise).
9. Was it difficult for you to do your regular household chores? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture difficulty with routine household chores of any kind, including indoors and outdoors. Difficulty may include direct physical or cognitive impairments, slowed performance, pushing though, reluctance, or avoidance.
10. Was it difficult for you to do activities because you were sensitive to light? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture the impact of photophobia on functioning, including premonitory, prodrome, postdrome, or interictal photophobia, and avoidance of activities by individuals whose migraine may be triggered by bright light.
11. Was it difficult for you to do activities because you were sensitive to smells? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture the impact of osmophobia on functioning, including premonitory, prodrome, postdrome, or interictal photophobia, and avoidance of activities by individuals whose migraine may be triggered by certain smells.
12. Was it difficult for you to do activities because you were sensitive to sound? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture the impact of phonophobia on functioning, including premonitory, prodrome, postdrome, or interictal photophobia, and avoidance of activities by individuals whose migraine may be triggered by noise.
13. Was it difficult for you to do errands? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture difficulty with ordinary errands of any kind. This item is intended to capture the ability to get out of the house as needed or wanted to take care of necessary business. Difficulty may include direct physical or cognitive impairments, slowed performance, pushing though, reluctance, or avoidance.

Subjective Cognitive Functioning Scale (Experiences of Difficulty with Cognitive Tasks)

Item and Response Scale	Intended Meaning
14. Was it difficult for you to concentrate? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture perceived experiences of difficulty concentrating or focusing attention in any way, including the sense that you have to force yourself to stay on task or the desire or practice of avoiding things that require concentration. This item purposefully reflects redundancy or overlap with items asking about feeling mentally slow or foggy, thinking clearly, and difficulty doing tasks that require concentration.
15. Was it difficult for you to speak clearly? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture perceived experiences of difficulty speaking smoothly and clearly, including stumbling over words, slurred or garbled speech, and avoidance of speaking. This item purposefully reflects redundancy or overlap with items asking about remembering words and having a conversation.
16. Was it difficult for you to remember the right word for something? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture perceived experiences of difficulty remembering the right word, including tip-of-the tongue and aphasia experiences as well as difficulty with word recall during speech that is caused by difficulty concentrating or thinking clearly. This item purposefully reflects redundancy or overlap with items asking about speaking clearly, concentrating, and having a conversation.
17. Was it difficult for you to have a conversation? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture perceived difficulty with carrying on a conversation, including one-on-one or group conversations. Difficulties may be connected to phonophobia, impairment of concentration or clear thinking, perceived speech impairment, or avoidance of conversation or interactions with others. This item purposefully reflects redundancy or overlap with items asking about difficulty speaking clearly and understanding speech.
18. Was it difficult for you to understand what was said to you? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture ability to comprehend speech (receptive language). Difficulty may include impairments caused by symptoms (e.g., pain, sound sensitivity, brain fog), or challenges with concentration or information processing. This item purposefully reflects redundancy or overlap with the item about having a conversation.
19. Was it difficult for you to understand what you were reading?	To capture reading comprehension (language) abilities. Difficulty may include impairments caused

Item and Response Scale	Intended Meaning
☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	by symptoms (e.g., pain, brain fog), or challenges with concentration or information processing. The item is not intended to capture avoidance of reading (or inability to read at all) due to light sensitivity alone, but to capture impact of migraine on ability to understand when reading.
20. Was it difficult for you to make day-to-day decisions? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture the simplest form of executive function, such as whether people are having difficulty making routine choices like what color pen to use or what to eat. Difficulty may include impairments caused by symptoms (e.g., pain, brain fog), challenges with concentration or information processing, or avoidance of decision-making due to migraine.
21. Was it difficult for you to carry out tasks that required many steps? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture ability to do multi-step tasks that rely on memory and executive function, such as complex work tasks or preparing meals that require following a recipe. The item is not intended to capture difficulty with tasks that require people to walk a lot of steps, but could be interpreted that way if it is taken out of the context of adjacent items and read literally.
22. Was it difficult for you to remember things that were important to you? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture challenges with memory recall that may result from migraine. The item is intended to capture impact on ability to remember significant things, such as important meetings, meaningful events, or who is picking up the children from school. It is not intended to capture issues with working memory, such as remembering what you were talking about, or short-term transient memory, such as remembering what you ate for breakfast.
23. Was it difficult for you to do tasks that required you to concentrate? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture ability to carry out tasks that require concentration. This item is intended to be narrower than the item asking about difficulty concentrating, but reflects duplication and overlap with that item. This item is intended to capture the direct impact of migraine on completion of tasks that require concentration, such as paying bills or participating in a committee meeting, as opposed to general difficulty with concentration that may affect passive activities like reading or watching television.

Social Role Functioning Scale (Experiences of Difficulty with Social Roles and Activities)

Item and Response Scale	Intended Meaning
24. Was it difficult for you to take care of people or pets that you usually take care of? ☐ Does not apply to me ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture ability to carry out caregiver roles. Difficulty can encompass impairments from symptoms, pushing through, reluctance, avoidance, and difficulty due to impairments of other functions (e.g., ability to move around, get out of the house, drive a car).
25. Was it difficult for you to manage your usual tasks and responsibilities at school or at work? ☐ Does not apply to me ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture ability to carry out work or school roles.
26. Was it difficult for you to keep plans you made? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture impact on general ability to function or interference with daily life. Difficulty may include pushing through, canceling or rescheduling planned activities, or missing out or skipping planned activities. This item purposefully reflects redundancy or overlap with items asking about reluctance to make plans, having to cancel/change social or recreation plans, enjoyment of social activity, and taking part in activities for fun.
27. How often were you reluctant to make plans with other people? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture impact on general ability to function or interference with daily life that results in reluctance to make plans or avoidance of planning ahead when it involves others who may be affected.
28. How often did you have to cancel or change your plans for social or recreation activities? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture impact on ability to engage in planned social and recreational activities.
29. Was it difficult for you to enjoy social activity with other people? ☐ Not difficult at all ☐ A little difficult ☐ Somewhat difficult ☐ Very difficult ☐ Unable to do	To capture impact on ability to enjoy social activities, which is intended to include pushing through to be present for social activity but not having a good time due to symptoms or other impacts of migraine.
30. Was it difficult for you to take part in activities you do for fun? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture impact on ability to engage in leisure and recreational activities of any kind, alone or with others. These activities may be passive/cognitive, such as reading or playing games, or active/physical, such as sports or travel.

Emotional Functioning Scale (Experiences of Emotional Impacts)

Item and Response Scale	Intended Meaning
31. How often did you feel you did not have control over your life? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture the subjective perspective of migraine unpredictability specifically in terms of disruptions and lack of control over life in general.
32. How often did you feel worried about having a migraine attack? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture anxiety or worry about migraine attacks.
33. How often were you concerned that your migraine attacks would affect other people's lives? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture anxiety or worry about how migraine affects other people, such as family, colleagues, or friends.
34. How often did you feel sad or depressed? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture feelings of sadness or depression.
35. How often did you feel frustrated? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture feelings of frustration, including anger.
36. How often did you feel irritable? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always	To capture feelings of irritability.

MODIFICATIONS FOR IMPLEMENTATION OF THE 24-HOUR INSTRUMENT

As noted previously, implementation of the proposed measures may necessitate modifications to the instruments to accommodate specific research goals, including the addition of questions associated with classifying responses according to specific clinical definitions of migraine day or headache day. Similarly, modifications may be desirable to reduce the burden of daily assessments during a study, such as simplifying the presentation of symptoms.

For the psychometric study of the 24-hour instrument, several such modifications were made, as follows:

1. Questions were added to permit characterizing migraine days according to specific diagnostic criteria, including headache duration, head pain that worsens with activity, throbbing/pounding head pain, and pain only or worse on one side of the head. Subsequent to these additions, the question "Did you have headache, head pain, or throbbing in your head?" was modified to remove the reference to 'throbbing' and implemented as "Did you have a headache or head pain?"

2. In alignment with these modifications, the item "Did you experience any migraine symptoms?" was modified to read "Did you have a migraine day?" This permitted the form of the question to mirror the planned assessment of migraine days using diagnostic criteria, thus permitting the study to assess whether self-reported migraine days are aligned with days that matched the selected diagnostic criteria. Use of the phrase "migraine day" was commonplace among participants in both concept elicitation and cognitive debriefing studies. The phrase was commonly used to denote a day during which migraine symptoms or impacts were present.

3. Two additional questions were added to ask about acute treatment use ("Did you take any medication to alleviate your head pain?") and healthcare utilization ("Did you seek care from a health care provider today because of your headache or head pain?"). These questions would often be important in a clinical trial context.

4. To permit convenient delivery of the instrument on a smartphone or tablet, as well as endeavor to minimize the time required to complete a daily instrument over several months, the items addressing migraine symptoms were reformulated to appear as a 'check all that apply' list preceded by the question "Did you experience any of the following?" and including the option "None of the above." If respondents checked any symptoms, they would receive follow-up questions asking them to rate the severity only of those symptoms they had checked. Because respondents would only rate severity for symptoms they reported having, the response options "did not have this symptom" and "I never experience this symptom" were removed. Similarly, questions about impacts on functioning were formatted in a similar checklist preceded by the question "Were any of the following difficult?" so that respondents were only asked to rate the level of difficulty for those impacts they checked. Implementation in this way achieved the benefit that, on days unaffected by migraine, respondents would only have to answer five questions. These implementation decisions necessitated minor

adjustment to the grammatical phrasing of items, such as rephrasing 'mentally slow or foggy' as 'mental slowness or fogginess' to match the noun format needed for a checklist.

5. To improve the amount of data that could be used for statistical analysis related to a potential cognition scale, two questions from the 7/14-day instrument were added to the 24-hour instrument and formatted in the same manner as the other questions about functioning. These additions ensured that the daily instrument included five items assessing cognitive concepts. The added items were "remembering the correct words for thing" and "speaking clearly." These items were selected on the basis of their level of endorsement and close conceptual connection to experiences of brain fog, difficulty concentrating, and difficulty thinking clearly.

Screenshots of the eCOA versions of the instruments can be found in Appendix C.

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APPENDIX A. LEGACY MEASURE CONTENT COMPARISON

MiCOAS Measure Framework Domain	**MiCOAS Measure Framework Component**	**24-hr MSQOL**	AIM-D	FIMQ	HANA	HDI	HImQ	HIT-6	MFIQ (v.2)	MIBS-4	MIDAS	MIG-SCOG	MPFID	MPQ-5	MSQ v. 2.1	MSQOL	MTAQ	PPMQr	# measures for concept	% measures for concept
Cognitive Function: Language	Ability to carry on a conversation																		0	0
Psychosocial Function: School/Work	Ability to carry out work/school/volunteer tasks and responsibilities			X			X		X	X	X						X		6	33
Cognitive Function: Concentration	Ability to concentrate	X	X	X	X	X		X	X			X	X		X				10	56
Cognitive Function: Language	Ability to converse											X							1	6
Cognitive Function: Concentration	Ability to make decisions																		0	0
Cognitive Function: Concentration	Ability to multi-task, do multi-step processes											X							1	6
Psychosocial Function: Family/Social/Leisure	Ability to participate in family/social/leisure activities	X	X	X	X	X	X		X		X			X	X	X		X	12	67
Cognitive Function: Language	Ability to read					X													1	6
Cognitive Function: Memory	Ability to recall words											X							1	6
Cognitive Function: Memory	Ability to remember what you are doing			X															1	6
Cognitive Function: Language	Ability to speak											X							1	6
Physical Function	Ambulate/move body		X	X					X				X						4	22
Psychosocial Function: Mood/Emotional State	Anxiety/worry	X			X	X			X					X	X	X			7	39
Psychosocial Function: Family/Social/Leisure	Avoiding/enjoying interactions with other people			X		X			X				X						4	22
Physical Function	Basic care of home		X	X			X		X		X		X						6	33
Physical Function	Basic care of self								X				X						2	11
Psychosocial Function: Family/Social/Leisure	Care of others/pets								X										1	6
Physical Function	Carry out routine activities	X				X		X	X				X	X	X			X	8	44
General Function	Cocooning			X			X	X					X						4	22

MiCOAS Measure Framework Domain	**MiCOAS Measure Framework Component**	**24-hr MSQOL**	AIM-D	FIMQ	HANA	HDI	HImQ	HIT-6	MFIQ (v.2)	MIBS-4	MIDAS	MIG-SCOG	MPFID	MPQ-5	MSQ v. 2.1	MSQOL	MTAQ	PPMQr	# measures for concept	% measures for concept
General Function	Comfort with making plans				X				X	X					X	X			5	28
Psychosocial Function: Mood/Emotional State	Depression/feel sad			X	X											X			3	17
Physical Function	Exertion/exercise		X						X				X						3	17
Psychosocial Function: Mood/Emotional State	Feel good/happy	X																	1	6
Psychosocial Function: Mood/Emotional State	Frustration/irritability			X		X		X	X						X	X		X	7	39
Physical Function	Get out of the home		X	X		X			X				X						5	28
Physical Function	Level of fatigue/energy	X		X	X		X	X	X						X				7	39
Cognitive Function: Concentration	Make errors																		0	0
Cognitive Function: Language	Math/numbers																		0	0
Cognitive Function: Concentration	Sustained attention																		0	0
Symptoms	Aura																		0	0
Symptoms	Mental acuity		X	X		X						X							4	22
Symptoms	Nausea	X					X												2	11
Symptoms	Neck pain																		0	0
Symptoms	Pain	X					X	X			X			X				X	6	33
Symptoms	Sensitivity to light, sound, smell	X							X									X	3	17
Symptoms	Vomiting																		0	0
Items not matched (e.g., domain n/a, item unclear)		3	0	0	1	8	0	0	1	2	0	0	0	0	0	13	8	2		
Total number of items in measure		15	11	20	7	25	16	6	26	4	7	9	13	5	14	25	9	16		
Number of MiCOAS concepts captured		9	7	13	6	9	7	6	16	2	4	6	9	4	7	5	1	5		
Percentage of MiCOAS concepts captured (out of 36)		25	19	36	17	25	19	17	44	6	11	17	25	11	19	14	3	14		

24-hour MSQOL: 24-hour Migraine Specific Quality of Life; AIM-D: Activity Impairment in Migraine-Diary; FIMQ: Functional Impact of Migraine; HANA: Headache Needs Assessment; HDI: Headache Disability Index; HImQ: Headache Impact Questionnaire; HIT-6: Headache Impact Test; HMSE: Headache Management Self-Efficacy Scale; HSLC: Headache-Specific Locus of Control Questionnaire; MFIQ: Migraine Functional Impact Questionnaire; MIBS-4:

Migraine Interictal Burden Scale; MIDAS: Migraine Disability Assessment; MIG-SCOG: Cognitive Impairment Scale for Migraine Attacks; MPFID: Migraine Physical Function Impact Diary; MPQ-5: Migraine Prevention Questionnaire; MSQ: Migraine-Specific Quality of Life; MSQOL: Migraine Specific Quality of Life Questionnaire; MTAQ: Migraine Therapy Assessment Questionnaire; PPMQr: Patient Perception of Migraine Questionnaire-revised

APPENDIX B. DISPOSITION OF ALL PROPOSED ITEMS, INCLUDING DUPLICATES AND ALTERNATES

The table below provides a per-item summary of selected interview data and decisions to keep, drop, or revised items over the four waves of cognitive debriefing interviews. The table includes numerous duplicates due to the same item language being tested with different response options. The response option applied may be discerned from the item ID. The item ID includes:

- a letter code that indicates the overall domain
    - CF = cognitive functioning
    - GF = general functioning and coping
    - PF = physical functioning
    - PSY = psychosocial functioning
    - S = symptoms
- a sequential number
- letter(s) or word indicating the response scale
    - d = difficulty
    - f = frequency
    - s = severity
    - yn = yes or no
    - days = select the number of days
    - pick = for the most bothersome symptom question only, pick from a list of symptoms

- when applicable, the letters “Rev” to indicate that the item was modified during debriefing; revised items retain the initial letters and numbers of the original item to provide an audit trail

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
CF01f	How often did you avoid doing things that required concentration?	Cognitive Function: Concentration: Ability to concentrate	Keep	Participants all reported that the need to push through (or preference for pushing through) would affect their responses to this question, thus underreporting may be a prominent issue for this item; one person thought that frequency of avoidance did not make sense to ask	Drop	Participants understood the question, but gave various reasons for disliking it or finding it unimportant; these included: it's not possible to avoid doing lots of things that require concentrating, people may not avoid but may slow down, people may avoid some tasks & not others (making it harder to answer the question)	-	-	-	-
CF02d	Was it difficult for you to concentrate?	Cognitive Function: Concentration: Ability to concentrate	Keep	All participants thought this was an important question to include	Keep	Participants related this item to questions about mental slowness / brain fog & concentration; one noted that keeping both types of questions was important	Keep	4 of 5 participants perceived a distinction between thinking clearly & concentrating	Keep	Kept in 24 hour instrument
CF02f	Was it difficult for you to concentrate?	Cognitive Function: Concentration: Ability to concentrate	Keep	All participants thought this was an important question to include	Keep	Participants varied in whether they viewed this item & the item "was it difficult for you to do tasks that required you to concentrate" as	Keep	Comments indicate that people correctly focused on difficulty concentrating because of migraine	Keep	Kept in 7/14 day instrument. One participant indicated that they might include factors other than migraine in

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
						redundant or distinct, & whether they thought both were of value				assessing concentration
CF03d	Was it difficult for you to do tasks that required you to concentrate?	Cognitive Function: Concentration: Ability to concentrate	Keep	Duplicate	Drop	Duplicate	-	-	-	-
CF03f	Was it difficult for you to do tasks that required you to concentrate?	Cognitive Function: Concentration: Ability to concentrate	Keep	Participants noted that this item overlapped with other items about concentration; three thought this was the best question because it was more specific to function, but one appeared to have difficulty recalling specific tasks that required concentration	Keep	Participants understood this item as intended & did not think exclusively of work/school (e.g., included driving); varied in whether they preferred this item or the broader item "what is difficult for you to concentrate" or thought both were important to ask	Keep	Comments suggest that the item will successfully capture a range of tasks from daily life as well as longer-term tasks such as learning.	Keep	Participants noted the similarity to the general question about ability to concentrate
CF04d	Was it difficult for you to concentrate on something for longer than 15 minutes?	Cognitive Function: Concentration: Sustained	Drop	Participants found the inclusion of the phrase "longer than 15 minutes" unnecessary & arbitrary, & one noted that contextual factors would influence their response;	-	-	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
				preferred an alternative item						
CF04f	Was it difficult for you to concentrate on something for longer than 15 minutes?	Cognitive Function: Concentration: Sustained	Drop	Duplicate	-	-	-	-	-	-
CF05d	Was it difficult for you to make choices that are usually easy for you?	Cognitive Function: Concentration: Make decisions	Drop	One participant misread/ misunderstood the item; others regarded this item as redundant with CF06 & preferred that question because it was simpler & more comprehensive of decision-making challenges (i.e., not just focused on "easy" decisions)	-	-	-	-	-	-
CF05f	Was it difficult for you to make choices that are usually easy for you?	Cognitive Function: Concentration: Make decisions	Drop	Duplicate	-	-	-	-	-	-
CF06d	Was it difficult for you to make day-to-day decisions?	Cognitive Function: Concentration: Make decisions	Keep	Three participants found the item relevant & valuable; one stated that the question seemed vague;	Keep	Participants referred to a variety of routine decisions; most preferred the difficulty scale but could answer with frequency; one	Keep	3 of 5 participants did not experience this	Keep	

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
				one participant did not discuss this item		found it hard to respond with frequency				
CF06f	Was it difficult for you to make day-to-day decisions?	Cognitive Function: Concentration: Make decisions	Keep	Duplicate	Drop	Duplicate	-	-	-	-
CF07f	Did you avoid tasks that required multiple steps?	Cognitive Function: Concentration: Multi-step tasks or multitasking	Drop	Participants perceived the avoidance of these tasks as overly specific & not as important compared to the difficulty in doing these tasks. Several participants expressed the inability to avoid tasks due to mandatory obligations or tendencies to push through	-	-	-	-	-	-
CF08d	Was it difficult for you to carry out tasks that required many steps?	Cognitive Function: Concentration: Multi-step tasks or multitasking	Keep	All participants understood this item as intended & thought it was important to ask	Keep	Participants based answers on things like work tasks & no one appeared to misinterpret this as physical steps	Keep	Participants understood the item as intended, with a focus on difficulty concentrating & keeping track of steps	Keep	3 of 4 participants understood the item as intended, with a focus on difficulty concentrating & keeping track. One participant interpreted the phrase to mean walking steps
CF08f	Was it difficult for you to carry out tasks that	Cognitive Function: Concentration: Multi-step	Keep	Duplicate	Drop	Duplicate	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
	required many steps?	tasks or multitasking								
CF09d	Was it difficult for you to do more than one thing at a time?	Cognitive Function: Concentration: Multi-step tasks or multitasking	Drop	Several participants thought the item was not important & one thought it was vague. This item was also seen as redundant of broader items about mental fog & concentration.	-	-	-	-	-	-
CF09f	Was it difficult for you to do more than one thing at a time?	Cognitive Function: Concentration: Multi-step tasks or multitasking	Drop	Duplicate	-	-	-	-	-	-
CF10d	Was it difficult for you to multi-task?	Cognitive Function: Concentration: Multi-step tasks or multitasking	Drop	Two participants thought this was an important concept to capture, one felt strongly that multi-tasking is not normal & should not be part of an assessment; participants saw the item as redundant with items about concentration & clear thinking	-	-	-	-	-	-
CF10f	Was it difficult for	Cognitive Function: Concentration:	Drop	Duplicate	-	-	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
	you to multi-task?	Multi-step tasks or multitasking								
CF11d	Was it difficult to do your usual tasks without making errors?	Cognitive Function: Concentration: Make errors	Drop	Participants found this item unclear, not relevant, or said they will avoid tasks when errors matter. One described this as a "miserable question" that requires judgments of what usual tasks to consider & what constitutes an error.	-	-	-	-	-	-
CF11f	Was it difficult to do your usual tasks without making errors?	Cognitive Function: Concentration: Make errors	Drop	Duplicate	-	-	-	-	-	-
CF12d	Was it difficult for you to speak clearly?	Cognitive Function: Language: Speak	Keep	Duplicate	Drop	Duplicate	-	-	-	-
CF12f	Was it difficult for you to speak clearly?	Cognitive Function: Language: Speak	Keep	Participants understood the question, but two referenced word recall as well	Keep	Two participants noted that speech can be affected by pain, not just cognitive impairment	Keep	Two participants conflated this concept with word recall	Keep	One participant appeared to interpret the item to mean interacting with people, rather than speaking without slurring or stumbling over words
CF13d	Was it difficult for you to speak	Cognitive Function:	Drop	Participants noted substantial	-	-	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
	clearly (i.e., without slurring or stumbling over words)?	Language: Speak		overlap with another, simpler question about speaking						
CF13f	Was it difficult for you to speak clearly (i.e., without slurring or stumbling over words)?	Cognitive Function: Language: Speak	Drop	Duplicate	-	-	-	-	-	-
CF14d	Was it difficult for you to understand what was said to you?	Cognitive Function: Language: Converse	Keep	All participants understood the item as intended, one indicated that this question did not apply to them	Keep	Participants preferred the difficulty scale for this question, with one participant noting that "it's not how often is that difficult, but, like, if you are having problem understanding, how severe is it, type of thing"	Keep	3 of 5 participants did not experience this	Keep	1 participant thought the question was confusing in the context of recalling experience over multiple days
CF14f	Was it difficult for you to understand what was said to you?	Cognitive Function: Language: Converse	Keep	Duplicate	Drop	Duplicate	-	-	-	-
CF15d	Was it difficult for you to have a conversation?	Cognitive Function: Language: Converse	Keep	Four participants liked the item & thought it was relevant to ask, one appeared to think the item was of less value because, although affected by	Keep	Participants understood the item as intended, including interpretations as difficulty concentrating or not feeling like talking to others, not just language issues	Keep	Comments suggest that the item will successfully capture an array of reasons why conversing is difficult.	Keep	

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
				migraine, they could still carry on a conversation if they had to						
CF15f	Was it difficult for you to have a conversation?	Cognitive Function: Language: Converse	Keep	Duplicate	Drop	Duplicate	-	-	-	-
CF16d	Was it difficult for you to express your thoughts?	Cognitive Function: Language: Converse	Drop	Three participants understood the item as intended & thought it was relevant; one participant interpreted the item as asking about ability to express feelings & one participant didn't find the item relevant to ask	-	-	-	-	-	-
CF16f	Was it difficult for you to express your thoughts?	Cognitive Function: Language: Converse	Drop	Duplicate	-	-	-	-	-	-
CF17f	Did you avoid reading because of migraine?	Cognitive Function: Language: Read	Keep	Most participants thought the concept was important, but preferred other questions	Drop	One person thought this item was best for capturing their experiences; others preferred alternate questions about reading & concentration	-	-	-	-
CF18d	Was it difficult for you to	Cognitive Function:	Keep	Participants thought the item was	Keep	Participants had different strategies for	Keep	4 of 5 participants understood the	Keep	3 of 4 participants understood the item as intended;

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
	understand what you were reading?	Language: Read		appropriate & useful to ask		responding depending on the scale (e.g., unable to do was used to express "avoided reading"); most participants preferred this item to the "avoid reading" item		item as intended (i.e., difficulty with comprehension). Comments suggest that people will indicate "no difficulty" when they avoid reading altogether		one referenced inability to see (due to watery eyes) rather than comprehension
CF18f	Was it difficult for you to understand what you were reading?	Cognitive Function: Language: Read	Keep	Duplicate	Drop	Duplicate	-	-	-	-
CF19d	Was it difficult for you to handle routine money transactions?	Cognitive Function: Language: Numbers/Math	Drop	Four participants thought it was not relevant or important to ask; one participant did not discuss the item	-	-	-	-	-	-
CF19f	Was it difficult for you to handle routine money transactions?	Cognitive Function: Language: Numbers/Math	Drop	Duplicate	-	-	-	-	-	-
CF20d	Was it difficult for you to do simple math without a calculator?	Cognitive Function: Language: Numbers/Math	Drop	Three participants thought it was unimportant to ask & one thought it was a "silly question"; one participant did not discuss this item	-	-	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
CF20f	Was it difficult for you to do simple math without a calculator?	Cognitive Function: Language: Numbers/Math	Drop	Duplicate	-	-	-	-	-	-
CF21d	Was it difficult for you to remember what you were doing (e.g., remember why you entered a room)?	Cognitive Function: Memory: Remember what you are doing	Drop	Duplicate	-	-	-	-	-	-
CF21f	Was it difficult for you to remember what you were doing (e.g., remember why you entered a room)?	Cognitive Function: Memory: Remember what you are doing	Keep	Two participants indicated that they have memory issues of this type due to other reasons, which influences responses; two found it not relevant to ask; & one person linked the concept to brain fog more broadly rather than memory	Drop	Participants noted that it can be difficult to tell if issues are due to migraine or something else; some participants equated this with difficulty concentrating	-	-	-	-
CF22d	Was it difficult for you to remember what you were talking about when speaking with someone?	Cognitive Function: Memory: Remember what you are doing	Drop	One participant equated this with word recall rather than following a train of thought; one participant thought it wasn't relevant	-	-	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
				to ask this & also discounted experiences with memory if they remembered "in a little bit"						
CF22f	Was it difficult for you to remember what you were talking about when speaking with someone?	Cognitive Function: Memory: Remember what you are doing	Drop	Duplicate	-	-	-	-	-	-
CF23d	Was it difficult for you to remember things that were important to you?	Cognitive Function: Memory	Keep	Duplicate	Drop	Duplicate	-	-	-	-
CF23f	Was it difficult for you to remember things that were important to you?	Cognitive Function: Memory	Keep	Reviewed by fewer than four participants	Keep		Keep	4 of 5 participants did not experience this often (or at all); one was unsure of the meaning	Keep	3 of 4 participants understood the item as intended, one wasn't sure what the question referred to
CF24d	Was it difficult for you to remember the right word for something?	Cognitive Function: Memory: Recall words	Keep	Duplicate	Drop	Duplicate	-	-	-	-
CF24f	Was it difficult for you to remember the right word for something?	Cognitive Function: Memory: Recall words	Keep	Three participants thought it was important	Keep		Keep		Keep	1 of 4 participant was unsure of the meaning

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
CF25d	Was it difficult for you to find the right words?	Cognitive Function: Memory: Recall words	Drop	Participants thought this was repetitive of other speech/memory items & this item was not preferred	-	-	-	-	-	-
CF25f	Was it difficult for you to find the right words?	Cognitive Function: Memory: Recall words	Drop	Duplicate	-	-	-	-	-	-
GF01f	How often did you spend time alone in a comfortable environment because of migraine?	General Function & Coping: Cocooning	Keep	Of the items related to cocooning, participants liked this one very much; one preferred this item because it did not include the term "soothing" & noted that it isn't always necessary to lie down	Revise to blend with other items	Participants varied in which item they preferred to capture cocooning	-	-	-	-
GF01fRev	How often did you want to spend time alone in a comfortable environment?	General Function & Coping: Cocooning	-	-	-	-	Keep	Most participants thought this question should be more specific (i.e., during headache or when you have symptoms)	Keep	
GF02f	How often did you need to lie down because of your migraines?	General Function & Coping: Cocooning	Drop	Of the items related to cocooning, participants liked this one the least	-	-	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
GF03f	How often did you want to be alone in a comfortable, soothing place because of your symptoms?	General Function & Coping: Cocooning	Keep	Of the items related to cocooning, participants also liked this one very much; the word "soothing" was important to one participant	Drop	Participants varied in which item they preferred to capture cocooning; soothing was considered unimportant to some	-	-	-	-
GF04d	Was it difficult for you to use a device with a lighted screen, such as a phone or computer?	General Function & Coping: Use devices with screen	Keep	Reviewed by fewer than four participants	Drop	Participants thought this item was relevant but redundant with questions about light sensitivity impacts; one participant thought this was unimportant because screens can be dimmed	-	-	-	-
GF04f	Was it difficult for you to use a device with a lighted screen, such as a phone or computer?	General Function & Coping: Use devices with screen	Keep	Duplicate	Drop	Duplicate	-	-	-	-
GF05d	Was it difficult for you to keep to your plans for the day?	Physical Function: Usual Activities	Keep	Participants liked the question & thought it was important to include	Keep	Participants thought it was important to include, & thought it should be asked with a 24-hour time frame	Keep		Keep	
GF05f	Was it difficult for you to keep to your plans for the day?	General Function & Coping: Comfort with making plans	Keep	Duplicate	Drop	Duplicate	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
		& commitments								
GF06d	Was it difficult for you to keep plans you made?	General Function & Coping: Comfort with making plans & commitments	Keep	Duplicate	Drop	Duplicate	-	-	-	-
GF06f	Was it difficult for you to keep plans you made?	General Function & Coping: Comfort with making plans & commitments	Keep	Four participants thought it was relevant & important to ask; one indicated that they experienced more issues with making, rather than keeping, plans	Keep	4 of 5 participants preferred the frequency scale for responding	Keep		Keep	
GF07f	How often were you reluctant to make plans with other people because of migraine?	General Function & Coping: Comfort with making plans & commitments	Keep	All participants thought it captured an important part of migraine experiences	Revise	Participants noted that it was similar to other questions about plans & that this item may capture more social information (as opposed to work / school, where people follow an imposed schedule)	-	-	-	-
GF07fRev	How often were you reluctant to make plans with other people?	General Function & Coping: Comfort with making plans & commitments	-	-	-	-	Keep	Participants interpreted this to mean social plans	Keep	

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
GF08f	How often did you feel you did not have control over your life?	General Function & Coping: Comfort with making plans & commitments	Keep	Reviewed by fewer than four participants	Keep	Most participants thought it was very important to include	Keep	1 of 5 interpreted this as asking whether a caregiver made decisions for you	Keep	2 of 4 participants thought of this question in terms of factors other than migraine, such as work or financial pressures
PF01d	Was it difficult for you to bend forward?	Physical Function: Ambulate / Move Body	Keep	Participants liked the question, found it relevant, but thought it should be asked daily	Keep	Participants thought it better to ask daily due to close connection to attacks (not an interictal issue)	Keep	One participant debated what "bend over" meant specifically	Keep	One participant noted that this is a motion they would avoid during migraine
PF01f	Was it difficult for you to bend forward?	Physical Function: Ambulate / Move Body	Drop	Duplicate	Drop	Duplicate	-	-	-	-
PF02d	Was it difficult for you to move your head?	Physical Function: Ambulate / Move Body	Keep	Participants liked the question, found it relevant, but thought it should be asked daily	Keep	Participants linked this item to exacerbation of symptoms	Keep		Keep	
PF02f	Was it difficult for you to move your head?	Physical Function: Ambulate / Move Body	Drop	Duplicate	Drop	Duplicate	-	-	-	-
PF03d	Was it difficult for you to walk?	Physical Function: Ambulate / Move Body	Keep	Participants liked the question, found it relevant, but thought it should be asked daily	Keep	Participants linked this item to exacerbation of symptoms	Keep	One participant responded based on limitations unrelated to migraine	Keep	Three participants did not experience this
PF03f	Was it difficult for you to walk?	Physical Function: Ambulate / Move Body	Drop	Duplicate	Drop	Duplicate	-	-	-	-
PF04d	Was it difficult for	Physical Function:	Keep	Participants liked the question, found	Keep	Some participants thought this question should	Keep	Three participants thought the	Keep	One participant interpreted this as exercise or

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	you to move your body?	Ambulate / Move Body		it relevant, but thought it should be asked daily; noted that this item is redundant with narrower questions about movement		come first & if people said no, the other questions would not appear; some participants thought that this question encompassed all the other more specific questions, but others had experienced some impacts & not others during attacks or expressed that the questions provide a sort of scale of severity		question was vague, but interpreted it as intended		activities more strenuous than usual, other participants listed movement that is covered by other questions (e.g., bending over, walking, moving the head)
PF04f	Was it difficult for you to move your body?	Physical Function: Ambulate / Move Body	Drop	Duplicate	Drop	Duplicate	-	-	-	-
PF05d	Was it difficult for you to do strenuous physical activities?	Physical Function: Exert	Keep	Participants interpret the item primarily in terms of exercise, but one participant mentioned other activities	Keep	Participants thought primarily about exercise, but some also considered lifting heavy weights or walking uphill; participants factored in avoidance due to strenuous activity being a trigger & one participant noted avoidance due to a comorbid condition	Keep	Participants thought about exercise & other taxing activities	Keep	
PF05f	Was it difficult for you to do	Physical Function: Exert	Keep	Duplicate	Drop	Duplicate	-	-	-	-

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	strenuous physical activities?									
PF06d	Was it difficult for you to do usual activities that require physical exertion, like going up stairs?	Physical Function: Exert	Keep	Duplicate	Drop	Duplicate	-	-	-	-
PF06f	Was it difficult for you to do usual activities that require physical exertion, like going up stairs?	Physical Function: Exert	Keep	All participants liked this question & found it relevant; several participants focused only on stairs, others referenced other activities	Keep	One participant focused exclusively on stairs; one indicated that climbing stairs didn't seem strenuous	Keep	One participant focused on stairs only	Keep	No participants in this group focused on stairs
PF07d	Was it difficult for you to get ready for the day (e.g., get showered & dressed)?	Physical Function: Basic Care of Self & Home	Keep	Two of 5 participants interpreted this as including other activities, such as letting the dog out	Keep	The item was not relevant to all participants (e.g., one person noted that they usually fine in the morning)	Keep		Keep	One participant noted this is not relevant if migraine occurred in the evening, another had a migraine only in the evening but applied this item to getting ready for bed
PF07f	Was it difficult for you to get ready for the day (e.g., get showered & dressed)?	Physical Function: Basic Care of Self & Home	Drop	Duplicate	-	-	-	-	-	-

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PF08d	Was it difficult for you to do your regular household chores?	Physical Function: Basic Care of Self & Home	Keep	Duplicate	Drop	Duplicate	-	-	-	-
PF08f	Was it difficult for you to do your regular household chores?	Physical Function: Basic Care of Self & Home	Keep	Most participants thought of routine cleaning & housekeeping tasks, one included routine outdoor maintenance activities; one participant thought it would be helpful to include examples of chores	Keep	Participants interpreted the item broadly in the context of their routine lifestyle; noted that there is great variation in chores & that some are more difficult than others; consequently, for a longer recall period, frequency was easier to answer for most people	Keep	Some participants thought about activity when affected by migraine while others thought about number of days on which this occurred. This results in a situation where answers like "rarely" & "always" actually denote the same experience because chores are not a daily activity for many people	Keep	
PF09d	Was it difficult for you to do errands (e.g., grocery shopping)?	Physical Function: Get out of the Home	Keep	Duplicate	Drop	Duplicate	-	-	-	-
PF09f	Was it difficult for you to do errands (e.g., grocery shopping)?	Physical Function: Get out of the Home	Keep	Participants interpreted errands broadly as things that require leaving the house & using transportation	Revise	Some participants factored in contextual elements, such as whether there was another person who could run errands for them or the level of	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
						importance of a specific err&				
PF09fRev	Was it difficult for you to do errands?	Physical Function: Get out of the Home	-	-	-	-	Keep	Participant responses indicate that the question will capture trigger avoidance & interictal burden	Keep	
PF10d	Was it difficult for you to do your usual activities outside your home?	Physical Function: Get out of the Home	Drop	One participant interpreted this to mean yardwork; two participants included errands in their interpretation & thought this item was redundant with the question about errands; one included leisure activities like going to the movies	-	-	-	-	-	-
PF10f	Was it difficult for you to do your usual activities outside your home?	Physical Function: Get out of the Home	Drop	Duplicate	-	-	-	-	-	-
PF11f	How often were you too tired to do your regular daily activities?	Physical Function: Fatigue /Energy, Physical Function: Usual Activities	Keep	Participants interpreted this question broadly & adaptively to their own lifestyle, as intended	Keep	Participants liked the specificity of this question, but not for 24 hours	Keep	Participant responses indicate they are focusing on fatigue due to migraine rather than other potential causes	Keep	Participants include tiredness not directly related to attacks, but that could result from life with regular migraines, medications used, & other causes

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PF12f	Did you feel tired because of migraine?	Physical Function: Fatigue /Energy	Keep	Participants thought this was an appropriate question, though one person noted that they feel tired all the time & another thought it might be burdensome to answer daily because they don't often experience fatigue	Drop	Participants thought this was easier/more accurate to report for 24 hours; one participant said it can be difficult to attribute fatigue uniquely to migraine itself (& not to medications &/or other factors)	-	-	-	-
PF12s	Did you feel tired because of migraine?	Physical Function: Fatigue /Energy	Keep	Some participants saw fatigue as a significant factor during attacks; others had prodrome or interictal fatigue & thus the "because of migraine" limited their response by implying that it should be an attack symptom	Revise	Some participants focused on attack, but others factored in post-attack fatigue	-	-	-	-
PF12sRev	Did you feel tired?	Physical Function: Fatigue /Energy	-	-	-	-	Keep	4 of 5 participants included tiredness unrelated to migraine; item might benefit from revision	Keep	Participants thought the item should specify 'because of migraine' since they are often tired for other reasons
PF13f	How often has migraine negatively	Physical Function:	Keep	Reviewed by fewer than four participants	Drop	Participants found the item redundant & some	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
	affected your energy level?	Fatigue /Energy				thought this item was more closely related to feelings of desire to do things than to fatigue				
PF14f	How often did you have to miss your regular daily activities because of migraine? Include times that you stopped early or started late.	Physical Function: Usual Activities	Keep	Reviewed by fewer than four participants	Revise	Participants this item highly relevant & closely related to level of disability caused by migraine	-	-	-	-
PF14fRev	How often did you have to miss your regular daily activities? Include times that you stopped early or started late.	Physical Function: Usual Activities	-	-	-	-	Keep	One participant did not absorb the "stopped early/started late" part of the question, which changed their answer on second reading	Keep	
PF15f	How often did you get help from someone else with daily activities or tasks?	Physical Function: Usual Activities	Drop	Participants liked the item, but noted that responses would be affected by contextual factors unrelated to migraine treatment (e.g., access to people who can help, other people's availability,	-	-	-	-	-	-

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				redundant of other questions asking about overall difficulty with task performance						
PF16d	Was it difficult for you to do your usual day-to-day activities?	Physical Function: Usual Activities	Keep	Duplicate	Drop	Duplicate	-	-	-	-
PF16f	Was it difficult for you to do your usual day-to-day activities?	Physical Function: Usual Activities	Keep	Participants interpreted this as intended & thought it was an appropriate question	Keep	Participants noted that the question was broad & could cover many, varied activities	Keep	Some participants included activities requiring concentration	Keep	
PSY01f	How often were you concerned that your migraine attacks would affect other people's lives?	Psychosocial Function: Mood /Emotional State: Anxiety/Worry	Keep	Reviewed by fewer than four participants	Keep	Participants noted the item will not apply to everyone	Keep	Most people thought about family & close companions only	Keep	Participants thought about family & close companions as well as coworkers
PSY02f	How often did you feel frustrated because of migraine?	Psychosocial Function: Mood /Emotional State: Frustration /Irritability	Keep	Three participants found this item very important; two did discuss it	Revise	Participants had mixed views on whether or not frustration overlaps with/is different from irritability	-	-	-	-
PSY02fRev	How often did you feel frustrated?	Psychosocial Function: Mood /Emotional State: Frustration /Irritability	-	-	-	-	Keep		Keep	Participants varied in whether they restricted their answer to migraine-related frustration or frustration from cases such as work
PSY03f	How often did you feel	Psychosocial Function:	Keep	Three participants	Revise	Participants had mixed views on	-	-	-	-

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	irritable because of migraine?	Mood /Emotional State: Frustration /Irritability		found this item very important; two did discuss it		whether irritability & frustration are the same/similar				
PSY03fRev	How often did you feel irritable?	Psychosocial Function: Mood /Emotional State: Frustration /Irritability	-	-	-	-	Keep		Keep	Participants varied in whether they restricted their answer to migraine-related irritability vs. irritability in general (e.g., one said they were 'an irritable person')
PSY04f	How often did you feel good?	Days: Crystal clear day	Keep	All participants understood the question as intended & thought it was good to include; one noted that it might be difficult to recall over a 14 day period	Keep	2 of 5 participants noted they weren't sure if this should be answered only based on migraine or in general	Keep	Participants understood this as intended even while expressing some doubt about the meaning	Keep	
PSY05f	How often did you have enough energy to do everything you planned to do?	Physical Function: Fatigue /Energy	Drop	One participant called this a "dumb question" & one thought it was irrelevant; one participant did not discuss the item; two thought it was relevant	-	-	-	-	-	-
PSY06f	How often were you able to enjoy all or part of a day?	Days: Crystal clear day	Keep	Most participants thought the item was relevant; one participant described the	Keep		Keep	Some participants spontaneously connected this question to the "feel good" question, seeing	Keep	

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
				question as "strange"; one thought				it as similar or better		
PSY07f	How often did you feel sad or depressed because of migraine?	Psychosocial Function: Mood /Emotional State: Depressed/Sad	Keep	Only two participants discussed this item	Revise	Most participants thought it was relevant; a participant with long-standing chronic migraine noted that they didn't consider the question relevant because they "don't let" it depress them anymore	-	-	-	-
PSY07fRev	How often did you feel sad or depressed?	Psychosocial Function: Mood /Emotional State: Depressed/Sad	-	-	-	-	Keep		Keep	Participants varied in whether they restricted their answer to migraine-related depression
PSY08d	Was it difficult for you to take care of any pets you have?	Psychosocial Function: Family /Social /Leisure /Recreation: Care of others/pets	Revise	One person questioned why people & pets were in separate questions; several noted that they either don't have pets or have pets that don't require a lot of care	-	-	-	-	-	-
PSY08f	Was it difficult for you to take care of any pets you have?	Psychosocial Function: Family /Social /Leisure /Recreation: Care of others/pets	Revise	Duplicate	-	-	-	-	-	-

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PSY09d	Was it difficult for you to take care of other people that you usually take care of?	Psychosocial Function: Family /Social /Leisure /Recreation: Care of others/pets	Revise	One participant wanted a more specific definition of what "taking care of" means	-	-	-	-	-	-
PSY09dRev	Was it difficult for you to take care of people or pets that you usually take care of?	Psychosocial Function: Family /Social /Leisure /Recreation: Care of others/pets	-	-	Drop	Duplicate	-	-	-	-
PSY09f	Was it difficult for you to take care of other people that you usually take care of?	Psychosocial Function: Family /Social /Leisure /Recreation: Care of others/pets	Revise	Duplicate	-	-	-	-	-	-
PSY09fRev	Was it difficult for you to take care of people or pets that you usually take care of?	Psychosocial Function: Family /Social /Leisure /Recreation: Care of others/pets	-	-	Keep	Participants understood the item as intended	Keep		Keep	
PSY10d	Was it difficult for you to enjoy social activity with other people?	Psychosocial Function: Family /Social /Leisure /Recreation: Avoiding /Enjoying	Keep	Three participants thought it was important to include; one noted that they avoid socializing in general & selected never, but also noted that this was largely because of migraine; one did not discuss this item	Keep	Most preferred the difficulty scale, citing concerns that frequency would not convey the level of difficulty experienced	Keep	1 of 5 participants was thrown off by the difficulty response scale	Keep	

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PSY10f	Was it difficult for you to enjoy social activity with other people?	Psychosocial Function: Family /Social /Leisure /Recreation: Avoiding /Enjoying	Keep	Duplicate	Drop	Duplicate	-	-	-	-
PSY11f	Did you avoid interacting with other people?	Psychosocial Function: Family /Social /Leisure /Recreation: Avoiding /Enjoying	Drop	Participants noted that their answer would be influenced by practices of avoiding social activity that have nothing to do with migraine	-	-	-	-	-	-
PSY12d	Was it difficult for you to take part in activities you do for fun?	Psychosocial Function: Family /Social /Leisure /Recreation: Ability to participate	Keep	Duplicate	Drop	Duplicate	-	-	-	-
PSY12f	Was it difficult for you to take part in activities you do for fun?	Psychosocial Function: Family /Social /Leisure /Recreation: Ability to participate	Keep	One participant noted their response was influenced by factors other than migraine	Keep	Most participants preferred to respond based on frequency	Keep		Keep	
PSY13d	Was it difficult for you to spend time with family or friends?	Psychosocial Function: Family /Social /Leisure /Recreation: Ability to participate	Drop	Participants found this item to be redundant & least preferred; three participants disliked the restriction to “family & friends”	-	-	-	-	-	-
PSY13f	Was it difficult for	Psychosocial Function:	Drop	Duplicate	-	-	-	-	-	

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	you to spend time with family or friends?	Family /Social /Leisure /Recreation: Ability to participate								
PSY14f	How often did you have to cancel or change your plans for social or recreation activities?	Psychosocial Function: Family /Social /Leisure /Recreation: Avoiding /Enjoying	Keep	Three participants thought the item was relevant; two did not discuss it	Keep	Participants noted strong overlap with other questions about making/keeping plans or missing events	Keep		Keep	
PSY15f	How often did you miss or have to leave a social or leisure event?	Psychosocial Function: Family /Social /Leisure /Recreation: Avoiding /Enjoying	Keep	Reviewed by fewer than four participants	Drop	Most participants noted overlap with other items	-	-	-	-
PSY16d	Was it difficult for you to manage your usual tasks & responsibilities at school or at work?	Psychosocial Function: School or Meaningful Work: Ability to carry out	Keep	Duplicate	Drop	Duplicate	-	-	-	-
PSY16f	Was it difficult for you to manage your usual tasks & responsibilities at school or at work?	Psychosocial Function: School or Meaningful Work: Ability to carry out	Keep	Participants noted that this is important to ask; one thought the question was not specific enough (e.g., should allow people to elaborate on their working situation)	Keep		Keep		Keep	
PSY17f	How often did you feel	Psychosocial Function:	Keep	3 participants thought this was	Keep	Three participants thought this was a	Keep	Responses suggest the	Keep	Responses suggest that successful

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	worried about having a migraine attack?	Mood/Emotional State: Anxiety/Worry		a very important question; one thought it irrelevant		key question to ask; one participant said it wasn't important because they would always be worried due to chronic migraine; one participant thought the question was confusing		question has the capacity to capture adaptation (e.g., people who have become accustomed to migraine may report less worry about having attacks)		treatment that prevents attacks would have an impact on this construct long-term
PSY18f	How often did you worry about how migraine would affect your daily life?	Psychosocial Function: Mood/Emotional State: Anxiety/Worry	Keep	Participants viewed this question as redundant of the broader, simpler question "how often did you feel worried about having a migraine attack" & one thought it was "useless"	Drop	Redundant: All participants identified this question as redundant with other items; Half of participants prefer the broader question (i.e., How often did you how often did you feel worried about having a migraine); one participant thought the question wasn't relevant to ask because they thought this would always be true for people with migraine	-	-	-	-
S00yn	Did you have any migraine symptoms?	Days: Migraine day	-	-	-	-	Keep	Participants understood the question as intended, including one who had had headache due to other causes &	Keep	

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								correctly indicated 'no' for this question		
S01y/n	Did you have a good day?	Days: Crystal clear day	Keep	Participants liked it being included in the questionnaire	Keep	Participants like the inclusion of this item; recognize that it will be subjective	Keep		Keep	Some participants noted they could have symptoms & still have a good day
S03f	Did you have headache, head pain, or throbbing in your head?	Symptoms: Pain	Keep	Duplicate	Drop	Participants thought this was best for 24 hours	-	-	-	-
S03s	Did you have headache, head pain, or throbbing in your head?	Symptoms: Pain	Keep		Keep	Participants wanted to see all symptoms at once, checklist style	Keep		Keep	
S04f	Did you have nausea?	Symptoms: Nausea	Keep	Duplicate	Drop	Participants thought this was best for 24 hours	-	-	-	-
S04s	Did you have nausea?	Symptoms: Nausea	Keep	One participant wondered if it counts as nausea if you don't actually vomit	Keep	Participants wanted to see all symptoms at once, checklist style	Keep		Keep	
S05s	Did you have sensitivity to light?	Symptoms: Sensitivities	Keep	Participants noted both ictal & interictal experiences	Keep	Participants wanted to see all symptoms at once, checklist style	Keep		Keep	
S06f	Did you have sensitivity to sound?	Symptoms: Sensitivities	Keep	Duplicate	Drop	Participants thought this was best for 24 hours	-	-	-	-
S06s	Did you have sensitivity to sound?	Symptoms: Sensitivities	Keep	Participants noted both ictal & interictal experiences	Keep	Participants wanted to see all symptoms at once, checklist style	Keep		Keep	Participant noted that not all sounds are equally bothersome
S07pick	Which of the following symptoms was most	Symptoms	Keep	Bothersomeness seen as impact on lifestyle /ability to function or	Revise	Need to add specification "other than pain"	-	-	-	-

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	bothersome to you?			suffering/ inability to cope with symptom						
S07pickREV	Which of the following symptoms other than pain was most bothersome to you?	Symptoms	-	-	-	-	Keep	1 of 5 participants picked a cardinal symptom; one thought all symptoms are equally bothersome & did not want to pick one	Keep	
S09f	Did you experience aura (e.g., visual spots or flashes of light, skin tingling or numbness)?	Symptoms: Aura	Keep	Duplicate	Drop	Participants thought this was best for 24 hours	-	-	-	-
S09s	Did you experience aura (e.g., visual spots or flashes of light, skin tingling or numbness)?	Symptoms: Aura	Keep	One participant thought the examples provided were misleading	Keep	Participants wanted to see all symptoms at once, checklist style	Keep		Keep	
S10f	Did you vomit?	Symptoms: Nausea	Keep	Duplicate	Drop	Participants thought this was best for 24 hours	-	-	-	-
S10s	Did you vomit?	Symptoms: Nausea	Keep	Participants thought this was an important question to include	Keep	Participants wanted to see all symptoms at once, checklist style	Keep		Keep - low endorsement	Most participants experience this rarely or never (item endorsed by 2 of 10 in waves 3-4)
S11f	Did you have neck pain?	Symptoms: Pain	Keep	Duplicate	Drop	Participants thought this was best for 24 hours	-	-	-	-
S11s	Did you have neck pain?	Symptoms: Pain	Keep	Participants understood as	Keep	Participants wanted to see all	Keep	Participants understood this	Keep	understood

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				intended & thought this was an important question to include		symptoms at once, checklist style		item & were able to respond		
S12f	How often did your migraine symptoms get worse when you moved around?	Symptoms: Sensitivities	Drop	Some participants found the question vague, weren't sure whether to include movement that triggers migraine; one noted that movement could worsen some symptoms and improve others	-	-	-	-	-	-
S13f	Did weather conditions make your migraine attack worse?	Symptoms: Sensitivities	Drop	Duplicate	-	-	-	-	-	-
S13s	Did weather conditions make your attack worse?	Symptoms: Sensitivities	Drop	Participants found the item vague and some were unsure how to respond; one thought it was incomplete (i.e., worse than what?); one thought the question was peculiar because weather conditions don't change that much where	-	-	-	-	-	-

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				they live; one had traveled and could answer both ways depending on which location's weather they included						
S14d	Was it difficult for you to do activities because you were sensitive to light?	Symptoms: Sensitivities, Physical Function: Usual Activities	Keep	Duplicate	Drop	Duplicate	-	-	-	-
S14f	Was it difficult for you to do activities because you were sensitive to light?	Symptoms: Sensitivities, Physical Function: Usual Activities	Keep	Participants thought this was an important item to include	Keep	Participants talked about attack impacts but also photophobia as a trigger	Keep	Responses indicate that the question will capture trigger avoidance & interictal burden	Keep	
S15d	Was it difficult for you to do activities because you were sensitive to sound?	Symptoms: Sensitivities, Physical Function: Usual Activities	Keep	Duplicate	Drop	Duplicate	-	-	-	-
S15f	Was it difficult for you to do activities because you were sensitive to sound?	Symptoms: Sensitivities, Physical Function: Usual Activities	Keep	Reviewed by fewer than four participants	Keep	Participants recognized that the question would be important to include even when they didn't experience phonophobia themselves	Keep		Keep	
S16d	Was it difficult for you to do	Symptoms: Sensitivities, Physical	Keep	Duplicate	Drop	Duplicate	-	-	-	-

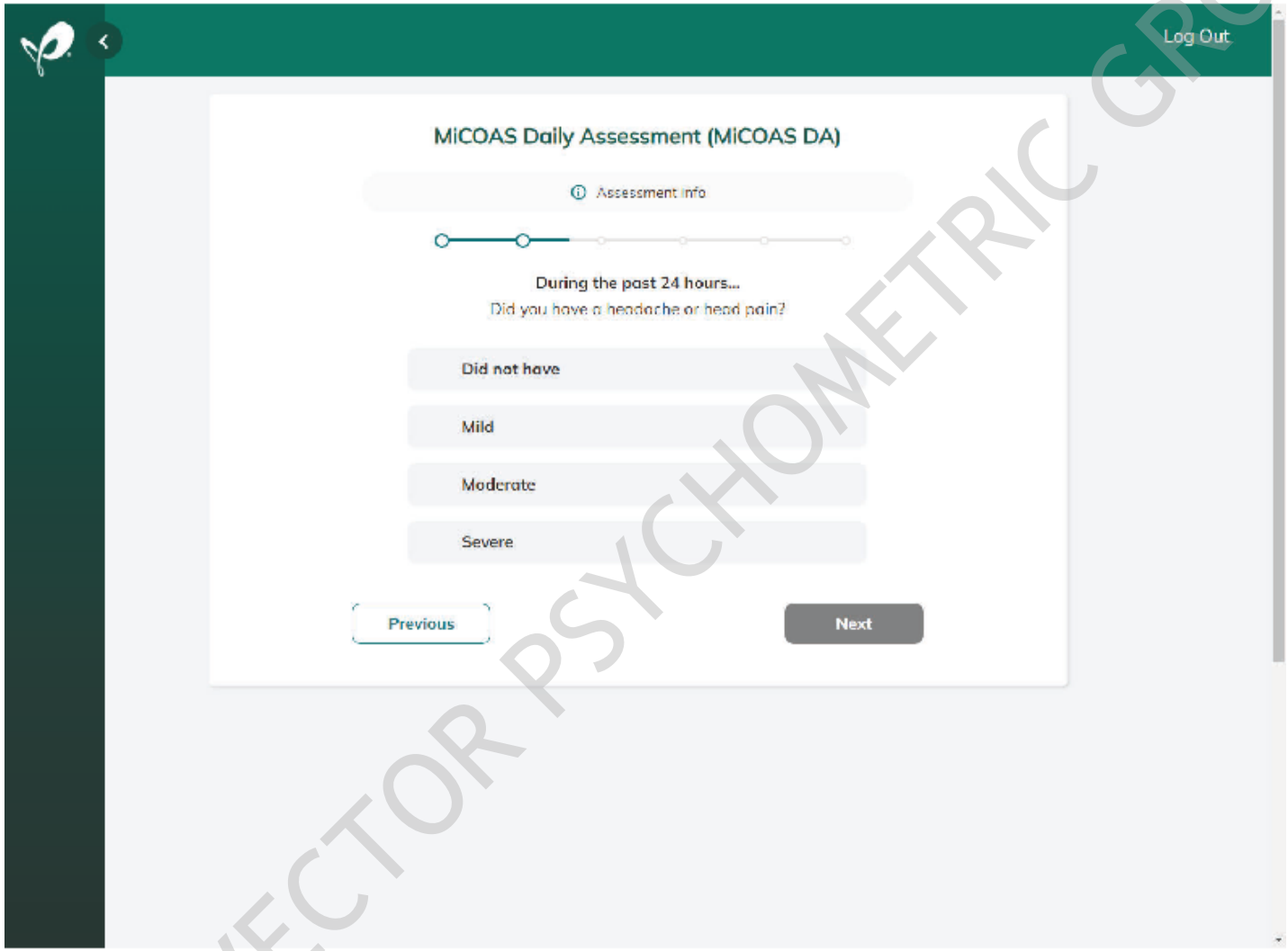
Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
	activities because you were sensitive to smells?	Function: Usual Activities								
S16f	Was it difficult for you to do activities because you were sensitive to smells?	Symptoms: Sensitivities, Physical Function: Usual Activities	Keep	Reviewed by fewer than four participants	Keep	Participants thought it would be important to include even if they don't experience osmophobia; one participant noted that this symptom was relevant only for their worst attacks	Keep		Keep	Responses indicate that the question will capture trigger avoidance & interictal burden, but may also reflect variance due to specific individual exposure to bothersome smells: for example, one participant noted that only cleaning product smells are an issue & these may not be regularly encountered
S17d	Was it difficult for you to do activities because you were sensitive to movement?	Symptoms: Sensitivities, Physical Function: Usual Activities	Drop	Participants found the item to be strongly redundant of other items asking about movement	-	-	-	-	-	-
S17f	Was it difficult for you to do activities because you were sensitive to movement?	Symptoms: Sensitivities, Physical Function: Usual Activities	Drop	Duplicate	-	-	-	-	-	-
S18d	Was it difficult for you to do activities because you were sensitive	Symptoms: Sensitivities, Physical Function: Usual Activities	Drop	As with other items asking about weather, some participants encountered	-	-	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
	to the weather?			difficulties recalling or responding to this item, or thought weather was not important to include						
S18f	Was it difficult for you to do activities because you were sensitive to the weather?	Symptoms: Sensitivities, Physical Function: Usual Activities	Drop	Duplicate	-	-	-	-	-	-
S19d	Was it difficult for you to think clearly?	Symptoms: Mental Acuity	Keep	Participants linked this item to the "mentally slow or foggy " item (S21) but one person recognized that it was asking "in a different way" & another noted that one could have brain fog/slowness & still be able to think clearly	Keep	Participants were divided in whether they thought this item reflected a similar concept to brain fog or difficulty concentrating, but the item resonated with all participants; most participants thought this was a better question for 24 hours	Keep	Participants thought about a variety of activities affected by thinking	Keep	
S19f	Was it difficult for you to think clearly?	Symptoms: Mental Acuity	Keep	Duplicate	Drop	Duplicate	-	-	-	-
S20f	How often did you feel less sharp than when you were not having a migraine attack?	Symptoms: Mental Acuity	Drop	One participant misinterpreted the item; two thought other questions were better; one liked the item;	-	-	-	-	-	-

Item ID	Item Text	Draft Framework Domain / Concept	Wave 1	Wave 1 Note	Wave 2	Wave 2 Note	Wave 3	Wave 3 Note	Wave 4	Wave 4 Note
				one was indifferent						
S21f	Did you feel mentally slow or foggy?	Symptoms: Mental Acuity	Keep	Duplicate	Drop	Duplicate	-	-	-	-
S21s	Did you feel mentally slow or foggy?	Symptoms: Mental Acuity	Keep	Multiple participants liked this item as a daily diary question for best accuracy	Keep	Some participants preferred questions about impairments of functioning to direct question about brain fog	Keep		Keep	
S22days	On how many days did you have head pain because of migraine?	Symptoms: Pain	Drop	Three participants indicated that daily tracking of migraine head pain would be “better” or “easier” because they may have head pain for multiple reasons in a 14-day period	Revise	-	-	-	-	-
S22days Rev	On how many days did you have head pain?	Symptoms: Pain	-	-	-	-	Keep	Participants understood the question as intended	Keep	

APPENDIX C. ECOA INSTRUMENT SCREENSHOTS

Daily Assessment (embedded Adobe PDF document)



7-day Assessment (embedded Adobe PDF document)

14-day Assessment (embedded Adobe PDF document)