

Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Preventive Pharmacological Treatments for Migraine

I. Background and Objectives for the Systematic Review

Migraine is a central nervous system disorder characterized by vascular headaches.¹ Migraine headaches range from moderate to very severe and last from 4 to 72 hours.² Pain from severe migraine headaches can be debilitating.³ In the United States, migraine affects 17 percent of women and 6 percent of men; among children, it affects 5 percent of boys^{4, 5} and 7.7 percent of girls.^{6, 7} The cumulative lifetime incidence of migraine in the U.S. population is 43 percent for women and 18 percent for men.⁸

For 8 to 13 percent of those who experience it, migraine is a chronic condition.⁹ The National Headache Foundation defines chronic migraine as headache, tension-type or migraine, that occurs >15 days per month for at least 3 months.^{10, 11} Chronic migraine significantly affects the physical, psychological, and social well-being of patients and can impose serious lifestyle restrictions.

Migraine also exacts a heavy economic toll. Each year, lost work time and diminished productivity from migraines costs American employers \$225.8 billion or \$1,685 per employee.¹²⁻¹⁴ Forty percent of people who get migraines might benefit from preventive medication,^{5, 15, 16} thus reducing lost productivity and work time. Yet, results from several studies demonstrate that only 12.4 percent of adults with migraine take preventive medication.^{4, 5, 15, 16}

Migraine pain results primarily from increased activity of several agents that regulate blood vessels and sensory function of the brain.¹ In about 15 percent of patients, migraine attacks may be accompanied by aura (visual, sensory, or language symptoms). Other accompanying symptoms may include photophobia (excessive sensitivity to light), phonophobia (fear of loud sounds), osmophobia (hypersensitivity to smells), nausea, or vomiting.²

Preventive medications presumably affect the pathophysiology of migraine.^{17, 18} The four drugs approved by the U.S. Food and Drug Administration (FDA) for migraine prevention in adults come from different drug classes and include propranolol, timolol, topiramate, and divalproex sodium.¹⁹ Botox is the only FDA-approved drug for chronic migraine. The FDA has approved no drugs for migraine prevention in children. Doctors also prescribe off-label drugs (approved for clinical conditions other than migraine) for migraine prevention, which include novel antiepileptic drugs, calcium channel modulators, glutamate blockers, and several other drug classes.^{19, 20}

Ideally, preventive treatment aims to fully eliminate headache pain.²¹⁻²³ Often, however, some degree of pain persists; therefore, treatment success is usually defined by a decrease in migraine frequency of at least 50 percent after 3 months.² In addition to pain relief, preventive drugs can also decrease severity of migraine attacks, normalize brain activity, and eliminate photophobia, phonophobia, nausea, and vomiting.^{24, 25}

Long-term adherence to preventive treatments is low. Between 17 and 29 percent of patients discontinue medication because of adverse effects such as anxiety, nausea, vomiting, sleep time reduction, drowsiness, or weakness.^{26, 27} Drug choices are based on efficacy and adverse effects,

doctors' beliefs about off-label medications, patient preferences, headache frequency, presence of aura, and comorbid conditions.^{10, 21, 22, 28-32} Some guidelines recommend preventive treatments for patients who have five or more migraine attacks per month,¹ while others suggest it for those who experience a headache on most days of the month.^{10, 11, 33} Often, preventive treatment is recommended for only 6 to 9 months; however, researchers have yet to fully examine migraine frequency after discontinuation of preventive treatment.²

Several gaps remain in published literature on preventive treatments for migraines in children and adults. Published systematic reviews have focused on efficacy of specific drugs rather than comparative effectiveness of all available pharmacological and nonpharmacological treatment options.³⁴ Little attention has been paid to the comparative effectiveness of off-label drugs to prevent migraine. Published reviews have not examined quality of life as an outcome. Clinical reviews have compared safety of a few but not all drugs.^{34, 35} No systematic reviews have examined the comparative effectiveness of models of comprehensive or coordinated care for patients with chronic migraine, such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring. Patients with chronic migraine represent the majority of patients seen in headache specialty clinics that practice multidisciplinary coordinated care.⁸

Our review focuses on the comparative effectiveness and safety of the drugs for preventing migraine attacks in children and adults; our results will help inform related treatment recommendations. By the nature of the question, the review focuses on outpatient care.

After discussion with key informants,³⁶ the Evidence-based Practice Center (EPC) formulated a list of eligible pharmacological classes. The EPC will evaluate comparative effectiveness of preventive pharmacological treatments following the principles in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter *Methods Guide*) developed by the Agency for Healthcare Research and Quality (AHRQ).^{37, 38}

II. The Key Questions

Question 1

What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in children and adults?

- a. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment?
- b. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments?
- c. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments?
- d. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone?
- e. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes? How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Question 2

What are the comparative harms from pharmacological treatments for preventing migraine attacks in adults and children?

- a. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment?
- b. What are the harms from preventive pharmacologic treatments when compared to active treatments?
- c. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Question 3

Which patient characteristics predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks in children and adults?

Public Comment

The draft Key Questions (KQs) were posted for public comment on the AHRQ Effective Health Care Program Web site for additional feedback from June 6, 2011, through June 30, 2011.

We made the following changes in the KQs based on the public comments received:

- We clarified the inclusion criteria for active treatments as monotherapy or drug therapy combined with nonpharmacological interventions; we clarified comparators as placebo, active drugs, or active nonpharmacological interventions.
- We added a question addressing the role of dosing regimens and duration of treatments on treatment effects.
- We included additional patient characteristics that could modify treatment effects, such as hormone-based birth control and hormone replacement, the onset of menarche and menopause, obesity, nutritional and dietary factors, aerobic fitness, previous head injury, psychological factors and social/family support system, and concomitant medications for comorbid conditions.
- We expanded the list of patient-centered outcomes to include composite outcomes defined as aggregate improvement of the outcomes on our original list.
- We added “number of moderate to severe headache days” and “number of physician/healthcare professional (HCP) visits” to the list of intermediate outcomes.
- To the list of harms we added medical resource utilization to manage adverse effects (e.g., prescription medication; urgent care/emergency services, physician/HCP visits).
- We clarified the review’s focus as prevention of episodic or chronic migraine as defined by the Headache Classification Committee of the International Headache Society,¹⁰ which does not include migraine variants or migraine equivalents with atypical symptomatic pain in regions other than the head.^{39, 40} Therefore, we would exclude the studies of basilar migraine, childhood periodic syndromes, retinal migraine, complicated migraines, and ophthalmoplegic migraine.⁴⁰ We also clarified our exclusion of hemiplegic migraine, a pathophysiologically distinct disorder with its own classification.⁴¹
- We stated that studies evaluating the efficacy of nonpharmacological treatments or economic outcomes are beyond the scope of this review.

PICOTS Framework

Population(s)

- Children and adults with episodic migraine, chronic daily headache, or chronic migraine as defined by the Headache Classification Subcommittee of the International Headache Society¹⁰ (see below for definitions).
 - Patient characteristics that can modify the effects of pharmacological treatments for preventing migraine attacks in children and adults:
 - Age
 - Gender
 - Pregnancy
 - Hormone-based birth control and hormone replacement
 - The onset of menarche and menopause
 - Race and ethnicity
 - Socioeconomic status
 - Education
 - Family history
 - Access to care, type of care, and residence in rural or urban areas
 - Definition of migraine
 - Presence of aura
 - Headache frequency
 - Prior treatments; overuse of drugs for acute migraine
 - Obesity
 - Nutritional and dietary factors, specifically caffeine
 - Aerobic fitness
 - Previous head injury
 - Psychological factors and social/family support system
 - Comorbidities (depression, bipolar disorder, anxiety, diabetes, hypertension, cardiovascular diseases, others)
 - Concomitant medications for comorbid conditions

Interventions

- Drugs approved by the FDA (such as propranolol, timolol, topiramate, and divalproex sodium) to prevent episodic migraine and to treat chronic migraine (such as Botox).
- Off-label medications available in the United States and previously examined in clinical trials for preventing migraine⁴² (Appendix A Table 1).
- Monotherapy.
- Multidrug interventions.
- Combined pharmacological with nonpharmacological modalities: behavioral interventions with education, exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, and dietary supplements.

Comparators

- Placebo.
- Drug treatments (comparative effectiveness).



- Nonpharmacological treatments: behavioral interventions with education, exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, and dietary supplements.

Outcomes

- Patient-centered outcomes:
 - Reduction of migraine attacks by >50 percent from baseline; primary outcome for the review.
 - Quality of life.
 - Patient satisfaction.
 - Composite patient centered outcomes defined as an aggregate improvement of the aforementioned outcomes.
 - Emergency visits, loss of work or school days; treatment failure.
- Intermediate outcomes:
 - Number of headache days.
 - Number of moderate to severe headache days.
 - Improvement in associated symptoms.
 - Use of drugs for acute migraine (prescribed or over-counter).
 - Physician/healthcare professional (HCP) visits.
- Harms:
 - All reported adverse reactions and effects (such as anxiety, nausea, vomiting, sleep time reduction, drowsiness, or weakness).
 - Treatment discontinuation due to adverse effects.
 - Additional medical resource utilization to manage adverse effects (e.g., prescription medication, urgent care/emergency services, physician/HCP visits).

Timing

- 6 months or more; optimally 12 months
- Any time of occurrence for the harms

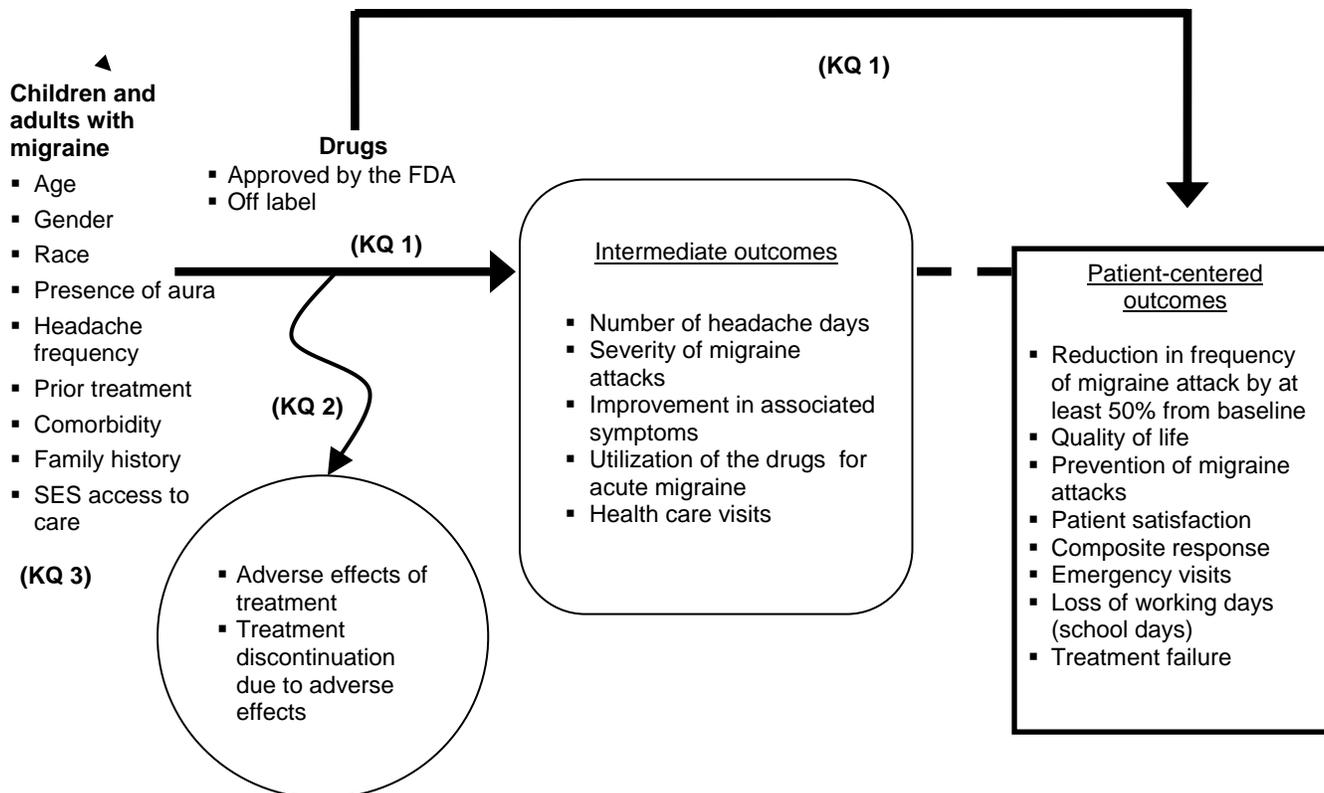
Setting

- Outpatient settings

III. Analytic Framework

The framework in Figure 1 was developed by following the AHRQ *Methods Guide* and the methods of the U.S. Preventive Services Task Force.⁴³⁻⁴⁵

Figure 1. Preventive treatments for migraine



Abbreviations: KQ = key question; SES = socioeconomic status

IV. Methods

The EPC will follow the AHRQ *Methods Guide* to select evidence from controlled trials and observational studies.⁴⁶ Three investigators will independently determine study eligibility according to recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions*.⁴⁷ The EPC will apply the best-available-evidence approach to include observational studies when evidence is not available from the randomized controlled trials (RCTs).⁴⁶

A. Criteria for Inclusion/Exclusion of Studies in the Review

The EPC will review published evidence of the efficacy and comparative effectiveness of preventive pharmacological treatments for migraine.

Inclusion Criteria:

1. Original epidemiologic studies that aimed to examine preventive pharmacological treatments for migraine, including randomized controlled clinical trials, nonrandomized multicenter clinical trials, and observational studies that used strategies to reduce bias.
2. Publication in English.
3. Target population of community-dwelling adults or children with episodic migraine, chronic daily headache, or chronic migraine defined according to International Headache Society criteria for chronic migraine.¹⁰
4. Eligible intermediate and patient-centered outcomes as listed above.
5. Drugs approved by the FDA for migraine prevention and off-label drugs examined in clinical trials.

We will review RCTs that included adults or children with migraine, comorbid headache disorders, or tension headache if they examined prevention of migraine.

Exclusion Criteria:

1. Studies that involved patients with acute migraine or other migraine variants, such as hemiplegic migraines, basilar migraine, childhood periodic syndromes, retinal migraine, complicated migraines, and ophthalmoplegic migraine; hospitalized patients; or patients in emergency rooms. Studies of short-term prevention of migraine, including menstrual migraines.
2. Studies that included some patients with migraine but did not separately report those outcomes.
3. Studies that involved surgical treatments for migraine.
4. Preclinical pharmacokinetic studies of eligible drugs; studies that examined the pathophysiology of migraine reporting instrumental measurements or biochemical outcomes.
5. Studies that did not test the associative hypotheses and did not provide adequate information on tested hypotheses (e.g., least square means, relative risk).
6. Noncomparative studies including case series when the evidence is available from RCTs.
7. Studies that examined eligible drugs on populations with other diseases.

To assess harms of treatments, we will include published and unpublished evidence of the adverse effects of drugs in patients with migraine.⁴⁸ The EPC will define harms as a totality of all possible adverse consequences of an intervention.⁴⁸ The EPC will analyze harms regardless of how authors perceived causality of treatments.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

We will search several databases including MEDLINE[®] (via Ovid and PubMed[®]), the Cochrane Library, and the SCIRUS bibliographic database to find published studies. For completed trials related to the key questions, we will search the FDA website to find medical and statistical reviews of the eligible drugs and clinical trial registries including ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry. Members of the Technical Expert Panel and peer reviewers may suggest additional sources of evidence. The

Scientific Resource Center will request Scientific Information Packets from appropriate manufacturers (shown in Appendix A, Table 2) per usual procedures. The EPC will not contact the investigators of the primary studies for missing data or clarifications.

The EPC has developed an *a priori* search strategy based on relevant medical subject heading (MeSH[®]) terms, text words, and weighted word-frequency algorithms to identify related articles. Exact search strategies can be found in Appendix A Table 3).

Searches for relevant literature will involve several steps: (1) evaluating previously published systematic reviews,⁴⁹ (2) conducting a comprehensive literature search in the databases listed above to retrieve the references that will be stored in a master library using EndNote[®] reference-management system, (3) screening abstracts against the inclusion/exclusion criteria listed above, and (4) retrieving and reviewing full-text articles on eligible studies to determine potential inclusion in the synthesis. We will update the literature search while the draft is under peer and public review.

To ensure consistency, all evaluators will attend a training session to discuss inclusion and exclusion criteria before the abstract review. In addition, the project team will meet after reviewing the first 25 abstracts to detect, discuss, and resolve disagreements and to further standardize the approach. A randomly selected 10 percent sample of excluded randomized studies will be reviewed by the project director to verify appropriate application of the exclusion criteria. We will document each recommended, included, and excluded study in the master library. We will develop a coding scheme to record and account for our reasons for excluding articles at full text review.

C. Data Abstraction and Data Management

Researchers will use standardized forms to extract data. We will conduct a double independent quality control for the data extracted from RCTs; one reviewer will abstract an article and a second will review the abstracted data for accuracy. Errors will be assessed by comparing established ranges for each variable and data charts from the original articles. Any detected discrepancies will be discussed. We will abstract the information relevant to the PICOTS framework. We will abstract minimum datasets to reproduce the results presented by the authors. For categorical variables we will abstract the number of events among treatment groups to calculate rates, relative risk, and absolute risk differences. Means and standard deviations of continuous variables will be abstracted to calculate mean differences with a 95 percent confidence interval (CI).

For RCTs in the quantitative analysis set, we will abstract the number randomized to each treatment group as the denominator to calculate estimates by applying intention-to-treat principles. We will abstract the time when the outcomes were assessed as weeks from randomization and the time of followup after treatments.

We will abstract inclusion and exclusion criteria, drug regime and doses, and patient characteristics including demographics and factors that can modify treatment effects.

D. Assessment of Risk of Bias in Individual Studies

We will evaluate the risk of bias in individual studies according to recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions*.⁴⁷ First, we will classify the study design as interventional (an RCT, a nonrandomized controlled clinical trial, or a nonrandomized uncontrolled clinical trial) or observational (cohort or case-control studies, cross-sectional studies, or case series).

Then, using the criteria from the Cochrane tool for bias in interventional studies, we will evaluate random allocation of the subjects to the treatment groups, adequacy of allocation concealment and randomization, masking of the treatment status, intention-to-treat principles, and selective outcome reporting. We will assume a low risk of bias when RCTs meet all the quality criteria; a moderate risk of bias if at least one of the quality criteria was not met; and a high risk of bias if two or more quality criteria were not met. We will conclude there is an unknown risk of bias for the studies with poorly reported quality criteria.

For observational studies, we will evaluate strategies to reduce bias in study design and analysis, including adjustment for confounding and valid measurements of the outcomes.

E. Data Synthesis

We will summarize the results into evidence tables. Our priority will be patient-centered outcomes, such as reduction in migraine attacks by greater than 50 percent from baseline, quality of life, patient satisfaction, and composite definitions of response. We will incorporate risk of bias in individual studies into the synthesis of evidence by using individual quality criteria rather than a global score or a ranking category of overall quality.^{50, 51} Synthesis of evidence about benefits of the treatments will be restricted to studies with low risk of bias.²¹

We will synthesize the evidence according to population characteristics that could modify treatment effect, including age, sex, race, duration of migraine, baseline frequency and severity of acute migraine attacks, presence of aura, previous drug treatments, history of drug overuse, and other patient characteristics described in the PICOTS framework. We will address the role of comorbidities and concomitant treatments in association with patient-centered outcomes. When possible, based on the reporting in original studies, we will conduct subgroup and sensitivity analyses according to patient characteristics, drug dose, and timing of followup.

Using Meta-Analyst⁵² and STATA^{®53} software at a 95 percent CI, we will calculate the relative risk and absolute risk difference from the abstracted events, and the mean differences in continuous variables from the reported means and standard deviations. We will use a logarithmic scale to analyze the adjusted regression coefficient with a standard error of association between treatments and patient-centered outcomes. We will use correction coefficients and intention to treat as recommended calculations for missing data.⁴⁷

Pooling criteria for KQs 1 and 2 will include the same active drug treatments and comparators and the same definitions of the outcomes. Standardized mean differences will be calculated for different continuous measures of the same outcome. We will not pool RCTs with nonrandomized studies, studies of children with those of adults, or studies of different pharmacological drug classes with each other.

We will test consistency in the results by comparing the direction and strength of the association⁵⁴ and will assess heterogeneity in results with Chi-square and I-square tests.^{55, 56} We will explore heterogeneity with meta-regression and sensitivity analysis and report the results from random effects models only.⁵⁷ We will choose the random effects model to incorporate in the pooled analysis any differences across trials in patient populations, baseline rates of the outcomes, dosage of drugs, and other factors.⁵⁸ We plan to explore heterogeneity by quality criteria of RCTs, disclosed conflicts of interest, study sponsorship, dose and duration of drug treatments, time of followup, inclusion of minorities, proportion of women and elderly adults, and other patient characteristics described above. To avoid ecological fallacy, we will not use patient level variables (for example, mean age or body mass index) in meta-regression.⁵⁷

The number needed to treat to achieve one event of a patient-centered outcome will be calculated as reciprocal to absolute risk differences (ARD) in rates of outcome events in the active and control groups.^{53,59} We will calculate means and 95 percent CIs for the number needed to treat as reciprocal to pooled ARD when ARD is significant.⁶⁰ The number of avoided or excess events (respectively) per population of 1,000 is the difference between the two event rates multiplied by 1,000.

F. Grading the Evidence for Each Key Question

We will assess strength of evidence according to risk of bias, consistency, directness, and precision for each patient-centered outcome and treatment discontinuation due to harms.⁵⁴ When appropriate, dose-response association, presence of confounders that would diminish an observed effect, strength of association, and reporting bias will also be included. We will evaluate the strength of the association, defining *a priori* a large effect when relative risk is >2 or <0.5 and a very large effect when relative risk is >5 or <0.2.⁴⁷ We will define low magnitude of the effect when relative risk is significant but <2.

We will assess reporting bias defined as publication bias, selective outcomes reporting, and multiple publication bias. We will not perform formal statistical tests quantifying the biases.⁶¹

We will define high level of evidence on the basis of consistent findings from well-designed RCTs (Table 1). The EPC will downgrade strength of evidence to moderate if at least one of the four strength-of-evidence criteria was not met, for example the studies have moderate risk of bias or the results not consistent or precise. We will downgrade strength of evidence to low if two or more criteria were not met. We will define evidence as insufficient when a single study with high

Table 1

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit a conclusion.

Risk of bias examined treatment effects or associations

G. Assessing Applicability

Applicability of the population will be estimated by evaluating the selection of adults or children with migraine in observational studies and clinical trials.⁶² Studies of community-dwelling adults or children that were followed up for 6 months or longer with drug treatments will have high applicability. Large observational cohorts based on national registries, population-based effectiveness trials, and nationally representative administrative and clinical databases will have high applicability.

V. References

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VI. Definition of Terms

- Migraine (as defined by the Headache Classification Subcommittee of the International Headache Society):¹⁰
Repeated attacks of headache lasting 4 to 72 hours in patients with a normal physical examination, no other reasonable cause for the headache, and:
 - At least two of the following features:
 - Unilateral pain
 - Throbbing pain
 - Aggravation by movement
 - Moderate or severe intensity
 - Plus at least one of the following features:
 - Nausea/vomiting
 - Photophobia and phonophobia
- Episodic migraine as an indication for preventive treatment:
 - Five or more attacks a month¹
 - Three or more attacks a month¹

- Definitions of chronic migraine (can be chronic from onset or transformed from episodic migraine):
 - FDA:
 - Chronic migraine is defined as having a history of migraine and experiencing a headache on most days of the month.³³
 - Revised International Headache Society criteria for chronic migraine:¹⁰
 - 1.5.1. Chronic migraine
 - A. Headache (tension-type and/or migraine) on ≥ 15 days per month for at least 3 months
 - * Characterization of a frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day by day for at least 1 month.
 - B. Occurring in a patient who has had at least five attacks.
 - C. On ≥ 8 days per month for at least 3 months headache has fulfilled C.1 and/or C.2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura.
 - 1. Has at least two of a–d
 - a. Unilateral location
 - b. Pulsating quality
 - c. Moderate or severe pain intensity
 - d. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) and at least one of (1) or (2):
 - (1). Nausea and/or vomiting
 - (2). Photophobia and phonophobia
 - 2. Treated and relieved by triptan(s) or ergot before the expected development of C.1 above
 - D. No medication overuse[†] and not attributed to another causative disorder

[†]Headache Classification Committee criteria for a medication overuse headache (A8.2)¹⁰

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose

potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.