Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Treatment for Phenylketonuria

Amendment Date(s) if applicable: March 29, 2011

(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Background

Phenylketonuria (PKU) is a metabolic disorder due to pathologic mutations in the gene that encodes a liver enzyme called phenylalanine hydroxylase (PAH). This deficiency leads to a buildup of an essential amino acid called phenylalanine (Phe) in the blood and tissues because PAH is required for the conversion of Phe into tyrosine, a neutral amino acid.[1] This abundance of Phe may cause intellectual disability, delayed speech, seizures, and behavior abnormalities.[2-4] Classic PKU is the most severe form of PKU, with a Phe concentration of >20 mg/dL at the time of diagnosis.[5] Maternal PKU occurs when PKU is not adequately treated during pregnancy, resulting in deleterious effect on the fetus, such as microcephaly. During a pregnancy, the placenta has higher concentrations of amino acids, including Phe. The concentration of Phe in the placenta amplifies the levels of Phe and thus the teratogenic effects on the fetus.[4,6]

Approximately 1 in every 13,500 to 19,000 infants in the United States is born with PKU.[5,7] The incidence of PKU varies based on ethnicity, with a higher prevalence seen among Native American and Caucasian individuals.[5,8] Detecting PKU early in life is crucial in order to prevent intellectual disability, so newborn screening for this disorder has become mandatory in the United States, although the implementation is inconsistent.[9]

Treatment for PKU is focused on maintaining a safe level of Phe concentration in the blood, promoting normal growth and health through life, and preventing intellectual disability, although there is no consensus on the optimal levels among clinics or across countries.[7,10] Patients with classic PKU require lifelong treatment, whereas patients with more mild forms of PKU may not require as stringent of treatment.[5,11] The main treatment has historically been for affected individuals to follow a Phe-restricted diet. This includes low-Phe medical food/formulas, which are semi-synthetic and adequate in other nutrients. The diet has minimal animal products, and consists of mostly vegetables and fruits that are high in carbohydrates, low in saturated and polyunsaturated fat, and low in cholesterol.[10] Because this diet restricts food from animal sources, it is possible for nutritional deficits (mainly from a lack of natural protein) to result.[10,12] Compliance with the diet can be difficult for patients and their families because the medical food/formula is unpalatable and expensive.[2-4] In addition to the low-Phe diet, many patients take amino acid supplements, vitamins, and minerals daily to replace other essential amino acids and nutrients absent from the restricted diet.[10] Patients with PKU may consume protein substitutes, but like the diet, they also have a poor taste.[13] Such supplementation could include large neutral amino acids (LNAAs), which primarily

decrease the brain Phe concentration by competing with Phe for transport across the blood-brain barrier.[14,15] LNAAs inhibit Phe influx into the brain as well as lower the blood-Phe concentration, preventing neurological damage.[16] In addition, the supplement may reduce the risk of depression by increasing tyrosine and thus decreasing dopamine in the brain.[16,17] Despite potential benefits, there is uncertainty about the efficacy and safety of the long-term use of LNAAs and the target patient population, including the appropriateness of its use in pregnant women with PKU.

In 2007, the United States Food and Drug Administration (FDA) approved sapropterin dihydrochloride (Kuvan, formerly known as Phenoptin) for the treatment of PKU under the stipulation that studies continue regarding the drug's efficacy and long-term safety. Current research on sapropterin dihydrochloride, the first pharmacologic treatment for PKU, suggests that it controls Phe concentrations and increases dietary Phe tolerance, potentially allowing a relaxation of the low-Phe diet (should be used in conjunction with diet).[18] Its mechanism of action is as a cofactor of the phenylalanine hydroxylase enzyme, thus increasing the activity level of the enzyme, leading to an increase in the amount of Phe that can be converted to tyrosine. Not all patients with PKU respond to sapropterin dihydrochloride; in clinical trials, approximately 20-56% of patients responded to treatment, and responsiveness can only be determined by a therapeutic trial.[5,19] The most common adverse events are minor, including headache, upper respiratory tract infection, rhinorrhea, pharyngolaryngeal pain, and gastrointestinal complaints, although these events are not significantly different compared to those experienced by individuals not on the drug. The long-term effects of sapropterin dihydrochloride have not been studied.[5,20-21] The role of sapropterin dihydrochloride in pregnant women with PKU is still unclear, but given the benefits of the drug in other groups of individuals with PKU, this is a population of patients with PKU that merit further study.[5] Like pregnant women, safety and efficacy of the use of sapropterin dihydrochloride in children under the age of 8, including infants, is unknown.[5,19]

It is well known among clinicians that negative fetal consequences occur in unplanned pregnancies in women with PKU, but management of maternal PKU is not formally standardized.[4] The guidelines from a National Institutes of Health (NIH) Consensus Development Conference suggest that management, in addition to traditional approaches, should include home-testing of Phe concentration levels for pregnant woman with PKU and outreach programs for pregnant woman with PKU and women with PKU who are of childbearing age to reinforce social support and positive attitudes about a controlled diet.[7] Genetic counseling for pregnant women with PKU is imperative to prevent negative fetal outcomes.[22] Management of the diet for some pregnant women is difficult to implement because individuals with mild forms of PKU are not often followed by healthcare professionals with expertise in PKU.[4] Management of the diet in adolescent girls with PKU is also difficult because they are not always monitored for high-risk behavior, such as sexual activity, drug use, and alcohol consumption.[4] In addition to the strict diet, in order to prevent malnourishment of the fetus, calcium, phosphorus, iron, folic acid, vitamin B_{12}, zinc, and selenium should be supplemented throughout the pregnancy.[22]

Scan of the Literature

A small body of literature reports on aspects of treatment of PKU; initial searches in the PubMed system identified just short of 2,000 papers published since 1963. The majority of the literature reports on aspects of the widely implemented low-Phe diet, but a smaller portion regards the use of sapropterin dihydrochloride in the management of PKU.

A recent Cochrane review of 4 RCTs of dietary interventions for PKU notes that blood Phe concentrations were lower in those on more restricted diets (an RCT comparing diet to the total absence of a diet cannot be done for ethical reasons) and that the low-Phe diet was beneficial for intelligence quotient (IQ); however, there remains uncertainty about the optimal Phe levels or when the diet could be relaxed, if at all.[23] Another recent Cochrane review of only 2 RCTs regarding use of sapropterin dihydrochloride reports that blood Phe concentration decreased and Phe tolerance increased in the treatment group.[18] Adverse events found included upper-respiratory tract infection, headache, vomiting, abdominal pain, diarrhea, pyrexia, and bone pain. These reviews only looked at RCTs and did not include observational studies or examination of subgroups. As of 2009, there were thirteen clinical trials yielding promising results of this drug, but long-term safety and efficacy are still not clear, as revealed by Hegge and colleagues.[5] While there is a growing body of evidence pertaining to the use of sapropterin dihydrochloride, there continues to be clinical uncertainty in the optimal management of the drug in children less than 4 years old or in pregnant women.[5]

Summary

PKU is a metabolic disorder that typically requires life-long management. Diagnosis is typically made by newborn screening, whereupon a treatment plan is implemented to prevent intellectual disability and other symptoms of the disease. A Phe-restricted diet is the primary treatment, with the addition of sapropterin dihydrochloride in recent years as a pharmacological aid to the traditional diet. Treating the disease also involves monitoring Phe concentrations in the blood on a regular basis, as well as adherence to a strict diet for women of childbearing age to prevent cognitive impairment in potential offspring. Existing literature cites few RCTs that predict with certainty the long-term effects of pharmacological treatment or the desired Phe concentration ranges for various patient populations.

II. The Key Questions

We developed the key questions (KQ) for this review based on input from key informants and experts. The questions were posted to the Effective Health Care Program Web site for public comment for approximately 4 weeks. Comments received on the posted KQs will be used in framing the report.

The comments generally supported our choice of key questions and indicated that the literature is sparse in this topic area. Comments also addressed some word choices and the need for clarification of some variables and outcomes.

Based on a comment suggesting that "cognitive decline" may not be the most accurate outcome description, we changed the phrase to "cognitive impairment," which is a more targeted and measureable outcome. We joined KQ1 with KQ2 to become KQ1a and KQ1b since the two are closely related and address the relationship between Phe levels and cognitive impairment.

We added the subgroup, "adults 21+ years old with PKU", to our effectiveness questions based on the public comments. We had addressed every other possible group of individuals with PKU, so it was logical to include this group as well. One comment suggested we look for studies where LNAAs are used instead of dietary therapy, not in addition to dietary therapy. We decided not to change this in KQ5 and KQ6 because our clinical experts indicated that LNAAs are offered to families who may have difficulty with adherence to the diet, but they would not consider offering the supplements instead of the diet because LNAAs are not an equivalent alternative.

Based on public comments, we clarified the wording of KQ7. It was previously unclear whether we intended to look for studies that included any one or more of the listed characteristics or all of the characteristics together. We intended the former, so we listed them as examples. Additional comments focused on the need for additional primary research, which we will keep in mind when writing the future research section of the eventual report.

Key Questions

KQ1a. What is the evidence that any specific phenylalanine (Phe) levels are optimal for minimizing or avoiding cognitive impairment in individuals with phenylketonuria (PKU)?

KQ1b. What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?

KQ2. What is the comparative effectiveness of sapropterin dihydrochloride with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status? Subgroups include the following:

- **a.** infants with PKU
- **b.** children ages 2 to 12 years old with PKU
- **c.** adolescents ages 13-21 years old with PKU
- **d.** adults 21+ years old with PKU

KQ3. What is the comparative effectiveness of sapropterin dihydrochloride with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

KQ4. What is the comparative effectiveness of large neutral amino acids (LNAAs) with dietary intervention versus dietary intervention alone for affecting outcomes including

measures of cognition (including executive function), quality of life, and nutritional status? Subgroups include the following:

a. infants with PKU
b. children ages 2 to 12 years old with PKU
c. adolescents ages 13-21 years old with PKU
d. adults 21+ years old with PKU

KQ5. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

KQ6. What are the harms, including adverse events, associated with the use of sapropterin dihydrochloride, LNAAs, and/or dietary intervention in individuals with PKU?

KQ7. What is the evidence for the effectiveness of the addition of sapropterin dihydrochloride or LNAAs to dietary intervention for affecting outcomes in subgroups of patients? The following are examples of potential defining characteristics of subgroups:

- demographic
- clinical
- genotypic
- adherence

PICOTS

Population

- Infants, children ages 2 to 12 years, adolescents ages 13-21 years, adults 21+ years, and pregnant women diagnosed and being treated for PKU. We will capture data on the type of PKU of patients in each study, including severity.

Interventions

- Pharmacological interventions, in addition to dietary intervention
  - Sapropterin Dihydrochloride
  - Large Neutral Amino Acids (LNAAs)

Comparators

- Dietary intervention only, including
  - Medical foods/formulas
  - Nutritional supplements
  - Phenylalanine restricted diet

Constructs for outcomes and adverse events to be extracted

At this time, we have identified a set of constructs for outcomes that we will assess in this review. As suggested by our TEP, we will look for each of these constructs and report on the way they are operationalized by the researchers. In this way, we intend to capture the maximum information available in light of the rarity of the condition and the paucity of treatment literature.

Primary outcomes in patient

1. Decreasing Phe levels in the blood

2. Improved nutritional status
3. Quality of life
4. Increased Phe tolerance
5. Normal growth
6. Cognitive development
7. Cognition, including measures of executive function

Primary outcomes in infant of PKU mother

1. Prevention of neurologic impairment
2. Prevention of cardiac defects
3. Normal growth
4. Typical cognitive development

Harms and adverse events, including but not limited to the following

1. Side effects from drug therapies
2. Nutritional deficiencies from dietary restrictions
3. Reduction in/negative influences on quality of life

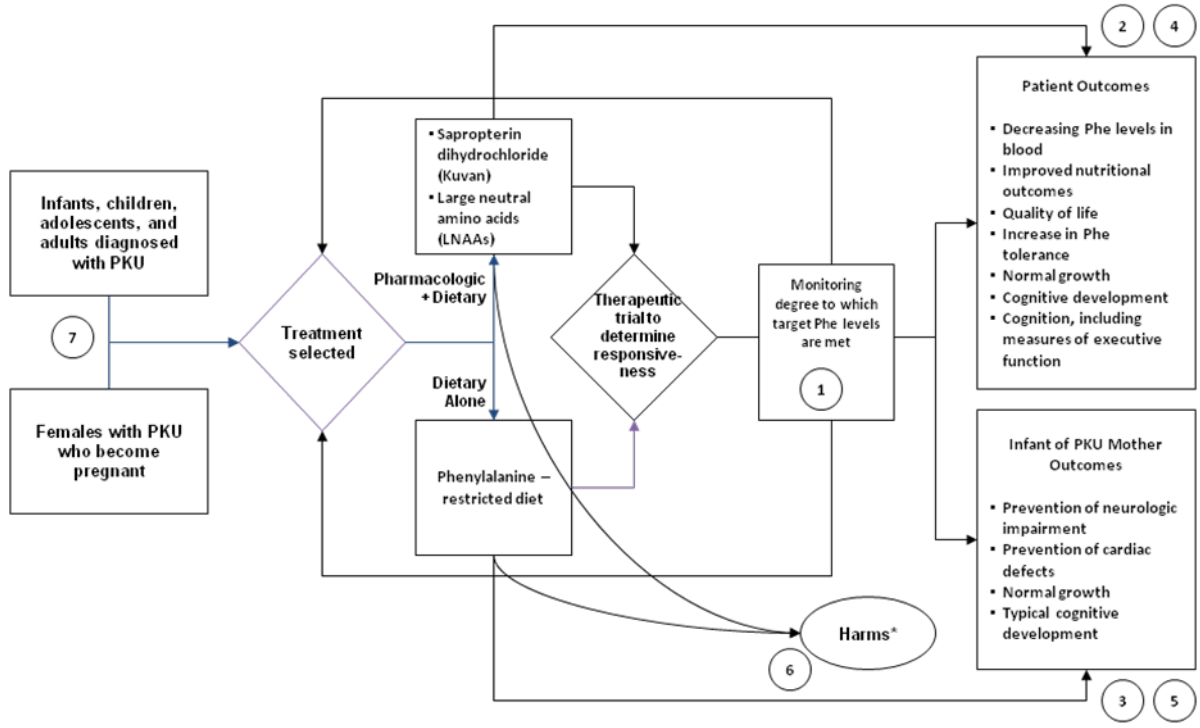
Timing

- We will consider all time frames without restriction. Most studies currently consider outcomes that occur within months of treatment, although some will continue for a few years. Ideally, longer term outcomes would be available, but such studies are exceedingly rare. Therefore, we have placed no limits on this factor in order to review all possible information.

Setting

- We will consider all settings

III. Analytic Framework



*Encompasses a full range of specific negative effects, including the narrower definition of adverse events. Can include costs, medical side effects, poor QOL, etc.

IV. Methods

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

Table 1 lists the inclusion/exclusion criteria we selected based on our understanding of the literature, the topic refinement phase, input from content experts, and established principles of methodological quality.

As an inclusion criterion, we will set the cut-off level for the study size of RCTs and prospective cohort studies at a minimum of 10 participants. PKU is an exceedingly rare condition and therefore recruitment into research studies is slow and challenging. Most studies enroll between one and 20 pariticipants. Although individual studies may lack power to definitively show effectiveness using traditional statistical methods, we will use appropriate methods for studies with small samples, individually and in combination, to utilize as much data as possible.

We will include only English language studies. Our technical experts concur that very few studies on PKU are published in other languages, and that those that are also are published in English.

Table 1: Inclusion/Exclusion Criteria

Category	Criteria
Study population	Humans only: Infants with *PKU <2 years of age Children with *PKU 2-12 years of age Adolescents with *PKU 13-21 years of age Pregnant women with *PKU Adults with *PKU 21+ years of age * PKU will be reported as operationalized by study authors.
Time period	All years
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs Controlled trials, prospective trials with historical controls, prospective cohort studies with N ≥ 10 Case series and retrospective studies with N ≥ 20 and harms or data relevant to KQs 1 & 2 Other criteria Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results Studies must include at least one outcome measure of an outcome listed in the PICOTS Studies must address one or more of the following for treatment for PKU: Sapropterin Dihydrochloride (Kuvan) Large Neutral Amino Acids (LNAAs) Dietary intervention (medical foods/formulas, nutritional supplements, Phe-restricted diet) Studies must include extractable data on relevant outcomes

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

Searching the Literature. To ensure comprehensive retrieval of relevant studies of treatment for PKU, we will use five key databases: the PubMed medical literature database, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), the EMBASE Drugs & Pharmacology database, the National Agricultural Library (AGRICOLA) interface database, and PsycINFO (CSA Illumina interface). The search strategies for each of these databases will focus specifically on terms related to PKU and its treatment, including key words, subject headings, and a combination of subject headings and/or key words (e.g., phenylketonuria, pharmaceutical preparations, dietary therapy).

During our reviews of abstracts and full-text articles, we will update the literature search quarterly by adding relevant studies as needed. We will also update the search when the draft report is submitted and add relevant studies as needed while the draft report is undergoing peer review. We will also incorporate studies that meet our inclusion criteria or are relevant as background material that may be identified by both public and peer reviewers.

We will carry out hand searches of the reference lists of recent systematic reviews or meta-analyses of PKU treatment; the investigative team will also scan the reference lists of articles that are subjected to the full-text review for studies that potentially could meet our inclusion criteria.

Searching for Grey Literature and Regulatory Information. Our research team will locate regulatory information from the Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency. We will look for information regarding the following treatment:

- Sapropterin dihydrochloride: Kuvan®

Initially, we will review regulatory data against published data to attempt to identify discrepencies. We will develop methods to incorporate relevant data from searches of the grey literature into the review as appropriate, and assess the impact of any lack of publication of regulatory information.

Initial Review of Abstracts. An abstract review form will be developed and pre-tested by all team members. It will be revised as needed before full abstract review begins. We will review all the titles and abstracts identified through our searches against our inclusion/exclusion criteria. Each abstract will be reviewed by at least two members of the investigative team. When differences between the reviewers arise, we will err on the side of inclusion. For studies without adequate information to make the determination, we will retrieve the full-text articles and review them against the inclusion/exclusion criteria.

Retrieving and Reviewing Articles. We will retrieve and review full articles that meet our predetermined inclusion/exclusion criteria or for which we have insufficient information at the abstract phase to make a decision about eligibility. A full text review form will be developed and pre-tested by all team members. Each article will be reviewed by at least two members of the investigative team. When differences between the reviewers arise, we will err on the side of inclusion.

After reviewing a sample of relevant articles, the Methods and Content Leads will design the data extraction forms and evidence tables for testing by the team. These forms will undergo revisions as needed until the team is satisfied that they are appropriate and then will be used to extract data from all full text articles that meet inclusion criteria.

We will develop a simple categorization scheme for coding the reasons that articles, at the stage of full review, are not finally included in the report. The abstractor will note the reason for exclusion on the article cover page. We will then record that code in an EndNote® (Thomson Reuters, New York, NY) bibliographic database so that we can later compile a listing of excluded articles and the reasons for such exclusions.

C. Data Extraction and Data Management

Deciding Which Outcomes Are To Be Extracted. With the support of our TEP, we identified critical constructs for outcomes related to PKU treatment. We will capture all validated outcome measures available within these constructs and report on their operationalization as part of the data extraction and analysis. With such a rare disease and a paucity of literature, it is ideal to remain flexible in which outcomes are sought in order to capture and utilize as much data as possible.

Monitoring Study Reviews. As reviews are conducted, the Project Coordinator and Administrative Support staff will track the status of each article. The Project Coordinator will maintain a master list of all the retrieved articles that indicates who was assigned the initial review and data extraction, its status in the review and data-extraction process, the results of the review (e.g., whether it was selected for a full review or the reason why it was not, the date the initial review and extraction were completed, etc.).

The Project Coordinator will also monitor the progress of reviews. During the review phase of the study, the Project Coordinator will report to the Methods and Content Leads on a weekly basis the number of abstracts and articles out for review, will contact the reviewers to determine their progress and to collect completed reviews, and will assess each evidence table entry for completeness. Twice a month, the project staff will meet to discuss the results and progress to date; review cases that have been particularly difficult to classify, abstract, interpret, or adjudicate; and address any questions the review team may have. In addition, all abstractors and other project team members will routinely use e-mail to communicate any concerns or questions that arise during the course of the reviews.

D. Assessment of Methodological Quality of Individual Studies

Assessing Study Quality. The quality of individual studies will be assessed by using specific assessment tools for each type of study. For RCTs, the fundamental domains will include: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, and freedom from selective reporting bias.

For observational studies, we will assess three broad characteristics: 1) the selection of the study groups; 2) the comparability of the study groups; and 3) either treatment exposure or the outcome of interest. For example, for a cohort study, the fundamental criteria will include: representativeness of the cohort, selection of a nonexposed cohort, ascertainment of treatment exposure, outcome of interest, comparability of cohorts,

assessment of outcome, adequate duration of followup, and adequate followup of the cohort. Other sources of bias would include imbalances in baseline measures, source of funding, stopping treatment early for benefit, and appropriateness of crossover design.

Decision rules regarding detailed use of the quality-assessment tools will be specified a priori by the review team. Two senior staff will independently perform quality assessment of the included studies; disagreements will be resolved through discussion or third-party adjudication as needed. We will record quality assessments in tables, summarizing for each study.

E. Data Synthesis

Preparing Evidence Tables. We will enter data into evidence tables by using predetermined abbreviations and acronyms consistently across all entries. Data entered into the evidence tables will be entered as they are presented in the papers. Decisions about transforming any data points will be made as an analytic plan is developed that is appropriate to the available data. The dimensions (i.e., areas of special focus, or the columns) of each evidence table may vary by KQ as appropriate, but the tables will contain some common elements, such as author, year of publication, study location (e.g., country, city, state) and time period, population description, sample size, and study type (e.g., RCT, prospective observational study, etc).

Data Analysis. Inference for several KQ will be, at least in part, model-based. We anticipate that the evidence garnered from the literature search described above will consist of small randomized clinical trials, retrospective studies, observational studies, and regulatory information. Because the combination, weighting and synthesis of potentially disparate sources of evidence is partly subjective, we want to formalize the process in the form of a meta-analytic model that makes the procedure explicit and verifiable. Using a Bayesian meta-analysis approach,[24] we can account for heterogeneity among types of information and among individual studies,[25] and include all relevant sources of uncertainty[26] in a unified modeling framework. In particular, assumptions regarding the quality of information sources and how they are weighted relative to one another (usually the primary source of subjectivity) can be formally incorporated as prior information, and its effect quantified. A major advantage of Bayesian hierarchical modeling in this context is the allowance for "partial pooling" of data sources, which shares information among studies without having to assume that studies are identical to each other.[27] We hope that such a model can be a useful tool for decision-makers that integrates available empirical evidence while accounting for that result from incomplete information.

F. Grading the Evidence for Each Key Question

Assessing the Strength of Evidence. We will also utilize explicit criteria for rating the overall strength of the collective evidence on each KQ into qualitative categories (e.g., low, moderate, high, insufficient). We will use established concepts of the quantity of

evidence (e.g., numbers of studies, aggregate ending sample sizes), the quality of evidence (from the quality ratings on individual articles), and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge. We will make these judgments as appropriate for each of the main KQs and any subquestions related to specific outcomes.

The strength of evidence evaluation will be that stipulated in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[28] which emphasizes the following four major domains: risk of bias (low, medium, high), consistency (inconsistency not present, inconsistency present, unknown or not applicable), directness (direct, indirect), and precision (precise, imprecise). Risk of bias is derived from the quality assessment of the individual studies that addressed the KQ and specific outcome under consideration. Each key outcome on each comparison of interest will be given an overall evidence grade based on the ratings for the individual domains.

The overall strength of evidence will be graded as "high" (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect), "moderate" (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate), "low" (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate), or "insufficient" (indicating that evidence is either unavailable or does not permit estimation of an effect).[29] When no studies are available for an outcome or comparison of interest, the evidence will be graded as insufficient.

Two senior staff will independently grade the body of evidence; disagreements will be resolved as needed through discussion or third-party adjudication. We will record strength of evidence assessments in tables, summarizing for each outcome.

G. Assessing Applicability

Assessing Applicability. Our team will assess the applicability of the results gathered from the literature according to EPC methods guidance.[28] This will be done to account for any factors limiting the ability to apply interventions to other populations or other settings, such as inadequate description of the intervention or failure to report follow-up data.We anticipate that important applicability factors will include age of the study participants, level of cognitive function at study entry and gender, among others.

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VI. Definition of Terms

PKU: "a rare metabolic disorder (and orphan disease) that usually results from a deficiency of a liver enzyme known as phenylalanine hydroxylase (PAH), […which] leads to elevated levels of the amino acid phenylalanine (Phe) in the blood and other

tissues; […this results in] mental retardation, microcephaly, delayed speech, seizures, eczema, behavior abnormalities, and other symptoms"[7]

Phe: phenylalanine; amino acid that metabolizes into the neutral amino acid tyrosine, which cannot occur in PKU patients due to a PAH deficiency[13]

LNAAs: large neutral amino acids that compete with Phe in transportation through the blood-brain barrier[14]

VII. Summary of Protocol Amendments

This amendment is to clarify methods described in the protocol for the Comparative Effectiveness of Treatment for Phenylketonuria (PKU). Table 2 summarizes the changes.

Table 2. Summary of protocol amendments

Date	Section	Protocol Deviation	Rationale
March 29, 2011	KQ 1a & 1b	Although it is not explicitly stated in the question, research on maternal Phe levels and related cognitive outcomes in their offspring will be included in this analysis. For this portion of the question we will utilize all studies available without implementing date limits.	Key Questions 1a and 1b pertain to the literature that examines the empirical relationship between Phe levels in the individual and cognitive outcomes. We needed to clarify that for pregnant women with PKU, we will examine outcomes in the offspring, not the women with PKU.
March 29, 2011	KQ 1a & 1b	We will begin with a review of existing reviews, using the methods described in EPC Methods Guidance*. That process includes a review of applicability of prior reviews to the current review/key questions, followed by a review of the quality of the prior reviews. At this point, a decision can be made regarding next steps, which could be to a) use the data from prior high-quality reviews in the current review; b) use the reference lists of prior high-quality reviews but extract data independently; or c) conduct an update only of prior reviews.	Prior systematic reviews have examined the relationship between Phe level and cognition in the individual with PKU.
March 29, 2011	KQ6	KQ6 will now read: What are the harms, including adverse events, associated with the use of sapropterin dihydrochloride and/or LNAAs in individuals with PKU?	This review focuses on the comparative effectiveness of two pharmacological treatments for PKU, sapropterin dihydrochloride and large neutral amino acids. Since we will not be examining the effectiveness of dietary interventions alone, we have changed the wording of KQ6 to capture harms associated with only the pharmacological treatments included in this review.

* White CM, Ip S, McPheeters M, et al. Using existing systematic reviews to replace de novo processes in conducting Comparative Effectiveness Reviews. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews [posted September 2009]. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60.

(NOTE THE FOLLOWING PROTOCOL ELEMENTS ARE STANDARD SECTIONS TO BE ADDED TO ALL PROTOCOLS)

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 multi-disciplinary group of clinical, content, and methodologic 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 healthy 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 methodologic 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 three 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.