AHRQ Comparative Effectiveness Review Surveillance Program

CER #56:
Adjuvant Treatment for Phenylketonuria (PKU)

Original release date:
February 2012

Surveillance Report:
January 2013

Key Findings:

- All conclusions for KQ1-7 are still considered valid
- No new significant safety concerns were identified.
- Several new studies were identified, but none challenged existing conclusions.

Summary Decision

This CER's priority for updating is **Low**

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Contents

Adjuvant Treatment for Phenylketonuria (PKU): An Assessment for the Need to Update the 2012 Evidence Review

1. Introduction

Comparative Effectiveness Review (CER) #56, Adjuvant Treatment for Phenylketonuria (PKU), was released in February 2012.[1] It was therefore due for a surveillance assessment in August, 2012.

2. Methods

2.1 Literature Searches

Using the search strategy employed for the original report, we conducted a limited literature search of Medline for the years 2011-October 24, 2012. This search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (Journal of Inherited and Metabolic Diseases, Molecular Genetics and Metabolism, European Journal of Pediatrics, Pediatrics, and Acta Paed). The specialty journals were those most highly represented among the references for the original report. Appendix A includes the search methodology for this topic.

2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

We shared the conclusions of the original report with 12 experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members, and peer reviewers) for their assessment of the need to update the report and their recommendations of any relevant new studies; 4 subject matter experts responded. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa

Method and/or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA/Health Canada reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the four-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.

- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 64 titles. After title and abstract review, 55 titles were rejected because they were editorials or letters or did not include topics of interest. The remaining 9 journal articles went on for further review. In addition to the searches, we also reference-mined articles that met inclusion criteria as well as non-systematic reviews identified by the literature searches but found no other articles. Four additional articles were reviewed at the suggestion of the experts: One had already been identified in our search (a published guideline[4] that was not considered in the decision regarding whether to update but is cited below), one was rejected for inclusion in the original report, one was rejected as a non-systematic review, and one was accepted. In addition, one piece of grey literature (a manufacturer's press release) was identified through a brief Google search, as the original project lead suggested several new treatments were in trials but could not provide more information.[5]

Thus, through literature searches and expert recommendations, 9 articles went on to full text review. Of these, 3 articles were rejected because they were non-systematic reviews or did not address a key question. Thus, 6 articles were abstracted into an evidence table (Appendix B).[6-11]

The FDA MedWatch, Health Canada, and MHRA UK searches identified no notifications of relevance.

3.2 Expert Opinion

The four experts were in unanimous agreement that none of the conclusions changed based on new evidence. Although one suggested new studies, he stated that several were not yet completed and none of the published studies would change the conclusions. One of the references mentioned by this expert was a guideline recently issued for the use of sapropterin in PKU; however this guideline cannot be interpreted as a recommendation for the use of sapropterin by any professional practice organization, as all 17 authors are employed by, or have received research support or honoraria from BioMarin, the manufacturer.[4]

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 1a: What is the evidence for optimal Phe Levels To Minimize Cognitive Impairment?				
Phe Levels and Impairments in IQ The data were analyzed according to two meta-analytic models The first represents the relationship of Phe and IQ when Phe was measured "historically" (more than 12 months before IQ measurement). In the second model, Phe and IQ were measured concurrently (within 6 weeks of each other). Evidence from 17 studies (mostly poor quality) suggests **increasing probability of low IQ at higher blood Phe levels**, regardless of whether IQ was measured during childhood or later, with a stronger association seen between Phe measured in early childhood and later IQ. There is a lack of strong association in measurements taken concurrently during the critical period. Dietary control—and reporting of dietary control—varied among the studies.	One new study assessed the effect of concurrent Phe levels and lifetime Index of dietary control (IDC) of Phe on pre-attentive processing in children with early and continuously treated PKU. Higher lifetime Phe and IDC were associated with increased visual evoked potential latencies and decreased mismatch negativity amplitudes (which differed with age), suggesting reduced ability to respond to stimulus change and the need to switch attention. (higher Phe: >360umol/L; lower lifetime Phe ≤360umol/L)[6] Another new study that compared early and late diagnosed individuals found that 97.7% of the early diagnosed patients had a normal IQ cf. only 25% of the late diagnosed. DQ/IQ were significantly inversely associated with IDC in early-dx children. Neurological and behavioral problems were significantly higher among	Not relevant	4/4 experts stated that there was no new evidence	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	behavioral problems differed significantly in prevalence between good, intermediary, and poor dietary control (as indicated by IDC)[7]			
Phe Levels and Impairments in Executive Function No measures of executive function have been validated for individuals with PKU. Nineteen unique studies determined to be too heterogeneous with respect to the neuropsychological measures used to allow pooling, showed that **overall, while Phe levels correlate with various assessments of executive function in some studies, the degree to which they are correlated and the correlation on individual measures are inconsistent.**	No studies identified	Not relevant	4/4 experts stated that there was no new evidence	Original conclusion is still valid and this portion of the original report does not need updating
Phe Levels and Impairments Related to Maternal PKU and Maternal PKU Syndrome Data predominantly from one longitudinal study, The Maternal PKU Collaborative Study, provide support for the observed increased risk of poor cognitive outcomes in the offspring of women with high maternal blood Phe concentrations. The study reported that timing of maternal metabolic control, defined as the	No studies identified	Not relevant	4/4 experts stated that there was no new evidence	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
number of weeks gestation before plasma Phe levels remained consistently lower than 605 µmol/L, was associated with lower child cognitive scores at 4 and 7 years of age.				
A model of the association between maternal blood Phe levels during pregnancy and effect on offspring during childhood confirmed that the relationship between maternal blood Phe and offspring cognitive outcomes was not linear: cognitive impairment was significantly more common in offspring of mothers with PKU than in controls at a Phe threshold of 360 µmol/L, and Phe levels were linearly related to cognitive outcomes only above this threshold. Importantly, while other factors, including maternal characteristics, severity of mutations, and offspring head circumference, contributed strongly to outcomes at 1 year of age, maternal Phe strongly overtook those other factors in predicting cognitive impairment by age 2.	A new study by Teissier (2012) that looked at birth outcomes in 115 pregnancies of 86 women with PKU in France found an increased risk for SGA among women who tightly controlled their diets and whose blood Phe levels were less than 120umol/L, demonstrating that low as well as high blood Phe may affect birth outcomes.[9]	Not relevant	4/4 experts stated that there was no new evidence but one mentioned a study by Teissier (2012)[9] that addressed the question of low serum Phe levels	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 1b: What is the Evidence for Optimal Phe Levels To Minimize Cognitive Impairment for Different Age Groups?				
We examined the potential effect of age in the meta-analysis of the relationship of Phe and IQ. Any influence of age was adequately represented by whether the Phe	A new study that analyzed lifetime Phe data showed that Phe levels at ages 4, 5, and 6 accounted for a higher proportion of the variance in	Not relevant	4/4 experts stated that there was no new evidence	Original conclusion is still valid and this portion of the original

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
measurements were historical or concurrent and whether they were taken in the critical period.	a particular aspect of VEP (P110 amplitude) than did concurrent Phe levels. Phe levels at age 9 also accounted for a higher proportion of the variance in N75 amplitude at occipital site 2 than did concurrent Phe.[6]			report does not need updating
Key Question 2. What is the Effectiveness of BH4 in Patients with PKU?				
Of the ten studies that evaluated the effects of BH4 in patients with PKU (relatively small, ranging in quality from poor to good, with varying doses, adherence rates, baseline Phe levels, and outcome measures), only 1 reported outcomes of interest, including measures of cognition and nutritional status (most participants had demonstrated responsiveness to BH4 in preloading trials). Phe levels were reduced by at least 30 percent in up to half of treated participants (32 to 50 percent) at dosages of 5 to 20 mg/kg/day and for up to 22 weeks of observation in comparative studies. In the one RCT that compared the effect of placebo on the likelihood of a 30-percent reduction in Phe, only 9 percent of those on placebo achieved this effect after 6 weeks, compared with 44 percent of the treated group. Data suggested a sustained response for up to 22 weeks duration, with 46 percent	One small new long-term (retrospective) study found that BH4 therapy, initiated in neonates or older children, significantly improved dietary Phe tolerance, allowing a 4-fold increase in Phe intake with a mean phenylalaninemia of 240±72uM, and 71±18% of Phe values within therapeutic targets (120-300uM). BH4 also improved metabolic control as measured by the decrease in mean phenylalaninemia (352±85 to 254±64um) and concomitant increases in the Phe values within therapeutic targets and a decrease in the values above target, and decreased the variance in blood Phe levels from 130±21uM to 93±27uM[8] A second new study found that metabolic control improved among BH4-	Not relevant	4/4 experts stated that there was no new evidence. One cites a case series on BH4 treatment of young children but the study was excluded from the original report.	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
achieving a 30-percent reduction in Phe levels. Responses varied by baseline Phe levels and other factors.	sensitive patients given BH4 while on a diet with twice the level of natural protein of usual PKU diets, but not among BH4-resistant participants. PKU patients reported higher physical well-being and HRQoL than age-matched healthy controls during the BH4 tx phase, but it was actually the resistant patients who had the higher HRQoL; BH4 sensitive patients did not increase their HRQoL.[11]			
BH4 use improved Phe tolerance over time. In the RCT, at a dosage of 20 mg/kg/day over 10 weeks, participants in the treatment group increased their Phe tolerance from 0 mg/kg at baseline to 20.9 mg/kg/day while maintaining blood Phe levels at <360 µmol/L, compared with an increase of 2.9 mg/kg/day in the placebo group. However, response varied substantially within the treatment group, with 33 percent tolerating an increase of between 31 and 50 mg/kg/day in supplement form but the rest of the participants tolerating lower levels of supplementary Phe. The degree to which this variability is associated with other factors possibly associated with Phe tolerance is	No studies identified	Not relevant	4/4 experts stated that there was no new evidence but one cites 2 studies supporting the original conclusion: one is a non-systematic review and the other is a set of guidelines for the use of BH4 (see text).[4]	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
unknown.				
One small case series reported on IQ and nutritional outcomes for up to 1 year on 5 mg/kg/day BH4 treatment. After 1 year of treatment, the 11 participants discontinued use of a medical food and normalized their diet. IQ scores after 12 months on BH4 were similar to scores before treatment and development quotients were within normal limits.	No studies identified	Not relevant	4/4 experts stated that there was no new evidence	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 3: What is the Effectiveness of BH4 in Pregnant Women with PKU?				
We did not identify any studies addressing this question.	No studies identified	Not relevant	4/4 experts stated that there was no new evidence (one stated that a new study has been completed but not yet published)	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 4. What is the Effectiveness of LNAAs in PKU?				
Three brief studies of poor to fair quality, using varying doses addressed the effects of LNAAs. Two of the three studies measured reductions in Phe levels, and one assessed cognitive outcomes. One fair-quality study reported a positive effect on executive functioning, specifically verbal generativity, cognitive flexibility, and self-monitoring. Overall, participants who were using a Phe-free medical food for their nutritional needs did not	No new studies identified	Not relevant	4/4 experts stated that there was no new evidence	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
experience a decrease in Phe, although those not adhering to diet or not using their formula did. In all three studies, blood Phe decreased after 1 week of treatment but remained above clinically acceptable levels.				
Key Question 5. What is the Effectiveness of LNAAs in Pregnant Women With PKU?				
We did not identify any studies addressing this question.	No new studies identified	Not relevant	4/4 experts stated that there was no new evidence	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 6: What are the Harms of Adjuvant Treatment for PKU?				
Of the 10 studies examining the effectiveness of BH4 in participants with PKU, 4 studies reported any type of harm related to the intervention drug. The most common side effects reported during BH4 trials were headache, throat pain, upper respiratory infection, diarrhea, abdominal pain, and nausea and vomiting, but harms were not significantly more common in the treatment - arm than in the placebo. One trial of LNAAs assessed neuropsychological outcomes and reported higher rates of anxiety associated with LNAA use.	No new studies identified.	Nothing reported by FDA, Health Canada or MHRA as of January 15, 2013	4/4 experts stated that there was no new evidence (one (one referred to a case series excluded from the original report)	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 7: What is the Effectiveness of BH4 and LNAAs for Subgroups of Individuals With PKU?				
We did not locate any studies addressing this question.	A new study whose aim was to identify genotypes	Not relevant	4/4 experts stated that there was no	Original conclusion is

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	associated with sapropterin responsiveness: 74 patients completed the trial, of whom 36 were sapropterin responsive. Genotypes occurring in 2 or more patients were consistently associated with results of the START test for sapropterin response. Thus particular alleles can be used to screen for responsiveness to sapropterin[10]		new evidence	still valid and this portion of the original report does not need updating

Are there new data that could inform the key questions that might not be addressed in the conclusions?

One expert mentioned a BioMarin PKU-016 study that measures outcomes of tetrahydrobiopterin in relation to neuropsychiatric symptoms; this study is scheduled for completion in Jan 2013. Another ongoing 7-year study in the PKU pediatric population will determine the effects, if any, on the development of children age 0-6 years who are using tetrahydrobiopterin.

A small Phase 2 trial of PEGylated phenylalanine ammonium lyase (PAL), an enzyme that breaks down Phe, was completed in September 2012; the Phase 3 trial is expected to begin in the 2nd quarter of 2013, according to a press release from the manufacturer dated 9/26/12.[5]

Legend: BH4 tetrahydrobiopterin; LNAA large neutral amino acids; Phe phenylalanine; PKU phenylketonuria; SCEPC Southern California Evidence-based Practice Center; SGA small for gestational age; tx treatment

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Appendices

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 6/1/2011-10/4/2012

LANGUAGE:
English

SEARCH STRATEGY:
phenylketonurias[mh] OR phenylketonuria[tiab] OR phenylketonurias[tiab] OR phenylalanine OR pku
AND
therapy[sh] OR pharmaceutical preparations[mh] OR therapeutics[mh] OR diet therapy[mh] OR "diet therapy"[Subheading] OR diet[tiab] OR dietary[tiab] OR 5,6,7,8-tetrahydrobiopterin[nm] OR sapropterin[tiab] OR tetrahydrobiopterin[tiab] OR bh4[tiab] OR kuvan[tiab] OR amino acids, neutral[mh] OR large neutral amino acid[tiab] OR large neutral amino acids[tiab] OR lnaa[tiab]
NOT
animal* NOT (human OR humans)

NUMBER OF RESULTS: 721

FILTERED IN ENDNOTE FOR THE FOLLOWING JOURNALS:
Annals of Internal Medicine
BMJ
JAMA
Lancet
New England Journal of Medicine

Acta Paediatrica
European Journal of Pediatrics
Journal of Inherited and Metabolic Diseases
Molecular Genetics and Metabolism
Pediatrics

NUMBER OF RESULTS AFTER FILTERING: 64

Appendix B. Evidence Table

Study Description	Intervention	Inclusion/Exclusion Criteria/ Population	Baseline Measures	Outcomes and Findings
Key Question 1a: What is the evidence for optimal Phe Levels To Minimize Cognitive Impairment?				
Author: De Sonneville, 2011[6] **Country:** Netherlands **Enrollment Period:** (see Huijbregts 2002)[12] **Funding:** Zorgonderzoek **Disclosures:** No influence of sponsor on content **Design:** Prospective cohort	None. 64 children with PKU dx at birth were divided into higher (Phe-H, >360umol/L) and lower lifetime Phe(Phe-L, Phe≤360umol/L) levels based on concurrent and lifetime midyear Phe levels and Index of Dietary Control (IDC)	**Inclusion Criteria:** PKU dx within first 2 weeks of birth, and treated early(<1 month after birth) and continuously with dietary restriction and regular monitoring (controls were 73 healthy children recruited from pts. families or peer groups) **Age, mean/yrs±SD (range):** 7-14 years **Other characteristics:** NR **Mean dose, mg/kg/day:** NR	Mean IDC for Phe-H group: 363umol/L For Phe-L group: 295umol/L Concurrent Phe was also measured throughout study	Pre-attentive processing was measured as follows: Visual evoked potentials (VEP) were measured using the checkerboard reversal task (CRT). Auditory evoked potentials were measured using the auditory oddball task (AOT). Serum Phe, EEG and eye movements were measured (via electro-oculogram) during the tasks, and visual and auditory acuity tests were also administered. Controls did not differ from children with PKU regarding overall VEP and mismatch negativity (MMN) indices. But higher lifetime Phe and IDC were associated with increased VEP latencies and decreased MMN amplitudes (which differed with age), suggesting reduced ability to respond to stimulus change and the need to switch attention.
Author: Gonzalez, 2011[7] **Country:** Spain	None: 121 children diagnosed with PKU in one hospital divided into groups by PKU control to assess association	**Inclusion Criteria:** PKU confirmed in their clinic with PAH deficiency confirmed by differential	IDC	88% of patients were on a protein-restricted diet and the rest were on BH4. 97.7% of the early diagnosed

Study Description	Intervention	Inclusion/Exclusion Criteria/ Population	Baseline Measures	Outcomes and Findings
Enrollment Period: 1985-2010 **Funding:** NR **Disclosures:** NR **Design:** Retrospective descriptive study	with IQ, developmental quotient (DQ), neurological complications, behavior. Mild PKU: 360-600umol/L; Moderate: 600-1200umol/l Classic: >1200 IDC calculated as half-year medians and mean of all medians	diagnosis or genetic analysis; pretreatment plasma Phe levels >360umol/L **Exclusion Criteria:** Late diagnosis and treatment or follow-up refusal; patients lost to follow-up; death due to cause unrelated to PKU **Age, mean/yrs±SD (range):** Median age 16 years, range 1 month-46 years (26%< 6 yrs., 13% 6-11 years; 16% 12-18 yrs., 45% adults) **Other characteristics:** 76% early diagnosed 12.4% mild PKU; 19% moderate; 69% classic **Mean dose, mg/kg/day:** NR		patients had a normal IQ cf. only 25% of the late diagnosed. DQ/IQ were significantly inversely associated with IDC in early-dx children. Neurological and behavioral problems were significantly higher among late diagnosed children than early dx. Neurological and behavioral problems differed significantly in prevalence between good, intermediary, and poor dietary control (as indicated by IDC)
Author: Teissier, 2012[9] **Country:** France **Enrollment Period:** 2002-2007 **Funding:** NR **Disclosures:** Authors declared as conflicts of interest, "None" **Design:** Retrospective cohort record review	No intervention. Independent variable was level of maternal Phe control achieved by dietary restriction (according to guidelines), based on monitoring indices	All French women with PKU who were pregnant between January 2002 and December 2007.	Serum Phe and 3 monitoring indices of levels over time	Study looked at birth outcomes in 115 pregnancies of 86 women with PKU in France found an increased risk for SGA among women who tightly controlled their diets and whose blood Phe levels were less than 120umol/L, demonstrating that low as well as high blood Phe may affect birth outcomes.[9]
Key Question 1b: What is the Evidence for Optimal Phe Levels To Minimize Cognitive Impairment for Different Age Groups?				
Author: De Sonneville, 2011[6] **Country:**	See KQ1a	See KQ1a	Mean IDC for Phe-H group: 363umol/L For Phe-L group: 295umol/L	Analysis of lifetime Phe data showed that Phe levels at ages 4, 5, and 6 accounted for

Study Description	Intervention	Inclusion/Exclusion Criteria/ Population	Baseline Measures	Outcomes and Findings
Netherlands **Enrollment Period:** (see Huijbregts 2002)[12] **Funding:** Zorgonderzoek **Disclosures:** No influence of sponsor on content **Design:** Prospective cohort			Concurrent Phe also measured throughout study	a higher proportion of the variance in a particular aspect of VEP (P110 amplitude) than did concurrent Phe levels. Phe levels at age 9 also accounted for a higher proportion of the variance in N75 amplitude at occipital site 2 than did concurrent Phe.
Key Question 2: What is the Effectiveness of BH4 in Patients with PKU?				
Author: Leuret, 2012[8] **Country:** France **Enrollment Period:** 2004-2010 **Funding:** NR **Disclosures:** None **Design:** Retrospective cohort	BH4 therapy initiated during the neonatal period (n=7) or later (n=8); median duration of treatment: 23 months (7-80)	**Inclusion Criteria:** Mild phenylketonuria Positive response to BH4 loading test **Age, mean/yrs±SD (range):** 7 neonates, 8 older children Mean age of children in older treatment group 13±12 months) **Other characteristics:** NR **Mean dose, mg/kg/day:** median daily dose 20mg/kg/d (8-24)	BH4 responsiveness as tested with 24-hour loading test, using single oral dose of 20mg/kg; responsiveness defined as reduction of >30% in blood Phe.	Long-term BH4 therapy significantly improved dietary Phe tolerance, allowing a 4-fold increase in Phe intake with a mean phenylalaninemia of 240±72uM and 71±18% of Phe values within therapeutic targets (120-300uM). The increase in ability to tolerate natural protein intake allowed Phe-free AA mixture to be discontinued in 7 pts or not introduced in 7. Only 1 pt., whose compliance was in doubt, continued the prescribed moderate Phe-restricted diet. BH4 also improved metabolic control as measured by the decrease in mean phenylalaninemia (352±85 to 254±64um) and concomitant increases in the Phe values within therapeutic targets and a decrease in the values above target…, and decreased the

Study Description	Intervention	Inclusion/Exclusion Criteria/ Population	Baseline Measures	Outcomes and Findings
				variance in blood Phe levels from 130±21uM to 93±27uM (The study did not compare children started on BH4 early vs. late)
Author: Ziesch, 2012[11] **Country:** Germany Enrollment Period: NR **Funding:** Merck-Serono **Disclosures:** NR **Design:** Prospective open clinical trial	Study conducted in 4 phases: Phase 1: baseline Phase 2: (2 weeks) doubling of natural protein intake Phase 3: (4 weeks) daily BH4 (20mg/kg) with increase natural protein intake Phase 4: (7 weeks) continuation of BH4 treatment by BH4-sensitive individuals	**Inclusion Criteria:** BH4 sensitivity established by mutational analysis and loading test **Age, mean/yrs±SD (range):** Range 4-18 years **Other characteristics:** NR **Mean dose, mg/kg/day:** NR	BH4 sensitivity, HRQoL	Metabolic control improved during Phase 3 in the BH4 sensitive patients but not the others. BH4-resistant participants, who consumed increased Phe during Phase 2, never regained their original blood Phe concentrations, even though they returned to pre-study consumption levels. PKU patients reported higher physical well-being and HRQoL than age-matched healthy controls during phase 3, but within this group, it was actually the resistant patients who had the higher HRQoL; BH4 sensitive patients did not increase their HRQoL (although responses to a set of supplementary questions suggested improved QoL). Parents of resistant patients, however, reported that their children's self-esteem decreased during the study period.
Key Question 3: What is the Effectiveness of BH4 in Pregnant Women with PKU?				
No studies identified				
Key Question 4: What is the Effectiveness of LNAAs in PKU?				
No studies identified				
Key Question 5: What is the Effectiveness of LNAAs in Pregnant Women With PKU?				
No studies identified				

Study Description	Intervention	Inclusion/Exclusion Criteria/ Population	Baseline Measures	Outcomes and Findings
Key Question 6: What are the Harms of Adjuvant Treatment for PKU?				
Leuret, 2012[8] **Country:** France **Enrollment Period:** 2004-2010 **Funding:** NR **Disclosures:** None **Design:** Retrospective cohort	BH4 therapy initiated during the neonatal period (n=7) or later (n=8); median duration of treatment: 23 months (7-80)	**Inclusion Criteria:** Mild phenylketonuria Positive response to BH4 loading test **Age, mean/yrs±SD (range):** 7 neonates, 8 older children Mean age of children in older treatment group 13±12 months) **Other characteristics:** NR **Mean dose, mg/kg/day:** median daily dose 20mg/kg/d (8-24)	Not relevant	No harms were reported by study participants
Key Question 7: What is the Effectiveness of BH4 and LNAAs for Subgroups of Individuals With PKU?				
Author: Utz, 2012[10] **Country:** US **Enrollment Period:** NR **Funding:** NR **Disclosures:** NR **Design:** RCT	Alternating placebo or sapropterin 1 week at a time, beginning with a week on sapropterin or placebo	**Inclusion Criteria:** PKU diagnosis, age 4 years or older **Exclusion criteria:** pregnancy, age less than 4 years, any clinical contraindication to sapropterin therapy **Age, mean/yrs±SD (range):** 18 adults, 18 youth **Other characteristics:** NR **Mean dose, mg/kg/day:** NR		Aim of study was to identify genotypes associated with sapropterin responsiveness. 74 patients completed the trial, of whom 36 were sapropterin responsive. Genotypes occurring in 2 or more patients were consistently associated with results of the START test for sapropterin response. Thus particular alleles can be used to screen for responsiveness to sapropterin

Table Notes: Legend: BH4 tetrahydrobiopterin; LNAA large neutral amino acids; Phe phenylalanine; PKU phenylketonuria; SCEPC Southern California Evidence-based Practice Center; SGA small for gestational age; tx treatment

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: **Adjuvant Treatment for Phenylketonuria (PKU)**

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1a: What is the evidence for optimal Phe Levels To Minimize Cognitive Impairment?			
Phe Levels and Impairments in IQ The data were analyzed according to two meta-analytic models The first represents the relationship of Phe and IQ when Phe was measured "historically" (more than 12 months before IQ measurement). In the second model, Phe and IQ were measured concurrently (within 6 weeks of each other). Evidence from 17 studies (mostly poor quality) suggests **increasing probability of low IQ at higher blood Phe levels**, regardless of whether IQ was measured during childhood or later, with a stronger association seen between Phe measured in early childhood and later IQ. There is a lack of strong association in measurements taken concurrently during the critical period. Dietary control—and reporting of dietary	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
control—varied among the studies.			
Phe Levels and Impairments in Executive Function No measures of executive function have been validated for individuals with PKU. Nineteen unique studies determined to be too heterogeneous with respect to the neuropsychological measures used to allow pooling, showed that **overall, while Phe levels correlate with various assessments of executive function in some studies, the degree to which they are correlated and the correlation on individual measures are inconsistent.**	☐	New Evidence:	☐
Phe Levels and Impairments Related to Maternal PKU and Maternal PKU Syndrome Data predominantly from one longitudinal study, The Maternal PKU Collaborative Study, provide support for the observed increased risk of poor cognitive outcomes in the offspring of women with high maternal blood Phe concentrations. The study reported that timing of maternal metabolic control, defined as the number of weeks gestation before plasma Phe levels remained consistently lower than 605 µmol/L, was associated with lower child cognitive scores at 4 and 7 years of age.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
A model of the association between maternal blood Phe levels during pregnancy and effect on offspring during childhood confirmed that the relationship between maternal blood Phe and offspring cognitive outcomes was not linear: cognitive impairment was significantly more common in offspring of mothers with PKU than in controls at a Phe threshold of 360 μ mol/L, and Phe levels were linearly related to cognitive outcomes only above this threshold. Importantly, while other factors, including maternal characteristics, severity of mutations, and offspring head circumference, contributed strongly to outcomes at 1 year of age, maternal Phe strongly overtook those other factors in predicting cognitive impairment by age 2.	☐	New Evidence:	☐
Key Question 1b: What is the Evidence for Optimal Phe Levels To Minimize Cognitive Impairment for Different Age Groups?			
We examined the potential effect of age in the meta-analysis of the relationship of Phe and IQ. Any influence of age was adequately represented by whether the Phe measurements were historical or concurrent and whether they were taken in the critical period.	☐	New Evidence:	☐
Key Question 2. What is the Effectiveness of BH4 in Patients with PKU?			
Of the ten studies that evaluated the effects of BH4 in patients with PKU (relatively small, ranging in quality from poor to good,		New Evidence:	

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
with varying doses, adherence rates, baseline Phe levels, and outcome measures), only 1 reported outcomes of interest, including measures of cognition and nutritional status (most participants had demonstrated responsiveness to BH4 in preloading trials). Phe levels were reduced by at least 30 percent in up to half of treated participants (32 to 50 percent) at dosages of 5 to 20 mg/kg/day and for up to 22 weeks of observation in comparative studies. In the one RCT that compared the effect of placebo on the likelihood of a 30-percent reduction in Phe, only 9 percent of those on placebo achieved this effect after 6 weeks, compared with 44 percent of the treated group. Data suggested a sustained response for up to 22 weeks duration, with 46 percent achieving a 30-percent reduction in Phe levels. Responses varied by baseline Phe levels and other factors.	☐		☐
BH4 use improved Phe tolerance over time. In the RCT, at a dosage of 20 mg/kg/day over 10 weeks, participants in the treatment group increased their Phe tolerance from 0 mg/kg at baseline to 20.9 mg/kg/day while maintaining blood Phe levels at <360 µmol/L, compared with an increase of 2.9 mg/kg/day in the placebo group. However, response varied substantially within the treatment group, with 33 percent tolerating an increase of between 31 and 50 mg/kg/day in supplement form but the rest of the	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
participants tolerating lower levels of supplementary Phe. The degree to which this variability is associated with other factors possibly associated with Phe tolerance is unknown.			
One small case series reported on IQ and nutritional outcomes for up to 1 year on 5 mg/kg/day BH4 treatment.59 After 1 year of treatment, the 11 participants discontinued use of a medical food and normalized their diet. IQ scores after 12 months on BH4 were similar to scores before treatment and development quotients were within normal limits.	☐	New Evidence:	☐
Key Question 3: What is the Effectiveness of BH4 in Pregnant Women with PKU?			
We did not identify any studies addressing this question.	☐	New Evidence:	☐
Key Question 4: What is the Effectiveness of LNAAs in PKU?			
Three brief studies of poor to fair quality, using varying doses addressed the effects of LNAAs. Two of the three studies measured reductions in Phe levels, and one assessed cognitive outcomes. One fair-quality study reported a positive effect on executive functioning, specifically verbal generativity, cognitive flexibility, and self-monitoring. Overall, participants who were using a Phe-free medical food for their nutritional needs	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
did not experience a decrease in Phe, although those not adhering to diet or not using their formula did. In all three studies, blood Phe decreased after 1 week of treatment but remained above clinically acceptable levels.			
Key Question 5: What is the Effectiveness of LNAAs in Pregnant Women With PKU?			
We did not identify any studies addressing this question.	☐	New Evidence:	☐
Key Question 6: What are the Harms of Adjuvant Treatment for PKU?			
Of the 10 studies examining the effectiveness of BH4 in participants with PKU, 4 studies reported any type of harm related to the intervention drug. The most common side effects reported during BH4 trials were headache, throat pain, upper respiratory infection, diarrhea, abdominal pain, and nausea and vomiting, but harms were not significantly more common in the treatment arm than in the placebo. One trial of LNAAs assessed neuropsychological outcomes and reported higher rates of anxiety associated with LNAA use.	☐	New Evidence:	☐
Key Question 7: What is the Effectiveness of BH4 and LNAAs for Subgroups of Individuals With PKU?			

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
We did not locate any studies addressing this question.	☐	New Evidence:	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			