Comparative Effectiveness Research Review Disposition of Comments Report

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

Draft review available for public comment from September 20, 2011 to October 14, 2011.

Research Review Citation: Lindegren ML, Krishnaswami S, Fonnesbeck C, Reimschisel T, Fisher J, Jackson K, Shields T, Sathe NA, McPheeters ML. Adjuvant Treatment for Phenylketonuria (PKU). Comparative Effectiveness Review No. 56. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No**.** HHSA 290-2007-10065-I.) AHRQ Publication No. 12- EHC035-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2012. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each comparative effectiveness research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or email. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #5	Executive summary	Background Etiology Inability to metabolize protein is not the problem, but inability to normally metabolize phenylalanine is.	Corrected
Peer reviewer #5	Executive summary	Newborn screening does not diagnose PKU. NBS does suggest a problem with metabolism of Phe, but a diagnostic work-up must be done to determine whether the problem is phenylaline hydroxylase deficiency, a biopterin synethsis defect or a biopterin regeneration defect since treatment is different.	Corrected
Peer reviewer #5	Executive summary	Treatment of PKU Animal protein is excluded in the diet after weaning. Diet consists mostly of grains (cereals), vegetables, fruits, fats, and medical foods (an exempt infant formula free of Phe in infants).	Corrected
Peer reviewer #5	Executive summary	ES-2 Medical foods are not supplements. They are the primary sources of protein equivalent (amino acids) in the diet. They are Phe free, not low Phe.	We have changed this terminology throughout the report.
Peer reviewer #5	Executive summary	Medical foods (except the new GMP-based one) are Phe-free, not low-Phe. Also, exempt infant formulas (medical foods) contain minerals , vitamins, and fats. Medical foods for children and adults made in the US contain minerals, vitamins and fats as well.	Corrected low Phe
Peer reviewer #5	Executive summary	Phe tolerance is based on several factors. These include genotype, gender, age, growth rate, pregnancy, illness, trauma, and whether bedridden.	Factors that impact Phe tolerance are included in the Introduction. The list is not meant to be exhaustive.
Peer reviewer #5	Executive summary	In addition to a Phe-restricted diet adequate in all nutrients and sapropterin in some patients another potential medical food for treatment of patients with PKU is large neutral amino acids, although they do not support adequate growth in children and do not maintain nitrogen balance in adolescence or young adults. 4 patients, 16-25 years of age fed 0.8 g/kg of LNAAs with 0.6 g/kg of protein in a low protein diet lost a mean 1.5 g N/day (range -2.99 – 15 g/days. J Inher Metab Dis. 1995; 18: 127-130)	LNAA are discussed as an adjuvant nutritional supplement in a following paragraph.
Peer reviewer #5	Executive summary	ES-3 Comparators Why is the term sapropterin used when tetrahydrobiopterin (BH4) is the ethical term to use?	We have used the term BH4 throughout the report

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #5	Executive summary	Why is genotype not included in this area since it is very important?	Genotype is believed to be important, but there are currently no consistent data supporting its use in the standard care of patients. Treatment is still based primarily on frequent Phe measurements. Genotype is included as one of the variables that may influence outcomes, and it is listed as a potential modifier in other KQs
Peer reviewer #5	Executive summary	Key Questions KQ1 Genotype should be included as a key question?	Genotype is believed to be important, but there are currently no consistent data supporting its use in the standard care of patients. Treatment is still based primarily on frequent Phe measurements. Genotype is included as one of the variables that may influence outcomes, and it is listed as a potential modifier in other KQs
Peer reviewer #5	Executive summary	KQ2 Sapropterin dihydrochloride is a manufactured product b Biomarin. Isn't it unethical to use the term in this material??	We have used the term BH4 throughout.
Peer reviewer #5	Executive summary	KQ4 and KQ5 LNAAs provide only essential amino acids, i.e. those that cannot be synthesized in the body. However, the non-essentials (those that can by synthesized if adequate amino groups and energy are fed) are necessary and part of protein synthesis in humans—i.e. glutamic acid, gluatmin, glycine, alanine, etc. without all amino acids present. When protein synthesis should occur, it does not occur and amino acids are deaminated and the NH2 groups lost in the urine. If LNAAs are the primary source of amino acids, a great amount must be fed, along with increased energy, in order that the so-called non-essential amino acids may be synthesized from their NH2 groups. Most human protein is about half non-essential amino acids.	The goal of this review is to examine treatment studies, not to provide a complete treatment of all PKU literature, mechanisms or background. Although we appreciate this information, it does not fit in the text of the report.

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Peer reviewer #5	Executive summary	Most human GI tracts do not tolerate hyperosmolar feeds without nausea, vomiting, distention, diarrhea and some infants have died due to it. The amino acids are small molecules that, if too concentrated when fed, can cause serious problems and have even in children and adults. If added to a medical food to administer they may make the mixture hyperosmolar.	This is useful information, but beyond the scope of this report, which does not provide recommendations about when or how to take the medical interventions.
Peer reviewer #5	Executive summary	Alone, LNAAs do not decrease blood Phe concentration adequately. Further, they contain no minerals, vitamins or fat which are required. LNAA mixes do not smell or taste good and for the woman with hyperemesis gravida, can be a major problem. About 50% of women in the US have hyperemesis gravida. Too large amounts of medical foods have always been problems with all patients.	Thank you for your comments. There are no data studying the use of LNAA in pregnant women with PKU.
Peer reviewer #5	Executive summary	ES-4 KQ5 And other malformations should be added.	The word "including" is used because the list in KQ5 is not meant to be exhaustive. Since there are no data regarding this questions, changing the wording in KQ5 is not necessary.
Peer reviewer #5	Executive summary	KQ6 and KQ7 Inappropriate use of term sapropterin dihydrochloride.	We have used the term BH4 throughout the report.
Peer reviewer #5	Executive summary	Analytic Framework Quality of life not likely to be increased by addiction of LNAAs which should not be used in pregnant women, only in non-pregnant adults. Add to "excessively high Phe concentrations in the maternal blood stream, amniotic fluid and fetal blood," We don't know fetal blood Phe concentration in early gestation only from about 19 weeks.	We have revised the framework.
Peer reviewer #5	Executive summary	ES-5 Figure ES-1 Genotype definitely should be added to diagnostic work-up. Sapropterin dihydrochloride should be changed to BH4 or only sapropterin.	I do not think that we can say genotype should definitely be done. There is no current guideline that endorses this view. We have used BH4 throughout the report.
Peer reviewer #5	Executive summary	ES-7 Data Synthesis and Analysis Evidence Synthesis Genotype should be included in all diagnostic work-ups in future studies.	Thank you for your comment; however, it is not the role of this report to make recommendations about diagnostic procedures.

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Peer reviewer #5	Executive summary	The use of IQ below 85 is interesting but in untreated or late treated patients other problems include hyperactive or bizarre behavior, skin depigmentation, delayed speech, skin rash and seizures with many having an IQ of 33 or less. See Clinical Picture. Koch R, Acosta P, Shaw KNF, et al. "Phenylketonuria and some other inborn errors of amino acid metabolism." Stuttgart: Georg Thieme Verlag, 1971, pp.20-25.	Is it accepted knowledge that untreated PKU is profoundly detrimental, and this includes severe intellectual disability, hypopigmentation, skin rash and possibly epilepsy.
Peer reviewer #5	Executive summary	ES-10 Phe Concentrations and Impairments Related to Maternal PKU Do you mean "poor cognitive outcomes in the offspring of women with high maternal blood Phe concentration?"	Corrected
Peer reviewer #5	Executive summary	ES-11 KQ2 Use of term sapropterin dihydrochloride seems unethical.	We have used the term BH4 throughout the report.
Peer reviewer #5	Executive summary	ES-12 Was the Phe administered as intact protein or pure L-Phe? There seems to be a different patient response depending on form of administration, in my experience.	Thank you for sharing your clinical experience. This was not a focus of the literature meeting criteria for this review.
Peer reviewer #5	Executive summary	What are references indicating that some patients, when taking BH4, could ingest up to 50 mg/kg/day more of PHE? What was diagnostic blood PHE of these patients and what was baseline blood PHE concentrations?	The Trefz 2009 RCT includes these data; see tables 10-12.
Peer reviewer #5	Executive summary	KQ4 There are only Phe-free medical foods in the US and GMP with some Phe recently begun.	Thank you for your comment. This systematic review is focused primarily on the treatment of PKU since it is funded by the United States government.
Peer reviewer #5	Executive summary	Insurance companies do not pay for supplements. Medical foods are not supplements	Thank you for your comment. We modified the text to refer to all formulas and Phe-restricted foods as "medical foods instead of "supplements."
Peer reviewer #5	Executive summary	ES-13 "Harms" sounds awkward. Why not just use "side-effects" or better "adverse events"?	Harms is the term used within the EPC program to refer to the totality of negative effects, including but not limited to side effects.

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Peer reviewer #5	Executive summary	Discussion Key Findings First paragraph is very unclear	We have edited the report.
Peer reviewer #5	Executive summary	ES-14 Applicability of Evidence What is meaning of “Nonetheless both studied populations likely to be seen in clinical care and clinicians should find the results applicable to some of their patients”?	Thank you for this comment; we have modified the text to clarify.
Peer reviewer #5	Executive summary	Overall, the lack of looking at anything but IQ and executive function as measures of outcome seem rather absurd. When a patient is in the clinical setting, many other aspects, without actual quantification, are evaluated. This manuscript ignores the large PKU collaborative study with its data, carried out between 1967 and about 1979, which evaluated growth, IQ, parental IQ and income when possible, etc. Nutrient intake, not just Phe intake, was carefully evaluated. Good nutrition status is essential for both growth and development.	We have included in this review all studies that met criteria, which were appropriate to answer the key questions. This is not intended to be a narrative review of all literature related to PKU.
Peer reviewer #5	Executive summary	Where are data from the Nat’l PKU Collaborative Study that included more than 100+ patients with PKU?	We have referenced this study in the background, but it did not meet criteria for inclusion to address our specific key questions.
Peer reviewer #5	Executive summary	Where are data from Elsas and Krause showing other problems, even with a normal IQ when blood Phe concentration was increased?	This study did not meet criteria for the review.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Pages ES-1 and ES-2. The statement, “Inability to properly metabolize protein” is inaccurate and should be changed to “Inability to properly metabolize the amino acid, phenylalanine.”	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	In the Background, Etiology section, the term, “hyperphenylalaninemia” is used in two conflicting situations. First, to describe a mild form of PKU (defined in this report as blood Phe = 120 - 1,000 mol/L) and second as a reference to PKU in general. While the report acknowledges that “exact cutoffs vary in the literature and in practice,” lack of accepted definitions is a vexing problem in research and clinical practice.	We have corrected the use of this term and generally deleted it. We agree that inconsistency in cutoffs makes assessment of the literature challenging.

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Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Additionally, with the emergence of tandem mass spectrometry for newborn screening, infants are now typically identified before their blood Phe levels exceed 1200 mol/L. With rapid initiation of treatment, the use of the classic cutoffs to categorize the type of PKU is not possible.	This comment may indeed be the case for some newborns with PKU. However, is this review we have adopted the definition for PKU that was used in the articles we reviewed. Perhaps the semiology needs to be modified, but that is beyond the scope of this systematic review.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Additionally, these definitions are an effort to have a common language and should not be used to restrict treatment options, which are patient specific. The Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference working groups are collectively addressing the definitions problem.	The language used in our report reflects that in the research literature. At no point in the Introduction do we suggest that only classic PKU should be treated, and our results certainly do not endorse this viewpoint.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Pages ES-1 and ES-2. The Treatment of PKU section includes an insufficient and inaccurate description of dietary treatment. The last sentence on ES-1, “The diet used for individuals with PKU rigidly restricts the intake of protein, including significant limitations on animal products” would be clearer and more succinct if worded as: “The diet for individuals with PKU involves restriction of intact protein tailored to the patients’ individual tolerance.”	We corrected this text.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	The statement that the diet consists mostly of vegetables and fruits is not accurate. Fruits and low-protein vegetables are incorporated into a diet that derives the largest amount of nutrients from medical foods. Additionally, placing an emphasis on “high in carbohydrates, low in saturated and polyunsaturated fat, and low in cholesterol” suggests that these nutrients are being targeted, which is not the case. We suggest the following rewording: “The diet consists mostly of vegetables, fruits, cereals, and fats to provide intact protein and nutrients. The remaining amount of protein and essential nutrients needed for body growth, development, and maintenance are provided by medical foods specifically designed for individuals with PKU. Medical foods are typically Phe-free, and vary in their micronutrient and macronutrient composition. However, they serve as medically-necessary vehicles for providing adequate protein and calories in a form that is tolerated. Low protein foods provide energy and contribute an acceptable quantity and quality of food.”	Thank you. We have reworded this statement as recommended.

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Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-2, first complete paragraph. The statement, "Based on the severity of the disease, individuals with PKU can tolerate different quantities of total Phe intake per weight. This is referred to [as] *Phe tolerance*." The amount of Phe that an individual can consume to keep blood Phe concentrations in the treatment range is not typically calculated based on weight beyond infancy.	We have corrected this sentence.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-2, first complete paragraph. Phe *concentrations* are monitored frequently and appropriate modifications to the total *dietary* Phe intake are made. This allows determination of the ideal dietary Phe tolerance for an individual patient. In a given individual, Phe tolerance changes with age and metabolic demand, for example, during periods of accelerated growth, pregnancy, and chronic and *acute illness*.	We have made the recommended changes to this section.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-2, first complete paragraph. The sentence, "As they get older Phe measurements become less frequent, and healthy adults with well-controlled PKU may only get Phe level measurements a few times a year," implies that it is acceptable to have less frequent blood Phe measurements. The recommendation, "diet for life," necessitates measuring blood Phe more frequently than a few times a year in all patients.	We have added text regarding the NIH recommendation for diet for life and continued monitoring.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-2. In the paragraph about LNAAs, it should be pointed out that LNAAs are not a Food and Drug Administration (FDA) approved drug.	We have clarified this fact.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	LNAAs decrease the concentrations of Phe crossing the blood brain barrier by competing for the shared amino acid transporters.	Added
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-2, Maternal PKU. "Poorly treated PKU in pregnant women can … even though the offspring do not have PKU." We suggest that the word "can" be removed, and the sentence read: "Poorly treated PKU in pregnant women will result …"	Corrected

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Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Also, because PKU is an autosomal recessive disorder and mothers with PKU have two mutated genes, if the father is a carrier, their offspring actually would have an increased risk over the general population of having PKU. Thus, the offspring of women with PKU may have PKU. This might be clarified by saying: "… even if the offspring does not have PKU."	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	The sentences, "Management of PKU can be very difficult. Some individuals may have loosened stringent dietary restrictions during adolescence, and restarting an unpalatable diet that strictly limits protein may be challenging," does not fully articulate the management issues during pregnancy. We suggest the following rewording: "Management of PKU can be very difficult. Restarting a restrictive and unpalatable diet during pregnancy is challenging. Complicating factors such as morning sickness, balancing severe protein restriction with adequate energy intake, insurance coverage limitations for medical foods and modified low protein foods, maturity of the expectant mother and her previous food lifestyle before pregnancy contribute to the challenges."	Added
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-2, Clinical Uncertainties. In the second sentence we suggest substituting "hyperphenylalaninemia" with "elevated blood Phe levels."	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-2, Clinical Uncertainties . The last sentence implies that LNAAs are a prescription drug, which they are not.	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-3, Objectives, Population, first sentence. Because LNAAs are classified as a medical food, they should not be lumped with "pharmacologic" treatment. We suggest "We focused this review on sapropterin and LNAA treatment for all …"	Corrected

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Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-4, Key Questions (KQ). How is KQ 7 different from the subgroup analysis done in KQ2 and KQ4?	KQ7 refers to any type of variation in patients, such as gender, race, socioeconomic setting, etc. KQ2 and KQ4 refer only to differences in age.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-4, Analytic Framework. Nutritional outcomes are referenced on ES-3 in Outcomes but not included here. We recommend that all secondary outcomes be referenced rather than just one: increasing quality of life.	We have revised the analytic framework.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	This framework reflects that LNAA may have a test for responsiveness, which is misleading.	We were not suggesting that LNAA has a test for responsiveness. What we were suggesting is that treatment decisions and plans are continually modified for either approach as the patients are monitored. The analytic framework does not include the loading test for sapropterin as studies about this were not included in the review. We have slightly revised the analytic framework so as not to create this confusion.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-6, Table ES-1. Inclusion and exclusion criteria. It would be helpful for additional information on the reasoning for the exclusions, such as limiting studies that had a minimum of 10 patients.	Details on the reasons for inclusion/exclude criteria are provided in the full report.

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Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Table ES-1 in the ES (page ES-6) is different than Table 1. (Inclusion and exclusion criteria) in the body of the report (page 10), despite identical titles. It seems only inclusion criteria are listed in Table 1, while exclusion criteria are listed in ES-1.	This is correct. The table in the executive summary is abridged.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-7, Results. "… (Comprising 43 unique studies) … "Were you able to control for the same IQ data that may have been published differently in more than one manuscript? Were you able to prevent "double dipping" of the same data in your final review?	Yes, we worked carefully to ensure that where there were "families" of papers using data from the same individuals that data were only extracted once.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-8, Phe levels and Impairments in IQ. Do we know whether the same individuals with PKU participated in more than one study cited; that is, are all the patient data unique?	Yes, we worked carefully to ensure that where there were "families" of papers using data from the same individuals that data were only extracted once.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-9, third paragraph. "… lower IQ at higher Phe measures …" For clarity, we would suggest changing to "higher blood Phe levels."	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-10, Phe Levels and Impairments in Executive function. An explanation of why a meta-analysis was not appropriate for any component of executive function would be helpful.	Thank you. We have clarified this text.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-11, first complete paragraph. In the sentence, "Importantly, while other factors, including maternal characteristics, severity of mutations and head circumference, contributed to outcomes …" does "head circumference" refer to the mother or the offspring?	Corrected

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Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-11 The end of the last sentence "(before Phe supplements began)," introduces a new element in the process of determining sapropterin responsiveness that is not discussed further. We suggest that clarification be made that the Phe intake among the individuals in the study did not change. We suggest: "At week 3, those receiving sapropterin had a greater reduction in Phe levels at their baseline dietary Phe intake."	We have made this change.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-12, second paragraph. In the sentence, "… examined the effect of sapropterin use on Phe tolerance …" We suggest clarifying that they are talking about responders by saying "... examined the effect on Phe tolerance in patients who responded to use of sapropterin ..."	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-12, KQ4. There is a discrepancy in assignment of "fair quality" vs. "poor quality" to citation 57. See page ES-13 KQ6.	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-12, KQ4, second paragraph. In the sentence, "Overall, participants who were using a low-Phe supplement to their nutritional needs …" is awkward. "Medical product" is the term used in the article to refer to the medical foods used by the subjects. All subjects maintained their usual Phe-restricted diet. If the term, "medical product" is used, put it in quotes. If it is not going to be used, we would recommend changing the sentence to read: "Overall, participants who were using a medical food did not experience a decrease in plasma Phe levels with the addition of LNAAs. Plasma Phe levels were lower, however, in those participants on LNAAs who did not also consume their medical food."	We have referred to Phe supplements as medical foods throughout the report.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-12, KQ5. It might be helpful to readers to note that LNAAs maybe contraindicated in pregnancy due to potential detrimental effects on the fetus.	We have noted that no studies addressing this question were located.

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Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-13, KQ6. There is no useful information given regarding the actual risk of using sapropterin. We would suggest that the incidence of adverse events be given rather than just listing them.	We have revised that text. In fact, the incidence of adverse events in patients receiving sapropterin did not differ compared to placebo.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-15, Future Research on Pharmacologic Treatment, first paragraph. In sentence five, we would suggest removing "including genotype" because potential modifiers can be added after sentence six to include genotype.	We have made this change.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-15, Future Research on Pharmacologic Treatment, In sentence six, the "unexplained" variability is likely to be multifactorial and may include individual patient and genotype differences, drug dose, and individual patient behavior such as dietary adherence.	Added
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-15, Future Research on Pharmacologic Treatment, first paragraph, last sentence. It is very important that calls for future research include the effects of sapropterin and LNAAs on nutritional status. If these treatments allow diet liberalization, the resulting consumption of greater quantities of whole foods and higher quality protein can result in long-term benefits to the patients.	Added
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Executive Summary	Page ES-16, Future Research, last paragraph. We appreciate the desire to have future studies be supported with public funding. However, in this current climate of funding cuts and shrinking budgets, the PKU community may have to rely, at least in part, on industry funding to conduct this important research. We would suggest that a recommendation be made to develop a set of very specific and stringent clinical research standards that include absolute transparency and availability of all research data, as well as rigorous double blinded, randomized control trials whenever possible.	We have noted the need for a consortium in the Future Research section of the report.

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Pharmacologic Interventions Working Group (PKU- PIWG)	Executive summary	Page ES-1 and ES-2: In the Background, Etiology section, the term, "hyperphenylalaninemia" is used in two conflicting situations. First, to describe a mild form of PKU (defined in this report as blood Phe = 120 - 1,000 umol/L) and second as a reference to PKU in general. We suggest that the second use of the term be changed to "elevated blood Phe."	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Pharmacologic Interventions Working Group (PKU- PIWG)	Executive summary	Page ES-1 and ES-2: The Treatment of PKU section includes an insufficient description of dietary treatment. The statement that the diet consists mostly of vegetables and fruits is simply not true. The emphasis on "high in carbohydrates, low in saturated and polyunsaturated fat, and low in cholesterol" suggests that these nutrients are being targeted. It lumps metabolic formulas with low protein foods which is confusing. While metabolic formulas are typically Phe-free, they vary in their micronutrient and macronutrient composition. Low-protein foods, on the other hand, are meant to supplement the diet with calories. We suggest that this section be rewritten to reflect these nuances.	We have clarified this section of text.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Pharmacologic Interventions Working Group (PKU- PIWG)	Executive summary	ES-4: How is Key Question 7 different from the subgroup analysis done in KQ2 and KQ4?	KQ7 addressed multiple variables unrelated to age, while KQ2 and KQ4 focused on different outcomes based on age.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Pharmacologic Interventions Working Group (PKU- PIWG)	Executive summary	**Comment 1:** ES-13 and Results page 20: The key findings mention that in the meta-analysis of studies associating Phe levels with IQ measurements, increasing Phe is associated with decreased IQ. We have no concerns with this statement for Classical PKU. However, we do not think that the studies support this data for some of the milder forms of the disease, especially those with Phe levels in the range of 360-600 umol/L. The studies that were analyzed in this meta-analysis are referenced in Table 3. The majority of these studies (10/16) only looked at individuals with Classical PKU. Only one study looked at patients with moderate or mild PKU and 5/16 of the studies did not classify the individuals.	We have noted that studies meeting our criteria included primarily participants with classic PKU and therefore the evidence may be primarily applicable to individuals with classic PKU.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Pharmacologic Interventions Working Group (PKU- PIWG)	Executive summary	We would suggest that this point be made clear; i.e., "For classical PKU patients, increasing blood PHE is clearly associated with decreased IQ…"	We have made this point in the text.

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Pharmacologic Interventions Working Group (PKU- PIWG)	Executive summary	We would also suggest adding a small section on the grey area of Phe levels in the range of 360-600 umol/L (See Hanley, Molecular Genetics & Metabolism. 104(1-2):23-6, 2011 Sep-Oct; van Spronsen Journal of Inherited Metabolic Disease. 34(3):651-6, 2011 Jun and reference 35 in the AHRQ report.	We concur that there are few data specifically on the effects of Phe in this range. We have added this consideration to the future research section.
Sara Copeland (affiliation not provided)	Executive Summary	I agree with the conclusion, my question is why did AHRQ feel this was necessary to be done? This is common practice among metabolic physicians and at this time, not controversial. It seems like investigation of issues where there is poor consensus would be a better use of this type of review.	Thank you for your comment. We agree that our findings support the standard of care for patients with PKU. However, we disagree that everything discussed in the report is uncontroversial, such as the use of LNAA and sapropterin. Our review seeks to clarify the data on these issues. The review also highlights areas that may be routinely practiced but are not based on quality data.
Peer Reviewer #1	Introduction	McPheeters et al. have compiled a 367 page, tour de force, systematic review assessing the comparative effectiveness of treatments for PKU. They have sought to tackle some of the toughest questions in the field of PKU management, and I congratulate them on their meticulous work, which has laid out the current state of evidence in one definitive document.	Thank you for your comments.
Peer reviewer #6	Introduction	Introduction and background (same comments apply to corresponding areas in Executive Summary) • Page 1: PKU…inability to properly metabolize protein" – PKU is an inability to metabolize the amino acid Phe only.	Corrected
Peer reviewer #6	Introduction	• P1: diet consists of carbs, fat and protein restriction with low-phe aa supplement, but not necessarily fruits and vegetables or low sat fat and low chol, foods.	Corrected

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Introduction	• P2: recommend adherence to a phe-restricted diet t/o life, but in practice, majority of older patients non-compliant and often outside of medical system an important point not noted. Current treatments often not reaching older patients, and examination of factors why is an important research question (only briefly mentioned on page 3 regarding maternal PKU, social support, home testing and outreach).	A reference for the recommendation that Phe-restricted diet be followed for life is now included in Introduction section. Future Research section modified to include a recommendation for studies to evaluate methods to improve adherence to diet throughout life.
Peer reviewer #6	Introduction	• P2: sapropterin not indicated to increase dietary Phe tolerance – was not adequately studied for "relaxation of low-phe diet", and not approved for this purpose. Authors note throughout no data to support this and sapropterin effects on long-term neurologic outcomes have not been studied.	Corrected
Peer reviewer #6	Introduction	• P3: seems to imply LNAA is a drug ("potential treatment") rather than an unregulated nutritional supplement of varying quality and composition- somewhat misleading	We have changed the word "treatment" in the first sentence of this section to "adjuvant therapy." Changed the term "medical foods" to "nutritional supplement" so LNAA are not confused with the medical foods we use for dietary restrictions.
Peer reviewer #6	Introduction	• P4: clinical uncertainties – being a rare disorder isn't only reason for limited data. Since patients treated at tertiary care and specialized centers, most patients identified on newborn screening for past several decades, and since relatively more common than a lot of other genetic disorders, a consistent public health effort to collect longer term data in registries potentially could have been performed (precedent for this in other rare disorders). A lack of coordinated efforts, commitment of public monies, and overall research plan to systematically address the gaps, among other factors, are additionally noted as contributing to uncertainties. Additionally, other clinical uncertainties noted in key questions (e.g., subgroups, phenotypes/genotypes, appropriate and consistent outcome tools, e.g., to assess executive functioning) and briefly noted in document (e.g., psychosocial factors affecting treatment, supporting factors) could be clustered here for a comprehensive list, perhaps using bullet points or numbering?	We have included this in the future research section.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Introduction	Definition of hyperphenylalaninemia in the phe range of >120 to < 1000 µmol/L – we are concerned that this range is too broad. A more recent review by Hanley in MGM, 2011 on hyperphenylalaninemia, provides a more appropriate definition of >120 to < 600 µmol/L. In this report, Campistol is also cited to be consistent with Hanley, defining hyperphenylalaninemia to be >120 to <600 µmol/L. We recommend that the definitions proposed by the NIH (Pediatrics 2001, 108:972-982) as well as in the publications by Scriver (Hum Mutat 2007, 28(9):831-845), Campistol and Hanley be included in the report.	We have clarified all uses of the word hyperphenylalanemia as it caused some confusion in the draft. We acknowledge that there are varying classification systems and do not present any particular one in the report. As noted, we used definitions provided by the authors of the studies and the use of these cutpoints did not affect our analysis.
BioMarin Pharmaceutical	Introduction	We request that the report correct the inaccurate statement that PKU is diagnosed using new-born screening (NBS). PKU is screened or detected using NBS. Diagnosis is confirmed through other biochemical testing.	We have corrected the text.
BioMarin Pharmaceutical	Introduction	Treatment of PKU Section - a. The draft report omits discussion of the literature on the low-phe diet in the management of PKU; it mentions only that diet is challenging to follow. The PKU diet has represented the standard of care in the management of PKU. This omission represents a significant limitation of the scope of the report.	Thank you for your comment. An explicit statement that Phe-restricted diet is the standard of practice has been added to the Introduction.
BioMarin Pharmaceutical	Introduction	Prevalence and Treatment Section - a. There is a statement that formula is described as low phe, though in the same sentence of the report it correctly states that the formula includes all essential amino acids except phe. This sentence is confusing and potentially misleading. We request that this be clarified.	We have clarified this sentence.
BioMarin Pharmaceutical	Introduction	Prevalence and Treatment Section - b.Monitoring phe just a few times a year in older individuals is contrary to what is recommended by the NIH suggesting monthly testing (NIH Consensus Statement PKU: Screening and Management. Volume 17, Number 3, Oct. 2000).	We have added text to this effect.
BioMarin Pharmaceutical	Introduction	Clinical Uncertainties Section - a. We are concerned that the studies from the maternal PKU collaborative study (Koch et al Pediatrics, 2003, 112:1523-1529) are incorrectly reported. We recommend that the reviewers incorporate the studies from the maternal PKU collaborative study (Koch et al Pediatrics, 2003, 112:1523-1529), as it would counter the report statement that pregnant women maintaining phe levels between 120 -360 µmol/L is uncertain.	We have added this reference and revised the section.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Introduction	We would encourage inclusion of published guidelines on management, patient selection, etc. of patients treated with sapropterin. These are described in papers by Levy et al in 2008 and Blau et al in 2009 in Molecular Genetics and Metabolism and Singh et al in 2009 in Topics of Clinical Nutrition (references cited below).	A review of guidelines would not be within the scope of this systematic review, but could provide additional information for individuals making treatment decisions or for future guidelines panels.
BioMarin Pharmaceutical	Introduction	b. The pivotal RCT which supported the FDA approval of sapropterin was done to look at the safety and efficacy of Kuvan combined with the phe-restricted diet in varying patient populations involving 579 subjects. We therefore believe this information should be reevaluated and more accurately reflected in the conclusions.	Our review did not include a review of loading data, which was used to assess potential response to Kuvan.The 579 participants noted here reflects all participants in the studies funded by BioMarin to gain approval for BH4. These studies included initial loading studies, which we interpreted as screening studies to identify potential responders. Our review was of the efficacy studies, which included only initial responders and are described in our report. Therefore, we focus on the longer term efficacy studies. Nonetheless, we have added a note in the results on the number of participants initially provided with Kuvan and the proportion who initially responded before being included in the efficacy trial that is included in our review.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Introduction	We would recommend inclusion of a discussion regarding psychological issues associated with prolonged hyperphenylalaninemia. Because of the importance of this issue, BioMarin is currently conducting the largest double blind placebo controlled study ever designed to evaluate the impact of Kuvan on psychological issues in PKU.	A comment about associated medical problems in treated PKU has been added to the Introduction. However, a systematic review of these psychological issues is beyond the scope of this review. Also, the data on treatment for these conditions is quite limited at this time. Therefore, comment about studying the psychological issues in treated PKU has been added to the Future Research section.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Introduction	**Body of Report** Please note that all comments made above regarding the ES also apply where the same text is included in the body of the report. We have not repeated these comments below.	We have revised the report.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Introduction	**Introduction** Page 1, Prevalence and Treatment, paragraph one. We recommended the following changes: "mainstay" to "established" "intake of *dietary* Phe ..."	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Introduction	Page 2, first complete paragraph. We recommended the following changes: Add "from food" to the end of the first sentence: "... individual ingests each day *from food*…	Corrected

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Introduction	We recommend that the sentence be changed as follows: “Based on the severity of the disease . . . can tolerate different quantities of total Phe intake. In infancy this prescribed amount of dietary Phe is based on body weight and growth. After early childhood it may be prescribed as a daily allowance."	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Introduction	Page 3, Role of LNAA, end of paragraph one. We recommend the following language: “Since LNAAs inhibit influx of abnormally elevated amounts of blood Phe into the brain ...” “In addition, LNAAs may lower blood Phe levels by competitively inhibiting ... tract.”	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Introduction	Page 3, paragraph two. The sentence, “Dosing is calculated by ... based on the amount of natural protein and Phe supplement in the diet.” The use of “Phe supplement” here is very confusing. Natural protein is the source of Phe in the diet. We suggest the following wording: “... based on the amount of natural protein (which provides the dietary Phe prescription) and Phe-free protein contained in the medical food.”	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Introduction	Page 3, paragraph three. Omit “as a second tier treatment.” Alternatively, include a statement that clarifies that a second tier treatment is an adjunct or alternate treatment. As stated, it implies that dietary compliance is a second tier treatment.	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Introduction	Page 3, Maternal PKU, paragraph three. It is unclear if the guidelines are recommending a home Phe monitor or just home collection of blood to send away for analysis. See comments for Maternal PKU section on Page ES-2 for further wording changes.	We clarified that the guidelines recommend frequent monitoring.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Introduction	Page 4, Clinical Uncertainties, third sentence. We recommend changing the sentence to read: “... when to prescribe sapropterin or LNAAs and in ...” This will remove the implication that LNAAs are drugs.	Corrected

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Introduction	Page 4. The last sentence: Implies that LNAAs are drugs.	We have been careful throughout to refer to LNAAs as nutritional supplements and not as drugs.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Pharmacologic Interventions Working Group (PKU- PIWG)	Introduction	**Comment 2:** Page 11 Study population The classification scheme that is used is not one that we have traditionally seen before. The referenced paper is from Spain and their figure I delineates the common classification systems used in differing countries. The USA more frequently uses a system where Classical PKU >1200 umol/L, mild PKU is 600-1200 and hyperphenylalaninemia (HPA) is 120-600. The Spanish group is proposing this new system based on their belief that all patients >360 umol/L need to be treated. While they make their case for using this particular classification system, they also state, "Controversy remains regarding at what level between 360 umol/L and 600 umol/L treatment may become necessary." We believe that the AHRQ should consider some of the more accepted classification systems or at least acknowledge the controversy.	In fact, we did not use a particular classification system in the report. Rather, as noted in the methods, we reported the classification system used by the authors of the included papers. We have removed the reference to Campistol paper as it caused some confusion but was intended as an example of a classification system.
Peer Reviewer #1	Methods	The inclusion and exclusion criteria are generally appropriate. In studies of Phe levels in relation to IQ, patients from 2-34 years. I didn't understand how a 2 year old's IQ could be measured.	Indeed, one study included young children and used developmental quotients for those individuals. This has been clarified in the results.
Peer Reviewer #1	Methods	Search strategy and listing of included and excluded articles is clearly stated. Definitions and diagnostic criteria are generally appropriate.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Methods	We could have a long debate about the validity of IQ testing methods and the high variability in the baseline IQ and standard deviations in the extraordinarily heterogeneous collection of Phe level studies. In addition, the authors themselves stated that choosing an IQ cutoff of 85 as a dichotomous variable is "subjective and problematic." It was reasonable in light of convenience of analysis, but not really defensible clinically. When it comes to loss of IQ in children with PKU, there is no tolerable level. However, I don't think that the authors would quarrel with my preceding statement, and nothing in the review supports and concept of "permissive hyperphenylalaninemia," so it is essentially a moot point.	We recognize the uncertainty related whether IQ is an optimal outcome, even among experts in the field. Nonetheless, it is an outcome frequently used in this body of literature and therefore amenable to analysis. The instruments used to assess IQ are standardized, valid and reliable in the age groups that they are designed for. IQ testing is used routinely in clinical practice and research assessments. The results frequently help guide the educational interventions that are provided to individuals with intellectual disability, learning disabilities, and other cognitive impairments.
Peer Reviewer #1	Methods	The statistical methods are appropriate.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	Methods	*Data sources and selection:* The decisions and comments regarding the literature available to review best reflect the lack of understanding permeating this report. The authors *a priori* excluded from consideration 97.5% of all literature published in the field in the review period. They claim that two thirds of the articles did not address the issues under consideration. This may be true, but given the lack of insight of the authors into the appropriate issues, it is impossible to be confident in their assertion without an extensive review of the articles excluded, a task well beyond the scope of this critique.	We have attempted to clarify these numbers. The initial literature review was purposely broad so as not to miss any relevant literature. The initial number reflects the total of abstracts and titles identified for all of the key questions, and included many publications that were not at all relevant (for example, animal studies). The proportion included in this review is consistent with other reviews in the EPC program, which take the perspective that it is better to begin with a review that is too broad so as not to miss relevant data. This results in more work up front and a higher exclusion rate, but ensures that we capture all possible studies.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	Methods	The authors then excluded over 90% of the remaining literature for not meeting requirements that were absurd in the context of rare disorders. For example, they included only clinical studies with greater than 10 patients, a ludicrous standard for rare disorder, and appear to make light of impressive double blind studies involving "only" 240 patients.	Thank you for your comment. In response, we have reviewed all treatment studies that were excluded solely for including fewer than 10 participants (Appendix A). There were fewer than 20 such studies, and inclusion of those small studies would not change the strength of evidence or any of the conclusions of this report. The list of studies excluded at the full text phase is provided in the appendix of the report as are the reasons for exclusion of each article.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	Methods	These latter studies represent a landmark in the field as they are the largest such ever conducted for any inborn error of metabolism. Instead of recognizing this achievement and the validity of the studies' conclusions, this review merely suggests that more data are necessary. No other rare diseases come even close to this level of evidence and thus the review essentially guts the entire field of treatment of inborn errors of metabolism.	We disagree that by reviewing the studies that do exist we have gutted an entire field. Rather, we hope we have shed light on the need for additional study. We acknowledge that smaller studies may contribute to the larger body of evidence. As noted above, in response to your comment and relevant concerns about exclusion of potentially important evidence, we analyzed those studies that had fewer than 10 participants (Appendix A). The intent of the review is to present in an unbiased manner the available evidence related to the key question, so that decisionmakers can make better informed decisions about care and also highlight areas where more research can benefit decisionmaking and outcomes for patients.
Peer reviewer #2	Methods	It is clear that the report should have considered small cases series, and even informative and well documented single case reports in reaching its conclusions.	We included case series in this report, and excluded only those with fewer than 10 participants. We believe this is appropriate for assessing efficacy. Nonetheless, as requested by this reviewer, we have assessed the potential impact of the studies excluded for including fewer than 10 participants

Commentator & Affiliation	Section	Comment	Response
			(Appendix A) and note that inclusion of those studies would not have changed any of our conclusions. Overall conclusions from these very small studies mirror those in the ones we included. Single case reports are considered anecdotal and such evidence is no more informative for treatment effectiveness rare diseases than it is for common ones. While it is true that very large, comparative and rigorous studies may never be possible, it is our responsibility to review what evidence exists and to assess the degree to which definitive conclusions can be made. It may be that for this rare disease, definitive conclusions may never be available based on the scientific evidence; individuals and panels making clinical decisions and guidelines will need to combine what scientific evidence there is with other information as noted above in determining a course of action.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	Methods	The likelihood of being able to conduct formal meta analyses in studies of rare diseases is low and should not be a goal of the report.	To the contrary, we were able to conduct a meta-analysis for Key Question 1 that we believe provides valuable information. Particularly in rare diseases in which studies are likely to be small, meta-analysis should be a goal as they can provide more rigorous scientific evidence by adding power to the studies.
Peer reviewer #6	Methods	Search strategies (P8-17) • Appear quite comprehensive and thorough.	Thank you for your comments.
Peer reviewer #6	Methods	• P7: analytic framework notes QOL as secondary outcome, but wasn't assessed in report. Secondary outcomes seemed to focus more on intermediate outcome measures, such as Phe levels.	We assessed the outcomes that were available in the literature. As noted in the methods, we sought longer term outcomes such as QoL but they were largely missing from the available research.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Methods	• P9 & 51-52: Unclear why regulatory reviews are “grey”. E.g., FDA uses raw data from clinical trials that are unbiased, independent analyses, and subject to site inspections to verify data – held to a higher standard than medical literature reports.	The term “grey” literature refers to data that is not published in the peer reviewed literature. It does not imply that they quality of research in this arena is less than the published literature. The reality, however, is that it is difficult to assess the quality of some grey literature, particularly conference abstracts, for example. There is also ample evidence of bias exisiting in FDA documentation due to selective outcome reporting, among other issues, so that work should be held to the same standards as published literature. There are ample references defining and explaining grey literature within the context of systematic reviews.
Peer reviewer #6	Methods	• P9 & 12: excluding studies of n<10 patients understandable, but since most of phe diet liberalization studies noted individual patient titration and were often, by necessity, quite small, may have limited this assessment in particular.	As noted previously, in response to comments during peer review, we assessed the potential for all studies excluded solely on the basis of size to change our conclusions. We determined that the totality of these studies would not have changed the conclusions of the review.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Methods	Inclusion/exclusion criteria and • Unclear why these age cut-points selected for children and adolescents, and for children overlaps critical and non-critical periods	We did not eliminate any studies based on ages of participants. We recognize that other subgroupings based on the critical age may have been appropriate and may be appropriate for future research.
Peer reviewer #6	Methods	Other criteria, synthesis, methods and analyses appear reasonable and appropriate. Rationale and descriptions are clearly stated and well-organized.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Methods	The limited body of literature from which to generate conclusions of this rare disease based on the minimum requirement of trial subjects (10 for this review), and for case reviews (20) demonstrate the issues associated with applying a standard CER framework to rare diseases. As a result of the above, inclusion of only 2 randomly controlled trials (RCT's) and 3 uncontrolled open label trials on sapropterin is extremely limiting, and illustrative of the challenges of applying the standard CER framework to a rare disease like PKU. The low prevalence of PKU makes it very difficult to conduct large studies. These criteria may have predisposed the authors to arrive at inconclusive results. We would suggest that a framework for the review of literature regarding rare diseases be developed that would make more allowance for small studies, case reports and grey literature as accepted and relevant scientific data to support evidence based treatment.	As noted above, in response to this concern, we have assessed the literature base of treatment studies with fewer than 10 participants (Appendix A). The findings of these smaller studies do not change our assessment. As noted above, we do not believe that the results are inconclusive; rather strength of evidence is a measure of our confidence that the current estimate will remain stable with further studies. The studies to date indicate that sapropterin is associated with a significantly greater lowering of Phe in the treated versus control participants, but that it is not effective in all initial responders and that we cannot predict the population in whom it will be effective, and that we do not have direct evidence on longer term outcomes. We anticipate that future research will be able to provide a much more stable and precise estimate of effect and ideally more direct evidence on cognitive effects.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Methods	We are concerned that the exclusion of the executive functioning data in the report is due to a restrictive definition. The report correctly states there are many tests to evaluate executive functioning. All of these tests will address one or more of the three domains of executive functioning including cognitive flexibility/shifting, inhibition control, and working memory. Additionally, processing speed, a related but not exclusive domain of executive functioning is not mentioned in this review, but it has been found to be impaired in PKU. By a broadened understanding of the array of executive functioning domains, we believe that evidence demonstrates a correlation between EF and phe levels.	We have added text to the report acknowledging the limitations of the methods for examining the impact of Phe on executive functioning. Certainly, this area of important research.
BioMarin Pharmaceutical	Methods	Key Questions Question 1: -We would like to suggest that to be more comprehensive and inclusive of the available literature, Question 1b should have age groups defined (see comments in Question 2 below).	The key questions for the report were developed with the assistance of key informants and were posted for public comment from November 8, 2010 – December 6, 2010. Therefore, we cannot change them at this time.
BioMarin Pharmaceutical	Methods	Key Questions Question 1: There are no questions addressing the dietary management of PKU despite it being the primary treatment for PKU. Please consider including this essential information in the report.	See the above response regarding the key questions and the scope of this particular review. This project is not intended to provide an overview of all treatments for PKU. A review of dietary management would have been a separate review and out of the scope of this project. Furthermore, dietary management is standard of care and it seems unlikely to meet the criteria of uncertainty for warranting a comparative effectiveness review, nor is it at all clear what the comparator would be in such a review.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Methods	Key Questions Question 1: -Review of the sapropterin product labeling would reveal that it should be used in conjunction with the phe restricted diet in the management of PKU. We are concerned that the report may not take into account the product labeling and the full body of literature supporting the FDA approval of sapropterin in the summary and conclusions of this report.	This systematic review consistently states that all treatments, including sapropterin, be considered as adjuvant treatments to dietary management. At no point does this review support or intimate endorsement of a treatment that does not include a Phe-restricted diet. Please see our comment above about why we excluded loading studies from this review, limiting the assessment to efficacy studies.
BioMarin Pharmaceutical	Methods	Key Questions Question 2: -We are concerned that to provide more meaningful understanding, subgroups should include the following to address this question: Where the report reads Adolescents ages 13 to 21 years old with PKU, we suggest that the report revisit how and why this age range was selected. Most studies we are familiar with classify the age range for adolescents with PKU between 13-18 years of age. We are concerned that by using a range up to 21 years old this report eliminated several studies, which could have supported adolescent outcomes and differing conclusions. In the US, many PKU clinics are oriented toward managing pediatric patients under 18. Thereafter, patients tend to leave clinic and manage their PKU by themselves without the benefit of support by qualified healthcare professionals. For this reason, most study investigators would likely use the 13-18 range for their study based on actual clinical experience.	As noted above, the key questions were established with input from the public and key informants and should not be retrofitted. That said, no data were available to conduct analyses by age groups. Studies were not excluded on the basis of age of the participants.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Methods	Article Selection Section – We are concerned that the criteria used to select the literature for this report led to the initial exclusion of 1672 of 2466 articles. Out of the remaining, a further exclusion of 728 articles resulted in the inclusion of only 66, comprising 43 unique studies. With only 43 unique studies to analyze, which are less than 5% of the total studies originally reviewed for consideration, we are concerned that it is difficult to arrive at conclusions regarding primary and secondary outcomes. These restrictive criteria and process do not seem to be consistent and appropriate with what might be a better way to evaluate literature in orphan diseases.	The proportion of initial citations included in our review is typical for this process. Our approach is to be widely inclusive at the search stage, which results in many titles and abstracts being included that do not include relevant data, but ensures that our search is highly sensitive and as such does not miss relevant data
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Methods	Page 7, Topic Development, paragraph one. Please include metabolic dietitians in the list of key informants as there were several involved in this process. Also, metabolic dietitians are primary clinicians who implement, monitor, and adjust dietary treatment for individuals with PKU.	Added
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Methods	Page 8, Figure 1 is missing in the draft report. While it is on ES-5, it would have been helpful to have it here as well.	We believe this was an issue with converting the report to a PDF file. The figure is visible in the final report.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Methods	Page 15, Grading the Body of Evidence. We like this more thorough description of important outcomes and suggest it be included in the ES.	We have added the more thorough description to the executive summary.
Peer Reviewer #1	Results	The attention to, and amount of, detail is a great strength of the review, and the characteristics of studies are clearly described. The key messages are stated succinctly and clearly.	Thank you for your comments.
Peer Reviewer #1	Results	Figure ES-1 is blurry. ES-3's print is too small, and the increments on the axes are too wide to read easily. In addition, the plasma phe concentration zone below 360 is not well visualized.	We have revised the figure.
Peer Reviewer #1	Results	I do not believe that the investigators overlooked any studies (and certainly no critical ones that I can think of).	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	Results	Key Question 1a: The report accurately acknowledges that high phe leads to lower IQ and serious anomalies in babies born to mothers with PKU. The report treats the issue of impairment of executive function in patients with high phe levels less intelligently. The report recognizes several key articles that demonstrate such an affect, but inappropriately dismisses them because they are not uniform in methodology and absolute outcome. This conclusion is inappropriate. It is essentially impossible to study every aspect of every rare disease in a classic clinical trial both due to a dearth of patients and a lack of funding for such studies. Instead, it is important to recognize clear trends indicated by studies that are conducted and include these in considering therapeutic recommendations.	No studies were excluded due to lack of uniformity in methods. Rather, we were unable to conduct a meta-analysis of heterogeneous papers. We provide what information we could in Appendix H and have ensured that all of the references are available for interested readers. In terms of the MPKU studies, we feel that our conclusions clearly acknowledge the relationship of maternal Phe and infant outcomes and that as we note, maternal Phe should be reduced as early as possible in pregnancy if not before to clinically acceptable levels.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	Results	Key Question 2. Development of medications to treat rare disorders is fraught with difficulty including available number of patients, ethical issues in the use of placebos that may lead to adverse outcomes due to natural progression of disease, and the dearth of funding to pursue such studies. In recognition of this, the FDA created its Orphan Products Office to encourage such development and help shape the studies in a way that will lead to clear answers in an ethically acceptable fashion. Sapropterin was the first (and still the only) medication approved by the FDA for treatment of PKU following a formal phase 3 clinical trials including a number of patientsunprecedented in a clinical trial for a rare disease. The phase 3 trials were preceded by equally unprecedented and stringent double blind placebo controlled trials. These studies clearly demonstrated a lowering of phe in nearly 50% of patients receiving the drug. In addition, some patients experienced an increase in phe tolerance leading to increased natural protein in their diet. The AHRQ report belittles these results, noting that a direct effect of Sapropterin on intellectual outcome was not demonstrated and acknowledges only that more study is necessary. This is a gross misunderstanding of the situation. In recognition of the nearly four decades of PKU research that unequivocally show that outcome in these patients is directly correlated with phe level, the FDA accepted lowering phe to be an acceptable surrogate marker in the Sapropterin studies. It is inappropriate to suggest that evaluation of every new therapy for a rare disease needs to recapitulate the knowledge base leading up to that study. The clear conclusion for Sapropterin is that it does lower phe in some patients, and its use is therefore justified in those patients as an aid to control their phe.	These points about the difficulty of conducting research on treatment for PKU are well taken and we have added comments to this effect in the background and discussion sections of the report. Our report examines the available evidence regarding the effect of sapropterin on both phe levels and tolerance and on longer term cognitive outcomes. We certainly do not intend to belittle the more immediate outcomes; to the contrary, we have provided separate evaluations for both types of outcomes. While it is true that the FDA accepted Phe levels as surrogate outcomes for the approval of sapropterin, they also requested additional commitment studies of longer term outcomes, We stress that both types of studies are important in order to understand the short term efficacy of the drug as well as longer term effectiveness.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	Results	Key Question 3. It is unlikely (and probably unethical) to examine the use of a medication known to lower phe in a pregnant woman with PKU. The report correctly notes that no studies were available, but an intelligent treatment of the topic should also acknowledge that based on the known teratogenic effects of phe, the use of Sapropterin is justified in those patients known to respond to it.	Again, the role of the EPC is not to make recommendations but to review the available scientific evidence for the specific key questions identified in this report. Groups and individuals making treatment and coverage decisions can incorporate contextual information into their decisionmaking.
Peer reviewer #2	Results	Key Question 4. There is no question that the use of LNAA's is less well established than Sapropterin in PKU. Nevertheless, existing data in the studies included in the report suggest it is a promising adjunct therapy in this disorder.	We stand by our assessment of the evidence. It is not our role to assess the degree to which evidence is promising but to assess the evidence as it currently exists.
Peer reviewer #2	Results	It should be noted that the report incorrectly states that LNAA's have not been shown to reduce phe in patients on a low phe diet. The referenced report by Matalon, et al, clearly demonstrated lowering of phe regardless of dietary phe intake.	We stand by our assessment that there is insufficient evidence to draw conclusions about the role of LNAAs in lowering Phe at this time, based on 3 very small studies.
Peer reviewer #2	Results	Key Question 5. Same comments as for Key Question 3.	Again, the role of the EPC is not to make recommendations but to review the available scientific evidence for the specific key questions identified in this report. Groups and individuals making treatment and coverage decisions can incorporate contextual information into their decision making.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	Results	Key Question 6. The conclusions of the report in this section perhaps best demonstrate the lack of attention and synthesis of the reviewed data shown by the review group. They quote a laundry list of side effects reported in the double blind Sapropterin trials but do not also report that they were no different or more frequent than the symptoms reported by subjects receiving placebo. Thus there were no demonstrable adverse effects attributable to Sapropterin. It is gross negligence on the part of the authors to suggest otherwise.	In fact, we report that the harms associated with sapropterin were mild, no more common than in the placebo when a comparison was available and that the drug was well tolerated. We have revised the text to make this point more clearly.
Peer reviewer #6	Results	Detail: • Limitations in the data are noted and bulk of evidence available for KQ1 only. Description and analysis for KQ1 are well done and informative. Key points in KQ1 objective and supported by descriptions in text.	Thank you for your comments.
Peer reviewer #6	Results	More breakdown by age subgroups for Q1b would be helpful if data permit – several more cutpoints are supplied in key question, but not incorporated in analysis (limited to critical and non-critical periods only). Conclusion is that need rigorous Phe control for life, but there appears to be very little data beyond young ages to fully support this conclusion, e.g., almost no data beyond adolescence.	As described previously, attempts to integrate age into the model were not successful.
Peer reviewer #6	Results	Study descriptions objective, clear, well-organized and thorough.	Thank you for your comments.
Peer reviewer #6	Results	Key points for KQ2-7 are informative, and particularly, note limitations that are supportive of overall findings of report.	Thank you for your comments.
Peer reviewer #6	Results	As previously stated, “harms” (KQ6) would have more meaning if consider risk-benefit in context of a serious disease with devastating neurological outcomes.	The assessment of risks versus benefits is the role of the users of this report. We have provided what evidence is available for the ability of interventions to change outcomes (short and long term Phe and cognitive outcomes) and have noted that harms observed were minor and no greater in the treatment versus placebo groups. That said, individuals using the report should also weigh the severity of potential outcomes of not treating in their development of guidelines.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Results	Figures and Tables: • P19: Figure 2 is a striking finding, especially very limited information in KQs 2-7. - suggest more emphasis in text in addition to figure.	The numbers in the PRISMA diagram are fairly typically for a comparative effectiveness review. We purposely begin with a broad and highly sensitive search in order to be sure not to miss any literature. Therefore, many papers are included in the intial numbers that are not relevant. We have noted that there is a lack of evidence overall for answering the key questions in this review.
Peer reviewer #6	Results	• P27&62: Figure 3&4 would benefit from a legend rather than having to refer back to the text.	The lines are labeled directly on the graph, so a legend is superfluous.
Peer reviewer #6	Results	• P29: Table 8 Detailed descriptions of outcome measures used in executive function very informative.	Thank you for your comments.
Peer reviewer #6	Results	Overlook any studies? • As previously noted, excluding studies with fewer than 10 patients understandable, but given rarity of disease, may have limited opportunity to assess some of key questions, such as diet liberalization.	Thank you for your comment. Studies with fewer than 10 patients have very limited statistical power and would in themselves offer very limited benefit for studying the key questions. Utilization of studies with fewer than 10 subjects could undermine the importance of our key questions. Nonetheless, we did assess the potential for those studies to influence our findings as noted above (Appendix A). Their inclusion would not have changed our conclusions.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Results	Regarding executive function, the omission of data from the large amount of published literature on the relationship between phe levels and EF limit the conclusions that can be made in this report.	We included all studies that met the criteria outlined in our methods.
BioMarin Pharmaceutical	Results	Also not included is the related literature on behavioral aspects of PKU (anxiety, depression, phobias, etc.).	This literature did not fit within the scope of this particular review. These areas are certainly of clinical importance. This report is a focused comparative effectiveness review, not a general overview of all literature related to PKU.
BioMarin Pharmaceutical	Results	We are concerned that the review suggests that both unpublished and gray literature were used to provide additional data, but only information that was submitted to the FDA for the evaluation of the safety and effectiveness of sapropterin is mentioned in the review. We request that the reviewers revisit and incorporate findings from existing unpublished and gray literature pertaining to all aspects of PKU disease, especially that regarding cognitive impairment in PKU.	As noted in the methods section, we searched extensively for grey literature, including, for example, conference abstracts and legal proceedings. The results represent what we were able to identify. This project had specific key questions, so grey literature not directly related to those questions could not have been incorporated.
BioMarin Pharmaceutical	Results	We are concerned that the exclusion of executive functioning data, and only including IQ data, greatly limits the utility of this report for adolescents and adults. This is because IQ is established in childhood. Therefore, the existing literature addressing executive function supports development of alternative outcome measures for adolescent and adult populations.	We agree that substantially more research, particularly treatment research, is needed in adolescents.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Results	We are concerned that there is confusion concerning the neurocognitive and psychological testing typically used in PKU. This confusion potentially compromises the ability to evaluate the research in this area. For example, very few studies (<5) were included on adult patients and IQ. Hence, we suggest that to do a meta-analysis and apply the outcome to all ages regarding optimal blood phe levels may not represent the most logical approach.	As indicated in the text, we initially added age as a covariate in the meta-analytic model, but this model was difficult to fit, and had convergence issues. The combination of the timing of measurement (concurrent and historical) and whether or not measurements were in the critical period does capture some characteristics of age. For example, if the measurement was concurrent and in the critical period, we know that they were children. If measurements were historical and not in the critical period, subjects had to be older (though not necessarily adults). Goodness of fit evaluation of the model showed good performance of the model for the adult studies (i.e. the data were reasonable samples from the posterior predictive distribution of the model for those studies)
BioMarin Pharmaceutical	Results	Also, the report authors observe there is a limited amount of data evaluating blood phe levels less than 500 µmol/L in adults. Current patient, payer, and health care system factors may impede adult PKU patients in many US jurisdictions from obtaining the needed healthcare support to maintain optimal phe levels. For this reason, we submit that it is difficult to truly determine the appropriate blood phe level recommendation in this age category. We observe that no mention was made of this unique clinical challenge in this report.	We have added a comment to this effect in the report in the section on applicability.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Results	We affirm that an appropriate association of phe levels and IQ data is made in this report. However, we are concerned that in the next section the authors describe their inability to associate optimal phe levels with executive functioning. The literature on the association of phe and IQ and phe and EF is very similarly compelling, which represents an inconsistency in the data reviewed for this report. (DeRoche et al Dev Neuro Psychology 2008, 33(4):474-504.	We did not identify a substantial literature meeting criteria for this key question. Furthermore, there is little agreement in the field about the degree to which individual measures of executive function can or should be combined in analyses. As noted in the Future Research section, this is an area that warrants substantial attention.
BioMarin Pharmaceutical	Results	There is no mention of the US Collaborative Study looking at long term outcomes of individuals with PKU, on and off diet, by Dr. Koch et al, which led to the recommendation of 'diet for life'. This was a positive and profound change in the historical management of PKU. This is therefore an extreme oversight in this report as this study has been incredibly important in the evolution of the current modern clinical management of PKU. (Koch et al JIMD 2002 25:333_346)	We have added this reference to the introduction and scope sections. Nonetheless, the goal of this systematic review is to review the literature that provides direct evidence to answer the key questions, not to provide an overview of the PKU literature. The Koch paper does not directly meet inclusion criteria for analysis.
BioMarin Pharmaceutical	Results	We are concerned with the observation that "a change to phe tolerance with sapropterin suggests that there is a large degree of variance in outcomes with sapropterin. This makes it difficult to predict response to medication due to this lack of uniformity of response in patients…" We would suggest inclusion of a discussion of all of the factors that impact blood phe and phe tolerance. A partial list of these factors would include the type of PKU mutation, severity of disease, growth, age, dietary Phe intake, physical activity, illness use of sapropterin, and the degree of response to sapropterin; all important variables explaining differences in outcome and response to the medication.	It is beyond the scope of this review to summarize the literature on all of the factors that may influence Phe levels. We do describe some of these in the background and a comment in the discussion.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Results	We too are concerned that there is limited data on use of sapropterin in pregnant women with PKU; this is challenging to study due to the rarity of these events. In light of appropriate current ethical standards in the US, no prospective study could be done in pregnancy with what has only been a therapy on the market for a few years. In this instance, the evidence cited in the report should include the existing case series published by Mosely and Koch and the abstract by the Tulane Medical group.	Thank you for this information about your ongoing studies. Case series with fewer than 10 individuals with PKU do not meet the inclusion criteria for this systematic review. They might be used, however, by groups making recommendations or guidelines.
BioMarin Pharmaceutical	Results	The report should also acknowledge that the PKUDOS registry, a post-marketing commitment being carried out by BioMarin, includes data on pregnant PKU patients in a sub-registry known as PKUMOMs.	This has been added
BioMarin Pharmaceutical	Results	We are concerned that the report does not acknowledge that the randomized clinical trials (RCTs) for sapropterin are multisite studies. This is an error in the information in the report. This leads to an unnecessary recommendation for the need for a multisite study.	We apologize for this oversight and have clarified that these are multisite studies.
BioMarin Pharmaceutical	Results	There are several studies that have evaluated genotype and sapropterin responsiveness. Several published studies report the inability to predict responsiveness based on genotype (Bercovich et al J Hum Genet 2008, Trefz et al JIMD, 2008, Zufluhet et al Human Mutation 2007).	We agree that to date genotype is not consistently predictive of responsiveness. This remains an area for future research.
BioMarin Pharmaceutical	Results	We are concerned that there is no discussion of brain white matter changes associated with blood phe levels in PKU or in relation to neurotransmitters and the impact of blood phe. We fear that this may suggest an inappropriately limited scope of the literature review and report regarding impact of blood phe and outcomes in PKU.	The association between white matter changes and Phe level is beyond the scope of this review and white matter changes were not a target outcome.
BioMarin Pharmaceutical	Results	We are concerned that discussions of other important outcomes in the management of PKU such as osteoporosis, obesity, as well as the full spectrum of neurologic complications are not included in the report.	We agree that these are important outcomes; however, they are currently not studies in the pharmacologic treatment literature.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	Results	In light of our observations about the limitations of the approach used in the evaluation of sapropterin in this draft review, we are concerned that studies regarding sapropterin, including at least 10 subjects are excluded from the report: Studies that should have been included regarding sapropterin, which have included at least 10 subjects are (complete reference listed below): a. Singh in JIMD 2010 assessing the impact of BH4 on nutritional status, b. Trefz in JIMD 2010 evaluating the long term effect of BH4 supplementation in children, c. Hennerman in MGM 2005 also looking at long term treatment of BH4, d. Vilaseca in Clin BioChem 2010 evaluating DHA levels in patients on BH4 compared to non-BH4 subjects, and e. Humphrey in MGM 2011 evaluating blood phe stability on BH4.	As noted above, we reviewed the treatment studies that were excluded solely on the basis of including fewer than 10 participants (Appendix A), and it is clear they their inclusion would not change the conclusions of the review. The Trefz and Humphrey studies were published after our literature pull, but have been added to the final version of the report.
BioMarin Pharmaceutical	Results	There are also several additional reports that include less than 10 subjects, particularly in the Maternal PKU literature with BH4 that should be included as well as abstracts and posters that have been reported at scientific meetings and which will soon be published. This would allow a more comprehensive analysis given that this medication has been recently approved. These references are listed below. Selected references pertaining to sapropterin: (as mentioned in above comments) Published Manuscripts: 1) Levy H, Burton B, Cederbaum S et al. Recommendations for evaluation of responsiveness to tetrahydrobiopterin (BH4) in phenylketonuria and its use in treatment. Mol Gen Metabol 2007; 92:287-291. 2) Blau N, van Spronsen FJ et al. Optimizing the use of sapropterin (BH(4)) in the management of phenylketonuria. Mol Genet Metab, April 2009, Vol.96, Pages 158-63. 3) Singh RH, Quirk ME, Douglas TD et al. BH4 therapy impacts the nutrition status and intake in children with phenylketonuria: 2-year follow-up. J Inherit Metab Dis 2010 DOI.1007/s10545-010-9224-1. 4) Burton BK. et al. Tetrahydrobiopterin Therapy for Phenylketonuria in Infants and Young Children. J Pediatrics March 01, 2011, Vol. 158, Pages 410-5. 5) Trefz FK, Scheible D, Frauendienst-Egger G. Long-term follow-up of patients with phenylketonuria receiving tetrahydrobiopterin treatment. J Inherit Metab Dis 2010 DOI 10.1007/s10545-010-9058-x. 6) Hennerman JB, Bűhrer C, Blau N et al. Long term treatment with tetrahydrobiopterin increases phenylalanine tolerance in children with severe phenotype of phenylketonuria. Mol Genet Metab 2005; 86:S86-S90. 7) Shintaku H, Kure S, Ohura T et al. Long-term treatment and diagnosis of tetrahydrobiopterin-responsive hyperphenylalaninemia with a mutant phenylalanine hydroxylase gene. Pediatr Res. 2004; 55: 425-430.	Thank you for these citations. Two of these studies met our criteria and are being included: Trefz FK, Scheible D, Frauendienst-Egger G. Long-term follow-up of patients with phenylketonuria receiving tetrahydrobiopterin treatment. J Inherit Metab Dis 2010 DOI 10.1007/s10545-010-9058-x. Humphreys M et al. Effect of BH4 on Phe/tyrosine ratio and variation in phe levels in BH4 responsive PKU patients. Molec Gen Metab 2011; doi:10.1016/j.ymgme.2011.05.011.

Commentator & Affiliation	Section	Comment	Response
		8) Vilaseca MA et al. Long term fatty acid status in PKU patients treated with BH4. Clin Biochem. 2010;43:411–415. 9) Humphreys M et al. Effect of BH4 on Phe/tyrosine ratio and variation in phe levels in BH4 responsive PKU patients. Molec Gen Metab 2011; doi:10.1016/j.ymgme.2011.05.011. Abstracts/Posters/Presentations presented at Scientific Conferences and soon to be published: 10) Gordon P, et al. Practice Patterns at Academic Medical Centers for Phenylketonuria (PKU) Patients previously enrolled in the SapropterinExpanded Access Program (SEAP) as compared to current commercial therapy for Sapropterin Dihydrochloride (Kuvan) Presented at ACMG Annual Clinical Meeting 2010. 11) Chapman M, Newman A, Gillis J. Diet Challenge as a Method of Determining Response to Sapropterin Dihydrochloride in a Patient with Well-Controlled PKU. Presented at ACMG Annual Clinical Genetics Meeting, March 2011. 12) Moseley KD, Azen C, Ottina MJ et al. Pilot study to evaluate the effects of Kuvan on adult individuals with phenylketonuria with measurable maladaptive behaviors. Presented at: SSIEM Annual Meeting, Istanbul, Turkey, Aug 31-Sept 4, 2010. 13) Burton B, Longo N, et al. Baseline characteristics of PKU patients enrolled in the PKUDOS registry. Presented at SIMD Annual Meeting, Asilomar, California February 27 - March 2, 2011. 14) White D, Grange D, Christ SE. Preliminary neurocognitive findings in individuals with phenylketonuria and treatment with sapropterin dihydrochloride (BH4). Poster presentation Presented at the Annual Society of the Study of Inborn Errors of Metabolism Symposium, 8-31 to 9-3-2010 Istanbul, Turkey 15) Adams D, Marra K, Clow C. Treatment with sapropterin in an individual with phenylketonuria and neurological impairment. Poster Presentation: Molecular Genetics and Metabolism 2009; 98: 17–38. 16) Christ SE, Peck D, Moffitt A et al. Brain function in individuals with PKU treated with Kvuan: evidence from functional magnetic resonance imaging (MRI). Poster Presentation: Presented at the Annual Society of the Study of Inborn Errors of Metabolism Symposium, 8-31 to 9-3-2010 Istanbul, Turkey 17) Cole A, Maritz C. Sapropterin treatment can lower blood phenylalanine levels and may allow dietary adjustment in adult patients: two case studies. Presented at European Phenylketonuria Group Symposium, Jan 22, Munich, Germany.	

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria (PKU) and Other Forms of Hyperphenylalaninemia Scientific Conference Pregnancy Working Group (PKU-PWG)	Results	Comment regarding Large Neutral Amino Acids in Maternal PKU Key Question 5 in the AHRQ report relates to the effectiveness of Large Neutral Amino Acids (LNAA) in pregnant women with PKU. The report concludes that the literature revealed no studies addressing this question. The report would be strengthened by including language cautioning that the use of LNAA therapy may not be appropriate in Maternal PKU (MPKU) because LNAA therapy does not reduce maternal blood Phe to a level safe for fetal development.	We indicated that no studies were located.
Phenylketonuria (PKU) and Other Forms of Hyperphenylalaninemia Scientific Conference Pregnancy Working Group (PKU-PWG)	Results	All medical foods for the treatment of MPKU contain some large neutral amino acids; traditional diet therapy for MPKU uses medical foods that also contain other amino acids (except Phe) and are used in conjunction with a Phe-restricted diet with the goal of reducing blood Phe. However, “LNAA therapy” refers to using medical foods that provide large amounts of the amino acids that share a common transport system with Phe across the blood:brain barrier in order to reduce brain levels of Phe (vonSpronsen 2010). LNAA therapy is used with a more liberal diet and is not intended to reduce plasma Phe. The primary target organ is the brain. Although studies have shown that LNAA therapy may also reduce plasma Phe by blocking uptake at the gut (Matalon 2006, 2007, Schindeler, 2007), the reduction was not sufficient to bring plasma Phe to a range safe for pregnancy (120-360 umol/L). In fact, The AHRQ report states: “three very small studies (total number of participants was 47) assessed LNAAs and reported no evidence that Phe levels were reduced to clinically meaningful levels”.	Text changed accordingly based on this comment.

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria (PKU) and Other Forms of Hyperphenylalaninemia Scientific Conference Pregnancy Working Group (PKU-PWG)	Results	LNAA alone may not support positive nitrogen balance needed for pregnancy. When only essential amino acids are fed, non-essential amino acids must be synthesized by the body. LNAA did not support positive nitrogen balance in 16-24 year olds with PKU who were fed large neutral amino acids without added lysine (Dotremont, 1995). During pregnancy, nitrogen requirements are greater than in the non-pregnant state due to protein synthesis within maternal and fetal tissues. The role of osmolarity of the LNAA mixture must also be considered since L-amino acids are small molecules that contribute to the osmolarity of medical foods. Hyperosmolar mixtures can cause abdominal cramping, diarrhea, distention and nausea, which is of concern given that 50% of women experience some hyperemesis gravidarum during pregnancy (Baylis, 1983) and the consumption of LNAA may exacerbate these symptoms. References: Baylis JM, Leeds AR, Challacombe DN. Persistent nausea and food aversions in pregnancy. A possible association with cow's milk allergy in infants. Clin Allergy. 1983 May;13(3):263-9. Dotremont H, Francois B, Diels M, Gills P. Nutritional value of essential amino acids in the treatment of adults with phenylketonuria. J. Inher. Metab. Dis. 1995 18:127-130. Matalon R, Michals-Matalon K, Bhatia G, Burlina AB, Burlina AP, Braga C, Fiori L, Giovannini M, Grechanina E, Novikov P, Grady J, Tyring SK, Guttler F. Double blind placebo control trial of large neutral amino acids in treatment of PKU: effect on blood phenylalanine. J Inherit Metab Dis. 2007 Apr;30(2):153-8. Matalon R, Michals-Matalon K, Bhatia G, Grechanina E, Novikov P, McDonald JD, Grady J, Tyring SK, Guttler F. Large neutral amino acids in the treatment of phenylketonuria (PKU). J Inherit Metab Dis. 2006 Dec;29(6):732-8. Schindeler S, Ghosh-Jerath S, Thompson S, Rocca A, Joy P, Kemp A, Rae C, Green K, Wilcken B, Christodoulou J. The effects of large neutral amino acid supplements in PKU: an MRS and neuropsychological study. Mol Genet Metab. 2007 May;91(1):48-54	We have noted that no studies addressing the use of LNAA in pregnancy were located.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Results	Page 20, Key Points, third bullet. Please clarify what is meant by this bullet. Is this referring to a historical average measurement rather than a single measurement? If so, the term, “historical” should then be used throughout the report.	We clarified this text in the Results section.

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Results	Page 31, Phe Levels and Maternal PKU, Key Points, second bullet. "…with a target of 10 weeks postconception to mitigate poor outcomes." This sentence appears to say that a pregnant woman would have to achieve control by 10 weeks. This is the end of organogenesis. Using this as the target focuses on cognitive outcomes only and is misleading when establishing an overall target to prevent the other consequences of MPKU.	We have revised this text to make it clear that ideally women should have appropriate Phe levels before conception.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Results	Additionally, in the Detailed Analysis that follows, the third sentence from the bottom of the page states that "children of mothers who were treated prior to pregnancy had the best outcomes..." Not including this in bullet two may mislead readers.	We have added this phrase to the bullet.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Results	Page 36. The word "supplements" used in this context to refer to the Phe added to a patient's diet above their usual dietary Phe intake, pre-sapropterin needs to be defined as such. We suggest "supplementary Phe added in controlled amounts to a patient's usual dietary intake."	We have revised this sentence to be more clear.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Results	Page 45, Table 13, Overview of Studies. Since brain Phe is mentioned in the body of the report, it would be important to identify that "Phe Levels" in the column heading is referring to blood Phe (assuming this is always the case in the articles reviewed).	We have made this change.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Results	Page 47, Clinical Trials, paragraph three. In line five, a reference is made to "median brain Phe level <450 mol/L" which we believe is refers to blood Phe, not brain Phe. We suggest that reference 112 be carefully reviewed to determine accuracy of this statement.	Corrected

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Results	Page 51, Grey Literature. We do not see that professional association sources, such as genetic and dietetic associations, were searched for grey literature. We feel this is an important oversight.	We did an extensive grey literature search. Please note that we would only include information from the grey literature that met inclusion requirements; ie. Grey literature would need to provide data related to treatment effectiveness. There is important information for patients and clinicians available through professional organizations, but not effectiveness data from studies that meet criteria for inclusion in our review.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Results	Pages 54 and 55. The post-marketing commitment study 7) is not listed on page 54.	Corrected
Peer Reviewer #1	Discussion	My main argument with the review is the following conclusion drawn by the authors: "the strength of evidence for the effects of saproprterin on Phe levels is low." I disagree. The strength of evidence, based on two randomized controlled trials as well as open label extension studies, is high, by my reading of the Methods Guide. The existing research has defined an estimate of the effect that is unlikely to change (given the experimental circumstances of the trial). As the authors noted, "At the end of 6 weeks of treatment, 32 percent of the treated group had achieved Phe <360 µmol/L, compared to 2 percent in the placebo group (p<0.001)." This is certainly not a subtle effect of sapropterin on Phe levels, albeit under tightly controlled experimental conditions, and with a run-in responsiveness phase. This is convincing, likely stable, evidence of efficacy, and there is no reason to believe that a larger clinical trial is needed to re-investigate the question of sapropterin's efficacy on Phe levels. No need to reinvent that wheel.	The strength of evidence is assessed separately for each outcome. In order to better present the strength of evidence for this review, we have further parsed the results to assess SOE for the short term effect of sapropterin on Phe levels separately from longer term cognitive effects, taking into account the moderate strength of evidence for understanding the Phe-IQ relationship. We have reworded the conclusions about strength

Commentator & Affiliation	Section	Comment	Response
			of evidence to be much more specific and to recognize that, as noted, sapropterin is clearly associated with a clinically relevant decrease in Phe levels over the short term, in a subset of individuals. It is unclear why it is effective in some individuals but not others, nor is is possible to predict which individuals will have a positive response. We maintain that the strength of the evidence on the relationship between sapropterin and cognitive outcomes is low because although there is moderate strength of evidence for the relationship of sapropterin and Phe and for the relationship of Phe and cognitive outcomes, the relationship between sapropterin and cognitive outcomes is indirectly assessed and based on few studies. We note further that SOE does not equate to effectiveness; it simply describes the level of confidence that we have in the estimate of effect currently seen in the limited literature. Future research may provide a more accurate and precise measurement of the degree to which sapropterin affects

Commentator & Affiliation	Section	Comment	Response
			cognitive outcomes Furthermore, the evidence threshold to change clinical practice is something that is determined by decisionmakers, and not by an evidence report. For this reason, evidence reports inform clinical practice guidelines, and do not replace the judgment of providers especially in areas where there is uncertainty.
Peer Reviewer #1	Discussion	In addition, while I share the concerns listed by the authors about the broader applicability of existing sapropterin research on important clinical outcomes such as quality of life and cognition, and agree with the complaint that, if only 32% of patients met the < 360 goal, that leaves 68% who didn't, 32% success is enormously better than 2%. I think the argument is really about whether, and to what degree, patients can be coaxed to achieve better dietary control of Phe levels, without reliance on sapropterin. Clearly, this is a question of value rather than efficacy. Sapropterin clearly lowers Phe levels in certain patients defined as "responders." Do the authors dispute that? Or am I misreading their use of the term "low" level of evidence.	It is important to note that SOE does not equate to effectiveness; it simply describes the level of confidence that we have in the current estimate of effect currently seen in the limited literature as one unlikely to change with further examination. Future research may provide a more accurate and precise measurement of the degree to which sapropterin affects cognitive outcomes. The evidence threshold to change clinical practice is something that is determined by decisionmakers, and not by an evidence report. For this reason, evidence reports inform clinical practice guidelines, and do not replace the judgment of providers especially in areas where there is

Commentator & Affiliation	Section	Comment	Response
			uncertainty. We have reworded the conclusions about strength of evidence to be much more specific and to recognize that, as noted, sapropterin is clearly associated with a clinically relevant decrease in Phe levels over the short term, in a subset of individuals. It is unclear why it is effective in some individuals but not others, nor is is possible to predict which individuals will have a positive response. We maintain that the strength of the evidence on the relationship between sapropterin and cognitive outcomes is low because although there is moderate strength of evidence for the relationship of sapropterin and Phe and for the relationship of Phe and cognitive outcomes, the relationship between sapropterin and cognitive outcomes is indirectly assessed at this time and based on few treatment studies.
Peer Reviewer #1	Discussion	I believe that the authors need to carefully reword their conclusions to stress the limitations and insufficient evidence of broad effectiveness on a wide range of clinically meaningful outcomes while also acknowledging convincing proof of efficacy in the setting of randomized controlled trials. I consider myself to be exceptionally skeptical, but I do not doubt that sapropterin lowers Phe levels in certain patients. Nor do my patients seem to have any doubts.	We have reworded the conclusions about strength of evidence to be much more specific and to recognize that, as noted, sapropterin is clearly associated with a clinically relevant decrease in Phe

Commentator & Affiliation	Section	Comment	Response
			levels over the short term, in a subset of individuals. It is unclear why it is effective in some individuals but not others, nor is is possible to predict which individuals will have a positive response. We maintain that the strength of the evidence on the relationship between sapropterin and cognitive outcomes is low because although there is moderate strength of evidence for the relationship of sapropterin and Phe and for the relationship of Phe and cognitive outcomes, the relationship between sapropterin and cognitive outcomes is indirectly assessed and based on few studies. We note further that SOE does not equate to effectiveness; it simply describes the level of confidence that we have in the estimate of effect currently seen in the limited literature. Future research may provide a more accurate and precise measurement of the degree to which sapropterin affects cognitive outcomes. Furthermore, the evidence threshold to change clinical practice is something that is determined by decisionmakers, and not by

Commentator & Affiliation	Section	Comment	Response
			an evidence report. For this reason, evidence reports inform clinical practice guidelines, and do not replace the judgment of providers especially in areas where there is uncertainty
Peer Reviewer #1	Introduction	McPheeters et al. have compiled a 367 page, tour de force, systematic review assessing the comparative effectiveness of treatments for PKU. They have sought to tackle some of the toughest questions in the field of PKU management, and I congratulate them on their meticulous work, which has laid out the current state of evidence in one definitive document.	Thank you for your comments.
Peer reviewer #6	Introduction	Introduction and background (same comments apply to corresponding areas in Executive Summary) • Page 1: PKU…inability to properly metabolize protein" – PKU is an inability to metabolize the amino acid Phe only.	Corrected
Peer reviewer #6	Introduction	• P1: diet consists of carbs, fat and protein restriction with low-phe aa supplement, but not necessarily fruits and vegetables or low sat fat and low chol, foods.	Corrected
Peer reviewer #4	Meta analysis	The authors used a Bayesian hierarchical model to estimate the association between blood phenylalanine levels with IQ with detailed information about the model provided in Appendix F. The overall model framework is sound. The description of the model for the individual patient level data is clear.	Thank you for your comments.
Peer reviewer #4	Meta analysis	However, the description of using summary data from some studies is needs more clarification. Presumably information from the summary data would be combined with the estimates from individual level data (and as suggested by the DAG), however, this is not reflected in the description of the methods and it is not clear whether μ_α and α_1 are estimated using information from both sources. It also helps to associate μ_α and α_1 with Baseline or Critical period effect (not exactly an effect) to improve clarity.	The DAG (Appendix F) provides some clarification. mu_alpha and alpha_1 both have direct parent-child relationships with the slopes for both sources of data. We did not model the baseline effect as a function of these parameters, but rather as a pure random effect. The Methods text specifies where components of the model differ based on the type of data provided by the studies.

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Peer reviewer #4	Meta analysis	The interest of statistical inference should be μ_α and α_1. However, for summary data, the description of methods seems to be reversed. For example, for $\rho_j = \beta_{1j}\left(\frac{s_{xj}}{s_{yj}}\right)$, estimate of β_{1j} is not usually not known from the published study and needs to be calculated from the correlation coefficient. It is not clear about the usefulness of $\operatorname{arctanh}(r_j) \sim N\left(\operatorname{arctanh}(\rho_j), \frac{1}{\sqrt{n_j-3}}\right)$ in this context -- get the SE for β_{1j}? Methods need to be described on how to estimate μ_α and $\alpha_1$from the reported data and how to combine with individual patient level data.	We changed the equation by solving for beta_1. We have added additional text to clarify the utility of the arctan(r) distribution – it is ultimately a measure of precision of the estimated slope for that study. The DAG explicitly relates how information is combined, and we have attempted to clarify further in the text.
Peer reviewer #4	Meta analysis	Delete the paragraph on partial pooling and later reference. Random effects models are routinely used in meta-analysis and the term of partial pooling is not widely accepted in the Meta-analysis literature. It is confusing to use the term.	Although the term may not be commonplace in this literature, it is a very important concept, and useful in communicating with non-statisticians. Since the term has been explained in the text, it should not be confusing for anyone.
Peer reviewer #4	Meta analysis	Also independently and identically distributed (iid) is not any tenuous assumption – iid random variables are exchangeable.	iid random variables are exchangeable, but exchangeable variables are not necessarily iid. We are assuming exchangeability here, not independence.
Peer reviewer #4	Meta analysis	It is useful to do a sensitivity analysis using a different cutoff points such as 70 for the probability of impairment.	That is beyond the scope of this current review, but we anticipate conducting such a sensitivity analysis in the future.

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Peer reviewer #4	Meta analysis	In the results section, the results from the linear mixed model were greatly over-interpreted. Although Bayesian inference does not have a P-value to claim significance, however, the 95% BCI has been used as evidence to indicate "significant" results. Based on Table 6, 95% CI for the estimate of critical period effect includes zero for both Historical and Concurrent models. The 95% CI for the estimate of baseline effect seems to be borderline for the concurrent model. Therefore except for Baseline Phe effect for the historical model, the results from the linear mixed model do not provide convincing evidence for the other effects, and the results should be interpreted so. However, the report presented the results as if there are associations for each of the four cases, which is true. Estimates for critical period effect for historical vs. concurrent model also have different direction, adding more uncertainty to these results.	We are not hypothesis testing in this review, so the notion of statistical significance is irrelevant. This is an estimation exercise, so the calculation of precision is what is relevant. Choosing the overlap of an interval with zero is arbitrary and not related to any clinical notion of significance.
Peer reviewer #4	Meta analysis	Page 20, most key points are over-statement without statistical basis and should be rewritten. For the concurrent model, it needs to show there is an association first, instead of saying "lack of strong association".	We have revised some of these points, but we believe the conclusions are reasonable based on the estimates illustrated in Figure 3, and particularly in light of the Bayesian approach that properly integrates uncertainty among modeled parameters.

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Peer reviewer #4	Meta analysis	Similarly, for table 7 and figure 3/Figure (and Figure 4 – they are the same plot), they are created based on the same over-interpretation of the results. It is not justified to create two lines (columns) for each model. There are always numerical differences when looking at a variable like critical period but an association could only be claimed with enough evidence. In relating to Table 7 and Figure 3, the description of results in pages 25-27 needs to be revised accordingly.	The figures are presented in the results section and the discussion. We prefer to retain both. Table 4, however, warrants 4 columns, as they represent 2 different groups from 2 different models. The probabilities in these tables and figures are the results of integrating over the posterior predictive distribution for IQ, across the specified range of Phe. So, it accounts for parametric uncertainty throughout each model. Hence, we believe this to be evidence of a clear relationship between these two variables. This is outlined in Appendix F, though we thought the details to be too technical for the main report.
Peer reviewer #4	Meta analysis	The discussion part for KQ1 results should also be revised accordingly.	See previous response
Peer reviewer #4	Meta analysis	Tables 4 and 5 For the column of Type of measurement, it is more clear to create two columns, one as historical vs. concurrent and the other is the status of critical period. -- Could all available data be classified into one of these four categories?	There was a 3rd time period – recent measurement (>6 weeks but <1 year)--but there were no studies in our meta-analysis set that included such data.
Peer reviewer #4	Meta analysis	ES – 7 It is confusing to say “the primary outcome was an IQ below 85” for the analysis in the meta-analysis section. For the statistical model, the outcome (dependent variable is IQ score itself).	We have replaced this sentence.
Peer reviewer #4	Meta analysis	Page 16, line 33 “readily combines both fixed and random effects”? -- not accurate way to describe the methods.	We have edited this.

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Peer reviewer #4	Meta analysis	Page 17, line 19, continuous parameters? Just say linear model coefficients.	We have changed text accordingly
Peer reviewer #4	Meta analysis	Page 17, line 23-24, it is the association between Phe and IQ, not effect.	We have changed text accordingly
Peer reviewer #4	Meta analysis	Page 17, line 29-30 "for each combination of predictors" – well, except for blood phenylalanine levels, there is only one more predictor (critical period) in the model and won't be a real combination. Describe the methods more accurately.	We have clarified this sentence.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Discussion	Page 64, paragraph four. We recommend omitting "surprisingly" as it is an editorial comment. There are at least 13 studies enrolling subjects listed on ClinicalTrials.gov as of October 14, 2011. This prospective body of research is not reflected in this discussion.	Deleted surprisingly
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Discussion	Page 65, paragraph two. The sentence describing liberalization of diet, "The practical implication of this result . . . she might be able to liberalize her diet by consuming an additional 8 ounces of milk, or adding 8 about 1 ounce of meat, or . . ." should be omitted or clarified. Is the intent to refer to a routine liberalization used for short periods of time during a study or to editorialize and suggest that this is a specific level of liberalization that would be achieved for all patients on sapropterin? Since the response was not uniform in the study, this example can be misleading.	We have clarified that this is an example.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Discussion	Page 72, first paragraph, last two sentences. These differences in study populations of the two RTCs reflect the trend in the PKU population as they age from childhood into adolescence and adulthood of relaxing dietary control, resulting in increases in blood Phe levels. It should be noted that the 2000 NIH Consensus Development Conference Statement (NIH, 2000) specifically recommended maintenance of blood Phe levels between 2 and 6 mg/dL from infancy through 12 years of age. For adolescents and adults, Phe levels were recommended to be maintained between 2 and 15 mg/dL, an implicit relaxation of dietary control. While the NIH Consensus Development Conference Statement cutoffs for adolescents and adults have not been embraced by all metabolic specialists, it confounds the conclusion that older participants had poor dietary control.	We have clarified the sentence.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Discussion	Also, please provide the citation for the "two RTCs" mentioned in the second line at the top of page 72.	Added

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Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Discussion	Page 72, paragraph one: Change line 6 to "*blood* Phe"	Corrected
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Discussion	Page 72, paragraph two: Omit "surprisingly" as inappropriate judgment.	Deleted
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Discussion	Page 73, second paragraph, last sentence: We would like to see more documentation for the statement that "some proportion of individuals who have an initial response do not have a durable response even over a few weeks."	All of the individuals in the trials were initial responders as an early response to sapropterin is a requirement for inclusion. Therefore, the fact that more than 60% did not demonstrate a positive response is evidence that some proportion of individuals do not have a durable response. We have added clarification.
Peer Reviewer #1	Discussion/ Conclusion	The implications of major findings are clearly stated, though I don't necessarily agree with all the conclusions, as I will describe below in section f. The limitations of the observational studies are underemphasized, and the limitations of the randomized controlled trials and subsequent open-label trials of sapropterin are overstated, in my opinion.	Please see revised conclusions in which we have provided additional information.
Peer Reviewer #1	Discussion/ Conclusion	No important literature was omitted.	Thank you for your comments.
Peer Reviewer #1	Discussion/ Conclusion	The future research section needs more thought. What more do we need to know about the cognitive hazards of Phe levels in different age groups? Tight control in all age groups, if patients are able to adhere to diet, is the current standard of care. Perhaps more research is needed in order to know just how imperative such tight dietary control is across the lifespan. We know little in older adults, for example. I would challenge the authors to be more explicit and creative in coming up with suggestions for future research.	We have substantially revised and expanded the section on Future Research, taking into account your suggestions.

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Peer Reviewer #1	Discussion/ Conclusion	In addition, with respect to future research on sapropterin, the current approach is to try it and see if Phe levels decline. It will be challenging to define groups in which there is no possibility of benefit, so that individuals in such groups can be confidently told by their physicians that a trial of sapropterin is futile. I don't see this as a key avenue for future research.	Future research may indeed identify a subpopulation of individuals with PKU in whom sapropterin does not work or the harms outweigh the benefits. I think this should stay in the Future Research section.
Peer Reviewer #1	Discussion/ Conclusion	What seems most important to me is to determine exactly what benefits (and/or harms) patients are deriving from sapropterin. A more precise and comprehensive idea of the value of this drug would be important for policymakers, particularly given the expense of the drug.	We could not agree more. This review already seeks to identify the benefits and potential harms of sapropterin. Given the limited data to date on this topic, additional research in this area is imperative to address this comment.
Peer reviewer #2	Discussion/Conclusions	Overall, this is a troubling and flawed report by the AHRQ review group that fails to reach the obvious conclusions based on the overwhelming level of evidence in the literature. The authors correctly note that lowering phe is beneficial and that medications such as Sapropterin and LNAAs can lower phe They fail to make the critical connection that these medications are therefore valuable adjuncts to diet in the treatment of PKU. The report should be rejected as unacceptable.	As a systematic review, the goal of this project is not to make recommendations but the assess the current state of the research. Your comment is directed toward groups making guidelines or individuals making clinical decisions who may take into account additional information in addition to a systematic review in making those decisions.
Peer reviewer #6	Discussion/Conclusions	Major findings clearly stated? • Yes, and generally conform to key points in results section	Thank you for your comments.
Peer reviewer #6	Discussion/Conclusions	Limitations clearly state? • Yes. Current gaps in knowledge are substantial, stated repeatedly throughout the document, and well-supported by study descriptions and literature review.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Discussion/Conclusions	Discussion points • P65: goals of short-term sapropterin studies were to demonstrate pharmacodynamic effect of treatment on Phe levels, not to achieve phe <360. Since incomplete response or, in many patients, non-response to treatment expected based on mechanism of action of drug, target levels without dietary intervention not basis of approval, and as noted by report authors, is a pharmacologic adjunct to treatment.	As mentioned earlier, we need to emphasize the mainstay of treatment is dietary intervention and needed efforts to address adherence, and effects of liberalization of diet in adolescents and adtuls…therefore BH$ adjunctive treatment (though the trials were conducted in an adult population who was noncompliant with the medication
Peer reviewer #6	Discussion/Conclusions	Additionally, risk of cognitive impairment rises with increments in phe level (to plateau of ~2000 per Figure 4), so attenuation of risk (or still unknown effect on executive function) rather than complete response to drug may still be of value, but clearly needs additional study.	We agree.
Peer reviewer #6	Discussion/Conclusions	Future research section clear and easily translated into new research? The most striking finding of this report is that despite many decades of diagnosis and identification of patients early on through newborn screening, and long-standing availability of an effective intervention (diet intervention and low-phe formulas), the authors have clearly documented a profound lack of reliable, long-term, prospective research into critical questions for PKU. As stated by the authors throughout the document, there is a need for more data on: • Exact relationship between Phe level and cognitive outcomes Consistent methodology to assess outcomes, including reliable clinical outcome assessment measures and tools (beyond IQ), and consistent data collection across treatment centers. • Lack of research into prognostic, predictive and response characteristics (e.g., phenotype/genotype), patient subgroups, and other characteristics. • Long-term effects on major clinical outcomes (neurocognitive development) and risk-benefit of sapropterin treatment, and reliable assessment of short- and long-term effects of LNAAs	Thank you for your comments. We have added to the Future Research section to emphasize some of these points.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Discussion/Conclusions	I believe this document would benefit from a clearer statement of specific research needs and strategies, and a ranking/listing of research priorities based on the authors findings.	We have substantially revised the future research section of the report. Ranking of research priorities is beyond the scope of the CER, and would be an appropriate part of a separate type of AHRQ project known as a Future Research Needs project.
Peer reviewer #6	Discussion/Conclusions	The future research goals stated on pages 70 - 72, although well supported by the findings in the report, are quite general, and don't appear to easily communicate specific needs for new research or how these goals will be achieved.	We have substantially revised the future research section of the report.
Peer reviewer #6	Discussion/Conclusions	If possible, a numerical list describing a comprehensive strategy to better meet the many and diverse needs of the patients could be generated. For example, drawing from experience in other rare genetic diseases (e.g., Cystic Fibrosis, muscular dystrophies) where long-term strategies and priority lists of research needs have resulted in considerable progress in patient care, targeted interventions, and outcome assessments, suggest the authors consider something similar for PKU. For example, this could include: • An overall PKU plan that considers all age groups and the multiple priorities noted in this report. The results in this report show poor neurologic outcomes in patients in recent studies, with resultant long-term educational and social support needs for patients and their families, so appears such a plan could be justified on a public health basis. For example, establishment and ongoing support of a steering/expert committee to define immediate and long-term research priorities and investment of public monies to ensure reliable support of this research (e.g., a 10-year plan).	See comment above about the scope of this effort vis a vis a Future Research Needs project.
Peer reviewer #6	Discussion/Conclusions	[future research needs] • Establishment of long-term prospective registries/natural history studies for PKU, or public-private support of the existing PKDOS, with a comprehensive listing of disease characteristics to be collected.	We have added this idea to the future research section.
Peer reviewer #6	Discussion/Conclusions	[future research needs] • Establishment of a research consortium to harmonize data collection, outcome assessments and patient care. Collaboration and harmonization with international research, funding and regulatory agencies could also be considered. Larger, multi-center, long-term study of LNAAs and sapropterin, as well as additional investigational agents as they become available, could be better supported by this consortium.	We agree with this excellent idea and have added it to the proposed future research section .
Peer reviewer #6	Discussion/Conclusions	[future research needs] Translational research to develop clinical outcome assessments into important aspects of the disease.	See previous comment.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Discussion/Conclusions	[future research needs] • Attention to patient care and intervention strategies to better support older patients, particular as findings in this report support tighter phe control throughout life.	See previous comment.
Peer reviewer #6	Discussion/Conclusions	[future research needs] Biorepositories to define PKU genotypes/phenotypes important to prognosis, and predictive of treatment response.	See previous comment.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Appendices	We commend the report authors for their efforts to summarize and provide the evidence tables in Appendices C and E. They are very nicely done.	Thank you for your comments.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	Appendices	The summary provided in Appendix H is very interesting and we acknowledge that even though the effects of diet on blood Phe levels are not specifically addressed in this report, it was noted in the evidence tables. It might be useful to readers of the report to be made aware of the contents of these appendices given that many people do not read beyond the body of the report.	The evidence tables reflect whatever data were available in the studies. However, they will in no way provide complete information on the effects of diet on blood Phe levels as we did not search systematically for the entirety of this literature base.
Peer Reviewer #1	Clarity and Usability	Clarity and Usability: The report is highly structured, and well organized. By design, it includes a lot of information that will be of interest only to particular readers. The conclusions can be used to inform policy and practice decisions. First and foremost, this review has aggregated and expertly analyzed the data that support the need to treat PKU and keep the levels below 360 if possible. There are still lingering questions about the effects of liberalizing the diet in adolescents and adults, but not in young children nor pregnant women.	Thank you for your comments.
Peer reviewer #4	Clarity and Usability	The report is clear.	We appreciate your thorough review of our statistical methods.
Peer reviewer #6	Clarity and Usability	Yes, well-organized, thorough, logical progressive and clear descriptions throughout report.	Thank you for your comments.
Peer reviewer #6	Clarity and Usability	Main points clear and easy to locate	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Clarity and Usability	• Conclusions are clear and supported, but defining future directions and research could benefit from a little more clarity (see Discussion and Conclusions section comments above)	Thank you for your comments. Changes have been made to the future directions and research sections to improve clarity
Peer Reviewer #1	General	This report is clinically meaningful, but unlikely to alter clinical practice. One of its merits is reinforcement of the necessity of maintaining phenylalanine levels as low as practically possible in children.	Thank you for your comment. Though not a primary goal of this review, we appreciate your comment that this study reinforces the cornerstone of treatment to maintain low Phe levels through the use of Phe-restricted diet and possibly other adjuvant therapies. It is important to note that the evidence review is not a clinical practice guideline. It may be used by guideline developers or other decision makers along with other clinical information, but it is meant to inform guidelines, but not intended to direct practice.
Peer Reviewer #1	General	The target population and audience are explicitly defined. Key questions are appropriate and explicitly stated. However, the key questions were not all answerable by the existing corpus of research. Some questions were more amenable than others, given the highly heterogeneous group of existing studies.	Since some of the key questions were not answerable by the existing corpus of research, we contend that these questions lend themselves to future research opportunities in this field as they delineate important issues for individuals with PKU.
Peer reviewer #2	General	This evidence review on comparative effectiveness of treatment for phenylketonuria (PKU) is enormously disappointing because it is essentially completely flawed. From determination of appropriate literature to consider to the conclusions based on that literature, the authors of the report show a stunning lack of understanding of the challenges and limitations inherent in dealing with ultra rare disorders such as	We acknowledge the challenges faced by researchers in this study of treatments for rare diseases. We have added

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		inborn errors of metabolism.	additional text about the challenges of studying PKU as it is an extremely rare disease. Furthermore, it is important to note that this is a review of the evidence and not a clinical guideline. We recognize that the consideration of benefits and harms may be different for those caring for individuals with rare diseases. This report can be used to inform guidelines and treatment decisions, but is not intended to direct them. This review presents the evidence so that decisionmakers in the care of individuals with PKU can make treatment decisions in light of both the scientific evidence and other considerations, including rarity of the disease, difficulty of researching it, and the potential for negative outcomes without treatment. Nonetheless, we stand by the scientific methods and the conclusions in this report. As part of our established procedures we engage experts in the field as part of a technical expert panel to provide valuable input into the review. Our technical expert panel provided

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			valuable input on parameters for our inclusion and exclusion criteria, as well as other methodological issues related to this evidence review.
Peer reviewer #2	General	In spite of its deficits,the report correctly acknowledges that reducing blood phe levels improves intellectual outcome in patients with PKU, then incomprehensibly concludes that there is insufficient data to recommend the use of therapies that reduce phe. The result is a report that at best is useless to the field (and in answering the question at hand) and at worse damaging in the potential to cause third party payers to refuse to cover PKU related services.	EPC reports do not make recommendations about practice. This report is assessing the evidence that saptopterin a) reduces Phe in the short term and b) has longer-term effects on cognitive outcomes. The report does not in any way conclude that treatment does not work; the absence of a strong evidence base should not be confused with evidence of no effect. Furthermore, the report does not make recommendations about whether or not saptopterin should be used in practice or paid for by insurance. Such a decision should be made by guidelines committees and payers and would incorporate issues such as the severity of disease, the potential for harm in the absence of treatment, the rarity of the disease and the associated difficulties in conducting research and the potential for additional research.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	General	The HRSA Secretary's Advisory Committee on Heritable Disorders in Childhood has shown that thoughtful, intelligent, and useful reviews are possible and of great value to the filed. This report reaches none of those marks and should be outright rejected by the NIH. If the methodology and conclusions of this report are allowed to stand, it has the even greater potential to make thoughtful treatment decisions on rare disorders based on evidence review of the literature literally impossible. Instead, it is essential that the work be repeated by a group more knowledgeable in evidence based reviews of rare genetic disorders.	We acknowledge the excellent work in systematic review for the HHS Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Our review was prepared under contract to AHRQ, not NIH, using accepted, standard EPC review methods, which are published and have been used for more than a decade to review many topics. Consistent with AHRQ EPC methods, we engaged a technical expert panel of experts in the field who advised us on issues such as inclusion/exclusion criteria, appropriate outcomes and other methodologic matters. As noted above, this is a systematic review of the evidence and not a guideline. We recognize that the threshold for decisionmaking around clinical care is likely to differ for a rare disease such as PKU, and expect that those individuals making decisions about care will take into account not only the scientific evidence but other contextual factors.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #3	General	In general, this is a thorough, well-written and provocative document. As the psychologist for the metabolism program at Children's Hospital Boston for 33 years, I have observed the wide range of outcomes in PKU and the many factors that contribute to these outcomes. As was made clear in the document, Phenylalanine levels do not have the same impact on all children and adults with PKU. Moreover, the impact may not be on IQ or executive functioning, but on other aspects of development that can have important implications for learning.	Thank you for your comments. The evidence is unequivocal that untreated PKU causes intellectual disability. Other effects of hyperphenylalaninemia may also occur, especially when the level is above normal but not as high as it would be if untreated, and we have noted these potential outcomes in the Introduction and Executive Summary.
Peer reviewer #3	General	Mention should be made of other "outcomes" that have been linked to elevated phe levels: Processing Speed Anxiety Depression Fine motor deficits Tremor	We have noted these outcomes.
Peer reviewer #3	General	My understanding of the literature is that there is a fundamental debate among neuropsychologists regarding the underlying cognitive deficit. The dopamine hypothesis proposed by Adele Diamond suggests that modest reductions in dopamine in the prefrontal cortex cause executive functioning deficits. Channon and others suggest a myelin hypothesis: reduce myelin causes reduction in processing speed. Clinically, my impression is that what is often described as attention deficits (part of executive functioning) may actually be a result of slower information processing. Children who do not process information quickly give up and stop paying attention.	Thank you for the information. The risk for attention problems has been added to the Introduction.
Peer reviewer #3	General	When looking at the impact of high phe levels at different ages it is important to keep in mind the types of deficits associated with PKU. Executive functions do not usually coalesce until age 11 years. Thus, younger children may not have noticeable learning deficits. Clinically, this is very obvious. Most children with PKU do well in the early grades, but have difficulties at about 4th grade, when they are expected to demonstrate comprehension and analytical reasoning. Prior to 4th grade, predominantly rote learning is required.	Thank you for this information. This degree of specificity is beyond the scope of the systematic review as the distinction between rote learning and executive function has not been published in detail.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #3	General	The authors seemed to have difficulties explaining why phe levels and IQ were not significantly correlated during the "critical period". I believe this is because the range of phe levels and the range of IQ is much smaller during those periods. Younger children are more adherent to treatment. Moreover, since executive functioning is less developed in all young children, it is not a significant component of IQ tests early on.	Thank you for this information. We have added this possible explanation to the results.
Peer reviewer #3	General	"Large scale" studies of neuropsychological functioning in PKU are very challenging for several reasons. First, most such studies rely on very specific tasks in which only small differences in the number of errors made or in the time it takes to respond are found. Whether or not these differences are clinically relevant is debatable. Second, pre-and post-tests are difficult because practice effects are hard to control for, especially in children. Some studies have found that children sometimes even perform less well on tasks the second time (for example when blood phe is lowered) simply because they are bored with the test. Third, since most neuropsychological tests are computerized, they are hard to standardize across centers.	We have addressed this issue in the Future Research section of the report.
Peer reviewer #3	General	Instead, behavioral indices or proximal measures of effect may be more suitable for determining comparative effectiveness. I noticed that the Behavioral Rating Index of Executive Function was mentioned, but no studies were reviewed that used the overall Global Executive Composite (which might actually be a better outcome measure). Other possible outcomes might be grades in school, length of employment, ratings of depression and anxiety.	We agree that these other outcomes are important for future research.
Peer reviewer #3	General	The recommendation that government funded studies are needed is extremely important. However, it has been almost impossible to obtain funding from the government for outcome studies in PKU or in any of the other metabolic disorders. The focus has been almost exclusively on expansion of newborn screening without attention to psychological outcome. Perhaps the point could be made that PKU serves as a model for other disorders. In order to develop evidenced based treatment guidelines, support must be given to conduct studies that can receive a "good" rating. The Mater	Thank you for your comments. We have added this recommendation to the Future Research section.
Peer reviewer #6	General	The authors have done an excellent job of comprehensively and thoroughly evaluating the existing evidence and research into PKU. Most notably, the compilation of existing research strongly supports the need for additional research and the need for a comprehensive public health plan/strategy to adequately support the needs of the patients and their families. This report is timely and much needed, and should be of considerable interest to the PKU community.	Thank you for your comments.
Peer reviewer #6	General	Yes. PKU is serious, chronic medical disorder with unmet medical needs, a difficult treatment regimen, and poor compliance particularly in older (adolescent and adult) patients. With a relatively new treatment for PKU commercially available (sapropterin), since last consensus statement (NIH 2000), and anecdotal/poorly supported use of LNAAs, a re-examination of existing, objective data is warranted.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	General	[Target population and audience explicitly defined?] Yes – consumers, health care providers and others in making informed choices among treatment alternatives. Additionally notes need to identify gaps in existing scientific evidence and research. Page 4 additionally notes overall goal is to "inform clinician and patient decisions about the treatment of PKU."	Thank you for your comments.
Peer reviewer #6	General	[Are the key questions appropriate and explicitly stated?] Clearly stated on pages ES-3-4, ES-8-14 and in the main body of the report in several places. For the most part, questions appear appropriate for the disorder, existing uncertainties and target audience.	Thank you for your comments.
Peer reviewer #6	General	However, Q7 somewhat redundant with subgroups in Q2 and 4.	Q2 and Q4 only address variation according to age or maternal PKU, but Q7 is addressing a multitude of other variations in patients, including ethnic background, environment, gender, etc.
Peer reviewer #6	General	For Q2 and 4, can it be clarified why age subgroup for children 2-12 and adolescents 13-21 years (instead of, for example children up to critical age and 6-12 subgroups, and adolescents ~13-16 or 18)?	We recognize that other subgroupings based on the critical age may have been appropriate and may be appropriate for future research. However the 2 published RCTs included in the review reflect age groups that are not based on critical period. Ultimately we were unable to do subgroup analyses regardless of the groupings.
Peer reviewer #6	General	Q6 assessment of "harms" may have been more useful if risk-benefit of intervention was assessed. In a serious disorder such as PKU, largely minor intolerances of, e.g., sapropterin should be considered in context.	We agree that developers of guidelines and users of this material should consider the minimal harms associated with sapropterin in light of the severity of this disease.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	General	Some key questions that were notably lacking: 1) Identification of most important areas where data/research are lacking (and why). Although was addressed in discussion sections throughout, could have been a stand-alone point since was stated as an objective of the study (and was one of the most notable findings of the report).	The key questions were developed with the assistance of a technical expert panel and posted for public comment from November 8, 2010 to December 6, 2010. They are by necessity tightly focused; the review is not intended to be an complete treatment of all important questions related to PKU. We hope that this review will be used in context with other important information and potentially other reviews by guidelines developers and other decisionmakers.
Peer reviewer #6	General	Some key questions that were notably lacking: 2) Examination of "best practices" and factors leading to non-compliance (e.g., psychosocial factors, supportive care) in addition to pharmacologic interventions, which impact compliance and outcomes. In other chronic genetic diseases (e.g., CF, muscular dystrophies), attention to best practices, even in absence of targeted therapies, can have a dramatic effect on outcomes, harmonize research/care practices, and stimulate research. For example, cost/coverage of low-phe formulas substantial burden to families, with public health implications.	See the comment above; an examination of best practices would not be in the scope of a comparative effectiveness review.
Peer reviewer #6	General	Some key questions that were notably lacking: 3) "Translational" research (aka fundamental research page ES-14), such as clinical outcome assessment tools development, which was also identified by the authors as being notably lacking for PKU. Evaluation of outcomes without adequate tools will limit ability to interpret results.	See the comments above. This is an important question, but beyond the scope of a CER focused on treatment. We hope that the identification of areas that are currently lacking in the evidence can be helpful to investigators and funders moving forward.
Peer reviewer #6	General	Some key questions that were notably lacking: 4) Assessment of growth.	See the above comments.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	General	PKU is a rare genetic condition and has been categorized by the FDA as an orphan disease. The rarity and severity of orphan disease makes it difficult to enroll and conduct large placebo controlled studies. In this spirit, we are concerned that the standard approach used for large population diseases such as diabetes or cardiovascular interventions does not fit for orphan diseases, as evidenced in this review and findings for PKU. Clinical information gleaned from small studies should be considered and case studies may have an appropriate and meaningful place in contributing to the understanding of the management of these rare diseases.	We have added text in the background and discussion sections of the report about the challenges of both conducting primary research on a rare disease and on conducting systematic reviews of rare diseases. To ensure that we did not miss important information from small studies, we assessed the studies that were excluded from our review because they included fewer than 10 participants (Appendix A). The results were essentially the same as those in the included studies. To add them to our current included literature would not change the conclusions,
BioMarin Pharmaceutical	General	We are concerned that the standard CER methodology approach used to perform the literature review is not appropriate for a rare condition like PKU. We believe that alternative methodological frameworks are required in order to perform an evidence based review for an orphan disorder, which could be applied for future rare disease reviews.	It is not clear to us why this would be the case. Risks of bias to research are the same across content areas. This is not to say that guidelines developers and individuals making clinical decisions should not use additional information in their decision-making, however.
BioMarin Pharmaceutical	General	We are concerned that the report does not clearly differentiate between sapropterin, a pharmacologic agent and large neutral amino acids (LNAAs) that are nutritional supplements. Sapropterin underwent extensive review by the FDA prior to receiving its marketing authorization in 2007. LNAA's s are marketed without a similar review process.	We have tried to make this clearer, including by revising the analytic framework.
BioMarin Pharmaceutical	General	We are concerned by the conclusion that "The use of pharmacologic adjuvant	Strength of evidence

Commentator & Affiliation	Section	Comment	Response
		therapy in PKU is novel and strength of the evidence is currently insufficient to low for effectiveness of treatment on interim or clinical outcomes." We request that the report provide the caveat that first in class drugs for orphan diseases such as PKU are often not approved based on long term studies, and that early results, by definition, will be limited in scope.	should not be conflated with an effect measure. Rather, it reflects our confidence that the true estimate of effect has been established by current research and will not shift with the addition of additional, future research. As noted above, we have modified our assessments to parse our assessments more distinctly for the positive effect of sapropterin on reducing Phe to clinical targets, the effect of Phe on improving cognitive outcomes (based on the meta-analysis) and the indirect link of sapropterin on cognitive outcomes. We consider there to be moderate strength of evidence that the effect observed in the first two is the effect likely to maintain, and low strength of evidence for the ability of sapropterin to improve cognitive outcomes because it is currently limited to indirect evidence with small numbers of individuals and few studies. That said, we have also been carefully to acknowledge that this is a rare disease and that research will be challenging. The fact that evidence for use of pharmacologic therapy is

Commentator & Affiliation	Section	Comment	Response
			novel should not be construed as criticism. As noted above, this is a systematic review of the evidence and not a guideline. We recognize that the threshold for decisionmaking around clinical care is likely to differ for a rare disease such as PKU, and expect that those individuals making decisions about care will take into account not only the scientific evidence but other contextual factors, including the challenges inherent in studying a rare disease and the likelihood of poor outcomes in the absence of some sort of treatment or management.

Commentator & Affiliation	Section	Comment	Response
BioMarin Pharmaceutical	General	We are concerned that in this report, pharmacologic management of PKU is addressed, but not dietary management, other than to say it is challenging to do with the goal of achieving the target phe level to minimize cognitive impairment. It is well documented that cognitive impairment can be due to dietary deficiencies from the PKU diet, but this is not reflected in this report.	Comparative effectiveness reviews are, by definition, specifically focused. It would not have been possible to review the entire literature on therapeutic approaches to PKU as a whole; and given that dietary management is the standard of care and well established, we focused on the role of pharmacologic treatment as adjuvant to dietary management. The key questions were determined and posted for public comment from November 8, 2010 to December 6, 2010. We agree that the role of dietary management is absolutely important, but that review could not be conducted within the framework of this project.
BioMarin Pharmaceutical	General	Also not included is the finding from the US Collaborative Study looking at long term outcomes of individuals with PKU, on and off diet, by Dr. Koch et al, 2002, JIMD 25:333-346. This led to the recommendation of 'diet for life'. This was a positive and profound change in the historical management of PKU.	As noted above, the scope of our contract was limited. This study did not address one of our key questions. We agree that this reference is important and have added it to the background section of the report.
BioMarin Pharmaceutical	General	We concur with the finding that industry has been the primary sponsor of the clinical studies. Very limited public or private funding has been dedicated to the treatment and to improving outcomes for PKU. Without industry funding, there would likely be few strides beyond the newborn screening initiatives. As a company working closely with the PKU community, committed to improving the lives of PKU patients, we would encourage more dedicated public-sector funding to PKU research.	We agree and have made this point explicitly in the revised text.

Commentator & Affiliation	Section	Comment	Response
Kathryn Moseley, M.S., R.D. Genetic Metabolic Dietitian, University of Southern California-Keck School of Medicine	General	The rationale: Since the discovery of PKU in 1934 the exact mechanism that causes damage to the brain has not been elucidated. However, in the early 1970's studies of the blood brain barrier and neurotransmitter deficits in PKU suggested that the high blood phenylalanine (phe) levels deprived the brain of other LNAA and was related to the mental retardation. (McKean C 1972, Olendorf 1973). Several other researches support these findings. (Surtees R 2000, Fernstrom JD 2007, van Spronsen FJ 2009) The idea of using LNAA in the treatment for PKU for lowering brain phe concentrations was postulated as early as 1976 (Andersen1976, Pratt 1980). Many small studies were performed at the John F. Kennedy Institute in Denmark using LNAA on adults and adolescents confirming that CSF neurotransmitters are decreased in individuals with PKU. With supplementation of LNAA, which increases neurotransmitter metabolism, no changes were noted in brain MRI in those individuals who have relaxed the diet. (Lykkelund et al 1988, Lou et al 1994, Guttler et al 1986; Nielsen et al 1988, Lou HC, Toft 1994). In 1999, Pietz et al confirmed that LNAA block the phe from entering the brain. The use of the LNAA has been used in Denmark since 1985 as an adjunct therapy for adults and adolescents who were not following clinical recommendations with no adverse effects. (Ahring K, 2010)	Thank you for this information. The references that met our criteria have been included in the review. We cannot comment on studies that did not meet our criteria.
Kathryn Moseley, M.S., R.D. Genetic Metabolic Dietitian, University of Southern California-Keck School of Medicine	General	Our experience: Our clinic has been using LNAA since 2003 for our adults and adolescents who cannot follow the phe-restricted diet. We originally studied 6 patients on LNAA for six months and documented a reduction in brain phe and an increase in both tyrosine and tryptophan in blood concentrations. (Koch R et al 2003). By giving these patients the LNAA they are allowed a more normal diet, their blood phe generally does not decrease, but the tyrosine blood levels are increased and the phe/tyr ratio is decreased. In our original study of the six patients for six months baseline phe/tyr for one of our patients was 69 after supplementation with LNAA the ratio was reduced to 6. They reported feeling better, less fatigue and an increase in concentration. Another study that we conducted with the use of the LNAA was with 10 individuals who were born before newborn screening and were severely affected. Ten subjects were observed for one year after LNAA supplementation. While the blood phe remained relatively stable there were significant increases in tyrosine and declines in phe/tyr ratios. Increased blood tyrosine levels were significantly associated with less aggression towards others and improvement on the Vineland Daily Living Scale. Cost comparisons of psychotropic medications obtained before and after the study revealed a cost savings of 50%. (manuscript in preparation) To date there is no consensus on what the blood phe levels for adults or adolescents should be. Furthermore, we have just completed a study in our clinical trials unit documenting that adults with PKU who are not taking a medical food product have lower levels of neurotransmitters and by supplementing with LNAA's the concentration of these neurotransmitters are increased without lowering of blood phe. (manuscript in preparation)	We appreciate this information from your clinical experience. The review of evidence includes all studies that meet criteria for inclusion. We encourage you to continue to publish as you accrue more data on the use of LNAA in patients with PKU and hope that enough additional research accrues that this review can be updated at some point.

Commentator & Affiliation	Section	Comment	Response
Kathryn Moseley, M.S., R.D. Genetic Metabolic Dietitian, University of Southern California-Keck School of Medicine	General	Evaluation of the use of LNAA is very difficult as blood phe cannot be used as the primary marker. In our experience, the blood phe level does not decrease appreciably. However, clinically these individuals are doing very well and are not deteriorating. The use of the LNAA has also resulted in a more normal amino acid profile (aside from elevated phe levels). (manuscript in preparation)	We appreciate this information from your clinical experience. The review of evidence includes all studies that meet criteria for inclusion. We encourage you to continue to publish as you accrue more data on the use of LNAA in patients with PKU and hope that enough additional research accrues that this review can be updated at some point.
Kathryn Moseley, M.S., R.D. Genetic Metabolic Dietitian, University of Southern California-Keck School of Medicine	General	Though it is true that there are not many studies using the LNAA one must remember that the early implementation of the phe-restricted diet was case studies until finally a Collaborative Study funded by the Maternal and Child Health Division of the Public Health Services was implemented to evaluate the treatment and put forth recommendations. There was also a follow up study from the original Collaborative study to locate these individuals and evaluate their present medical, nutritional, psychological and socioeconomic status. The results of that study indicated that early dietary discontinuation is associated with poorer outcomes in intellectual ability as well as increases in medical and behavioral problems. At the time of the testing, all of the subjects in the group that discontinued the diet (n=11) had blood phe levels over 1,000umol/l and 50% of the subjects on the phe-restricted diet (n=10) had blood phe levels over 1,000umol/l. Indicating that for some, despite high blood phe levels they had a good outcome. In the adults that we follow whether on a phe-restricted diet or on LNAA the phe levels are typically under 1200umol/l but certainly not in the 120-360umol/l range. Despite that, we have young adults in the top-notch schools, honors programs, college graduates and in good paying jobs. We have very few adults “off diet” and taking no medical products whatsoever. Probably because we can offer them an alternative that they can adhere to and this gets them to clinic for education and follow-up. Additionally, we are treating many late diagnosed PKU individuals with LNAA who were born before newborn screening and reside in group homes. Their maladaptive behaviors continue to improve and psychotropic medications are decreased.	We appreciate this information from your clinical experience. The review of evidence includes all studies that meet criteria for inclusion. We encourage you to continue to publish as you accrue more data on the use of LNAA in patients with PKU and hope that enough additional research accrues that this review can be updated at some point.

Commentator & Affiliation	Section	Comment	Response
Kathryn Moseley, M.S., R.D. Genetic Metabolic Dietitian, University of Southern California-Keck School of Medicine	General	We must find other measures in addition to the blood phe levels to justify maintaining low blood phe levels beyond adolescence. We must provide recommendations and treatments that are achievable.	We agree and have noted this in the report. We have noted these kinds of issues in the Future Research section of the review.

Commentator & Affiliation	Section	Comment	Response
Kathryn Moseley, M.S., R.D. Genetic Metabolic Dietitian, University of Southern California-Keck School of Medicine	General	The references below were not used in the report as they did not meet inclusion criteria but they are pertinent to clinical care. Andersen AE, Avins L. Lowering Brain Phenylalanine Levels by Giving Other Large Neutral Amino Acids, *Arch Neurol* 1976 33:684-686 Guttler F and H Lou. Dietary Problems of Phenylketonuria: Effect on CNS Transmitters and their Possible Role in Behaviour and Neuropsychological Function. *J. Inher. Metab. Dis. 9 Supple 2* 1986 169-177 Koch R, et al. Large neutral amino acid therapy and phenylketonuria: a promising approach to treatment. *Mol Gen* 2003 79:110-113 Lou HC, Lykkelund et al. Increased Vigilance and Dopamine Synthesis by Large Doses of Tyrosine or Phenylalanine Restriction in Phenylalanine Restriction in Phenylketonuria. *Acta Padiatr Scand* 1987 76: 560-565 Lou HC, Toft PB et al. Unchanged MRI of myelin in adolescents with PKU supplied with non-phe essential amino acids after dietary relaxation. *Acta Paediatr* 1994 83:1312-14 Lykkelund D, Nielsen JB, et al. Increased neurotransmitter biosynthesis in phenylketonuria induced by phenylalanine restriction or by supplementation of unrestricted diet with large amounts of tyrosine. *Eur. J. Pediatr.* 1988 148:238-245 McKean C. The effects of high phenylalanine concentrations on serotonin and catecholamine metabolism ni the human brain. *Brain Research* 1972 46: 469-476 Nielsen JB, Lou HC, Guttler F. Effects of diet discontinuation and dietary tryptophan supplementation on neurotransmitter metabolism in phenylketonuria. *Brain Dysfunction.* 1988 I: 51-56 Olendorf Wm. Saturation of Blood Brain Barrier Transport of Amino Acids in Phenylketonuria. *Arch Neurol.* Vol 28 1973: 45-48 Pietz J, Kreis R, et al. Large Neutral Amino acids block phenylalanine transport into brain tissue in patients with phenylketonuria. J Clin Inves. 1999 103:1169-1178 Pratt OE. A new approach to the treatment of Phenylketonuria. *J. Ment. Defic. Res.* 1980 24:203-217 van Spronsen FJ et al. Brain dysfunction in phenylketonuria: Is phenylalanine toxicity the only possible cause? *J Inherit Metab Dis* 2009 32:46-51	Thank you for providing these references. As you note, they did not meet criteria for inclusion in our review.

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria (PKU) and Other Forms of Hyperphenylalaninemia Scientific Conference Pregnancy Working Group (PKU-PWG)	General	Comment regarding nomenclature: To prevent confusion, the working group recommends that when referring to the fetus or newborn as having dysmorphology or malformations from uncontrolled or poorly controlled blood phenylalanine (Phe) in the mother, the term, "maternal PKU syndrome" be used. The term "maternal PKU" should be used only to refer to the pregnant women with PKU, or to the general concept of pregnancy with PKU. "Maternal PKU" should not be used to refer to the newborn. These terms were used inconsistently in the Executive Summary and body of the report.	We have revised this text.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	General	A consistent definition throughout the ES and the rest of the report needs to be made when talking about “phe measured 1 year before IQ tested.” We assume this refers to a historical measurement, thus we would suggest using “historical measurement” throughout the document.	The definitions in the report reflect those available in the studies.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	General	PKU-DCMWG wishes to commend AHRQ for contracting with an Evidence-based Practice Center to conduct this review. The emergence of new therapies for the treatment of PKU, such as sapropterin dihydrochloride (sapropterin) and large neutral amino acids (LNAAs), obligate clinicians to reconsider established practice decisions. The need for reliable information and guidelines to inform these decisions is critical to successful patient care. The CER-PKU was thoughtfully undertaken and will provide guidance for clinicians based on current evidence from the scientific literature. It is significant, however, that out of 2,466 citations identified in searches, only 66 papers representing 43 unique studies were retained. Sixteen unique studies representing 371 patients met criteria for the relationship between phenylalanine (Phe) levels and IQ (but only one study was rated as good quality) and eight studies were reviewed for effectiveness of sapropterin (one was rated as good quality). No studies were located that addressed key questions relative to the effectiveness of sapropterin or LNAAs in pregnant women. The lack of robust research in PKU points to the difficulties in conducting rigorous research in PKU treatment and management. We summarize these challenges below.	Thank you for your comments. We respond to specific comments below.

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	General	[Challenges in PKU research] As noted in the report, the number of individuals with PKU is very small compared to other chronic disease populations. The patient pool available for research is generally comprised of those who have chosen to continue a relationship with a clinical center. Thus, these patients may represent a best case scenario which may skew patient characteristics. Conducting multi-center trials is complicated by differences in long-term treatment protocols and varying Institutional Review Board requirements. Cognitive and behavioral deficits among patients with PKU may make compliance with research protocols difficult. Studies are typically conducted in a free-living environment which introduces inconsistencies among and across studies. Access to a controlled inpatient setting for research is limited to all but the largest genetic centers. The professionals who have the ability to conduct research in PKU are often the same people who provide clinical care to these patients, making time and staffing limitations significant.	We agree that all of these challenges are inherent in studying PKU and have added more commentary in the report to this effect. Nonetheless, it is important to expect that rigorous research be conducted so that we can be assured that individuals with PKU can receive optimal treatment. As noted in the report, we encourage Federal funding agencies to provide more attention to this important area of research.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	General	The strict criteria required for an evidence-based review of literature, and the value of the information gained through this robust process is undeniable. However, clinicians cannot limit themselves to knowledge and guidance found only in publications that meet strict criteria for an evidence-based review. The paucity of “gold standard,” randomized controlled trials, which is also seen in other rare diseases research, requires clinicians to utilize “grey literature” such as case studies and professional consensus documents to fill the gaps in the evidence.	We agree. Systematic reviews provide one source of information for individuals and groups making clinical and guideline decisions. The report is specifically not intended to provide specific guidance, but to provide a rigorous review of existing research to support the development of guidance or clinical decisionmaking by other individuals and groups.

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	General	We would ask that this report explicitly address the research limitations inherent in the PKU population as subjects.	We note in the report that the disease is exceedingly rare and thus difficult to study.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	General	We also ask that it be recognized that treatment of PKU must be based on clinical judgment in addition to information gleaned from evidenced-based literature reviews.	See comment above. As we note in the report, systematic reviews provide one source of information for individuals and groups making clinical and guideline decisions. The report is specifically not intended to provide specific guidance, but to provide a rigorous review of existing research to support the development of guidance.

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	General	Additionally, we are concerned that should this report be used alone "as a basis for reimbursement and coverage policies," as explicitly stated on page ii, appropriate clinical care for PKU patients may be limited or denied.	The language that you note in your comment is from the materials provided by the funding agency and not part of the report itself. The report is specifically not intended to provide specific guidance, but to provide a rigorous review of existing research to support the development of guidance. As noted in the report, systematic reviews provide one source of information for individuals and groups making clinical and guideline decisions. These groups may also have additional considerations beyond that of this evidence review that they must consider carefully in making decisions about coverage and reimbursement.

Commentator & Affiliation	Section	Comment	Response
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	General	We are very concerned that this report does not explicitly acknowledge the importance of dietary treatment in outcome for individuals with PKU. Despite the availability of other treatments, the majority of patients are still managed by dietary intervention alone. The current body of research and clinical observation has demonstrated that the pharmacological treatments available to date do not preclude the use of a Phe-restricted diet combined with specialized medical formulas medical foods and modified low protein foods. The lowering of blood Phe levels is accomplished by dietary treatment first and foremost. Unfortunately, the necessity of this standard of care treatment is being questioned by policy makers as they evaluate effective medical treatments for a national health care system. By not acknowledging the importance of dietary intervention in this report, treatment may be denied to individuals and ultimately undermine the effectiveness of the newborn screening system.	We have added text to this effect. As we note, dietary management is the standard of care, is known to be effective and is not the focus of this review. We acknowledge the importance of dietary intervention in the background section of this report. As noted previously, this work was a comparative effectiveness review focused on pharmacologic therapy. It is not intended to be a review of all treatments for PKU. We have attempted to further emphasize this point, and that diet for life continues to be the recommended course of care.
Phenylketonuria and Other Forms of Hyperphenylalaninemia Scientific Conference Diet Control and Management Working Group (PKU-DCMWG)	General	The terms used to describe the specialized products that comprise the bulk of the diet for patients with PKU need to be appropriately described and consistently used throughout the Executive Summary (ES) and the body of the report. “Supplement” is not an accurate term because of the large proportion of the diet represented by these products. We recommend the use of the regulatory definition to describe medical foods. **(US Food and Drug Administration. Guidance for Industry: Frequently Asked Questions About Medical Foods** www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/MedicalFoods/ucm054048.htm. Accessed October 17, 2010.)	We have clarified the language throughout and have used the term “medical foods.”

Commentator & Affiliation	Section	Comment	Response
Public reviewer (Anonymous)	General	**On p. ES-2 is the following statement:** "In addition to a Phe-restricted diet and sapropterin, another potential treatment for PKU is large neutral amino acids (LNAAs). LNAAs primarily decrease the brain Phe concentration by competing with Phe for transport across the blood-brain barrier.[3, 4] " And on p. ES-12 "Three studies addressed the effects of LNAAs,4, 57, 58 including a fair57 and poor58 quality RCT and a poor quality uncontrolled open label trial.[4] " … "This fair quality study[57] reported a positive effect on executive functioning, specifically verbal generativity, cognitive flexibility, and self-monitoring. Overall, participants who were using a low-Phe supplement to their nutritional needs did not experience a decrease in Phe, although those not adhering to diet or not using their formula did." **Do the authors of the Draft Report feel that the two references below are useful in providing more insight on this theme or do they think they are not relevant to this Draft Report?** Large neutral amino acids block phenylalanine transport into brain tissue in patients with phenylketonuria. Pietz J, Kreis R, Rupp A, Mayatepek E, Rating D, Boesch C, Bremer HJ. J Clin Invest. 1999 Apr;103(8):1169-78. No evidence for individual blood-brain barrier phenylalanine transport to influence clinical outcome in typical phenylketonuria patients. Pietz J, Rupp A, Burgard P, Boesch C, Kreis R Ann Neurol. 2002 Sep;52(3):382-3; author reply 383-4. No abstract available	Thank you for pointing out these references. Neither publication met criteria for the review.
Public reviewer (Anonymous)	General	**Below I listed literature that seems relevant to the other themes of the report that the report is not referring to. Did the authors of the report feel these publications did not full fill their criteria for inclusion or were a number of these publications possibly missed because they were published in supplements? Thank you very much for taking the time to look at this list.** **From Mol Genet Metab. 2010;99 Suppl 1:** Event-related potential correlates of selective processing in early- and continuously-treated children with phenylketonuria: effects of concurrent phenylalanine level and dietary control. de Sonneville LM, Huijbregts SC, van Spronsen FJ, Verkerk PH, Sergeant JA, Licht R. Mol Genet Metab. 2010;99 Suppl 1:S10-7. **As well as other articles from this Mol Genet Metab. 2010;99 Suppl 1 on:**	Thank you for providing this list of citations. These papers were all identified in our initial search and were all excluded, typically because they did not contain the type of data we required for answering our questions about Phe levels and measures of cognition.

Commentator & Affiliation	Section	Comment	Response
		'Phenylketonuria, Psychology and the Brain' **The Report cites this issue:** 9. Christ SE, Huijbregts SCJ, de Sonneville LMJ, et al. Executive function in early-treated phenylketonuria: Profile and underlying mechanisms. Molecular Genetics and Metabolism. 2009;99 (SUPPL.):S22-S32. I believe it is 2010 **And there are additional articles in that issue relevant to the theme of the report such as:** Disruption of prefrontal function and connectivity in individuals with phenylketonuria. Christ SE, Moffitt AJ, Peck D. Mol Genet Metab. 2010;99 Suppl 1:S33-40. **and others** **From Eur J Pediatr. 1996 Jul;155 Suppl 1:** Intelligence and professional career in young adults treated early for phenylketonuria. Schmidt H, Burgard P, Pietz J, Rupp A. Eur J Pediatr. 1996 Jul;155 Suppl 1:S97-100. PMID:8828621[PubMed - indexed for MEDLINE] Intellectual development of the patients of the German Collaborative Study of children treated for phenylketonuria. Burgard P, Schmidt E, Rupp A, Schneider W, Bremer HJ. Eur J Pediatr. 1996 Jul;155 Suppl 1:S33-8. PMID:8828606[PubMed - indexed for MEDLINE] Effects of concurrent phenylalanine levels on sustained attention and calculation speed in patients treated early for phenylketonuria. Schmidt E, Burgard P, Rupp A. Eur J Pediatr. 1996 Jul;155 Suppl 1:S82-6. PMID:8828617[PubMed - indexed for MEDLINE] Long-term follow-up of patients treated for phenylketonuria (PKU). Results from the Prague PKU Center. Cechák P, Hejcmanová L, Rupp A. Eur J Pediatr. 1996 Jul;155 Suppl 1:S59-63. Long-term follow up of patients with classical phenylketonuria after diet relaxation at 5 years of age. The Paris Study. Rey F, Abadie V, Plainguet F, Rey J. Eur J Pediatr. 1996 Jul;155 Suppl 1:S39-44. **And other articles from the Eur J Pediatr. 1996 Jul;155 Suppl 1 issue.**	

Commentator & Affiliation	Section	Comment	Response
		Psychopathology of patients treated early for phenylketonuria: results of the German collaborative study of phenylketonuria. Burgard P, Armbruster M, Schmidt E, Rupp A. Acta Paediatr Suppl. 1994 Dec;407:108-10. PMID:7766943[PubMed - indexed for MEDLINE] Psychological and social findings in adolescents with phenylketonuria. Weglage J, Fünders B, Wilken B, Schubert D, Schmidt E, Burgard P, Ullrich K. Eur J Pediatr. 1992 Jul;151(7):522-5. PMID:1396915[PubMed - indexed for MEDLINE] Results of psychological testing of patients aged 3-6 years. Michel U, Schmidt E, Batzler U. Eur J Pediatr. 1990;149 Suppl 1:S34-8. PMID:2091929[PubMed - indexed for MEDLINE]	