Effective Health Care Program

Future Research Needs Paper
Number 21

Adjuvant Treatment for Phenylketonuria: Future Research Needs

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Number 21

Adjuvant Treatment for Phenylketonuria: Future Research Needs

Identification of Future Research Needs From Comparative Effectiveness Review No. 56

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None of the investigators have any affiliation or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that is needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Executive Summary

Background

Phenylketonuria (PKU) is a metabolic disorder in which an inability to properly metabolize the amino acid phenylalanine (Phe) leads to a buildup of Phe in the blood, causing neurotoxicity and resulting in intellectual disability, delayed speech, seizures and behavior abnormalities. PKU is typically diagnosed at birth following abnormal newborn screening results. With adherence to a Phe-restricted diet, poor outcomes can be mitigated. Nonetheless, management of PKU can be difficult and onerous for the patient and the family, leading to interest in identifying new ways of managing this lifelong condition.

The mainstay for treatment of PKU is a diet that restricts the intake of Phe to control the Phe concentration in the blood. In 2007 the United States Food and Drug Administration approved sapropterin dihydrochloride (Kuvan®, formerly known as Phenoptin) for the treatment of PKU under the stipulation that studies regarding the drug's efficacy and long-term safety continue. Sapropterin dihydrochloride (hereafter, BH4) is presumed to work by enhancing residual enzyme activity present in some individuals with PKU. In addition to a Phe-restricted diet and BH4, another potential treatment for PKU is large neutral amino acids (LNAAs). In theory, LNAAs decrease the brain Phe concentration by competing with Phe for shared amino acid transporters to cross the blood-brain barrier.[1,2]

The Vanderbilt Evidence-based Practice Center completed an Agency for Healthcare Research and Quality (AHRQ)-funded systematic review of adjuvant treatments (BH4, LNAAs) for PKU (published February 2012). The report focused on Key Questions related to outcomes and harms of adjuvant treatment with BH4 and LNAAs in individuals with PKU, including pregnant women with PKU, and effects in subgroups (defined by demographic, clinical, genotypic, and adherence-related variables such as age, disease severity, genetic mutations, and dietary status). Key Questions also addressed evidence for optimal Phe levels for minimizing cognitive impairment.

Overall, evidence was graded as insufficient to moderate to address treatment-related questions. Dietary management remains the mainstay of treatment for PKU, and maintaining control over the lifetime is an appropriate goal. Nonetheless, there is potential to support patients in achieving their clinical goals and possibly liberalizing their diet with adjuvant therapy. BH4 has been shown in two RCTs and two open label trials to reduce Phe levels in some patients, with significantly greater reductions seen in treated versus placebo groups. Overall, harms associated with the drug were minor. To date, there are no data to directly establish the potential effects of BH4 on longer term clinically important outcomes, including cognition, executive function, and quality of life. Thus, while the strength of evidence is moderate for a large, positive effect of BH4 on reducing Phe levels over the short term in some groups of patients showing initial responsiveness, evidence for the effect of BH4 on longer term clinical outcomes is low, and based on indirect associations, including a meta-analysis of the relationship of Phe levels and IQ.

In theory, supplementation of a Phe-restricted diet with LNAAs might have a beneficial effect on cognition as LNAAs may competitively inhibit transportation of Phe through the blood-brain barrier, thereby offering protection by potentially decreasing brain Phe levels. However, there was insufficient evidence to suggest that LNAAs could be a viable treatment option for reducing Phe levels or increasing Phe tolerance.

Increasing Phe is clearly associated with decreased IQ, with a probability of IQ less than 85 exceeding the population probability (approximately 15 percent) at blood Phe over 400 µmol/L and leveling off at about 80 percent at 2000 µmol/L (moderate strength of evidence). This finding supports the typical target goal for blood Phe levels in individuals with PKU (120 to 360 µmol/L).

Methods

Table A outlines the project's methods, which were modified from those used in prior future research needs projects.[3] Briefly, we used a multistep process to identify evidence gaps, beginning with culling gaps as reported in the Comparative Effectiveness Review (CER) and gaps relevant to adjuvant treatment raised during a National Institutes of Health State of the Science conference session devoted to future research needs in PKU. We framed gaps as Population-Intervention-Comparators-Outcomes-Timing-Setting (PICOTS) questions by CER Key Question or as foundational or methodologic research for which greater understanding would benefit PKU treatment. We also indicated where ongoing research may begin to address questions.

Table A. Methods for developing future research needs

Approach to Evidence Gap Identification
1. Generate preliminary list of research gaps based on gaps noted in the CER
2. Form stakeholder workgroup with representatives from groups including patient/family/advocacy organizations, the provider community, the research community, and funding agencies
3. Locate ongoing trials and other funded research
4. Conduct conference call with stakeholders to refine initial list of evidence gaps
5. Review teleconference responses and refine list of research gaps related to adjuvant treatment for PKU
Approach to Prioritization and Stakeholder Engagement for Prioritization
6. Request that stakeholders prioritize research gaps
7. Cull list of prioritized gaps to top tier research needs based on stakeholder voting
8. Request that stakeholders assess top priority needs using modified EHC selection criteria
Approach to Research Question Development and Considerations for Potential Research Designs
9. Determine potential study designs to address final list of research needs
10. Develop research needs report
11. Request stakeholder input on the draft research needs report
12. Finalize research needs report

Abbreviations: CER=comparative effectiveness review; EHC=Effective Health Care Program; PKU=phenylketonuria

We then convened a group of stakeholders broadly representative of research, clinical care, patient/consumer, and funder perspectives to provide input on the list and add additional questions as necessary. We engaged stakeholders agreeing to participate in the project via an initial conference call to introduce the project and to add to the list of gaps identified from the report. This call was followed by an email message including the revised list of gaps and inviting stakeholders to edit or add questions as necessary.

We presented the expanded list of questions to stakeholders via a Web-based survey that asked stakeholders to allot a number of votes to each question to indicate priority. We asked stakeholders to consider the overall importance of the question for PKU research but did not prescribe specific criteria for prioritizing at this phase. We limited the number of votes available to roughly two-thirds of the number of questions identified to ensure that stakeholders selected

high-priority issues. We then compiled votes across stakeholders and questions to determine the top tier of research needs. We considered questions scoring at least 5 points to comprise the top tier.

We sent a second Web-based survey to stakeholders asking them to prioritize the top tier needs, divided into treatment/intervention- and methods-related questions, using the following modified Effective Health Care (EHC) program selection criteria:[4]

- Potential for significant health impact
- Potential to reduce variation in clinical practices
- Potential for significant economic impact
- Potential risk from inaction.
- Potential to address inequities
- Potential to allow assessment of ethical, legal, social issues pertaining to the condition
- Potential for new knowledge.

Stakeholders ranked each question on each of the criteria using a 1- (low) to 5- (high) point scale. We tallied scores across each criterion to determine an overall score for each question and divided questions into top, middle, and lower tiers for both treatment- and methods-focused needs according to overall scores. We determined research considerations for each of the top tier treatment-related needs by considering factors including the availability of relevant data sets; alignment with the system of care for PKU; and recruitment issues in rare diseases.

Results

Stakeholders

Stakeholders broadly represented clinical, research, and advocacy perspectives in PKU. The panel comprised nine stakeholders, including a physician from a pharmaceutical company, an advocate who has children with PKU, representatives from government agencies that fund research on developmental disabilities, a dietician and nutritionist, clinical researchers with expertise in generics and metabolism, and experts in developmental medicine and in bioethics. We generated lists of potential stakeholders via a review of potential Technical Expert Panel members and key informants for the CER, review of investigators in studies included in the CER, review of advocacy and other agencies relevant to PKU, and through consultation with our Task Order Officer (TOO). Eight of nine stakeholders had participated in the National Institutes of Health (NIH) PKU Scientific Review Conference: State of the Science and Future Research Needs conference.

Research Needs

Table B lists the combined list of research questions from the CER and those generated by stakeholders, broadly categorized into methodologic-related and treatment-related questions.

Table B. Research needs identified in CER and by stakeholders

Methodologic/Other-Related Questions
Which domains of executive function (e.g., planning, inhibitory control) are most sensitive to changes in Phe in individuals with PKU?
Which measures, including executive function and affective disorder screens, are shown to be associated with changes in cognitive outcomes related to Phe level in individuals with PKU?
To what degree do measures of executive function vary with cognition, in the context of varying levels of Phe?
What is the validity, reliability, and responsiveness to change of existing tools for measuring executive function in individuals with PKU?
When measuring executive function in individuals with PKU, when and how frequently should these measures be assessed?
Which measures of ADHD are valid, sensitive, and reliable for use in individuals with PKU?
What are the clinical benefits and limitations of distinguishing attention-related symptoms due to elevated Phe levels vs. from non-PKU-related factors such as individual behavior?
To what degree does Phe level affect domains of social and emotional functioning in PKU?
What is the relationship between clinical measures of executive function and "real world"/adaptive functioning?
What are the effects of nutritional status on measures of executive function or emotion?
To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?
What is the effectiveness of spectroscopy or other imaging techniques in assessing the effects of LNAAs on neurotransmission of Phe?
What CNS biomarkers are effective for assessing the effects of LNAAs on the brain in individuals with PKU?
What methods are effective for measuring brain amino acid absorption?
Are passive registries as effective as ongoing cohort studies for collecting adequate data to assess long-term effectiveness of adjuvant therapies?
In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?
What are the components of an effective system of care for individuals with PKU?
What treatment-related factors at different ages are the greatest source of concern to families / caregivers?
In individuals with PKU, what timing of Phe monitoring is optimal for fine tuning diet and treatment?
What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?
What is an appropriate study duration for understanding cognitive and other effects in individuals with PKU?
How can nutritional status be effectively measured in PKU?
What is the role of functional neuroimaging in PKU?
How should registry data collection be modified to allow for collection of efficacy data?
Treatment-Related Questions
In children ≤4 years old with PKU, what is the effect of BH4 plus diet compared with placebo plus diet/standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and growth and development?
In individuals with PKU responsive to BH4, what is the effect of BH4 plus diet compared with diet/standard care on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, family functioning, and harms of treatment over the long term (>2 years)?
What characteristics of the individual or family moderate responsiveness to BH4 in individuals with PKU?
What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological comorbidities in individuals with PKU?
What characteristics of the individual, including disease severity, or characteristics of the family are associated with early vs. late initial response to BH4?
In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care?
How does treatment with BH4 modify other care processes, including the transition to care as an adult?

Table B. Research needs identified in CER and by stakeholders (continued)

Treatment-Related Questions
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet/standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?
What harms to the mother and offspring are associated with BH4 use in pregnant women with PKU?
In individuals with PKU, what are the long-term effects (>6 months) of LNAAs on cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet and harms of LNAAs?
What harms are associated with LNAA use in individuals with PKU?
In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of LNAAs in promoting return to care?
How does treatment with LNAAs modify other care processes?
How can the effects of LNAAs be measured and when should measurement occur?
What are short-term effects of BH4 on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet, and harms of BH4 in specific subgroups (defined by age, dietary control, disease type)?
Among individuals with PKU using pharmacologic therapy, are supportive adherence models effective in increasing adherence?
Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes?
Among effective adherence support systems, have individual components been shown to drive effectiveness?
Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?
What are the pharmacokinetic, pharmacodynamic, and pharmacogenomic factors associated with treatment response in individuals with PKU?
What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?
Which biomarkers are effective for demonstrating response to treatment or therapeutic efficacy in PKU?
What is the utility of the plasma Phe/Tyrosine ratio compared with plasma Phe level as a measure of Phe control in PKU?
Are medical foods adequate to overcome vitamin and mineral deficiencies over the lifetime in individuals with PKU?
What is the role of combination therapy in PKU?
How can the effectiveness of combination therapies be measured?

Abbreviations: ADHD=attention deficit hyperactivity disorder; BH4=sapropterin dihydrochloride; CER=comparative effectiveness review; CNS=central nervous system; IQ=intelligence quotient; LNAA=large neutral amino acid; QOL=quality of life; PKU=phenylketonuria

Round One Prioritization

In the first prioritization (round one) survey, stakeholders prioritized needs by allotting a limited number of points to the questions. Eight of nine stakeholders completed the survey. The highest priority questions (questions scoring at least 5 points, n=27/50 needs) identified via the round one survey are outlined in the full report.

Final Prioritization

We then asked stakeholders to rate each of the 27 high-priority questions, divided into the broad categories of methodologic- or treatment-focused, on the EHC criteria listed above. Eight of nine stakeholders completed the survey. Tables C and D list the highest priority questions (in alphabetical order within each category).

Table C. Highest priority methodologic and other research questions

Question/Need	Tier
How can the effectiveness of combination therapies be measured?	Top
How should registry data collection be modified to allow for collection of efficacy data?	Top
In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?	Top
To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?	Top
What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?	Top

Abbreviations: Phe=phenylalanine; PKU=phenylketonuria

We broke down treatment-related questions into PICOTS elements and provide potential study designs as determined by the EPC team (Table D). The full report lists all questions by priority tier (top, middle, lower).

Table D. Highest priority treatment-related research questions, PICOTS elements, and potential study designs

Question/Need	Tier	Population	Intervention	Comparator	Outcomes	Timing	Setting	Potential Study Designs*
Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes? Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?	Top	Individuals with PKU	Adherence models, including social supports, electronic /online tools, print-based programs	Usual care without specific adherence support	Phe control, adherence, IQ, executive function, QOL	>6 months (ideally 12-24 months)	Clinic and community	RCT, prospective cohort
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet/standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?	Top	Pregnant women with PKU	BH4+diet	Placebo+diet	Maternal outcomes: Phe control, QOL, liberalization of diet, pregnancy outcomes Child outcomes: Cognitive outcomes (IQ and measures of executive function), QOL, growth and development	>5 years	Obstetrical care setting	Prospective cohort, Registry studies
What are the components of an effective system of care for individuals with PKU?	Top	Individuals with PKU	System of care	Usual care	Phe control, patient satisfaction, retention in care, QOL	>6 months	Community care, clinical care	RCT, time series, stepped wedge

Table D. Highest priority treatment-related research questions, PICOTS elements, and potential study designs (continued)

Question/Need	Tier	Population	Intervention	Comparator	Outcomes	Timing	Setting	Potential Study Designs*
What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological comorbidities in individuals with PKU?	Top	Individuals with PKU	BH4+diet	Diet	Changes in measures of behavioral and psychological comorbidities (e.g., ADHD, depression, anxiety)	--	Clinical care	
In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care?	Top	Individuals with PKU not adherent to diet or other treatment	Availability of BH4	--	Phe control, patient satisfaction, retention in care, QOL	--	Community and clinic	Pre-post designs, stepped wedge
What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?	Top	Individuals with PKU not adherent to treatment	Systems of health communication, education and adherence support directed to individuals not in treatment	--	Rate of return to treatment, continuation of treatment for a designated period of time. For women trying to become pregnant, ability to establish Phe control prior to conception.	--	Combination of clinica and community	Pre-post designs, stepped wedge

*See glossary of study designs at end of report

Abbreviations: ADHD=attention deficit hyperactivity disorder; BH4=sapropterin dihydrochloride; Phe=phenylalanine; PICOTS=population-intervention-comparator-outcomes-timing-setting; PKU=phenylketonuria; QOL=quality of life; RCT=randomized controlled trial

Discussion

Research gaps in PKU are due in part to the rarity of the disease, and many fundamental questions remain unanswered. The research gaps and needs identified through both the initial review of the CER and the stakeholder process fell into two primary categories: those that were methodologic or foundational in nature and those that were directly related to treatment intervention (and thus fit more directly into the comparative effectiveness rubric). The methodologic work is necessary to undergird the study of interventions and the two types of priority efforts should be considered in tandem.

Measuring combinations of therapeutic approaches, rather than isolating individual treatments is challenging under any circumstances. With a rare disease, the numbers of individuals on any specific combination of therapies will be small, increasing the complexity and difficulty of demonstrating effectiveness. Furthermore, the current dependence on blood Phe as a measure of dietary control is far from ideal. Because it requires laboratory time, it cannot be used to provide instant feedback that might support ongoing modifications to care. Efforts to develop technology to provide instant feedback on Phe have failed to date, but work is and should continue to provide families with the ability to obtain rapid feedback. One methodologic question focused on the need to understand how and under what circumstances registry data could be used for effectiveness research. The use of registries (as is currently being done with pregnant women) is likely to be a key part of improving care for PKU patients. Finally, the identification, prevention and role of dietary deficiencies in affecting the outcomes of patients with PKU was seen by the stakeholders as a worthy focus of future research.

Six intervention questions were designated as highest priority.

Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes? Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?

Understanding how to support PKU patients in adherence to what may be an evolving care approach has potential implications for achieving effective Phe management and positive cognitive outcomes. Ideally, studies of adherence support will take the form of RCTs comparing adherence support to usual care/practice and comparing various approaches to adherence support, as well as prospective cohort studies with good assessment and analytic management of confounders. In particular, it would be helpful to know whether adherence approaches aimed at particular developmental stages are successful at instilling habits that persist, even as children age and move through other developmental stages. It may be that RCTs are best able to capture early gains, while well-conducted prospective cohort studies with advanced analytics can describe trajectories of effects as participants age and develop**.**

In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet/standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?

Studying the effects of BH4 in addition to diet among pregnant women is complicated by lack of safety data and ethical issues related to conducting randomized trials in this vulnerable population. Prospective cohort studies with good assessment and analytic management of

confounders are rigorous approaches, and registry data will provide additional crucial information. In addition, measures of cognitive outcomes in children require long-term follow-up of both mothers and children. Cognitive outcomes are also driven by maternal IQ and must be controlled for analytically. Investigators should consider techniques to reduce bias and confounding in evaluation studies, including randomly selecting subjects, or including all subjects who received the intervention for assessment; retaining as many subjects in the evaluation over time as possible; having comparison groups that are equivalent at baseline on severity of PKU, age and maternal IQ; and using data analytic techniques that control for potential confounders

What are the components of an effective system of care for individuals with PKU?

Research is needed that both describes and evaluates systems of care for individuals with PKU (including the medical home), and that rigorously assesses the contribution that individual components make to effective care. Particular challenges related to this research include the need to document carefully the intervention so that it could be replicated, to fully characterize patients and patient characteristics to assess their impact on effectiveness, to include enough variation to understand and measure the impact in the heterogeneous PKU population, and the use study designs that are able to produce causal estimates and usable measures of effect. Potential study designs would include RCTs, time series, stepped wedge designs and other designs used extensively in the field of quality improvement. Outcomes should include clinical outcomes as well as satisfaction and quality of life.

What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological comorbidities in individuals with PKU?

RCTs are needed to examine the impact of BH4 and improved dietary management compared with diet alone on Phe control and whether improved Phe control affects the symptoms of ADHD, anxiety, depression or other psychological comorbidities. In addition to ongoing studies assessing behavioral effects of sapropterin in PKU, prospective cohort studies with good assessment and analytic management of confounders offer another rigorous approach. Studies evaluating behavioral and psychological outcomes will require comparison groups equivalent at baseline on severity of PKU, age, and type of psychological comorbidity as well as long-term followup. Reliable and valid assessment of behavioral and psychological outcomes is critical, and validated tests in PKU populations may not be available.

As the following questions are very closely related, we address them together.

In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care? What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?

It is likely that most studies will take the form of pre- and postinvestigations, but these studies will be unable to assess what proportion of the nonadherent population returned to treatment. It may be possible to do comparative studies by implementing different approaches at different clinical sites, or using a stepped wedge design across sites. Such a study would assume that the numbers of nonadherent individuals in different geographic regions are essentially equivalent. This study design would have challenges related to cross-contamination, given the strong communication network within the PKU community at large. Thus, it will be important to work with individuals who do return to treatment to understand exactly what motivated them to

return, and then to study carefully what elements of a support system help them to continue with their treatment.

Underpinning the ability to conduct the specific research described in this document is the need for investment in the type of infrastructure that supports the study of a rare disease. In particular, we recommend the establishment of a multi collaborator consortium that includes a public-private partnership. Collaborators in this consortium could develop or identify an agreed upon set of standardized data collection tools, especially for cognitive outcomes beyond IQ. Such a consortium should include guidelines for data sharing and comprehensive reporting, not only of intervention and outcome data, but of important, potentially confounding variables.

Stakeholders also emphasized the need for a health services research agenda on issues such as variation in care and in insurance access for medical foods. A related question is the ability to obtain care and treatment once children with PKU become adults. Finally, our stakeholders warned that the current workforce for caring for individuals with PKU is inadequate, and that the field needs to encourage and support training for a range of providers, including nonmetabolic nutritionists (for understanding exigencies of PKU) as well as psychiatrists and psychologists.

Conclusions

The existing research gaps related to the use of adjunct pharmacologic therapy in PKU are both substantive and methodologic. Specific deficiencies range from the substantive need for more trials that include more individuals to methodologic gaps in our understanding of the longer term implications of intermediate outcomes. In both cases, research is fundamentally challenging because the disease is so rare, making accrual of adequate numbers of participants difficult, if not impossible, for specific studies. Our multistep process identified high-priority methodologic needs related to measurement of outcomes and dietary control and treatment-related needs including understanding adherence to treatment and an optimal system of care for affected individuals, the effects of BH4 on pregnant women, and effects on mental health and behavioral comorbidities. While ongoing research may begin to provide some answers, addressing research needs in PKU will require further long term, rigorously designed, comparative studies. Further research also requires expanding our foundation of understanding of critical aspects of the disease including its natural history, biologic mechanisms of disease, and ways to measure elevated Phe to better understand its effects on cognition. Stakeholders also emphasized that clinical decisionmaking will, by necessity be based on a range of factors, including the rarity of the disease, the devastating consequences of not treating and the association of treatment with quality of life and family functioning. Future comparative effectiveness research should include additional contextual data to support decisionmaking and increase its utility.

Background

Context

Phenylketonuria (PKU) is a metabolic disorder in which an inability to properly metabolize the amino acid phenylalanine (Phe) leads to a buildup of Phe in the blood, causing neurotoxicity and resulting in intellectual disability, delayed speech, seizures and behavior abnormalities. Individuals with PKU are also susceptible to other adverse outcomes, including impaired executive function, reduced processing speed, attention problems, impaired fine motor skills, and mental health concerns (such as anxiety and depression symptoms).[5,6] PKU is typically diagnosed at birth following abnormal newborn screening results. With adherence to a Phe-restricted diet, poor outcomes can be mitigated. Nonetheless, management of PKU can be difficult and onerous for the patient and the family, leading to interest in identifying new ways of managing this lifelong condition. Further, questions remain as to the empirical basis for the selection of specific blood Phe levels as targets to reflect good dietary control.

The mainstay for treatment of PKU is a diet that restricts the intake of Phe to control the Phe concentration in the blood. In general, the usual treatment goal is a blood Phe level of 120 to 360 µmol/L. However, there is some variation in the target Phe level between clinics and across countries.[7,8] In addition to the low-Phe diet, many patients take vitamins and minerals daily to replace the nutrients that are absent in their restricted diet.[8] Historically, Phe levels were only monitored closely during the first 6 years of life (the "critical period") because elevated Phe after that age was not believed to be detrimental. However, based on accumulated evidence over the last few decades, it is now standard of care to recommend strict adherence to a Phe-restricted diet and routine monitoring of Phe levels throughout life.[7,9]

In 2007 the United States Food and Drug Administration (FDA) approved sapropterin dihydrochloride (Kuvan®, formerly known as Phenoptin) for the treatment of PKU under the stipulation that studies regarding the drug's efficacy and long-term safety continue. Sapropterin dihydrochloride (hereafter, BH4) is presumed to work by enhancing residual enzyme activity present in some individuals with PKU. Although treatment with BH4 would potentially allow a relaxation of the low-Phe diet, it is not intended to serve as a complete substitute for dietary intervention.[10]

In addition to a Phe-restricted diet and BH4, another potential treatment for PKU may be large neutral amino acids (LNAAs). LNAAs are considered nutritional supplements and are not subject to FDA approval. In theory, LNAAs decrease the brain Phe concentration by competing with Phe for shared amino acid transporters to cross the blood-brain barrier.[1,2] When used in clinical practice, LNAAs generally are offered to individuals who are unable to maintain dietary adherence.

A Phe-restricted diet throughout life has been well established as the cornerstone of treatment for PKU by studies such as the PKU Collaborative Study.[9] Yet PKU is a rare metabolic disease, and there are limited data on the best adjunct treatment in addition to diet for different ages. Although most clinics use a blood Phe level of 120 to 360 µmol/L as the goal treatment range, evidence is mixed on a specific optimal range for minimizing the clinical and cognitive effects of elevated blood Phe levels across different ages of individuals, including pregnant women. Furthermore, the efficacy, safety, and target populations for the concomitant use of BH4 or LNAAs with a Phe-restricted diet have not been established, and clinicians lack evidence-based support for when to prescribe BH4 or LNAAs and in which patients.

The implications of liberalizing the diet in those patients who do achieve blood Phe levels below treatment goals are currently unknown in terms of their effect on short- and long-term clinical and cognitive effects. Finally, the safety and efficacy of the use of BH4 and LNAAs in pregnant women and in children, including infants, are unknown.[11,12] Further complicating clinical decisionmaking is the difficulty in studying such a rare disease. Not only is research challenging logistically, but little Federal funding is available to support such research. The availability and quality of research evidence is unlikely to reach the level of more common clinical conditions; nonetheless, we know with certainty that failure to treat this condition with a Phe-restricted diet with or without concomitant use of BH4 or LNAAs leads to very poor outcomes. Clinicians, patients, and their families must make the best decisions possible about what treatment avenues to pursue in the presence of uncertainty.

Adjuvant Treatment for PKU Systematic Review

In 2010, the Vanderbilt Evidence-based Practice Center completed an Agency for Healthcare Research and Quality (AHRQ)-funded systematic review of adjuvant treatments (BH4, LNAAs) for PKU. The report focused on the following Key Questions related to adjuvant treatment:

Key Question 1a. What is the evidence that any specific Phe levels are optimal for minimizing or avoiding cognitive impairment in individuals with PKU?

Key Question 1b. What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?

Key Question 2. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status? Subgroups include the following:

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

Key Question 3. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

Key Question 4. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status? Subgroups include the following:

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

Key Question 5. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

Key Question 6. What are the harms, including adverse events, associated with the use of BH4, LNAAs, and/or dietary intervention in individuals with PKU?

Key Question 7. What is the evidence for the effectiveness of the addition of BH4 or LNAAs to dietary intervention for affecting outcomes in subgroups of patients? The following are examples of potential defining characteristics of subgroups:

- demographic
- clinical
- genotypic
- adherence

Key Findings of the Evidence Report

Phe Levels and Cognitive Outcomes

Seventeen studies were included in the meta-analysis, providing data on 432 individuals who ranged from age 2 to 34 years. The CER modeled the association of IQ less than 85 with blood Phe level, accounting for time of Phe measurement relative to cognitive testing, and whether or not the measurement occurred in the critical period (<6 years of age). Increasing Phe is clearly associated with decreased IQ, with a probability of IQ less than 85 exceeding the population probability (approximately 15 percent) at blood Phe over 400 µmol/L and leveling off at about 80 percent at 2000 µmol/L. This finding supports the typical target goal for blood Phe levels in individuals with PKU (120 to 360 µmol/L).

Studies of the association of blood Phe and executive function targeted many specific outcomes, precluding straightforward quantitative analysis of the data. Some studies clearly suggest that elevated Phe is likely associated with poorer outcomes but data are inconsistent across types of measures.

BH4

Ten studies evaluated the effects of BH4[13-22] in patients with PKU. Phe levels were reduced by at least 30 percent (the level used in studies submitted to the FDA to assess responsiveness) in up to half of treated participants (32 to 50 percent) at dosages of 5 to 20 mg/kg/day and for up to 22 weeks of observation in comparative studies. In the one RCT that comparing the effect of placebo on likelihood of a 30 percent reduction in Phe, only 9 percent of those on placebo achieved this effect, compared with 44 percent of the treated group after 6 weeks.[14] Data from the uncontrolled open label trial following [13] this RCT[14] suggested a sustained response for up to 22 weeks duration, with a 46 percent achieving a 30 percent reduction in Phe levels. Two trials[15,18] also examined the effect of BH4 use on Phe tolerance in individuals responsive to BH4, as did three case series.[17,19,21] In all five studies, Phe tolerance improved over time. One small case series reported on IQ and nutritional outcomes for up to 1 year on 5 mg/kg/day BH4 treatment.[19] After 1 year of treatment, the 11 participants discontinued use of a medical food and normalized their diet. IQ scores after 12 months on BH4 were similar to scores before treatment and development quotients were within normal limits.

Of the 10 studies examining the effectiveness of BH4 in participants with PKU, 4 studies[13-15,20] reported any type of harm related to the intervention drug. The most common side effects reported during BH4 trials were headache, throat pain, upper respiratory infection, diarrhea, abdominal pain, and nausea and vomiting, but harms were not significantly more common in the treatment arm than in the placebo.

LNAAs

Three studies addressed the effects of LNAAs.[2,23,24] The studies included a total of 47 participants. The trials were short, with treatment between 1 and 8 weeks, and dosages ranged from 250 mg/kg/day to 1g/kg/day. Two of the three studies measured reductions in Phe levels,[2,24] and one assessed cognitive outcomes.[23] This fair quality study[23] reported a positive effect on executive functioning, specifically verbal generativity, cognitive flexibility, and self-monitoring. Overall, participants who were using a Phe-free medical food to their nutritional needs did not experience a decrease in Phe, although those not adhering to diet or not using their formula did. In all three studies, blood Phe decreased after one week of treatment but remained above clinically acceptable levels. One trial of LNAAs[23] assessed neuropsychological outcomes and reported higher rates of anxiety associated with LNAA use.

Subgroups of Individuals With PKU

We did not identify any studies meeting our criteria and addressing adjuvant therapies in pregnant women with PKU of the effectiveness of adjuvant therapies for subgroups of individuals with PKU.

Strength of Evidence

Table 1 outlines the strength of the evidence (confidence that the current effect estimate will not change with future research) for the effects of BH4 and LNAAs as determined in the review.

Table 1. Intervention, strength of evidence domains, and strength of evidence for key outcomes

Outcome	Intervention	Study Type (N studies of type reporting outcome)	Risk of Bias	Consistency	Direct-ness	Precision	SOE
Reduction in Phe levels over the short term (≤12 weeks) in responders	BH4	RCT (2)[14,15] Uncontrolled open label (3)[13,18,20] Case series (3)[16,19,21]	Medium	Consistent	Direct	Precise	Moderate
	LNAAs	RCT (2)[23,24] Uncontrolled open label (1)[2]	High	Inconsistent	Direct	Imprecise	Insufficient
Reduction in Phe levels over the long term (>12 weeks) in responders	BH4	Case series (4)[16,17,19,21]	High	Consistent	Direct	Imprecise	Insufficient data to calculate an effect

Table 1. Intervention, strength of evidence domains, and strength of evidence for key outcomes (continued)

Outcome	Intervention	Study Type (N studies of type reporting outcome)	Risk of Bias	Consistency	Direct-ness	Precision	SOE
Phe tolerance	BH4	RCT (1)[15] Uncontrolled open label (1)[18] Case series (3)[17,19,21]	High	Consistent	Direct	Imprecise	Insufficient
	LNAAs	NR	NR	NR	NR	NR	Insufficient
Phe variability	BH4	Case series (1)[16] Cohort study (1)[22]	High	Unknown	Direct	Imprecise	Insufficient
	LNAAs	NR	NR	NR	NR	NR	Insufficient
Cognitive outcomes	BH4	Case series (1)[19] plus indirect evidence from RCTs plus meta-analysis	High	Unknown	Direct	Imprecise	Low
	LNAAs	RCT (1)[23]	High	Unknown	Direct	Imprecise	Insufficient
Nutritional status	BH4	Case series (1)[19]	High	Unknown	Direct	Imprecise	Insufficient
	LNAAs	NR	NR	NR	NR	NR	Insufficient
Lack of significant harms	BH4	RCT (2)[14,15] Uncontrolled open label (2)[13,20] Cohort study (1)[22]	High	Consistent	Direct	Precise	Moderate
	LNAAs	RCT (1)[23]	High	Unknown	Direct	Imprecise	Insufficient
Quality of life	BH4	NR	NR	NR	NA	NR	Insufficient
	LNAAs	NR	NR	NR	NA	NR	Insufficient

Abbreviations: LNAAs=large neutral amino acids; NA=not applicable; NR=not reported; RCT=randomized controlled trial; SOE=strength of the evidence

Evidence Gaps

The existing research gaps related to the use of adjuvant pharmacologic therapy in PKU are both substantive and methodologic. Research is fundamentally challenging because the disease is so rare, making accrual of adequate numbers of participants difficult, if not impossible, for some studies. Furthermore, in part because it affects so few people, funding for PKU research is limited, and to date, treatment research is almost exclusively supported by the pharmaceutical industry.

Phe Level and Cognitive Outcomes

A significant limitation in the current body of research on the relationship between blood Phe level and cognitive outcomes is the lack of consistent methodologies using standardized tools and measures and consistent data collection across centers. The result is that many studies provide incomplete data that cannot be used in meta-analyses, despite a clear need for research to occur across sites in order to accrue adequate numbers for analysis. Complete reporting of data and results in future studies would ensure that future research can be considered in more robust meta-analyses and can contribute to an improved understanding of the relationship between Phe and IQ.

In addition, some studies that did provide appropriate data for inclusion did not provide information on potentially confounding or modifying factors in the relationship between Phe and IQ. In future research, details about familial IQ, socioeconomic status, maternal education, age at initial treatment and concurrent medications should be fully described so they might be used in a

more extensive meta-analysis of Phe-IQ associations. One basic need is to better understand the degree to which the perceived association changes by age, with the practical implication of understanding the degree of dietary control necessary across age groups. Certainly if patients are able to adhere to diet, then tight control is the standard of care, but understanding of the specific implications of looser control, especially in older adults, is lacking and could inform clinical practice. Because tight control is important, an understanding is needed of the supports that might be helpful as individuals age over the lifespan. Related to this is the need for additional measures to assess adequate control beyond blood Phe. This requires an understanding of what outcomes are clinically important, and their relative value to patients and their families. For this to be possible, complete and accurate measure of Phe and cognition over fairly long periods of time is necessary, perhaps through a long-term follow up study or through the multisite collaboration suggested above. Finally, the effects of mild hyperphenylalaninemia as opposed to classic, mild and moderate PKU, should also be clarified, including the impact on cognition, executive functioning, attention, behavioral problems, and other psychological issues.

Ideally, future studies or a complete registry could provide repeated measures (e.g., index of dietary control) of blood Phe that can more precisely characterize an individual's Phe level over relevant time intervals, and standard deviations around those measures so that we can determine the effect of variation in Phe on IQ. Also, rather than relying solely on IQ, alternative outcomes could allow for modeling the degree to which increased Phe is associated with differences between an individual's realized and expected outcomes.

Although research is being conducted on executive function outcomes for individuals with PKU, there is no consensus on which measures of executive function are most appropriate. This highlights the need for fundamental research, because measures of executive function tend to be better reflections of success with day-to-day activities than targeted measures such as IQ. It is plausible that some measures of executive function may be more sensitive to changes in Phe than IQ, and therefore better at identifying impairment. By the same token, establishing the degree to which measures of executive function can and should be combined in analyses would be helpful for synthesizing the currently disparate body of literature. Nonetheless, the sensitivity, validity and acceptability of individual executive function measures in PKU has yet to be established or agreed upon, and current research reflects a reliance on a wide range of outcomes, making synthesis of relationships and pooling of results difficult.

Given the reported association between PKU and an increased incidence of inattention, anxiety and depressive symptoms, additional studies on these and other psychological issues in PKU are also warranted. Some of this work is ongoing, and we encourage more work examining the full range of outcomes associated with PKU.

BH4

Research on the use of BH4 as an adjuvant therapy in PKU management consists of small, tightly controlled multisite efficacy studies, two of which are RCTs. The greatest research need in this area is thus for larger studies. Given the known difficulty of accruing large numbers of participants, however, researchers should also use existing data sets, and, as recommended, use a consortium and multisite approach to gathering data. Ideally, studies will be conducted in both tightly controlled and nonadherent populations, and among different age groups, with appropriate design and power for subgroup analyses. Research should continue to include RCTs, but prospective cohort studies that may have the potential to provide additional effectiveness data—including outside of a controlled clinical setting—adherence and longer term evidence

would also be helpful to support understanding of the role of BH4 in clinical care. These studies should provide substantially more detail on the range of benefits and harms associated with treatment. For example, a better understanding is needed of the effects of BH4 in children less than 4 years of age and pregnant women, and while it may be challenging or inappropriate to conduct RCTs in these populations, observational cohorts or registry data are essential.

Data are not currently available to understand potential modifiers of treatment effectiveness in order to select the best populations for targeting further research and treatment. Moreover, the variability in responsiveness to BH4 is unexplained, and subpopulations that have a unique response to this medication have not been well characterized. Causes of variability may be multifactorial and likely include individual patient and genotype differences, drug dose, and individual patient behavior such as dietary adherence. It is unclear, in particular, why a high proportion of individuals who have an initial response in loading studies at screening do not have a durable response in efficacy trials, even while those who do have a response demonstrate a significant effect. The degree to which this observed variation may be associated with suboptimal adherence should be assessed.

Another area of potential research is the use of adherence supports for both drug and diet to optimize potentially positive outcomes. It is assumed that support at familial, social and system levels may be helpful and this idea should be empirically addressed.

Long-term efficacy outcomes beyond 22 weeks and safety outcomes beyond 3 years are currently unavailable, as are measures of behavioral change and cognition and patient-reported outcomes including quality of life. The degree to which reductions in blood Phe are associated with measurable cognitive outcomes or even patient perception of increased mental clarity is unknown. Furthermore, explicit assessment of the potential for liberalization of the diet, and the subsequent nutritional effects has yet to be conducted.

Future research should comprise larger studies designed to allow subgroup analysis of the effectiveness of adjuvant pharmacologic therapy for PKU. Although the current literature does not provide evidence for effectiveness in all target patients, some benefit is seen in some patients. Whether these patients differ from the overall population in terms of genotype is an area of current research focus that has the potential to allow targeting of treatment.

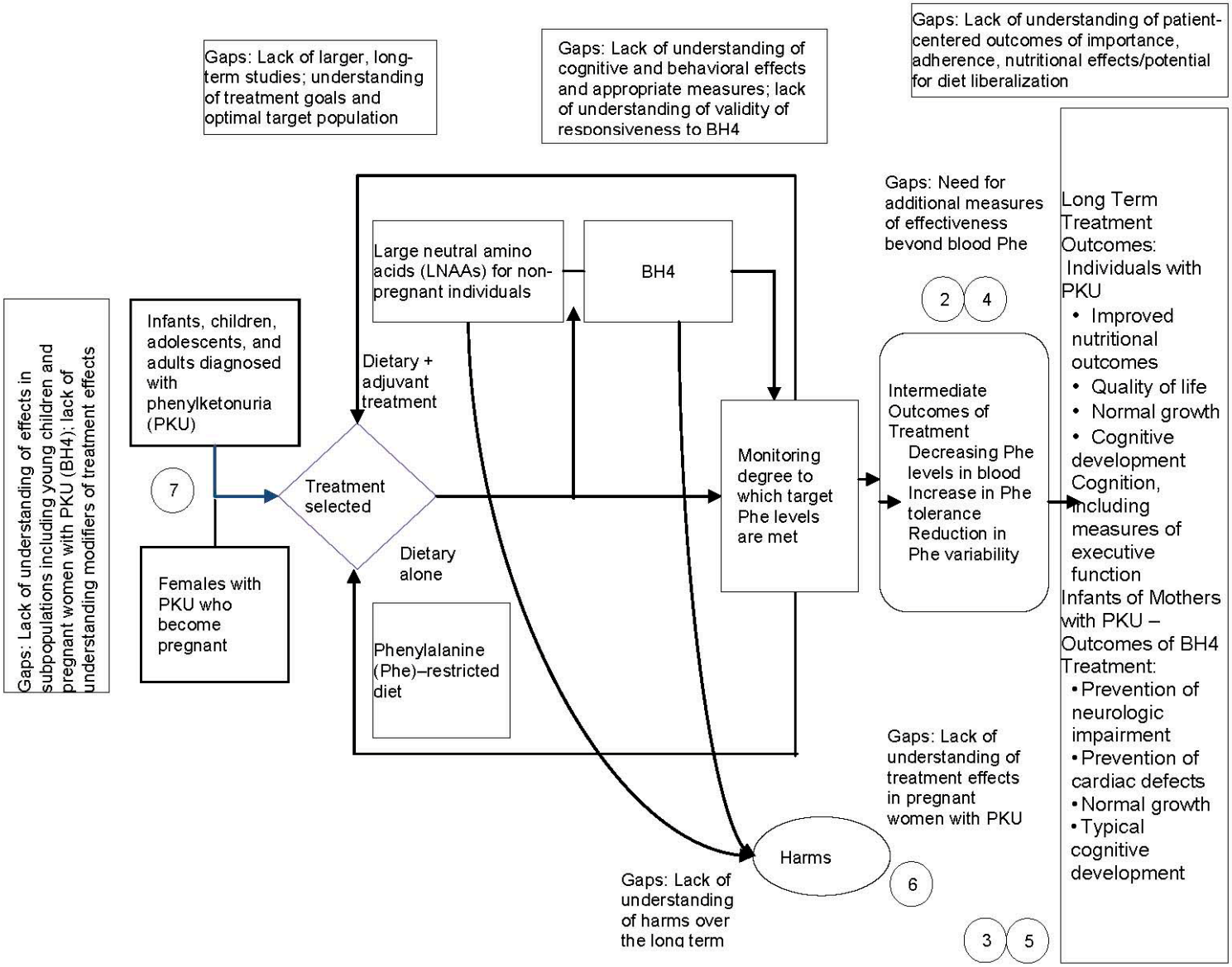
A number of studies are reportedly underway to address gaps in the current literature. These include a long-term study of the effect of BH4 on neurocognitive function in young children, a study of the effect in adolescent patients with attention deficit hyperactivity disorder, and a registry that includes pregnant women. However, we stress the importance of making data available and note that several commitment studies have been listed as completed, but have yet to make findings available. These include the studies on cardiac effects of BH4. Another commitment study that is reported as fulfilled is an open label study to study the safety and efficacy of BH4 for treating patients with hyperphenylalaninemia, yet no results have been made available. Finally, publicly funded studies to confirm and expand on reported efficacy and effectiveness data are needed.

LNAAs

The three very small studies of LNAAs cannot be considered as more than proof of concept at this time, and if further work is to occur in this area, it should be done in well-conducted RCTs of adequate size. The mechanism by which LNAAs may work should be clarified, as should the optimal target population and specific treatment goals. The current formulations that have been tested require taking many pills per day and so the formulations should be made more palatable.

Figure 1 illustrates these treatment-related evidence gaps within the analytic framework of the evidence report.

Figure 1. Analytic framework illustrating intervention-related evidence gaps



Methods

Table 2 outlines the methods we used to identify and prioritize research needs. We expand on the table's brief description in each of the following sections.

Table 2. Methods for developing future research needs related to adjuvant therapies for PKU

Approach to Evidence Gap Identification
1. Generate preliminary list of research gaps based on the gaps noted in the CER
2. Form stakeholder workgroup with representatives from groups including patient/family/advocacy organizations, the provider community, the research community, and funding agencies
3. Locate ongoing trials and other funded research
4. Conduct conference call with stakeholders to refine initial list of evidence gaps
5. Review teleconference responses and refine list of research gaps related to adjuvant treatment for PKU
Approach to Prioritization and Stakeholder Engagement for Prioritization
6. Request that stakeholders prioritize research gaps
7. Cull list of prioritized gaps to top tier research needs based on stakeholder voting
8. Request that stakeholders assess top priority needs using modified EHC selection criteria
Approach to Research Question Development and Considerations for Potential Research Designs
9. Determine potential study designs to address final list of research needs
10. Develop research needs report
11. Request stakeholder input on the draft research needs report
12. Finalize research needs report

Abbreviations: CER=comparative effectiveness review; EHC=Effective Health Care Program; PKU=phenylketonuria

Identification of Evidence Gaps

We identified evidence gaps that limited conclusions that could be drawn about each Key Question from primarily the Discussion and Future Research sections of the report. One investigator extracted research gaps from the review. A senior investigator then reviewed the list for accuracy and completeness and added gaps as appropriate. We augmented this preliminary list of gaps as identified in the review with gaps/needs discussed at the National Institute of Child Health & Human Development PKU Scientific Review Conference: State of the Science and Future Research Needs held on February 22–23, 2012.

We framed gaps as Population-Intervention-Comparators-Outcomes-Timing-Setting (PICOTS) questions by CER Key Question or as nonresearch issues for which greater understanding would benefit PKU treatment (Appendix A). We also indicated where ongoing research may begin to address questions.

Identification of Ongoing Research

We searched clinical research repositories and research-related sites including ClinicalTrials.gov, AHRQ's Grants Online database, CenterWatch, NIH Reporter, the Canadian Institute for Health Research, OrphaNet, the UK Medical Research Council, Wellcome Trust, the World Health Organization Clinical Trials Registry, Current Controlled Trials, and the European Union Clinical Trials Register. We also searched the Web sites of relevant advocacy organizations including the Children's PKU Network, the National PKU Alliance, National Society for PKU, Canadian Association for Rare Disorders, Children Living with Inherited Metabolic Diseases organization, Canadian PKU and Allied Health Disorder Organization,

National Organization for Rare Disorders, Genetic Metabolic Dieticians International, Eurordis, Society for the Study of Inborn Errors of Metabolism, British Inherited Metabolic Disease Group, Society for Inherited Metabolic Disorders, International Rare Diseases Research Consortium, and the March of Dimes. Appendix B includes a summary of findings from these searches.

Engagement of Stakeholders, Researchers, and Funders

We then convened a group of stakeholders broadly representative of research, clinical care, patient/consumer, and funder perspectives to provide input on the list and add additional questions as necessary. We generated lists of potential stakeholders via a review of potential Technical Expert Panel members and key informants for the CER, review of investigators in studies included in the CER, review of advocacy and other agencies relevant to PKU, and through consultation with our Task Order Officer (TOO). We reviewed potential stakeholder candidates with the TOO to determine a final set of invitees. Stakeholders completed conflict of interest forms, and none was deemed by the AHRQ TOO to have conflicts that would preclude their participation.

We engaged stakeholders agreeing to participate in the project via an initial conference call to introduce the project and to add to the list of gaps identified from the report. This call was followed by an email message including the revised list of gaps and inviting stakeholders to edit or add questions as necessary.

Criteria for Prioritization

Round One Prioritization

We presented the expanded list of questions to stakeholders via a Web-based survey implemented in the RTI-UNC EPC Prioritization Software.[25] The survey asked stakeholders to allot a number of votes to each question to indicate priority. We asked stakeholders to keep in mind EHC prioritization criteria when considering importance but did not require "votes" by each specific criterion at this phase. Based on processes used in prior future research needs projects,[3] we limited the number of votes available to roughly two-thirds of the number of questions identified to ensure that stakeholders selected high-priority issues. We then compiled votes across stakeholders and questions. We a priori considered those questions receiving at least 5 points to comprise the top tier of research needs for further prioritization.

Round Two Prioritization

We sent a second Web-based survey (created using RedCap survey software[26]) to stakeholders asking them to further prioritize the high-priority needs using modified EHC program selection criteria (Table 3) as described in AHRQ EHC methodologic guidance[4]). Stakeholders ranked each question on each criterion below using a 1 (low) to 5 (high) point scale (Appendix C). Questions were divided by broad category of focus (treatment or methodologic/other).

Table 3. EHC criteria used to prioritize top-tier research needs*

• Potential for significant health impact on the current and future health status of people with respect to burden of the disease and health outcomes: mortality, morbidity, and quality of life
• Potential to reduce important inappropriate (or unexplained) variation in clinical practices known to relate to quality of care. Potential to resolve controversy or dilemmas in what constitutes appropriate health care. • Potential to improve decision-making for patient or provider, by decreasing uncertainty
• Potential for significant (nontrivial) economic impact related to the costs of health service; to reduce unnecessary or excessive costs; to reduce high costs due to high volume use; to reduce high costs due to high unit cost or aggregate cost. Costs may impact consumers, patients, health care systems, or payers
• Potential risk from inaction (Including unintended harms from lack of prioritization of proposed research; opportunity cost of inaction)
• Potential to reduce health inequities (Addresses inequities, vulnerable, diverse populations , including issues for patient subgroups)
• Potential to allow assessment of ethical, legal, social issues pertaining to the condition
• Potential for new knowledge (Research would not be redundant or question not sufficiently researched, including completed and in-process research; utility of available evidence limited by changes in practice, e.g., disease detection or evolution in technology)

* Criteria outlined in Prioritization Criteria Methodology for Future Research Needs Proposals Within the Effective Health Care Program[4]

Abbreviation: EHC=Effective Healthcare Program

We tallied the number of points for each question across all criteria in each category and present questions by tier of priority (top, middle, lower). Appendix D outlines the highest scoring questions on each criterion.

Research Question Development and Research Considerations

Once we had determined the top-tier questions/needs, the core project team discussed potential research designs and considerations relevant to each top tier treatment-related question. This discussion was informed by AHRQ guidance and input received from stakeholders during prior calls. We considered factors including the following:

- Ethical, legal, and social considerations
- Resource utilization
- Availability of relevant datasets
- Alignment with the system of care for PKU
- Challenges in assessing outcomes
- Recruitment issues in rare diseases

Results

Stakeholders

Stakeholders represented clinical, research, and advocacy perspectives in PKU. The panel comprised nine stakeholders, including a physician from a pharmaceutical company, an advocate who has children with PKU, representatives from government agencies that fund research on developmental disabilities, a dietician and nutritionist, clinical researchers with expertise in generics and metabolism, and experts in developmental medicine and in bioethics. Appendix E includes a summary of discussion from the initial stakeholder call

Research Needs

Needs Identified in CER and via Stakeholder Input

Table 4 lists the research needs identified in the CER and those generated via stakeholders organized by Key Question. Where identified, possibly relevant ongoing research is included.

Table 4. Research needs identified in CER and by stakeholders

Key Question	Research Question	Potentially Relevant Ongoing Research
1a. What is the evidence that any specific Phe levels are optimal for minimizing or avoiding cognitive impairment in individuals with PKU? 1b. What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?	Which domains of executive function (e.g., planning, inhibitory control) are most sensitive to changes in Phe in individuals with PKU?	None identified
	Which measures, including executive function and affective disorder screens, are shown to be associated with to changes in cognitive outcomes related to Phe level in individuals with PKU?	
	To what degree do measures of executive function vary with cognition, in the context of varying levels of Phe?	
	What is the validity, reliability, and responsiveness to change of existing tools for measuring executive function in individuals with PKU?	
	When measuring executive function in individuals with PKU, when and how frequently should these measures be assessed?	
	Which measures of ADHD are valid, sensitive, and reliable for use in individuals with PKU?*	
	What are the clinical benefits and limitations of distinguishing attention-related symptoms due to elevated Phe levels vs. from non-PKU-related factors such as individual behavior?*	
	To what degree does Phe level affect domains of social and emotional functioning in PKU?*	
	What is the relationship between clinical measures of executive function and “real world”/adaptive functioning?*	
	What are the effects of nutritional status on measures of executive function or emotion?*	
	To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?*	

Table 4. Research needs identified in CER and by stakeholders (continued)

Key Question	Research Question	Potentially Relevant Ongoing Research
2. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status?	In children ≤4 years old with PKU, what is the effect of BH4 plus diet compared with placebo plus diet/standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and growth and development?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392) • Safety, and Population Pharmacokinetics of Sapropterin Dihydrochloride (Kuvan®) in Phenylketonuria (PKU) Patients <4 Years Old. (SPARK) (NCT01376908) • A Phase 3b Open-Label Study to Evaluate the Effect of Kuvan® on Neurocognitive Function, Maintenance of Blood Phenylalanine Concentrations, Safety, and Population Pharmacokinetics in Young Children With Phenylketonuria (NCT00838435)
	In individuals with PKU responsive to BH4, what is the effect of BH4 plus diet compared with diet/standard care on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, family functioning, and harms of treatment over the long term (>2 years)?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What characteristics of the individual or family moderate responsiveness to BH4 in individuals with PKU?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological comorbidities in individuals with PKU?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392) • A Double-blind, Placebo-controlled, Randomized Study to Evaluate the Safety and Therapeutic Effects of Sapropterin Dihydrochloride on Neuropsychiatric Symptoms in Subjects With Phenylketonuria(NCT01114737)
	What characteristics of the individual, including disease severity, or characteristics of the family are associated with early vs. late initial response to BH4?	None identified

Table 4. Research needs identified in CER and by stakeholders (continued)

Key Question	Research Question	Potentially Relevant Ongoing Research
2. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status?	In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care? *	None identified
	How does treatment with BH4 modify other care processes, including the transition to care as an adult? *	
3. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?	In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet/standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What harms to the mother and offspring are associated with BH4 use in pregnant women with PKU?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)

Table 4. Research needs identified in CER and by stakeholders (continued)

Key Question	Research Question	Potentially Relevant Ongoing Research
4. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status?	In individuals with PKU, what are the long-term effects (>6 months) of LNAAs on cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet and harms of LNAAs?	• Effects of short term increase of phenylalanine levels on neuropsychological functions and well-being in adults with phenylketonuria: the "diet for life" study- supplement of amino acids (NTR1056)
	What harms are associated with LNAA use in individuals with PKU?	• Effects of short term increase of phenylalanine levels on neuropsychological functions and well-being in adults with phenylketonuria: the "diet for life" study- supplement of amino acids (NTR1056)
	What is the effectiveness of spectroscopy or other imaging techniques in assessing the effects of LNAAs on neurotransmission of Phe?*	None identified
	What CNS biomarkers are effective for assessing the effects of LNAAs on the brain in individuals with PKU?*	
	In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of LNAAs in promoting return to care?*	
	How does treatment with LNAAs modify other care processes?*	
	How can the effects of LNAAs be measured and when should measurement occur?*	
	What methods are effective for measuring brain amino acid absorption?*	

Table 4. Research needs identified in CER and by stakeholders (continued)

Key Question	Research Question	Potentially Relevant Ongoing Research
7. What is the evidence for the effectiveness of the addition of BH4 or LNAAs to dietary intervention for affecting outcomes in subgroups of patients?	What are short-term effects of BH4 on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet, and harms of BH4 in specific subgroups (defined by age, dietary control, disease type)?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392) • Effects of Sapropterin on Brain and Cognition in Individuals With Phenylketonuria (NCT00730080) • Evaluation of Behavior, Executive Function, Neurotransmitter Function and Genomic Expression in PKU "Nonresponders" to Kuvan(NCT01274026) • Treatment of hyperphenylalaninemia with Sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) and its influence on the amino acids and fatty acids patterns from childhood to adulthood, a Phase IV, longitudinal, unblinded, controlled, single-centre, retrospective and prospective clinical study(ISRCTN77098312)
Overall / Foundational Questions	Among individuals with PKU using pharmacologic therapy, are supportive adherence models effective in increasing adherence?	None identified
	Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes?	
	Among effective adherence support systems, have individual components been shown to drive effectiveness?	
	Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?	
	What are the pharmacokinetic, pharmacodynamic, and pharmacogenomic factors associated with treatment response in individuals with PKU?	
	Are passive registries as effective as ongoing cohort studies for collecting adequate data to assess long-term effectiveness of adjuvant therapies?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)

Table 4. Research needs identified in CER and by stakeholders (continued)

Key Question	Research Question	Potentially Relevant Ongoing Research
Overall / Foundational Questions	In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What are the components of an effective system of care for individuals with PKU?	None identified
	What treatment-related factors at different ages are the greatest source of concern to families / caregivers?	• 5-year Follow-up of the Comparison of Life and Physical Health in Adult Patients With PKU and Healthy Age Matched Controls (NCT01096758)
	In individuals with PKU, what timing of Phe monitoring is optimal for fine tuning diet and treatment?	• The effects of online availability of individual phenylalanine levels to patients with phenylketonuria (NTR1171)
	What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?*	None identified
	Which biomarkers are effective for demonstrating response to treatment or therapeutic efficacy in PKU? *	
	What is the utility of the plasma Phe/Tyrosine ratio compared with plasma Phe level as a measure of Phe control in PKU? *	
	Are medical foods adequate to overcome vitamin and mineral deficiencies over the lifetime in individuals with PKU? *	
	What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU? *	
	What is an appropriate study duration for understanding cognitive and other effects in individuals with PKU? *	
	How can nutritional status be effectively measured in PKU? *	
	What is the role of functional neuroimaging in PKU? *	
	What is the role of combination therapy in PKU? *	
	How can the effectiveness of combination therapies be measured? *	
	How should registry data collection be modified to allow for collection of efficacy data? *	

*Questions derived from stakeholder calls

Abbreviations: ADHD=attention deficit hyperactivity disorder; BH4=sapropterin dihydrochloride; IQ=intelligence quotient; LNAA=large neutral amino acids; Phe=phenylalanine; PKU=phenylketonuria; QOL=quality of life

Stakeholders also identified several research questions that fell out of the scope of the current project's Key Questions and analytic framework. Therefore, these questions could not be

included in the prioritization process. They are, however, important questions to the field, and therefore we list them here:

- What is the effectiveness of medications to treat ADHD, anxiety, depression, and other mental health comorbidities in individuals with PKU?
- What methods are effective for identifying and reaching individuals with PKU not currently under care?
- What is the natural history of PKU?
- How does defining responsiveness in terms of Phe level or Phe tolerance or in terms of cognition or other long-term outcomes affect care for individuals with PKU?

We also identified a number of nonresearch issues/recommendations in the report and expanded with stakeholder feedback; we include these issues in the Discussion section of the report. We did not ask stakeholders to prioritize these nonresearch issues but note that further exploration would benefit our understanding of PKU.

Round One Prioritization

As noted, we presented the expanded list of research needs in Table 5 to stakeholders in an initial survey (round one survey). We requested that stakeholders review EHC prioritization criteria and then assign a number of points to each question to indicate priority. Eight of nine stakeholders completed the survey.

Table 5 lists the highest priority questions (questions scoring at least 5 points) identified via the round one survey. We organized questions broadly by area of focus (methodologic/other or treatment) and present them by category in no particular order.

Table 5. Questions indentified as high priority in round one survey

Treatment-Oriented Questions
Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes?
Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?
In children ≤4 years old with PKU, what is the effect of BH4 plus diet compared with placebo plus diet/standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and growth and development?
In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care?
In individuals with PKU responsive to BH4, what is the effect of BH4 plus diet compared with diet/standard care on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, family functioning, and harms of treatment over the long term (>2 years)?
In individuals with PKU, what are the long-term effects (>6 months) of LNAAs on cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet and harms of LNAAs?
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet/standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?
What are short-term effects of BH4 on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet, and harms of BH4 in specific subgroups (defined by age, dietary control, disease type)?

Table 5. Questions indentified as high priority in round one survey (continued)

Treatment-Oriented Questions
What are the components of an effective system of care for individuals with PKU?
What characteristics of the individual, including disease severity, or characteristics of the family are associated with early vs. late initial response to BH4?
What harms are associated with LNAA use in individuals with PKU?
What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological comorbidities in individuals with PKU?
What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?
Methodologic-Oriented/Other Questions
How can the effectiveness of combination therapies be measured?
How should registry data collection be modified to allow for collection of efficacy data?
In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?
To what degree do measures of executive function vary with cognition, in the context of varying levels of Phe?
To what degree does Phe level affect domains of social and emotional functioning in PKU?
To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?
What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?
What is the effectiveness of spectroscopy or other imaging techniques in assessing the effects of LNAAs on neurotransmission of Phe?
What is the relationship between clinical measures of executive function and “real world”/adaptive functioning?
What is the validity, reliability, and responsiveness to change of existing tools for measuring executive function in individuals with PKU?
What methods are effective for measuring brain amino acid absorption?
When measuring executive function in individuals with PKU, when and how frequently should these measures be assessed?
Which domains of executive function (e.g., planning, inhibitory control) are most sensitive to changes in Phe in individuals with PKU?
Which measures, including executive function and affective disorder screens, are shown to be associated with changes in “real world”/adaptive functioning related to Phe level in individuals with PKU?

Abbreviations: BH4=sapropterin dihydrochloride; IQ=intelligence quotient; LNAA=large neutral amino acids; Phe=phenylalanine; QOL=quality of life; PKU=phenylketonuria

Final Prioritization

In our round two/final survey we requested that stakeholders score each of the 27 high-priority needs (Table 5) on each of the following EHC selection criteria[4] using a 1 (low) to 5 (high) point scale:

- Potential for significant health impact
- Potential to reduce variation in clinical practices
- Potential for significant economic impact
- Potential risk from inaction
- Potential to address inequities
- Potential to allow assessment of ethical, legal, social issues pertaining to the condition
- Potential for new knowledge

Eight of nine stakeholders completed the survey. We tallied the scores for each need/question on each criterion to determine an overall score and divided the questions by range of scores into top, middle, and lower tiers (presented in no particular order within each tier in Table 8); we combined and clarified two treatment questions related to adherence supports into one as one question was effectively a subquestion addressing modifiers of adherence program effects. Thus, six needs/questions comprise the top tier/highest priority treatment-related needs.

The results are presented below in two sections: first, the top-tier methodologic questions (Table 6), followed by those that received lower priority scores, and second, the top tier treatment-related questions (Table 7), followed by lower priority treatment questions.

Of note, the scores were all very close, and no set of recommended studies should be considered low priority. The rating provides a relative measure; all of the research questions are important, but a subset comprises a priority set that should be addressed first. We broke down top tier treatment-related questions into PICOTS elements (Table 7). As methods-related questions typically do not involve effectiveness outcomes, we did not delineate PICOTS.

Highest Priority Research Agenda

The questions below are those that were prioritized into the top tier of the potential research questions. We have expanded on specific issues that might warrant consideration by investigators wishing to study any of the highest priority research questions. Clearly, across the board, studies should be rigorous and include appropriate comparison groups. They should be adequately powered to assess effects, and followup should continue for an adequate period of time so as not to limit measurement to immediate or short-term outcomes. We outline specific considerations for the top tier of methodologic questions and for the top tier intervention research questions below.

Table 6. Highest priority methodologic and other questions

Question/Need	Tier
How can the effectiveness of combination therapies be measured?	Top
How should registry data collection be modified to allow for collection of efficacy data?	Top
In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?	Top
To what extent are poor cognitive outcomes related to dietary deficiencies versus Phe levels?	Top
What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?	Top

Abbreviations: Phe=phenylalanine; PKU=phenylketonuria

Many, if not most, individuals with PKU are likely to be treated with combination approaches, and methods for designing studies that assess the effectiveness of different combinations, rather than individual treatments, should be developed and validated. The question of whether or how registry data can support this and other types of effectiveness research warrants consideration by the PKU community.

Three primary measurement issues reached top priority level. First, there is an urgent need to identify approaches beyond blood Phe, which cannot be assessed immediately, for capturing the degree to which individuals are maintaining dietary control. This information is critical for guiding treatment, and to the degree that it is possible the effects of dietary deficiencies themselves on cognitive outcomes should be disaggregated from the effects of increasing Phe so that future studies can account for any potential effect of nutrition that may confound studies

focused on Phe. Finally, related to this question, is a need for more research identifying biomarkers that can identify vitamin and mineral deficiencies.

The intervention research questions that were prioritized into the top tier are presented in Table 7. Where appropriate we specify design-related issues as identified by the EPC team for investigators to consider. We also identify and describe methodologic challenges inherent in studying these questions that will warrant attention by the investigators who choose to pursue them in the Discussion chapter.

Table 7. Highest priority treatment-related research questions, PICOTS elements, and potential study designs

Question/Need	Tier	Population	Intervention	Comparator	Outcomes	Timing	Setting	Potential Study Designs*
Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes? Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?	Top	Individuals with PKU	Adherence models, including social supports, electronic /online tools, print-based programs	Usual care without specific adherence support	Phe control, adherence, IQ, executive function, QOL	>6 months (ideally 12-24 months)	Clinic and community	RCT, prospective cohort
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet/standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?	Top	Pregnant women with PKU	BH4+diet	Placebo+ diet	Maternal outcomes: Phe control, QOL, liberalization of diet, pregnancy outcomes Child outcomes: Cognitive outcomes (IQ and measures of executive function), QOL, growth and development	>5 years	Obstetrical care setting	Prospective cohort, Registry studies
What are the components of an effective system of care for individuals with PKU?	Top	Individuals with PKU	System of care	Usual care	Phe control, patient satisfaction, retention in care, QOL	>6 months	Community care, clinical care	RCT, time series, stepped wedge

Table 7. Highest priority treatment-related research questions, PICOTS elements, and potential study designs (continued)

Question/Need	Tier	Population	Intervention	Comparator	Outcomes	Timing	Setting	Potential Study Designs*
What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological comorbidities in individuals with PKU?	Top	Individuals with PKU	BH4+diet	Diet	Changes in measures of behavioral and psychological comorbidities (e.g., ADHD, depression, anxiety)	--	Clinical care	RCTs, prospective cohort studies
In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care?	Top	Individuals with PKU not adherent to diet or other treatment	Availability of BH4	--	Phe control, patient satisfaction, retention in care, QOL	--	Community and clinic	Pre-post designs, stepped wedge
What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?	Top	Individuals with PKU not adherent to treatment	Systems of health communication, education and adherence support directed to individuals not in treatment	--	Rate of return to treatment, continuation of treatment for a designated period of time. For women trying to become pregnant, ability to establish Phe control prior to conception.	--	Combination of clinic and community	Pre-post designs, stepped wedge

*See glossary of study designs at end of report

Abbreviations: ADHD=attention deficit hyperactivity disorder; BH4=sapropterin dihydrochloride; IQ=intelligence quotient; LNAAs=large neutral amino acids; Phe=phenylalanine; PKU=phenylketonuria; QOL=quality of life; RCT=randomized controlled trial

Middle and Lower Priority Research Agenda

None of the research questions identified through this process was considered unimportant, and certainly, this is a field with substantial room for research growth. The questions listed in Table 8 might be considered second tier in terms of immediacy and need for answers, but they are, nonetheless important. Our focus for this project is on identifying a highest priority subset for immediate action, so we do not discuss the questions in this section but provide them for use by investigators and funders in the field. They also provide insight for policy makers into areas that are currently lacking in definitive, research-based evidence.

Table 8. Middle and lower priority research questions

Type of Question	Question	Tier
Methodologic	To what degree do measures of executive function vary with cognition, in the context of varying levels of Phe?	Middle
Methodologic	To what degree does Phe level affect domains of social and emotional functioning in PKU?	Middle
Methodologic	What methods are effective for measuring brain amino acid absorption?	Middle
Methodologic	When measuring executive function in individuals with PKU, when and how frequently should these measures be assessed?	Middle
Methodologic	Which measures, including executive function and affective disorder screens, are shown to be associated with to changes in cognitive outcomes related to Phe level in individuals with PKU?	Middle
Methodologic	What is the effectiveness of spectroscopy or other imaging techniques in assessing the effects of LNAAs on neurotransmission of Phe?	Lower
Methodologic	What is the relationship between clinical measures of executive function and "real world"/ adaptive functioning?	Lower
Methodologic	What is the validity, reliability, and responsiveness to change of existing tools for measuring executive function in individuals with PKU?	Lower
Methodologic	Which domains of executive function (e.g., planning, inhibitory control) are most sensitive to changes in Phe in individuals with PKU?	Lower
Treatment	In children ≤4 years old with PKU, what is the effect of BH4 plus diet compared with placebo plus diet/standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and growth and development?	Middle
Treatment	In individuals with PKU responsive to BH4 plus diet compared with diet/standard care on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, family functioning, and harms of treatment over the long term (>2years)?	Middle
Treatment	In individuals with PKU, what are the long-term effects (>6months) of LNAAs on cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet and harms of LNAAs?	Middle
Treatment	What are short-term effects of BH4 on outcomes including Phe control, Phe tolerance cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, and harms of BH4 in specific subgroups (defined by age, dietary control, disease type)?	Lower
Treatment	What characteristics of the individual, including disease severity, or characteristics of the family are associated with early vs. late initial response to BH4?	Lower
Treatment	What harms are associated with LNAA use in individuals with PKU?	Lower

Abbreviations: BH4=sapropterin dihydrochloride; IQ=intelligence quotient; LNAAs=large neutral amino acids; Phe=phenylalanine; PKU=phenylketonuria; QOL=quality of life

Discussion

We used a multistep process adapted from prior AHRQ EPC future research needs projects to identify top tier research needs related to adjuvant pharmacologic therapies for PKU. Research gaps in PKU are due in part to the rarity of the disease, and many fundamental questions remain unanswered. The scope of the current project was limited by the scope of the original CER to research regarding the use of pharmacologic therapies in addition to dietary restriction to improve short and long-term outcomes. While this limitation can prove challenging in some future research needs processes, for this topic the large number of critical questions within the topic did not put excessive limitations on our process or the product.

In the first phase of the process, we developed a list of initial research gaps from the CER and invited stakeholders to add to or modify that initial list during two conference calls. We then invited stakeholders to review the list on their own time and to add any additional questions that they thought would be important to include. This snowballing process allowed us to develop a comprehensive list from which to identify highest priority areas. Providing stakeholders adequate opportunity to build this list increased its comprehensiveness and ensured that at the prioritization phase there were adequate choices amongst which to identify the highest priorities. Once this list was developed, stakeholders participated in a two-step prioritization exercise. In the first step they identified a high-priority set of questions from the list, culling the initial list of questions down to a high-priority tier of 27 questions. In the second step, they further prioritized these high-priority questions. We then divided questions by points allotted into top, middle and lower tier research needs, divided roughly by thirds.

The results of this process are presented in this manuscript, with a focus on those that were designated as highest priority in the final prioritization round. We discuss lessons learned from the process, then the high-priority research recommended by the stakeholders. The stakeholder process itself was facilitated by the integration of the original CER into a NIH Scientific Review Conference (PKU Scientific Review Conference: State of the Science and Future Research Needs), and we encourage further integration of efforts related to the conference. The CER report was presented at the conference, providing an opportunity for the team to achieve greater understanding of the research challenges in the field and for potential stakeholders to be educated on the AHRQ EPC program and the particular process of this topic. Even so, we did not get complete participation from the invited stakeholders, with eight invitees not responding to or declining our invitation. Most of the stakeholders (eight of nine individuals) who participated in the project had attended the NIH conference.

Once stakeholders were engaged, we held two conference calls in order to accommodate busy schedules. While it can be helpful to have all stakeholders on one call to facilitate a comprehensive conversation (i.e., with all viewpoints represented), we found that the smaller groups meant that individuals could each participate more and all members were actively engaged. There was substantial congruency in the information across the calls. We found the stakeholders were quickly responsive to requests for snowballing or prioritization on line, with all stakeholders completing all portions of the process. In part, we believe this reflects a strong commitment on the part of the stakeholders to raising the visibility of PKU as a priority area for research. A consistent theme at the conference and in our interactions with stakeholders was that this area of research is substantially underfunded and warrants attention, particularly in light of the potentially devastating effects of nontreatment.

The research gaps and needs identified through both the initial review of the CER and the stakeholder process fell into two primary categories: those that were methodologic or

foundational in nature and those that were directly related to treatment intervention (and thus fit more directly into the comparative effectiveness rubric). Therefore, we have discussed the two types of research separately here. The methodologic work is necessary to undergird the study of interventions and the two types of priority efforts should be considered in tandem.

Research Considerations: Methodologic and Treatment Questions

There were five methodologic issues identified as high priorities for immediate research attention:

- How can the effectiveness of combination therapies be measured?
- In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?
- How should registry data collection be modified to allow for collection of efficacy data?
- To what extent are poor cognitive outcomes related to dietary deficiencies versus Phe levels?
- What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?

Two of these are clearly measurement issues. Measuring combinations of therapeutic approaches, rather than isolating individual treatments is challenging under any circumstances. With a rare disease, the numbers of individuals on any specific combination of therapies will be small, increasing the complexity and difficulty of demonstrating effectiveness. Furthermore, the current dependence on blood Phe as a measure of dietary control is far from ideal. Because it requires laboratory time, it cannot be used to provide instant feedback that might support ongoing modifications to care. Efforts to develop technology to provide instant feedback on Phe have failed to date, but work is and should continue to provide families with the ability to obtain rapid feedback. One methodologic question focused on the need to understand how and under what circumstances registry data could be used for effectiveness research. The PKU community is motivated to collect and analyze data that might support better understanding of both questions of natural history and treatment. The use of registries (as is currently being done with pregnant women) is likely to be a key part of improving our ability to properly care for PKU patients. Finally, the identification, prevention and role of dietary deficiencies in affecting the outcomes of patients with PKU was seen by the stakeholders as a worthy focus of future research. They noted particularly that some cognitive effects perceived to be associated with increased Phe could in fact be caused by dietary deficiencies. As such, understanding what vitamin and mineral deficiencies may occur, how to identify them and how they correspond to cognitive outcomes would be of benefit both for clinical care and to understand outcomes observed in effectiveness research.

Research on the use of BH4 as an adjuvant therapy in PKU management is relatively new and consists of small, tightly controlled multisite efficacy studies, two of which are RCTs. The greatest research need in this area is thus for larger studies that include adequate numbers of participants. Given the known difficulty of accruing large numbers of participants, however, researchers should also use existing data sets and, as recommended, use a consortium and multisite approach to gathering data. Ideally, studies will be conducted in both tightly controlled and nonadherent populations, and among different age groups, with appropriate design and

power for subgroup analyses. Research should continue to include RCTs, but prospective cohort studies that may have the potential to provide additional effectiveness data—including outside of a controlled clinical setting—adherence and longer term evidence would also be helpful to support understanding of the role of BH4 in clinical care. Six specific treatment/intervention questions were designated as highest priority; we outline the questions and provide discussion on each below.

Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes? Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?

Because of the life-long nature of PKU, treatment occurs over the life course, including dietary restriction, use of medical foods and formula, and pharmacologic therapy. Treatment effectiveness will be modified by the degree to which individuals are able to adhere to their prescribed course of treatment. Thus, understanding how to support patients with PKU in consistent and appropriate adherence to what may be an evolving care approach has potential implications for achieving effective Phe management and positive cognitive outcomes. Interventions to support adherence are likely to include social support in group or individual formats, online support that may or may not include tailored approaches, telephone and text reminder systems as well as print-based tools. Adherence support may take place in a clinical setting or in the community and may or may not be part of one's clinical care.

Ideally, studies of adherence support will take the form of RCTs comparing adherence support to usual care/practice and comparing various approaches to adherence support, as well as prospective cohort studies with good assessment and analytic management of confounders. It is imperative that studies include comparison groups. Investigators will be challenged to include in their studies adequate numbers of participants to assess the potential modifiers of success listed above. In particular, it would be helpful to know whether adherence approaches aimed at particular developmental stages are successful at instilling habits that persist, even as children age and move through other developmental stages. Identifying an ideal developmental target would help in the development of effective materials and approaches. Furthermore, such studies will require long term follow up that is conducted in such a way that the effects of interventions provided at specific points can be isolated, regardless of future interventions. It may be that RCTs are best able to capture early gains, while well-conducted prospective cohort studies with advanced analytics can describe trajectories of effects as participants age and develop**.**

In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet/standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?

Elevated maternal Phe level during pregnancy is teratogenic. Abnormalities include intrauterine growth restriction, microcephaly, congenital heart defects, developmental delays, and intellectual disability in children born to women with poorly controlled PKU during pregnancy. The effects of uncontrolled maternal PKU occur regardless of whether the fetus has PKU. The Maternal PKU Collaborative Study, the largest study to prospectively follow women with PKU who were pregnant, followed 572 pregnancies with 412 live births from 1984 to 2002.[27-31] Results of this important study demonstrated that the best observed neonatal outcomes

occurred when strict control of maternal blood Phe (120-360 µmol/L) was initiated before pregnancy or by 8 weeks post conception. This level of strict compliance with a Phe-restricted diet during both preconception and periconception is challenging. It is complicated by potential nausea and vomiting during the first trimester that may limit adherence to a strict diet and result in poor maternal nutrition. However, identifying and educating women about the importance of adherence before conception is also difficult as most women do not realize they are pregnant until they have missed a period. Many young women with PKU have lost adherence to dietary control by late adolescence, dropped out of pediatric care and may not have transitioned to adult care settings, and if they do seek care from a PKU clinic it is often after 8 weeks of pregnancy. However, BH4 may provide an impetus for women to return to PKU care, thus providing access to family planning and preconception care, including management of Phe levels, early identification of pregnancies and better management in early pregnancy, when strict control is especially critical.

Studying the effects of BH4 in addition to diet among pregnant women is complicated by lack of safety data and ethical issues related to conducting randomized trials in this vulnerable population. Prospective cohort studies with good assessment and analytic management of confounders are a rigorous approach, and registry data will provide additional crucial information. In addition, measures of cognitive outcomes in children require long-term follow-up of both mothers and children. Cognitive outcomes are also driven by maternal IQ and must be controlled for analytically. Investigators should consider techniques to reduce bias and confounding in evaluation studies, including randomly selecting subjects, or including all subjects who received the intervention for assessment; retaining as many subjects in the evaluation over time as possible; having comparison groups that are equivalent at baseline on severity of PKU, age and maternal IQ; and using data analytic techniques that control for potential confounders

What are the components of an effective system of care for individuals with PKU?

The system of care in place to support individuals with PKU includes a complex set of stakeholders in the health care system. “System of Care” is itself a specific approach and has been studied in the mental health field for a number of years.[32-34] Care related to PKU requires participation by clinical experts in genetics, developmental pediatrics, nutrition, and psychology, and may also include support for health advocacy, attainment of insurance coverage, legal and social support as well as family education and support. Care and support that is coordinated may be more effective at helping PKU patients reach their individual goals related to Phe management, cognition and high quality of life, but specific systems of care are currently not described or evaluated in the scientific literature.

Research is needed that both describes and evaluates systems of care for individuals with PKU (including the medical home), and that rigorously assesses the contribution that individual components make to effective care. Particular challenges related to this research include the need to document carefully the intervention so that it could be replicated, to fully characterize patients and patient characteristics to assess their impact on effectiveness, to include enough variation to understand and measure the impact in the heterogeneous PKU population, and the use study designs that are able to produce causal estimates and usable measures of effect. Potential study designs would include RCTs, time series, stepped wedge designs and other designs used extensively in the field of quality improvement. Outcomes should include clinical outcomes as well as satisfaction and quality of life.

What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological comorbidities in individuals with PKU?

In several studies, populations with PKU have been found to have higher prevalence rates of behavioral difficulties and other psychological comorbidities, including ADHD, anxiety, and depression, compared with the general population. Few studies have evaluated the relationship of these psychological outcomes to Phe control. Challenges include the difficulty distinguishing behaviors related to Phe control and intellectual status, socio-demographic factors, or underlying neurobiology. Studies have also been limited by small populations with large variations in behaviors scores, Phe levels, and IQ. Psychological comorbidities (e.g., ADHD) may overlap in neurobiologic mechanism, as populations with PKU and ADHD are both thought to have low levels of dopamine, especially in the prefrontal cortex, and this hypodopamine state has direct effect on behavior. Thus, if strict dietary management and BH4 improve Phe control and the symptoms of ADHD or other psychological outcomes are reduced, there may be no need for treatment (e.g., stimulant medications), but if symptoms are related to overlapping mechanisms, even with improved Phe control these symptoms may persist and require treatment.

There is a need for rigorously designed evaluation studies to evaluate the comparative effectiveness of BH4 in addition to diet on behavioral and psychological comorbidities. Ideally, RCTs are needed to examine the impact of BH4 and improved dietary management compared with diet alone on Phe control and whether improved Phe control impacts the symptoms of ADHD, anxiety, depression or other psychological comorbidities. Three studies are currently evaluating behavioral effects of sapropterin in PKU. One BioMarin-sponsored study is a US- and Canada-based RCT recruiting 200 individuals with PKU 12 years of age and older to evaluate the effect of BH4 compared with placebo on ADHD symptoms. The second is studying effects on behavior in 6- to 18-year old individuals (N=20) with PKU (sponsored by Washington University School of Medicine collaborating with BioMarin and the University of Missouri-Columbia, Northwestern University, and Oregon Health and Science University). The third study, from the University of Southern California collaborating with BioMarin, is evaluating behavior in 13 participants with PKU taking sapropterin.

Additionally, prospective cohort studies with good assessment and analytic management of confounders is another rigorous approach. It is imperative that studies include comparison groups. To reduce bias and confounding in evaluation studies, investigators should consider several techniques including randomly assigning participants to the intervention group; randomly selecting subjects, or including all subjects who received the intervention, for assessment; retaining as many subjects in the evaluation over time as possible; having comparison groups that are equivalent at baseline on severity of PKU, age-group, and type of psychological comorbidity; and using data analytic techniques that control for potential confounders (IQ, maternal IQ, etc).

These studies evaluating behavioral and psychological outcomes will require more long term followup. Reliable and valid assessment of behavioral and psychological outcomes is critical and validated tests in PKU populations may not be available.

As the following questions are very closely related, we address them together.

In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care? What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?

A fundamental challenge in care for individuals with PKU is the high rate of nonadherence, particularly as individuals with PKU age through adolescence and into adulthood. With increasing data confirming that lifelong Phe management is ideal for all individuals, and essential for women who may become pregnant, clinicians face the challenge of bringing individuals back to treatment that they may have abandoned.7-9,35 Restarting a restrictive diet can be unpleasant and difficult.

The question of how the medical system can encourage individuals to return to treatment crosses clinical, health behavior and health education lines, and warrants multidisciplinary research that reflects each of these fields. In addition to the promise of BH4, as in the research question above, the issue is to establish what type of education and health communication systems, combined with clinical diet training and adherence support, is most effective and leads to the highest rate of return to care.

Investigators wishing to study this question will be challenged first by a lack of an unequivocal denominator. It is unknown precisely how many individuals have ceased to be adherent to treatment. It is likely that most studies will take the form of pre- and postinvestigations, but these studies will be unable to assess what proportion of the nonadherent population returned to treatment. It may be possible to do comparative studies by implementing different approaches at different clinical sites, or using a stepped wedge design across sites, given that the sites treating where individuals with PKU are treated are well known and often collaborate on research. Such a study would assume that the numbers of nonadherent individuals in different geographic regions are essentially equivalent. This study design would have challenges related to cross-contamination, given the strong communication network within the PKU community at large. Thus, it will be very important to work with individuals who do return to treatment to understand exactly what motivated them to return, and then to study carefully what elements of a support system help them to continue with their treatment.

Other Considerations

Underpinning the ability to conduct the specific research described in this document is the need for investment in the type of infrastructure that supports the study of a rare disease. Other rare conditions have benefited from an overall research agenda. To this end, we recommend that a multicollaborator process that includes a public-private partnership which could create a powerful tool for the future of PKU research in the form of implementing a longer term (perhaps 10-year) research agenda. Furthermore, because the metabolic centers that treat patients with PKU are identifiable, and because PKU patients are almost inevitably treated in such a center if they are receiving care, there is tremendous potential for development of a multicenter research consortium to comprehensively evaluate the complete system of care for individuals with PKU. Such a collaborative effort is necessary for a number of the potential research tracks described above, including describing systems of care, and supporting the expansion of registries. Collaborators in this consortium could also develop or identify an agreed upon set of standardized data collection tools, especially for cognitive outcomes beyond IQ. Such a consortium should include guidelines for data sharing and comprehensive reporting, not only of intervention and outcome data, but of important, potentially confounding variables.

Stakeholders also emphasized the need for a health services research agenda that might better document issues such as variation in care and in insurance access for medical foods. Given good evidence that Phe is ideally controlled across the lifespan, a related question is the ability to obtain care and treatment once children with PKU become adults.

Finally, our stakeholders warned us that the current workforce for caring for individuals with PKU is inadequate, and that the field very much needs to encourage and support training for a range of providers, including nonmetabolic nutritionists (for understanding exigencies of PKU) as well as psychiatrists and psychologists.

Conclusions

The existing research gaps related to the use of adjunct pharmacologic therapy in PKU are both substantive and methodologic. Specific deficiencies range from the substantive need for more trials that include more individuals to methodologic gaps in our understanding of the longer term implications of intermediate outcomes. In both cases, research is fundamentally challenging because the disease is so rare, making accrual of adequate numbers of participants difficult, if not impossible, for specific studies. Our multistep process identified high-priority methodologic needs related to measurement of outcomes and dietary control and treatment-related needs including understanding adherence to treatment and an optimal system of care for affected individuals, the effects of BH4 on pregnant women, and effects on mental health and behavioral comorbidities. While ongoing research may begin to provide some answers, addressing research needs in PKU will require further long term, rigorously designed, comparative studies. Further research also requires expanding our foundation of understanding of critical aspects of the disease including its natural history, biologic mechanisms of disease, and ways to measure elevated Phe to better understand its effects on cognition. Stakeholders also emphasized that clinical decisionmaking will, by necessity be based on a range of factors, including the rarity of the disease, the devastating consequences of not treating and the association of treatment with quality of life and family functioning. Future comparative effectiveness research should include additional contextual data to support decisionmaking and increase its utility.

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Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AHRQ	Agency for Healthcare and Research Quality
BH4	Sapropterin Dihydrochloride
CER	Comparative Effectiveness Review
EHC	Effective Health Care Program
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
HPA	Hyperphenylalaninemia
IQ	Intelligence Quotient
KAMPER	Kuvan® Adult Maternal Pediatric European Registry
LNAA	Large Neutral Amino Acids
N	Number
Phe	Phenylalanine
PICOTS	Population-Intervention-Comparators-Outcomes-Timing-Setting
PKU	Phenylketonuria
PKUDOS	Phenylketonuria Demographic, Outcomes, and Safety Registry
NIH	National Institutes of Health
QOL	Quality of Life
RCT	Randomized Controlled Trial
SER	Systematic Evidence Review
SOE	Strength of Evidence
SPARK	Safety, and Population Pharmacokinetics of Sapropterin Dihydrochloride (Kuvan®)
TEP	Technical Expert Panel
TOO	Task Order Officer

Glossary of Study Designs

Pre-post design:	Study designs that collect data before and after an intervention
Prospective cohort study:	Research study that follows groups of individuals over time and compares them for a given outcome
Randomized controlled trial:	Controlled clinical trial that assigns participants randomly to two or more groups
Registry studies:	Studies that use data from registries of patient information, which typically collect data on patients with a given diagnosis or condition or undergoing specific procedures or treatments
Stepped wedge:	Study design in which interventions are typically sequentially rolled out or staggered over a number of time periods
Time series:	Study design employing measurement of data at successive time points at specific time intervals

Appendix A. Preliminary Evidence Gaps Identified From CER

Research Questions Derived From Gaps Noted in Report by Key Question

Key Question 1a. What is the evidence that any specific Phe levels are optimal for minimizing or avoiding cognitive impairment in individuals with PKU?

Key Question 1b. What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?

	Research Questions	Potentially Relevant Ongoing Research
	Which domains of executive function (e.g., planning, inhibitory control) are most sensitive to changes in Phe in individuals with PKU?	None identified
	Which measures of executive function are shown to be associated with to changes in cognitive outcomes related to Phe level in individuals with PKU?	
	To what degree do measures of executive function vary with cognition, in the context of varying levels of Phe?	
	What is the validity and reliability of existing tools for measuring executive function in individuals with PKU?	
	When measuring executive function in individuals with PKU, when and how frequently should these measures be assessed?	

Key Question 2. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status?

	Research Questions	Potentially Relevant Ongoing Research
	In children ≤4 years old with PKU, what is the effect of BH4 plus diet compared with placebo plus diet or standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and growth and development?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392) • Safety, and Population Pharmacokinetics of Sapropterin Dihydrochloride (Kuvan®) in Phenylketonuria (PKU) Patients <4 Years Old. (SPARK) (NCT01376908) • A Phase 3b Open-Label Study to Evaluate the Effect of Kuvan® on Neurocognitive Function, Maintenance of Blood Phenylalanine Concentrations, Safety, and Population Pharmacokinetics in Young Children With Phenylketonuria (NCT00838435)
	In individuals with PKU responsive to BH4, what is the effect of BH4 plus diet compared with diet/standard care on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, and harms of treatment over the long term (>2 years)?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What characteristics of the individual moderate responsiveness to BH4 in individuals with PKU?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological comorbidities in individuals with PKU?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392) • A Double-blind, Placebo-controlled, Randomized Study to Evaluate the Safety and Therapeutic Effects of Sapropterin Dihydrochloride on Neuropsychiatric Symptoms in Subjects With Phenylketonuria(NCT01114737)
	What characteristics of the individual, including disease severity, are associated with early vs. late initial response to BH4?	• Sapropterin for treatment of patients with Phenylketonuria: Identification of subpopulations with substantial clinical benefit (Canadian Institute for Health Research—completion status not clear)

Key Question 3. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

	Research Questions	Potentially Relevant Ongoing Research
	In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet or standard care on Phe control, cognitive outcomes (IQ and measures of executive funtion), QOL, liberalization of diet, and pregnancy outcomes?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What harms to the mother and offspring are associated with BH4 use in pregnant women with PKU?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)

Key Question 4. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status?

	Research Questions	Potentially Relevant Ongoing Research
	In individuals with PKU, what are the long-term effects (>6 months) of LNAAs on Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet and harms of LNAAs?	• Effects of short term increase of phenylalanine levels on neuropsychological functions and well-being in adults with phenylketonuria: the "diet for life" study- supplement of amino acids (NTR1056)
	What harms are associated with LNAA use in individuals with PKU?	• Effects of short term increase of phenylalanine levels on neuropsychological functions and well-being in adults with phenylketonuria: the "diet for life" study- supplement of amino acids (NTR1056)

Key Question 7. What is the evidence for the effectiveness of the addition of BH4 or LNAAs to dietary intervention for affecting outcomes in subgroups of patients?

	Research Questions	Potentially Relevant Ongoing Research
	What are short-term effects of BH4 on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet, and harms of BH4 in specific subgroups (defined by age, dietary control, disease type)?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392) • Effects of Sapropterin on Brain and Cognition in Individuals With Phenylketonuria (NCT00730080) • Evaluation of Behavior, Executive Function, Neurotransmitter Function and Genomic Expression in PKU "Nonresponders" to Kuvan(NCT01274026) • Treatment of hyperphenylalaninemia with Sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) and its influence on the amino acids and fatty acids patterns from childhood to adulthood, a Phase IV, longitudinal, unblinded, controlled, single-centre, retrospective and prospective clinical study(ISRCTN77098312)

Overall/Foundational Questions

	Research Question	Potentially Relevant ongoing Studies
	Among individuals with PKU using pharmacologic therapy, are supportive adherence models effective in increasing adherence?	None identified
	Are supportive adherence models effective at improving long-term cognitive outcomes?	
	Among effective adherence support systems, have individual components been shown to drive effectiveness?	
	Is the effectiveness of adherence models moderated by characteristics of the individual, including age, gender, family structure and severity of disease?	
	What are the pharmacokinetic, pharmacodynamic, and pharmacogenomic factors associated with treatment response in individuals with PKU?	
	Are passive registries as effective as ongoing cohort studies for collecting adequate data to assess long-term effectiveness of adjuvant therapies?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What are the components of an effective system of care for individuals with PKU?	None identified
	What treatment-related factors at different ages are the greatest source of concern to families / caregivers?	• 5-year Follow-up of the Comparison of Life and Physical Health in Adult Patients With PKU and Healthy Age Matched Controls (NCT01096758)
0	In individuals with PKU, what timing of Phe monitoring is optimal for fine tuning diet and treatment?	• The effects of online availability of individual phenylalanine levels to patients with phenylketonuria (NTR1171)

Additional (nonresearch) recommendations/needs:

- Increased understanding of long-term implications of intermediate outcomes
- Multi-collaborator consortium that includes a public-private partners to outline research agenda; evaluate needs for comprehensive system of care; develop/expand prospective registries to include collection of outcome data including measures of executive function, nutritional status, growth, and quality of life; and biorepository
- Understanding of the role of international collaboration and differences in diet, culture, genotype/phenotype, etc. in planning for multicenter consortia
- Standardized data collection tools, especially for cognitive outcomes
- Standards/guidelines for data sharing and comprehensive reporting (including reporting of measures of variance, potential cofounding and modifying factors, etc.)
- Standardized collection and reporting of potential confounders and modifiers (e.g., familial IQ, SES, maternal education, concurrent medications, age at initial treatment, level of dietary control)
- Increased understanding of outcomes of importance to patients and families
- Understanding of quality of life for patients and families and factors that affect quality of life
- Understanding approaches to studying adjuvant therapies in pregnant women with PKU (e.g., registry, cohort study)
- Understanding of study designs that can provide high-quality data while taking into account difficulties in accrual in rare diseases
- Studies appropriately designed and powered to allow subgroup analyses
- Understanding of the potential role of observational studies in providing effectiveness data
- Publicly funded studies
- Understanding of potentially useful research models from other rare disease

Appendix B. Ongoing/Recently Completed Studies Related to Adjuvant Therapies in PKU and Ongoing Studies Search Strategies

Table B-1. Potentially relevant ongoing/recently completed studies

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry **Identifier(s):** NCT00778206 PKUDOS-01, PKUDOS Registry	**Start date:** Sept 2008 **Estimated study completion date:** No date given **Estimated primary completion date:** September 2023 (Final data collection date for primary outcome measure)	**Purpose:** To evaluate the safety of long-term treatment with Kuvan **Study design:** Observational Model: Cohort Time Perspective: Prospective **Condition(s):** Phenylketonuria, Hyperphenylalaninaemia **Intervention(s):** Drug: Sapropterin dihydrochloride **Estimated enrollment:** 3500	**Sponsor OR PI:** BioMarin Pharmaceutical **Collaborator(s):** None listed	ClinicalTrials.gov Accessed at: http://ClinicalTrials.gov/ct2/show/NCT00778206?
Title: A Phase IV, Prospective, Open-label, Uncontrolled, Multi-centre Cohort Trial to Assess the Responsiveness of Subjects With Phenylketonuria (PKU) to Treatment With Kuvan® 20 mg/kg/Day for 28 Days **Identifier(s):** NCT01082328 EMR 700773-503 2009-018168-81	**Start date:** May 2010 **Estimated study completion date:** No date given **Estimated primary completion date:** April 2012 (final data collection date for primary outcome measure)	**Purpose:** To evaluate the proportion of responders [≥30% reduction from baseline in blood phenylalanine (Phe) level] to 20 mg/kg/day sapropterin dihydrochloride treatment at several time points during 28±1 days **Study design:** Endpoint Classification: Safety/Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Supportive Care **Condition(s):** Phenylketonuria **Intervention(s):** Drug: Kuvan® (Sapropterin dihydrochloride) **Estimated enrollment:** 70	**Sponsor OR PI:** Merck KGaA **Collaborator(s):** • Merck Serono Norway • Smerud Medical Research International AS	ClinicalTrials.gov Accessed at: http://ClinicalTrials.gov/ct2/show/NCT01082328

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: A Phase IIIb, Multicentre, Open-Label, Randomized, Controlled Study of the Efficacy, Safety, and Population Pharmacokinetics of Sapropterin Dihydrochloride (Kuvan®) in Phenylketonuria (PKU) Patients <4 Years Old (SPARK) **Identifier(s):** NCT01376908 EMR 700773-003 EudraCT Number: 2009-015768-33	**Start date:** June 2011 **Estimated study completion date:** June 2015 **Estimated primary completion date:** Aug 2012 (final data collection date for primary outcome measure)	**Purpose:** To evaluate efficacy, safety and population pharmacokinetics of Kuvan® in infants and children with PKU (<4 years of age at the time of study entry). A pharmacogenetic sub-study as optional part of this study will be also conducted **Study design:** Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** PKU **Intervention(s):** • Experimental: Kuvan® + Phe-restricted diet • Phe-restricted diet alone **Estimated enrollment:** 50	**Sponsor OR PI:** Merck KGaA **Collaborator(s):** None listed	ClinicalTrials.gov Accessed at: http://ClinicalTrials.gov/ct2/show/NCT01376908

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency **Identifier(s):** NCT01016392 EMR700773-001 EudraCT: 2009-015769-29	**Start date:** November 2009 **Estimated study completion date:** No date given **Estimated primary completion date:** July 2025 (final data collection date for primary outcome measure)	**Purpose:** **Primary:** To assess the long-term safety in subjects treated with Kuvan® **Secondary:** To provide additional information regarding: • Safety in specific subject groups • Growth and neurocognitive outcomes for subjects with hyperphenylalaninemia (HPA) who are receiving treatment with Kuvan® • Progress and outcome of pregnancy for women with HPA who become pregnant while receiving Kuvan® (these women will be enrolled in a dedicated sub-registry) • Assessment of adherence to diet and to Kuvan® • Assessment of long-term sensitivity to Kuvan® treatment **Study design:** Observational Model: Cohort; Time Perspective: Prospective **Condition(s):** Hyperphenylalaninemia (HPA) due to Phenylketonuria (PKU) or Tetrahydrobiopterin (BH4) Deficiency **Intervention(s):** No diagnostic, therapeutic or experimental intervention is involved. Subjects will receive clinical assessments, medications and treatments solely as determined by their study physician. **Estimated enrollment:** 625	**Sponsor OR PI:** Merck KGaA **Collaborator(s):** None listed	ClinicalTrials.gov Accessed at: http://ClinicalTrials.gov/ct2/show/NCT01016392

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: A Double-blind, Placebo-controlled, Randomized Study to Evaluate the Safety and Therapeutic Effects of Sapropterin Dihydrochloride on Neuropsychiatric Symptoms in Subjects With Phenylketonuria **Identifier(s):** NCT01114737 PKU-016 PKU Ascend	**Start date:** June 2010 **Estimated study completion date:** January 2013 **Estimated primary completion date:** January 2013 (Final data collection date for primary outcome measure)	**Purpose:** To evaluate the safety and therapeutic effects of sapropterin on neuropsychiatric symptoms in subjects with PKU **Study design:** Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Primary Purpose: Treatment **Condition(s):** Phenylketonuria **Intervention(s):** Drug: Sapropterin dihydrochloride Drug: Placebo **Estimated enrollment:** 200	**Sponsor OR PI:** BioMarin Pharmaceutical **Collaborators:** None listed	ClinicalTrials.gov Accessed at: http://ClinicalTrials.gov/ct2/show/NCT01114737
Title: Effects of Sapropterin on Brain and Cognition in Individuals With Phenylketonuria **Identifier(s):** NCT00730080	**Start date:** July 2008 **Estimated study completion date:** July 2009 **Estimated primary completion date:** July 2009 (Final data collection date for primary outcome measure)	**Purpose:** Primary objective is two-fold: • determine if cognition (particularly executive abilities) improves in patients with PKU who have been treated with sapropterin for a period of 6 months • determine if the structure and functional integrity of the brain improves in patients with PKU who have been treated with sapropterin for a period of 6 months. In addition, the interrelationships between changes in cognition and brain will be examined. **Study design:** Observational Model: Case Control Time Perspective: Prospective **Condition(s):** PKU **Intervention(s):** Drug: Sapropterin (Kuvan) **Estimated enrollment:** 35	**Sponsor OR PI:** Washington University School of Medicine **Collaborators:** • BioMarin Pharmaceutical • University of Missouri-Columbia	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT00730080

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: A Phase 3b Open-Label Study to Evaluate the Effect of Kuvan® on Neurocognitive Function, Maintenance of Blood Phenylalanine Concentrations, Safety, and Population Pharmacokinetics in Young Children With Phenylketonuria **Identifier(s):** NCT00838435 PKU-015	**Start date:** February 2009 **Estimated study completion date:** December 2018 **Estimated primary completion date:** December 2018 (Final data collection date for primary outcome measure)	**Purpose:** To evaluate the safety of Kuvan® and its effect on neurocognitive function, blood Phe concentration, and growth in children with PKU who are 0-6 years old **Study design:** Endpoint Classification: Safety/Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** PKU **Intervention(s):** Drug: sapropterin dihydrochloride **Estimated enrollment:** 230	**Sponsor OR PI:** BioMarin Pharmaceutical **Collaborator(s):** None listed	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT00838435
Title: Baseline Evaluation and Long-term Follow-up of Nutritional Status and Neurotransmitter Concentrations in Phenylketonuria Patients Initiating Treatment With Sapropterin Dihydrochloride (KuvanTM), a Tetrahydrobiopterin Analog **Identifier(s):** NCT00688844 IRB-7828	**Start date:** October 2008 **Estimated study completion date:** February 2010 **Estimated primary completion date:** February 2010 (final data collection date for primary outcome measure) Per ClinicalTrials.gov: The recruitment status of this study is unknown because the information has not been verified recently.	**Purpose:** • To record nutritional biomarkers, body composition, bone density, and measures of nutrient intake in a phenylketonuria subject group at baseline and for one year after start of KuvanTM therapy • To investigate changes in monoamine neurotransmitter synthesis in a phenylketonuria subject group at baseline and for one year after start of KuvanTM therapy • Evaluate changes in quality of life (QOL) for PKU subjects beginning KuvanTM therapy **Study design:** Observational Model: Cohort Time Perspective: Prospective **Condition(s):** PKU **Intervention(s):** None listed **Estimated enrollment:** 62	**Sponsor OR PI:** Emory University **Collaborators:** • BioMarin Pharmaceutical • Clinical Interaction Network (CIN) of the Atlanta Clinical and Translational Science Institute	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT00688844

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Evaluation of Behavior, Executive Function, Neurotransmitter Function and Genomic Expression in PKU "Nonresponders" to Kuvan® (Sapropterin Dihydrochloride) **Identifier(s):** NCT01274026 183590-1	**Start date:** January 2011 **Estimated study completion date**: January 2012 **Estimated primary completion date:** August 2011 (Final data collection date for primary outcome measure)	**Purpose:** To correlate any change in behavior and executive function skills of PKU patients who are non-responsive to sapropterin effect on the PAH enzyme, as defined by lowered blood Phe levels, with urine neurotransmitter levels and broad gene expression prior to and after sapropterin administration **Study design:** Endpoint Classification: Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Phenylketonuria, Behavior and Behavior Mechanisms, PAH Gene Expression **Intervention(s):** Drug: sapropterin dihydrochloride **Estimated enrollment:** 30	**Sponsor OR PI:** Tulane University School of Medicine **Collaborator(s):** None listed	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT01274026
Title: Multimodal Neuroimaging and Neurocognitive Assessment of Biomarkers and Response to Sapropterin Dihydrochloride Treatment in Phenylketonuria **Identifier(s):** NCT01412437 BMRN 9956	**Start date:** April 2011 **Estimated study completion date**: December 2012 **Estimated primary completion date:** March 2012 (final data collection date for primary outcome measure)	**Purpose:** The investigators will use different types of brain imaging (MRI) in patients with phenylketonuria (PKU) who are currently not on a strict diet to test the hypothesis that there is improvement in brain circuitry and biochemistry after return to diet and/or sapropterin dihydrochloride (Kuvan). **Study design:** Allocation: Randomized Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Diagnostic **Condition(s):** PKU **Intervention(s):** Dietary Supplement: diet Drug: sapropterin dihydrochloride **Estimated enrollment:** 38	**Sponsor OR PI:** Children's Research Institute **Collaborator(s):** Georgetown University	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT01412437

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Behavioral Effects of Kuvan in Children With Mild Phenylketonuria **Identifier(s):** NCT00827762	**Start date:** January 2009 **Estimated study completion date:** January 2010 **Estimated primary completion date:** January 2010 (Final data collection date for primary outcome measure)	**Purpose:** To determine whether improvements in behavior occur in children with PKU who are taking Kuvan **Study design:** Observational Model: Case-Only Time Perspective: Prospective **Condition(s):** PKU **Intervention(s):** Drug: Kuvan **Estimated enrollment:** 20	**Sponsor OR PI:** Washington University School of Medicine **Collaborator(s):** • BioMarin Pharmaceutical • University of Missouri-Columbia • Northwestern University • Oregon Health and Science University	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT00827762
Title: The Effects of Kuvan on Functional Brain Connectivity in Individuals With Phenylketonuria (PKU) **Identifier(s):** NCT00964236	**Start date:** August 2009 **Estimated study completion date:** August 2011 **Estimated primary completion date:** August 2010 (Final data collection date for primary outcome measure)	**Purpose:** To determine whether Kuvan™ (sapropterin) improves the strength of the functional connectivity between brain regions in individuals with PKU **Study design:** Observational Model: Case Control Time Perspective: Prospective **Condition(s):** PKU **Intervention(s):** Drug: Sapropterin (Kuvan) **Estimated enrollment:** 20	**Sponsor OR PI:** University of Missouri-Columbia **Collaborator(s):** BioMarin Pharmaceutical	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT00964236

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Pilot Study to Evaluate the Effects of Kuvan on Adult Individuals With Phenylketonuria With Measurable Maladaptive Behaviors **Identifier(s):** NCT00728676 BioMarin-300	**Start date:** August 2008 **Estimated study completion date:** February 2010 **Estimated primary completion date:** December 2009 (Final data collection date for primary outcome measure)	**Purpose:** To validate the outcome measures and the tolerability of Kuvan treatment in the improvement of behavioral symptoms in 10 selected adults with PKU with or without mental retardation **Study design:** Observational Model: Case Control Time Perspective: Prospective **Condition(s):** PKU **Intervention(s):** None listed, observational trial **Estimated enrollment:** 13	**Sponsor OR PI:** University of Southern California **Collaborator(s):** BioMarin Pharmaceutical	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT00728676
Title: Pilot Study to Evaluate Melatonin Secretion as a Marker of Decreased Serotonin in Individuals With PKU: Evaluation of the CNS Effects of Tetrahydrobiopterin **Identifier(s):** NCT01617070	**Start date:** May 2012 **Estimated study completion date:** December 2013 **Estimated primary completion date:** December 2013 (Final data collection date for primary outcome measure)	**Purpose:** This study examines the effect of tetrahydrobiopterin (Kuvan) and Large Neutral Amino Acid (LNAA) therapy on melatonin and dopamine levels in individuals with Phenylketonuria (PKU). **Study design:** Endpoint Classification: Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Phenylketonuria (PKU) **Intervention(s):** Drug: Kuvan Dietary Supplement: Large Neutral Amino Acid Therapy **Estimated enrollment:** 12	**Sponsor OR PI:** University of Southern California **Collaborator(s):** BioMarin Pharmaceutical	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT01617070

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Bone Mineral Density in Adults With Hyperphenylalaninemia on Kuvan Therapy **Identifier(s):** NCT01541397 HSC-MS-11-0119	**Start date:** June 2011 **Estimated study completion date:** October 2012 **Estimated primary completion date:** October 2012 (Final data collection date for primary outcome measure)	**Purpose:** Prospective study to compare the bone mineral density in adults with HPA on KUVAN™ therapy to those not on therapy **Study design:** Allocation: Non-Randomized Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Hyperphenylalaninemia, PKU **Intervention(s):** Drug: Sapropterin **Estimated enrollment:** 20	**Sponsor OR PI:** The University of Texas Health Science Center, Houston **Collaborator(s):** BioMarin Pharmaceutical	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT01541397
Title: The Ability of Kuvan® (Sapropterin Dihydrochloride) to Prevent Meal-induced Lipid Peroxidation and Endothelial Dysfunction in Patients With Phenylketonuria: a Pilot Study **Identifier(s):** NCT01395394 IRB-00046153	**Start date:** June 2011 **Estimated study completion date:** No date given **Estimated primary completion date:** December 2012 (Final data collection date for primary outcome measure)	**Purpose:** To see how tetrahydrobiopterin therapy affects measures of oxidative stress and endothelial function in patients with PKU **Study design:** Allocation: Non-Randomized Intervention Model: Single Group Assignment Masking: Open Label **Condition(s):** PKU **Intervention(s):** Drug: Kuvan Other: Meal Challenge **Estimated enrollment:** 50	**Sponsor OR PI:** Emory University **Collaborator(s):** None listed	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT01395394

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: The effects of online availability of individual phenylalanine levels to patients with phenylketonuria **Identifier(s):** NTR1171 07/292	**Start date:** date of first enrollment/planned start date: 1-April-2008 **Estimated completion date:** Planned closing date: 1-Oct-2009 Recruiting/open, per website as of 5/29/2012	**Purpose:** The aim of this study is to evaluate the effect of online availability of individual phenylalanine (Phe) levels to patients with PKU on plasma Phe levels, on the frequency of Phe measurements and on the frequency of contact with the dietician. **Study design:** Randomized: Yes Masking: None Control: Active Group: Parallel Type: 2 or more arms, randomized **Condition(s):** Phenylketonuria (PKU) **Intervention(s):** During a period of twelve months, one group will have online access to the individual phenylalanine results and the other group will continue the present procedure. Patients who have online access to their phenylalanine results will no longer be called by the dietician about results outside the recommended range. These patients personally can adjust their diet to the phenylalanine levels and determine the frequency of blood-sampling. **Target sample size:** 90	**Sponsor OR PI:** Academic Medical Center (AMC) **Collaborator(s):** NR	WHO ICTRP Search Portal Accessed at: http://apps.who.int/trialsearch/Trial.aspx?TrialID=NTR1171 Nederlands Trial Registry http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1171
Title: Effects of short term increase of phenylalanine levels on neuropsychological functions and well-being in adults with phenylketonuria: the "diet for life" study **Identifier(s):** NTR1056 07/262 07.17.1461	**Start date:** date of first enrollment/planned start date: 1-Jan-2008 **Estimated completion date:** Planned closing date: 1-Sep-2008 Recruiting/open, per website as of 5/29/2012	**Purpose:** To evaluate the effects of short term supplementation of Phe to levels comparable to levels observed in adult patients who fully discontinued their diet, on neuropsychological functions and wellbeing of adult patients with PKU **Study design:** Randomised: Yes Masking: Triple Control: Placebo Group: Crossover Type: [default] **Condition(s):** Phenylketonuria (PKU) **Intervention(s):** Supplementation of phenylalanine (Phe) to levels that simulate full discontinuation of dietary treatment. **Target sample size:** 20	**Sponsor OR PI:** Academic Medical Center (AMC) **Collaborator(s):** NR	WHO ICTRP Search Portal Accessed at: http://apps.who.int/trialsearch/Trial.aspx?TrialID=NTR1056 Nederlands Trial Registry http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1056

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Ö-PKU 1 – Evaluation of a Test for the identification of BH4 responsive PKU patients **Identifier(s):** EudraCT Number: 2010-019767-11 Sponsor Protocol Number: Ö-PKU1	**Start date:** 2010-09-08 **Estimated completion date:** NR Status: ongoing, per database as of 5/29/2012	**Purpose:** **Primary:** Evaluation of a test to identify BH4 responsive patients **Secondary:** • responsive genotypes • correlation of initial blood phe levels and results in the two respective tests • frequency of deviations from blood phenylalanine target range in both tests • frequency and reasons for deviations from test algorithm **Study design:** Controlled, Open, Cross over - Yes Randomised, Single blind, Double blind, Parallel group, Other - No **Condition(s):** Hyperphenylalaninaemia (HPA) in adult and pediatric patients of 4 years of age and over with phenylketonuria (PKU). **Planned number of subjects:** 30	**Sponsor OR PI:** Graz Medical University **Collaborator(s):** NR	EU Clinical Trials Register Accessed at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-019767-11/AT
Title: Sapropterin for treatment of patients with Phenylketonuria: Identification of subpopulations with substantial clinical benefit **Identifier(s):** NR	**Start date:** 03/01/2012 **Estimated completion date:** 02/28/2013	**Purpose:** We will establish a national network to test patients for their response to sapropterin and develop national criteria to identify those who benefit most**.** **Study design:** NR **Condition(s):** Phenylketonuria **Intervention(s):** Sapropterin **Estimated enrollment:** NR	**Sponsor OR PI:** Sylvia Stockler (at University of British Columbia) **Collaborator(s):** Co-investigators: Rollin Frederick Brant, Bruce C. Carleton, Jean-Paul Collet, John James Mitchell, Sandra Michelle Sirrs	Canadian Institutes for Health Research website

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Phase 2 Study of Glycomacropeptide VS. Amino Acid Diet for the Management of PKU **Identifier(s):** NCT01428258 1R01FD003711-01A1 H-2010-0165	**From NIHReporter:** **Start date:** 15-Aug-2011 **End date:** 31-Jul-2015 **From ClinicalTrials.gov:** **Start date:** September 2011 **Estimated study completion date:** April 2015 **Estimated primary completion date:** April 2015 (Final data collection date for primary outcome measure)	**For Description in NIHReporter, see:** http://projectreporter.nih.gov/project_info_description.cfm?aid=8022162&icde=12661476&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC **ClinicalTrials.gov:** **Purpose:** For individuals with Phenylketonuria (PKU), the investigators hypothesize that glycomacropeptide will provide an acceptable form of low-phenylalanine dietary protein that will improve dietary compliance, blood phenylalanine levels, cognitive function, and ultimately quality of life compared with the usual amino acid based diet. **Study design:** Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Crossover Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** PKU **Intervention(s):** Dietary Supplement: Glycomacropeptide (GMP) diet given first Dietary Supplement: Amino Acid (AA) Diet Given First **Estimated enrollment:** 30	**Sponsor OR PI:** **NIHReporter:** **PI:** Ney, Denise M (at University of Wisconsin Madison) **ClinicalTrials.gov:** **Sponsor:** University of Wisconsin, Madison **Collaborator(s):** Children's Hospital Boston	NIHReporter Accessed at: http://projectreporter.nih.gov/project_info_description.cfm?aid=8022162&icde=12661476&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT01428258

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Study of a National Cohort of Adult Patients With Phenylketonuria **Identifier(s):** NCT01619722 PHRN10/FM-ECOPHEN	**Start date:** February 2012 **Estimated study completion date:** February 2019 **Estimated primary completion date:** February 2019 (Final data collection date for primary outcome measure)	**Purpose:** The aim off this study is to follow a French cohort of young adult patients with PKU to: • Describe the evolution of the disease in adulthood and neurological complications associated neuropsychological detect, investigate the prognostic factors for complications • Describe the metabolic balance of patients • Collect data on nutritional status, • Detect osteoporosis • Studying social integration and quality of life of adult patients with PKU • Collect biological samples for further study (markers of bone turnover) **Study design:** Observational Model: Cohort Time Perspective: Prospective **Condition(s):** PKU, Hyperphenylalaninemia, BMD, Quality of Life **Intervention(s):** None listed, observational trial **Estimated enrollment:** 220	**Sponsor OR PI:** University Hospital, Tours **Collaborator(s):** Institut National de la Santé Et de la Recherche Médicale, France	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT01619722
Title: Phase 2, Open-Label Dose-Finding Study to Evaluate the Safety, Efficacy, and Tolerability of Multiple Subcutaneous (SC) Doses of rAvPAL-PEG in Subjects With PKU **Identifier(s):** NCT00925054 PAL-002	**Start date:** September 2009 **Estimated study completion date:** December 2012 **Estimated primary completion date:** December 2012 (Final data collection date for primary outcome measure)	**Purpose:** To evaluate whether weekly injections of phenylalanine ammonia lyase (rAvPAL-PEG) can reduce blood phenylalanine concentrations in PKU subjects and whether repeated administration is safe **Study design:** Allocation: Non-Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** PKU **Intervention(s):** Drug: rAvPAL-PEG **Estimated enrollment:** 45	**Sponsor OR PI:** BioMarin Pharmaceutical **Collaborator(s):** None listed	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT00925054

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Long-term Extension of a Phase 2, Open-Label Dose-Finding Study to Evaluate the Safety, Efficacy, and Tolerability of Multiple Subcutaneous Doses of rAvPAL-PEG in Subjects With PKU **Identifier(s):** NCT00924703 PAL-003	**Start date:** January 2010 **Estimated study completion date:** August 2017 **Estimated primary completion date:** May 2017 (Final data collection date for primary outcome measure)	**Purpose:** This study is an extension of the dose-finding study (PAL-002), and also as an extension for the dose and frequency finding study (PAL-004). Administration of rAvPAL-PEG will be continued to assess whether long-term dosing of rAvPAL-PEG is safe and can maintain reduced blood Phe concentrations in PKU subjects. **Study design:** Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** PKU **Intervention(s):** Drug: rAvPAL-PEG **Estimated enrollment:** 50	**Sponsor OR PI:** BioMarin Pharmaceutical **Collaborator(s):** None listed	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT00924703
Title: A Phase 2, Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of Subcutaneous Dose Levels of rAvPAL-PEG Administered Daily in Subjects With **Phenylketonuria** **Identifier(s):** NCT01212744 PAL-004	**Start date:** March 2011 **Estimated study completion date:** September 2012 **Estimated primary completion date:** September 2012 (Final data collection date for primary outcome measure)	**Purpose:** To evaluate the effect of daily administration of rAvPAL-PEG on the reduction of blood Phe concentrations in subjects with PKU **Study design:** Allocation: Non-Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** **Phenylketonuria** **Intervention(s):** Drug: rAvPAL-PEG **Estimated enrollment: 16**	**Sponsor OR PI:** BioMarin Pharmaceutical **Collaborator(s):** None listed	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT01212744

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: A Phase II, Multi-center, Open-label, Dose-finding Study to Evaluate Safety, Efficacy and Tolerability of Subcutaneously (SC) Administered rAvPAL-PEG in Patients With PKU for 24 Weeks **Identifier(s):** NCT01560286 165-205	**Start date:** May 2012 **Estimated study completion date:** May 2013 **Estimated primary completion date:** May 2013 (final data collection date for primary outcome measure)	**Purpose:** To evaluate the effect of dosing regimens of multiple subcutaneous (SC) doses of rAvPAL-PEG to induce an early and sustained Phe reduction while decreasing the frequency and severity of hypersensitivity reactions in patients with PKU **Study design:** Allocation: Non-Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Phenylketonuria **Intervention(s):** Biological: rAvPAL-PEG **Estimated enrollment:** 24	**Sponsor OR PI:** BioMarin Pharmaceutical **Collaborator(s):** None listed	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT01560286
Title: Quantitative Requirements of Docosahexaenoic Acid for Neural Function in Children With Phenylketonuria **Identifier(s):** NCT00909012 455-08	**Start date:** May 2009 **Estimated study completion date:** March 2012 **Estimated primary completion date:** July 2011 (Final data collection date for primary outcome measure)	**Purpose:** This multicentric double-blind randomized trial aims at determining quantitative DHA requirements for optimal neural function in PKU children. **Study design:** Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Primary Purpose: Basic Science **Condition(s):** PKU **Intervention(s):** Dietary Supplement: high oleic sunflower oil Dietary Supplement: microalgal oil **Estimated enrollment: 125**	**Sponsor OR PI:** Ludwig-Maximilians - University of Munich **Collaborator(s):** European Union	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT00909012

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: The Impact of Docosahexaenoic Acid on Neuropsychological Status in Females With Phenylketonuria **Identifier(s):** NCT00892554	**Start date:** June 2007 **Estimated study completion date:** January 2010 **Estimated primary completion date:** January 2010 (final data collection date for primary outcome measure) Per ClinicalTrials.gov: The recruitment status of this study is unknown because the information has not been verified recently.	**Purpose:** To determine if taking supplemental DHA improves measures of processing speed and executive function in teen and adult women with PKU **Study design:** Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Primary Purpose: Prevention **Condition(s):** Phenylketonuria **Intervention(s):** Dietary Supplement: Docosahexaenoic Acid Dietary Supplement: Corn/soy oil **Estimated enrollment:** 35	**Sponsor OR PI:** Emory University **Collaborator(s):** Atlanta Clinical and Translational Science Institute	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT00892554
Title: Hepatocyte Transplantation for Phenylketonuria **Identifier(s):** NCT01465100 PRO10100525	**Start date:** December 2011 **Estimated study completion date:** December 2014 **Estimated primary completion date:** November 2014 (Final data collection date for primary outcome measure)	**Purpose:** To determine whether partial irradiation of the liver and liver cell transplantation can reduce the need for dietary and medical management or could possibly eliminate the need for a special diet and medications to treat this disease for patients with phenylketonuria (PKU) by normalizing phenylalanine levels in the body. **Study design:** Endpoint Classification: Safety/Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** PKU **Intervention(s):** Radiation: Preparative Radiation Therapy Procedure: Hepatocyte Transplant Drug: Immunosuppression **Estimated enrollment:** 10	**Sponsor OR PI:** University of Pittsburgh **Collaborator(s):** None listed	ClinicalTrials.gov Accessed at: http://clinicaltrials.gov/ct2/show/NCT01465100

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: FIT for PKU - Family Integrated Training for patients with Phenylketonuria (PKU**)** **Identifier(s):** ORPHA102819	**Start date:** NR **Estimated completion date:** NR	**Purpose:** NR **Study design:** NR **Type of research project:** health sociology study **Condition(s):** PKU **Intervention(s):** NR **Estimated enrollment:** NR	**Sponsor OR PI:** Dr Peter Burgard (at Universitätsklinikum Heidelberg, Klinik für Kinderheilkunde I - Sektion für Angeborene Stoffwechselkrankheiten) **Collaborator(s):** NR	ORPHANET website Accessed at: http://www.orpha.net/consor/cgi-bin/ResearchTrials_ResearchProjects.php?lng=EN&data_id=51204&ResearchProjectName=FIT-fur-PKU--Familienintegratives-Training-fur-Patienten-mit-Phenylketonurie--PKU&title=FIT-fur-PKU--Familienintegratives-Training-fur-Patienten-mit-Phenylketonurie--PKU&search=ResearchTrials_ResearchProjects_Simple
Title: Nutritional status and metabolic syndrome in patients with Phenylketonuria **Identifier(s):** ORPHA283470	**Start date:** NR **Estimated completion date:** NR	**Purpose:** NR **Study design:** NR Type of research project: human physiopathology study, observational clinical study **Condition(s):** PKU **Intervention(s):** NR **Estimated enrollment:** NR	**Sponsor OR PI:** • Pr Nuno Borges (at Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto) • Dr Júlio C Rocha (at Unidade de Genética Médica - Departamento de Genética CGMJM - Centro de Genética Médica Jacinto Magalhães) **Collaborator(s):** NR	ORPHANET website Accessed at: http://www.orpha.net/consor/cgi-bin/ResearchTrials_ResearchProjects.php?lng=EN&data_id=87865&ResearchProjectName=Estado-nutricional-e-s-ndrome-metab-lica-em-doentes-com-Fenilceton-ria&title=Estado-nutricional-e-s-ndrome-metab-lica-em-doentes-com-Fenilceton-ria&search=ResearchTrials_ResearchProjects_Simple

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Dietary therapy and outcome in early treated PKU patients in adulthood **Identifier(s):** ORPHA100202	**Start date:** NR **Estimated completion date:** NR	**Purpose**: NR **Study design:** NR Type of research project: observational clinical study **Condition(s):** PKU **Intervention(s):** NR **Estimated enrollment:** NR	**Sponsor OR PI:** Pr Anibh Martin Das (at Arbeitsgruppe Stoffwechselerkrankungen und Neuropädiatrie Medizinische Hochschule Hannover) **Collaborator(s):** NR	ORPHANET website Accessed at: http://www.orpha.net/consor/cgi-bin/ResearchTrials_ResearchProjects.php?lng=EN&data_id=49879&ResearchProjectName=Diatetische-Therapie-und-Outcome-bei-fruhbehandelten-PKU-Patienten-im-Erwachsenenalter&title=Diatetische-Therapie-und-Outcome-bei-fruhbehandelten-PKU-Patienten-im-Erwachsenenalter&search=ResearchTrials_ResearchProjects_Simple

Title/Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Effect of docosahexaenoic acid treatment on the neurodegenerative changes of visual functions in patients with phenylketonuria (Phase IV) **Identifier(s):** ORPHA240466	**Start date:** NR **Estimated completion date:** NR	**Purpose:** NR **Study design:** NR Type of research project: drug clinical trial **Condition(s):** PKU **Intervention(s):** NR **Estimated enrollment:** NR	**Sponsor OR PI:** **PI**: Dr Jaume Campistol Plana (of Unidad de enfermedades metabólicas) **Sponsor:** NR Funding body listed as Instituto de Salud Carlos III (ISCIII) **Collaborator(s):** NR	ORPHANET website Accessed at: http://www.orpha.net/consor/cgi-bin/ResearchTrials_ClinicalTrials.php?lng=EN&data_id=76415&ClinicalTrialName=Efecto-del-tratamiento-con--cido-docosahexanoico-sobre-los-cambios-neurodegenerativos-de-las-funciones-visuales-en-pacientes-con-fenilcetonuria--Fase-IV-&title=Efecto-del-tratamiento-con--cido-docosahexanoico-sobre-los-cambios-neurodegenerativos-de-las-funciones-visuales-en-pacientes-con-fenilcetonuria--Fase-IV-&search=ResearchTrials_ClinicalTrials_Simple

Table B-2. Search strategies

Resource URL	Search Parameters	Search Terms/Strategy
Canadian Institute for Health Research http://www.cihr-irsc.gc.ca/	Funding Decisions Data field searched	phenylketonuria, PKU, hyperphenylalaninemia, hyperphenylalaninaemia
CenterWatch www.centerwatch.com	Conditions field	Phenylketonuria
ClinicalTrials.gov http://clinicaltrials.gov/	Advanced search, Conditions field used	Phenylketonuria OR phenylketonurias OR PKU OR Phenylketonuric OR "phenylalanine hydroxylase" OR hyperphenylalaninemia
EU Clinical Trials Register https://www.clinicaltrialsregister.eu/	NA	PKU OR phenylketonuria OR hyperphenylalaninemia OR hyperphenylalaninaemia
NIH Reporter http://projectreporter.nih.gov/reporter.cfm	Projects field searched	phenylketonuria or PKU or hyperphenylalaninemia or hyperphenylalaninaemia
ORPHANET http://www.orpha.net/	Research Projects and Clinical Trials fields searched	phenylketonuria, PKU, hyperphenylalaninemia, hyperphenylalaninaemia
World Health Organization International Clinical Trials Registry Platform Search Portal http://apps.who.int/trialsearch/	Searched Condition field, Recruitment status = ALL	Phenylketonuria OR PKU OR hyperphenylalaninemia or hyperphenylalaninaemia

Note: Web sites of agencies/organizations such as the National PKU Alliance, Children's PKU Network, National Society for PKU, Canadian Association for Rare Disorders, Children Living with Inherited Metabolic Diseases (CLIMB) organization, Canadian PKU and Allied Health Disorder organization, National Organization for Rare Disorders, Genetic Metabolic Dieticians International, Society for the Study of Inborn Errors of Metabolism, British Inherited Metabolic Disease Group, and the Society for Inherited Metabolic Disorders also searched using combinations of terms including phenylketonuria, PKU, hyperphenylalaninemia.

Appendix C. Prioritization Surveys

Round One Survey Questions

Future Research Needs: Adjuvant Therapies for PKU

Please prioritize these areas for future research related to adjuvant therapies for PKU by adding stars to an item listed below. More stars indicate higher priority. You are given a total of 35 stars which you may allocate to any of the 52 items listed below. You may use up to five stars per item. To add stars to a selection, position your mouse over the dots in the right hand column.

Please complete this survey by 5 June 2012.

If you have any questions or difficulty with this system, please contact nila.sathe@vanderbilt.edu

Remaining stars: (35 of 35)

- Which domains of executive function (e.g., planning, inhibitory control) are most sensitive to changes in Phe in individuals with PKU?
- Which measures, including executive function and affective disorder screens, are shown to be associated with changes in cognitive outcomes related to Phe level in individuals with PKU?
- To what degree do measures of executive function vary with cognition, in the context of varying levels of Phe?
- What is the validity, reliability, and responsiveness to change of existing tools for measuring executive function in individuals with PKU?
- When measuring executive function in individuals with PKU, when and how frequently should these measures be assessed?
- Which measures of ADHD are valid, sensitive, and reliable for use in individuals with PKU?
- What are the clinical benefits and limitations of distinguishing attention-related symptoms due to elevated Phe levels vs. from non-PKU-related factors such as individual behavior?
- To what degree does Phe level affect domains of social and emotional functioning in PKU?
- What is the relationship between clinical measures of executive function and "real world"/adaptive functioning?
- What are the effects of nutritional status on measures of executive function or emotion?
- To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?
- In children ≤4 years old with PKU, what is the effect of BH4 plus diet compared with placebo plus diet or standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and growth and development?
- In individuals with PKU responsive to BH4, what is the effect of BH4 plus diet compared with diet/standard care on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, family functioning, and harms of treatment over the long term (>2 years)?

- What characteristics of the individual or family moderate responsiveness to BH4 in individuals with PKU?
- What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological comorbidities in individuals with PKU?
- What characteristics of the individual, including disease severity, or characteristics of the family are associated with early vs. late initial response to BH4?
- In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care?
- How does treatment with BH4 modify other care processes, including the transition to care as an adult?
- In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet or standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?
- What harms to the mother and offspring are associated with BH4 use in pregnant women with PKU?
- In individuals with PKU, what are the long-term effects (>6 months) of LNAAs on cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet and harms of LNAAs?
- What harms are associated with LNAA use in individuals with PKU?
- What is the effectiveness of spectroscopy or other imaging techniques in assessing the effects of LNAAs or other therapies on neurotransmission of Phe?
- What CNS biomarkers are effective for assessing the effects of LNAAs on the brain in individuals with PKU?
- In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of LNAA in promoting return to care?
- How does treatment with LNAAs modify other care processes?
- How can the effects of LNAAs be measured and when should measurement occur?
- What methods are effective for measuring brain amino acid absorption?
- What are short-term effects of BH4 on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet, and harms of BH4 in specific subgroups (defined by age, dietary control, disease type)?
- Among individuals with PKU using pharmacologic therapy, are supportive adherence models effective in increasing adherence to medication?
- Are supportive adherence models (diet and/or drug) effective at improving long-term cognitive outcomes?
- Among effective adherence support systems, have individual components been shown to drive effectiveness?
- Is the effectiveness of adherence models moderated by characteristics of the individual, including age, gender, family structure and severity of disease?
- What are the pharmacokinetic, pharmacodynamic, and pharmacogenomic factors associated with treatment response in individuals with PKU?
- Are passive registries as effective as ongoing cohort studies for collecting adequate data to assess long-term effectiveness of adjuvant therapies?
- In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?

- What are the components of an effective system of care for individuals with PKU?
- What treatment-related factors at different ages are the greatest source of concern to families / caregivers?
- In individuals with PKU, what timing of Phe monitoring is optimal for fine tuning diet and treatment?
- What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?
- Which biomarkers are effective for demonstrating response to treatment or therapeutic efficacy in PKU?
- What is the utility of the plasma Phe/Tyrosine ratio compared with plasma Phe level as a measure of Phe control in PKU?
- Are medical foods adequate to overcome vitamin and mineral deficiencies over the lifetime in individuals with PKU?
- What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?
- What is an appropriate study duration for understanding cognitive and other effects in individuals with PKU?
- How can nutritional status be effectively measured in PKU?
- What is the role of functional neuroimaging in PKU?
- What is the role of combination therapy in PKU?
- How can the effectiveness of combination therapies be measured?
- How should registry data collection be modified to allow for collection of efficacy data?
- Are there critical periods of development during which promotion of adherence would facilitate long-term adherence to care?

Round Two Prioritization Survey Questions

Future Research Needs—Adjuvant Therapies for PKU

Thank you again for your participation in this project. The highest ranking research questions (separated into treatment-related and methodologic/other) resulting from the previous ranking survey are below. **In this final survey, we ask that you rank each question from 1 (lowest) to 5 (highest) across seven AHRQ prioritization criteria:**

- **Potential for significant health impact** on the current and future health status of people with respect to burden of the disease and health outcomes (mortality, morbidity, and quality of life).
- **Potential to reduce important inappropriate (or unexplained) variation in clinical practices** known to relate to quality of care, including potential to resolve controversy or dilemmas in what constitutes appropriate health care, and potential to improve decision-making for patient or provider, by decreasing uncertainty.
- **Potential for significant (nontrivial) economic impact related to the costs of health service** to reduce unnecessary or excessive costs, to reduce high costs due to high volume use, to reduce high costs due to high unit cost or aggregate cost. Costs may impact consumers, patients, health care systems, or payers.
- **Potential risk from inaction** Unintended harms from lack of prioritization of proposed research; opportunity cost of inaction.
- **Potential to address inequities**, vulnerable, diverse populations (including issues for patient subgroups); potential to reduce health inequities.
- **Potential to allow assessment of ethical, legal, social issues** pertaining to the condition.
- **Potential for new knowledge** Research would not be redundant or the question is not sufficiently researched, including completed and in-process research; utility of available evidence is limited by changes in practice (e.g., disease detection or evolution in technology).

When all surveys are returned we will tally "scores" per question and present the highest ranking questions for each criterion.

Thank you!

Question	Health impact	Variation in care	Economic impact	Risk from inaction	Inequities	ELSI	New knowledge
Treatment Questions							
In individuals with PKU responsive to BH4 plus diet compared with diet/standard care on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, family functioning, and harms of treatment over the long term (>2years)?							
In children ≤4 years old with PKU, what is the effect of BH4 plus diet compared with placebo plus diet or standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and growth and development?							
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet or standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?							
What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological co-morbidities in individuals with PKU?							
What are short-term effects of PH4 on outcomes including Phe control, Phe tolerance cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, and harms of BH4 in specific subgroups (Defined by age, dietary control, disease type							
In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care?							
What are the components of an effective system of care for individuals with PKU?							
Are there critical periods of development during which promotion of adherence would facilitate long-term adherence to care?							
Are supportive adherence models (diet and/or drug) effective at improving long-term cognitive outcomes?							
What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?							
What characteristics of the individual, including disease severity, or characteristics of the family are associated with early vs. late initial response to BH4?							
In individuals with PKU, what are the long-term effects (>6months) of LNAAs on cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet and harms of LNAAs?							
What harms are associated with LNAA use in individuals with PKU?							

Question	Health impact	Variation in care	Economic impact	Risk from inaction	Inequities	ELSI	New knowledge
Methodologic/Other							
What is the validity, reliability, and responsiveness to change of existing tools for measuring executive function in individuals with PKU?							
Which measures, including executive function and disorder screens, are shown to be associated with changes in cognitive outcomes related to Phe level in individuals with PKU?							
What methods are effective for measuring brain amino acid absorption?							
What is the relationship between clinical measures of executive function and "real world"/ adaptive functioning?							
In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?							
To what degree do measures of executive function vary with cognition, in the context of varying levels of Phe?							
What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?							
How should registry data collection be modified to allow for collection of efficacy data?							
Which domains of executive function (e.g., planning inhibitory control) are most sensitive to changes in Phe in individuals with PKU?							
When measuring executive function in individuals with PKU, when and how frequently should these measures be assessed?							
To what degree does Phe level affect domains of social and emotional functioning in PKU?							
To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?							
What is the effectiveness of spectroscopy or other imaging techniques in assessing the effects of LNAAs on neurotransmission of Phe?							
How can the effectiveness of combination therapies be measured?							

Thank you for participating in this project. We will notify you when the draft report is available for comment.

Appendix D. Highest Ranking Questions by Prioritization Criteria

We present the highest ranking (top 5) research needs/questions for each prioritization criterion organized by broad area of focus (treatment- or methods-related). Questions appear in alphabetical order under each criterion. Prioritization criteria were as follows:

- Potential for significant health impact
- Potential to reduce variation in clinical practices
- Potential for significant economic impact
- Potential risk from inaction.
- Potential to address inequities
- Potential to allow assessment of ethical, legal, social issues pertaining to the condition
- Potential for new knowledge.

Treatment Questions

Table D-1. Highest ranking treatment-related questions by prioritization criterion

Potential for significant health impact
Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes? Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?
In children ≤4 years old with PKU, what is the effect of BH4 plus diet compared with placebo plus diet / standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and growth and development?
In individuals with PKU responsive to BH4 plus diet compared with diet/standard care on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, family functioning, and harms of treatment over the long term (>2years)?
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet / standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?
What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological co-morbidities in individuals with PKU?
Potential to reduce variation in clinical practices
Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes? Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?
In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care?
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet / standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?
What are the components of an effective system of care for individuals with PKU?
What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological co-morbidities in individuals with PKU?
Potential for significant economic impact*
Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes? Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?
In individuals with PKU responsive to BH4 plus diet compared with diet/standard care on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, family functioning, and harms of treatment over the long term (>2years)?
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet /standard care on

Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?
What are the components of an effective system of care for individuals with PKU?
What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological co-morbidities in individuals with PKU?
What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?
Potential risk from inaction
Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes? Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?
In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care?
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet / standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?
What are the components of an effective system of care for individuals with PKU?
What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological co-morbidities in individuals with PKU?
Potential to address inequities*
Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes? Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?
In children ≤4 years old with PKU, what is the effect of BH4 plus diet compared with placebo plus diet / standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and growth and development?
In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care?
In individuals with PKU responsive to BH4 plus diet compared with diet/standard care on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, family functioning, and harms of treatment over the long term (>2years)?
In individuals with PKU, what are the long-term effects (>6months) of LNAAs on cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet and harms of LNAAs?
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet /standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?
What are the components of an effective system of care for individuals with PKU?
What harms are associated with LNAA use in individuals with PKU?
What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological co-morbidities in individuals with PKU?
What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?
Potential to allow assessment of ethical, legal, social issues pertaining to the condition
Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes? Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?
In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care?
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet /standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?
What are the components of an effective system of care for individuals with PKU?
What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?
Potential for new knowledge
Do interventions intended to increase adherence to diet or drug treatment in individuals with PKU lead to improved short-term and long-term cognitive outcomes? Are promotion of adherence and related positive outcomes that occur over the long term modified by important factors that include developmental stage of the individual, age, family factors, Phe level, historical adherence, and type of PKU?
In children ≤4 years old with PKU, what is the effect of BH4 plus diet compared with placebo plus diet / standard

care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and growth and development?
In individuals with PKU, what are the long-term effects (>6months) of LNAAs on cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet and harms of LNAAs?
In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet or /standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and pregnancy outcomes?
What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological co-morbidities in individuals with PKU?

*Some questions received identical scores

Abbreviations: BH4=sapropterin dihydrochloride; IQ=intelligence quotient; LNAAs=large neutral amino acids; Phe=phenylalanine; PKU=phenylketonuria; QOL=quality of life

Methods Questions

Table D-2. Highest ranking methods-related questions by prioritization criterion

Potential for significant health impact*
How can the effectiveness of combination therapies be measured?
How should registry data collection be modified to allow for collection of efficacy data?
To what degree does Phe level affect domains of social and emotional functioning in PKU?
To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?
What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?
Which measures, including executive function and affective disorder screens, are shown to be associated with to changes in cognitive outcomes related to Phe level in individuals with PKU?
Potential to reduce variation in clinical practices*
How can the effectiveness of combination therapies be measured?
How should registry data collection be modified to allow for collection of efficacy data?
In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?
To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?
What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?
When measuring executive function in individuals with PKU, when and how frequently should these measures be assessed?
Potential for significant economic impact*
How can the effectiveness of combination therapies be measured?
How should registry data collection be modified to allow for collection of efficacy data?
To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?
What is the effectiveness of spectroscopy or other imaging techniques in assessing the effects of LNAAs on neurotransmission of Phe?
What methods are effective for measuring brain amino acid absorption?
Which measures, including executive function and affective disorder screens, are shown to be associated with to changes in cognitive outcomes related to Phe level in individuals with PKU?
Potential risk from inaction
How can the effectiveness of combination therapies be measured?
How should registry data collection be modified to allow for collection of efficacy data?
To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?
What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?
What is the effectiveness of spectroscopy or other imaging techniques in assessing the effects of LNAAs on neurotransmission of Phe?
Potential to address inequities
How can the effectiveness of combination therapies be measured?
How should registry data collection be modified to allow for collection of efficacy data?
In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?
When measuring executive function in individuals with PKU, when and how frequently should these measures be assessed?
Which measures, including executive function and affective disorder screens, are shown to be associated with to changes in cognitive outcomes related to Phe level in individuals with PKU?
Potential to allow assessment of ethical, legal, social issues pertaining to the condition
How should registry data collection be modified to allow for collection of efficacy data?
In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?

To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?
What is the relationship between clinical measures of executive function and "real world"/ adaptive functioning?
When measuring executive function in individuals with PKU, when and how frequently should these measures be assessed?
Potential for new knowledge*
How can the effectiveness of combination therapies be measured?
How should registry data collection be modified to allow for collection of efficacy data?
In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?
To what degree do measures of executive function vary with cognition, in the context of varying levels of Phe?
To what degree does Phe level affect domains of social and emotional functioning in PKU?
To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?
What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?
What methods are effective for measuring brain amino acid absorption?

*Some questions received identical scores

Abbreviations: Phe=phenylalanine; PKU=phenylketonuria; QOL=quality of life

Appendix E. Summary of Stakeholder Calls

Future Research Needs—Adjuvant Therapies for Phenylketonuria
May 15 and 16, 2012 Stakeholder Call Summary

Objective:

To review and expand on research gaps and potential research questions outlined in the Adjuvant Therapies for PKU comparative effectiveness review in preparation for prioritizing research needs identified.

The team and stakeholders reviewed the preliminary list of gaps identified by key question. Stakeholders offered suggestions for additional questions, refinements to questions, and additional points to consider. We summarize stakeholder discussion by Key Question below. Tables following the summary reflect additional questions/points suggested by stakeholders.

Key Question 1 (Evidence for specific Phe levels in minimizing cognitive impairment)

- Stakeholders suggested referencing the grid developed during NIH PKU state of the science meeting and outlining cognitive screening tools and screenings by age.
- Stakeholders agreed that establishing the validity of measures of cognition and executive function is a critical issue.
- Stakeholders noted difficulty in understanding issues related to attention--is the incidence of ADHD increased in the PKU population versus the general population or are attention-related symptoms in PKU due to effects of Phe levels? To what extent is ADHD a comorbidity of PKU or a feature of the PKU phenotype?
- Stakeholders also noted a lack of understanding of the effectiveness of ADHD medications in individuals with PKU.
- Stakeholders recommended specific questions dealing with the validity and sensitivity of measures to assess ADHD in PKU.
- Stakeholders noted that measures of executive function may not assess real world functioning; questions should clearly note that a clinical measure and assessment of real world/adaptive functioning are important. A grid developed by the PKU NIH conference long-term functioning workgroup may be useful as background material. Suggested research issues include: to what degree does Phe level affect domains of social and emotional functioning? What is the relationship between clinical measures of executive function and real world functioning?
- Stakeholders also noted the importance of understanding the relationships among executive function deficits, other cognitive deficits, and educational functioning in PKU.
- Stakeholders suggested that questions about the validity of measurements also address a tool's responsiveness to change.
- Stakeholders noted that nutritional status can affect cognitive function. Research is needed to address biomarkers and techniques to measure nutritional status, the impact of nutritional status on health and thus on cognition and measure of emotion or conditions such as anxiety.
- Understanding the role of neuroimaging in PKU is an additional area to consider.

- An important question that remains unanswered is what is the mechanism by which elevated Phe (or its metabolites) is toxic to the brain and affects cognition?

Key Question 2 (Effects of BH4 on Phe, cognition, QoL, and nutritional status)

- Stakeholders and team noted that research on BH4 related to effects in young children and longer-term outcomes is in process. Stakeholders noted that while currently ongoing research will provide valuable insight, it will not be able to answer questions related to long-term outcomes.
- Stakeholders recommended revising the wording of some questions to clarify that diet is the standard of care, despite variation in adherence to diet.
- Stakeholders noted that while answering comparative effectiveness questions is critical, the final report should acknowledge that answers to questions/the research base are not sufficient for informing policy decisions. Such decisions must weigh effects on outcomes including family functioning, quality of life, nutritional status, and cognition. Comparative effectiveness research (CER) should acknowledge the gap between the CER process and the reality of implementing policy and care. CER can improve efforts to incorporate contextual information in order to increase utility.
- Stakeholders noted that a high percentage of adults with PKU are currently not under clinical care. New treatments may serve to draw people back to the clinic and potentially to diet/adjuvant treatment.
- Stakeholders noted that a potential research area is exploring the effects of adjuvant therapy (BH4 or LNAAs) in promoting a return to care and in modifying the process of care. Research should address how to identify patients not under care and the best ways to reach this population as well as how adjuvant therapy may affect the transition to care as an adult.
- Another area of research recommended by stakeholders relates to defining responsiveness to BH4 treatment and whether responsiveness as defined by Phe levels or tolerance differs from responsiveness as defined by changes in cognition or other long-term outcomes.
- Stakeholders also recommended that research address the optimal study duration for assessing cognitive or other effects.
- Family functioning was recommended by stakeholders as both an outcome of interest and potential modifier of treatment effectiveness; stakeholders noted that defining/developing a valid measure of family functioning will be necessary.

Key Question 3 (Effects of BH4 in pregnant women with PKU)

- Stakeholders strongly supported the use of registry data and data that is available to address questions in pregnant women and noted a need to ensure that registry data collection is modified to collect efficacy data appropriately. The team discussed the drawbacks of a lack of comparative data (women not treated with BH4) in registries but noted the potential to use historical data.
- Stakeholders noted that, despite the fact that little is known about safety of BH4 in pregnant women, a lack of dietary restriction will lead to poor outcomes.

Key Question 4 (Effects of LNAAs on cognition, QoL, and nutritional status)

- Despite the lack of existing high quality research suggesting benefit for LNAAs, stakeholders agreed that further research on LNAAs is critical.
- Stakeholders noted that critical areas for research are finding CNS markers for changes in neurotransmitters, understanding if amino acid/precursor production leads to neurotransmitter production, understanding how to measure brain amino acid absorption, and understanding the role and potential of spectroscopy to assess amino acid changes. Significant work needs to be done to understand technologies for measuring brain effects. Stakeholders noted that animal models for understanding protein synthesis and blood-brain Phe transport would be useful and that some for PKU in general do exist.
- Stakeholders agreed that monitoring Phe levels in the brain would be useful in PKU in general; validating biomarkers that would demonstrate either response to treatment or therapeutic efficacy across the board is important.
- Stakeholders felt that outcomes of interest for questions related to the effectiveness of LNAAs should emphasize cognition and executive function (vs. effects on Phe). It is also important to understand how and how often to measure effects on outcomes of LNAA use.
- Stakeholders brought up the need to understand combination therapies and noted that the use of combination therapies will outstrip the research, thus understanding safety and efficacy is critical. Questions include the role of combination therapy in PKU and how to measure effectiveness.

Key Question 7 (Evidence of treatment effectiveness for subgroups of individuals with PKU) and overarching issues

- Team noted that understanding adherence in subgroups is an area for research: What are the particular drivers of adherence both to diet and drug in this population? What motivates adherence, at what age groups? Stakeholders noted that there may be critical developmental periods for promoting adherence to promote lifelong care.
- Stakeholders noted a need to understand markers of treatment effectiveness better. Blood Phe is not the ideal ultimate outcome, but understanding of the sensitivity of other measures is lacking. The Phe-Tyrosine ratio may be a good candidate for further study.
- Stakeholders noted a need to understand the overlap of cognitive effects due to vitamin and mineral deficiencies and cognitive and neuro-cognitive outcomes related to PKU itself. A pressing research question is how to differentiate between outcomes as a result of the disease versus those as a result of a dietary deficiency. In patients who consume adequate amounts of medical foods, it is not known whether those adequately meet nutritional needs across life stages.
- Stakeholders agreed that an understanding of the natural history of PKU is lacking as is an understanding of outcomes at older ages.
- Stakeholders indicated a need for standardized data collection tools for dietary analysis.
- Stakeholders also discussed the implications of spotty insurance coverage of medical foods after age 18 and implications both for the individual and for research if a significant number of individuals cannot maintain the standard of care.
- Stakeholders and the team discussed the need to explore alternate means of data collection as trial accrual in rare diseases is slow and there is a need to study outcomes in pregnant women while maximizing safety. Registries and observational studies can provide useful data but research should explore ways to modify registry data collection so

that efficacy data is collected appropriately. The final report should include a summary of novel study designs and considerations for each.

- Stakeholders noted that the report should also acknowledge new therapies beginning to be studies including newer formulations of LNAAs, PegPAL, and glycomacropeptide (GMP) protein formulas. Additionally, stakeholders noted that the goal of therapy is to maximize outcomes for the patient, so clinicians may prescribe medications such as anxiolytics. Research should begin to study the effects of additional treatments in individuals with PKU and to understand the real world effects of combination therapies.
- Stakeholders advocated research exploring means to monitor Phe levels more easily.
- Stakeholders noted that an understanding of how to incorporate the patient perspective in determining relevant study end points is important as is incorporating measures of quality of care as outcomes of research.
- Stakeholders commented that ensuring a skilled workforce is increasingly critical as individuals with PKU age. Clinicians and nutritionists need training appropriate for understanding unique needs in metabolic disease.

Research Questions Derived from Gaps Noted in Report and Stakeholder Additions by Key Question

Key Question 1a. What is the evidence that any specific Phe levels are optimal for minimizing or avoiding cognitive impairment in individuals with PKU?

Key Question 1b. What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?

	Research Questions Derived from Report	Potentially Relevant Ongoing Research
	Which domains of executive function (e.g., planning, inhibitory control) are most sensitive to changes in Phe in individuals with PKU?	--
	Which measures, including executive function and affective disorder screens, are shown to be associated with to changes in cognitive outcomes related to Phe level in individuals with PKU?	--
	To what degree do measures of executive function vary with cognition, in the context of varying levels of Phe?	--
	What is the validity, reliability, and responsiveness to change of existing tools for measuring executive function in individuals with PKU?	--
	When measuring executive function in individuals with PKU, when and how frequently should these measures be assessed?	--
Additional Questions from Stakeholder Calls		
	Which measures of ADHD are valid, sensitive, and reliable for use in individuals with PKU?	
	What are the clinical benefits and limitations of distinguishing attention-related symptoms due to elevated Phe levels vs. from non-PKU-related factors such as individual behavior?	
	To what degree does Phe level affect domains of social and emotional functioning in PKU?	
	What is the relationship between clinical measures of executive function and “real world”/adaptive functioning?	
	Which measures, including executive function and affective disorder screens, are shown to be associated with to changes in “real world”/adaptive functioning related to Phe level in individuals with PKU?	
	What are the effects of nutritional status on measures of executive function or emotion?	
	To what extent are poor cognitive outcomes related to dietary deficiencies compared with Phe levels?	

Key Question 2. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status?

	Research Questions Derived from Report	Potentially Relevant Ongoing Research
	In children ≤4 years old with PKU, what is the effect of BH4 plus diet compared with placebo plus diet or standard care on Phe control, cognitive outcomes (IQ and measures of executive function), QOL, liberalization of diet, and growth and development?	•PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) •Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392) •Safety, and Population Pharmacokinetics of Sapropterin Dihydrochloride (Kuvan®) in Phenylketonuria (PKU) Patients <4 Years Old. (SPARK) (NCT01376908) •A Phase 3b Open-Label Study to Evaluate the Effect of Kuvan® on Neurocognitive Function, Maintenance of Blood Phenylalanine Concentrations, Safety, and Population Pharmacokinetics in Young Children With Phenylketonuria (NCT00838435)
	In individuals with PKU responsive to BH4, what is the effect of BH4 plus diet compared with diet/standard care on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, liberalization of diet, family functioning, and harms of treatment over the long term (>2 years)?	•PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) •Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What characteristics of the individual or family moderate responsiveness to BH4 in individuals with PKU?	•PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) •Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What is the comparative effectiveness of BH4 in addition to diet, relative to diet alone, to reduce behavioral and psychological comorbidities in individuals with PKU?	•PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) •Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392) •A Double-blind, Placebo-controlled, Randomized Study to Evaluate the Safety and Therapeutic Effects of Sapropterin Dihydrochloride on Neuropsychiatric Symptoms in Subjects With Phenylketonuria(NCT01114737)
	What characteristics of the individual, including disease severity, or characteristics of the family are associated with early vs. late initial response to BH4?	--
Additional Questions from Stakeholder Calls		
	In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of BH4 in promoting return to care?	
	How does treatment with BH4 modify other care processes, including the transition to care as an adult?	

Key Question 3. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

	Research Questions Derived from Report	Potentially Relevant Ongoing Research
	In pregnant women with PKU, what is the effect of BH4 plus diet compared with placebo plus diet or standard care on Phe control, cognitive outcomes (IQ and measures of executive funtion), QOL, liberalization of diet, and pregnancy outcomes?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What harms to the mother and offspring are associated with BH4 use in pregnant women with PKU?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)

Key Question 4. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status?

	Research Questions Derived from Report	Potentially Relevant Ongoing Research
	In individuals with PKU, what are the long-term effects (>6 months) of LNAAs on cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet and harms of LNAAs?	• Effects of short term increase of phenylalanine levels on neuropsychological functions and well-being in adults with phenylketonuria: the "diet for life" study-supplement of amino acids (NTR1056)
	What harms are associated with LNAA use in individuals with PKU?	• Effects of short term increase of phenylalanine levels on neuropsychological functions and well-being in adults with phenylketonuria: the "diet for life" study-supplement of amino acids (NTR1056)
Additional Questions from Stakeholder Calls		
	What is the effectiveness of spectroscopy or other imaging techniques in assessing the effects of LNAAs on neurotransmission of Phe?	
	What CNS biomarkers are effective for assessing the effects of LNAAs on the brain in individuals with PKU?	
	In individuals with PKU not currently adherent to diet or receiving treatment for PKU, what are the effects of LNAA in promoting return to care?	
	How does treatment with LNAAs modify other care processes?	
	How can the effects of LNAAs be measured and when should measurement occur?	
	What methods are affective for measuring brain amino acid absorption?	

Key Question 7. What is the evidence for the effectiveness of the addition of BH4 or LNAAs to dietary intervention for affecting outcomes in subgroups of patients?

	Research Questions Derived from Report	Potentially Relevant Ongoing Research
	What are short-term effects of BH4 on outcomes including Phe control, Phe tolerance, cognitive outcomes (IQ and executive function), quality of life, and liberalization of diet, and harms of BH4 in specific subgroups (defined by age, dietary control, disease type)?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392) • Effects of Sapropterin on Brain and Cognition in Individuals With Phenylketonuria (NCT00730080) • Evaluation of Behavior, Executive Function, Neurotransmitter Function and Genomic Expression in PKU "Nonresponders" to Kuvan(NCT01274026) • Treatment of hyperphenylalaninemia with Sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) and its influence on the amino acids and fatty acids patterns from childhood to adulthood, a Phase IV, longitudinal, unblinded, controlled, single-centre, retrospective and prospective clinical study(ISRCTN77098312)

Overall/Foundational Questions Derived from Report

	Research Question	Potentially Relevant ongoing Studies
	Among individuals with PKU using pharmacologic therapy, are supportive adherence models effective in increasing adherence?	--
	Are supportive adherence models (diet and/or drug) effective at improving long-term cognitive outcomes?	--
	Among effective adherence support systems, have individual components been shown to drive effectiveness?	--
	Is the effectiveness of adherence models moderated by characteristics of the individual, including age, gender, family structure and severity of disease?	--
	What are the pharmacokinetic, pharmacodynamic, and pharmacogenomic factors associated with treatment response in individuals with PKU?	--
	Are passive registries as effective as ongoing cohort studies for collecting adequate data to assess long-term effectiveness of adjuvant therapies?	• PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) • Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)

	In addition to blood Phe, what measures provide valid assessments of dietary control in individuals with PKU?	•PKUDOS: Phenylketonuria (PKU) Demographic, Outcomes, and Safety Registry (NCT00778206) •Kuvan® Adult Maternal Pediatric European Registry (KAMPER): Observational Study on the Long Term Safety of Kuvan® Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (NCT01016392)
	What are the components of an effective system of care for individuals with PKU?	--
	What treatment-related factors at different ages are the greatest source of concern to families / caregivers?	•5-year Follow-up of the Comparison of Life and Physical Health in Adult Patients With PKU and Healthy Age Matched Controls (NCT01096758)
0	In individuals with PKU, what timing of Phe monitoring is optimal for fine tuning diet and treatment?	•The effects of online availability of individual phenylalanine levels to patients with phenylketonuria (NTR1171)
Additional Questions from Stakeholder Calls		
	What medical supports can bring individuals with PKU back to treatment and/or dietary adherence?	
	Which biomarkers are effective for demonstrating response to treatment or therapeutic efficacy in PKU?	
	What is the utility of the plasma Phe/Tyrosine ratio compared with plasma Phe level as a measure of Phe control in PKU?	
	Are medical foods adequate to overcome vitamin and mineral deficiencies over the lifetime in individuals with PKU?	
	What biomarkers are valid for understanding the effects of vitamin and mineral deficiencies in PKU?	
	What is an appropriate study duration for understanding cognitive and other effects in individuals with PKU?	
	How can nutritional status be effectively measured in PKU?	
	What is the role of functional neuroimaging in PKU?	
	What is the role of combination therapy in PKU?	
0	How can the effectiveness of combination therapies be measured?	
1	How should registry data collection be modified to allow for collection of efficacy data?	
2	Are there critical periods of development during which promotion of adherence would facilitate long-term adherence to care?	

Additional (non-research) recommendations/needs:

- Increased understanding of long-term implications of intermediate outcomes
- Multi-collaborator consortium that includes a public-private partners to outline research agenda; evaluate needs for comprehensive system of care; develop/expand prospective registries to include collection of outcome data including measures of executive function, nutritional status, growth, and quality of life; and biorepository
- Understanding of the role of international collaboration and differences in diet, culture, genotype/phenotype, etc. in planning for multicenter consortia
- Standardized data collection tools, especially for cognitive outcomes
- Standards/guidelines for data sharing and comprehensive reporting (including reporting of measures of variance, potential confounding and modifying factors, etc.)
- Standardized collection and reporting of potential confounders and modifiers (e.g., familial IQ, SES, maternal education, concurrent medications, age at initial treatment, level of dietary control)
- Increased understanding of outcomes of importance to patients and families
- Understanding of quality of life for patients and families and factors that affect quality of life
- Understanding approaches to studying adjuvant therapies in pregnant women with PKU (e.g., registry, cohort study)
- Understanding of study designs that can provide high-quality data while taking into account difficulties in accrual in rare
- Studies appropriately designed and powered to allow subgroup analyses
- Understanding of the potential role of observational studies in providing effectiveness data
- Publicly funded studies
- Understanding of potentially useful research models from other rare diseases

Additional points from stakeholder calls:

- Need for standardized dietary data collection tools
- Need to understand how well medical foods meet nutritional needs across the lifespan
- Understanding of the effects of lack of insurance coverage of medical foods and treatment needs after age 18/26 for many individuals with PKU and individual and research implications for maintaining the standard of care
- Exploration of techniques to monitor Phe levels more easily, including home monitoring
- Understanding of methods for incorporating the patient perspective in determining relevant study end points
- Animal studies to increase understanding of protein synthesis and blood-brain transport and mechanisms of toxicity of Phe and/or its metabolites in the brain
- Appropriate training to ensure knowledgeable workforce as case identification increases with newborn screening
- Appropriate training for non-metabolic nutritionists in understanding exigencies of PKU
- Appropriate training for psychiatrists and psychologists in understanding PKU
- Understanding of how to incorporate quality of care as an outcome

Additional Questions from Stakeholder Calls—Out of Scope of Adjuvant Therapies (will be noted in final report but not prioritized by stakeholders)

- What is the effectiveness of medications to treat ADHD, anxiety, depression, and other mental health comorbidities in individuals with PKU?
- What methods are effective for identifying and reaching individuals with PKU not currently under care?
- What is the natural history of PKU?
- How does defining responsiveness in terms of Phe level or Phe tolerance or in terms of cognition or other long-term outcomes affect care for individuals with PKU?

Next Steps:

We will send stakeholders the link to a Web-based survey to prioritize the expanded list of research needs. Prioritization will occur in two rounds: In the first round stakeholders will allot a number of points to each question to indicate the top tier/highest priority questions. We will compile "votes" across stakeholders and cull the expanded list to the highest priority research needs. In the second round, stakeholders will prioritize the top tier list of needs using criteria including the potential for significant health impact, potential for risk from inaction, and potential for significant economic impact.