EE316

An iterative survey of phenylketonuria (PKU) medical experts to inform health economic modeling methods

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1. Background & Objectives:

Phenylketonuria (PKU) is an inherited, genetic disease. The condition results in elevated blood phenylalanine (Phe) which leads to a wide range of clinical outcomes, including neurocognitive and neurobehavioral impairments.[1]

- Burdensome, lifelong dietary management is required to maintain blood Phe at or below the recommended level.[2] Poor adherence to Phe-restricted diets has been observed[3] and the potential for suboptimal management of blood Phe levels leading to neurological damage remains.
- Two pharmacological treatment options have regulatory approval for PKU: sapropterin dihydrochloride and pegvaliase.

- Health technology assessments (HTA) for the reimbursement of sapropterin and pegvaliase have involved varying approaches to cost-effectiveness analysis (CEA). Evaluations of these HTA processes have highlighted a number of limitations with the approaches used including:
  - Failure to capture long-term impacts of uncontrolled Phe; health state definitions not aligning with utility/cost impacts; a lack of support for diet liberalization modeling; implausible or lack of discontinuation modeling; and an absence of modeling of PKU-associated comorbidities, caregiving impacts, and impacts on mothers and/or unborn children in maternal PKU.[4]

- Consensus on a clinically accurate CEA model structure would be valuable for future assessments of treatments for PKU.

The objective of this study was to identify and establish agreement on key components of a clinically accurate CEA model structure through expert consensus.

2. Methods:

- A modified Delphi panel[5] comprising international, multidisciplinary experts in PKU is currently in progress.

Preparatory phase

1. A targeted review of sapropterin and pegvaliase HTA evaluations was conducted to characterize challenges with the approaches used.[4]
2. Subsequently, the results of the targeted review were used to inform a process which sought to identify clinical outcomes of greatest importance to model in CEA for PKU. This involved:
   - Initial qualitative discussions held with N=8 PKU medical experts.
   - A subsequent scoping survey in which 17 distinct clinical outcomes in PKU (**Figure 1**), identified based on input from the previous steps, were rated.
     - In the survey, the experts rated each outcome on their importance for CEA on a specified numerical scale. Consideration was given to the degree to which they affect:
       - Prognosis for other PKU outcomes/comorbidities
       - Patient/family/caregiver quality of life
       - Patient healthcare resource use/costs
       - Other direct (e.g., medical foods, paid caregiving) or indirect (e.g., employment outcomes, informal caregiving) costs

Figure 1. Scoping survey outcomes rated for importance for CEA

Outcome		Description
Physiological/ neurologic	Blood Phe concentration	controlled vs. uncontrolled, or more segmented levels
	Physiological growth/development	height, weight, body mass index
	Neurologic symptoms - acute/short-term	e.g., tremors, epilepsy
	Neurologic symptoms - chronic/longer-term	e.g., dementia
	Comorbid conditions	e.g., overweight/obesity, chronic fatigue, diabetes mellitus, ischemic heart disease, dental issues, anemia, asthma, renal insufficiency, eczema, alopecia, osteoporosis
Psychiatric	Intellectual disability	severe reduction in intelligence quotient (IQ)
	Mild-moderate reduction in IQ	
	Executive function deficit disorders	e.g., attention-deficit/hyperactivity disorder
Psychological/ behavioral	Behavioral conditions	e.g., anger, autism spectrum disorder
	Psychological outcomes - acute/short-term	e.g., anxiety, confusion, poor mood
	Psychological outcomes - chronic/longer-term	e.g., depression, relationship satisfaction, other psycho-social manifestations
Dietary/ pharmacotherapeutic management	Tolerance of natural Phe/protein	
	Nutritional deficiencies	e.g., deficiencies vs. recommended dietary allowances for essential vitamins and minerals
	Adverse events of treatment	e.g., hypersensitivity reactions
Maternal PKU	Mother's physiological health	e.g., management of morning sickness / hormone changes while on restricted diet, childbirth complications, nutritional deficiency
	Mother's psychological health	e.g., anxiety with stricter dietary control in pregnancy, concern for the unborn child
	Child's physiological health	e.g., spontaneous abortion, developmental delay and/or intellectual disability, microcephaly, congenital heart defects, low birth weight

Modified Delphi panel

- Purposive sampling was used to recruit the panel to capture potential heterogeneity in clinical perspectives.[8,9]
  - Eleven participants were identified representing a range of experience (pediatrics, metabolics, and genetics specialists; guideline development for PKU; clinical care; clinical study involvement; dietary management) and five countries:

France (n=1), Germany (n=1), Japan (n=1), UK (n=2), USA (n=6)

- An e-Delphi panel comprising two rounds of questions and an intermediate review of responses (to allow for participants to observe others' anonymized responses between rounds) is underway.
- Prior to launch of Round 1, pilot testing was conducted with N=4 experts, to ensure that the process, instructions, and questions were clear to the participants.

Round 1: Survey including 14 questions related to clinical outcomes, diet liberalization, target population, Phe-level classification, and treatment discontinuation.

- The questions were posed as qualitative statements and asked the participant to rate their level of agreement / disagreement using a 5-point Likert scale (as well as a "Don't know" option).
- For some questions, additional details were requested (e.g., measurement parameters) based on whether the participant agreed or disagreed with the statement.
- With the completion of Round 1, participants were provided a summary of anonymized responses and encouraged to share further comments via an online forum.

Round 2: Survey including questions that did not achieve consensus in Round 1, refined based on comments from Round 1 responses and the intermediate review.

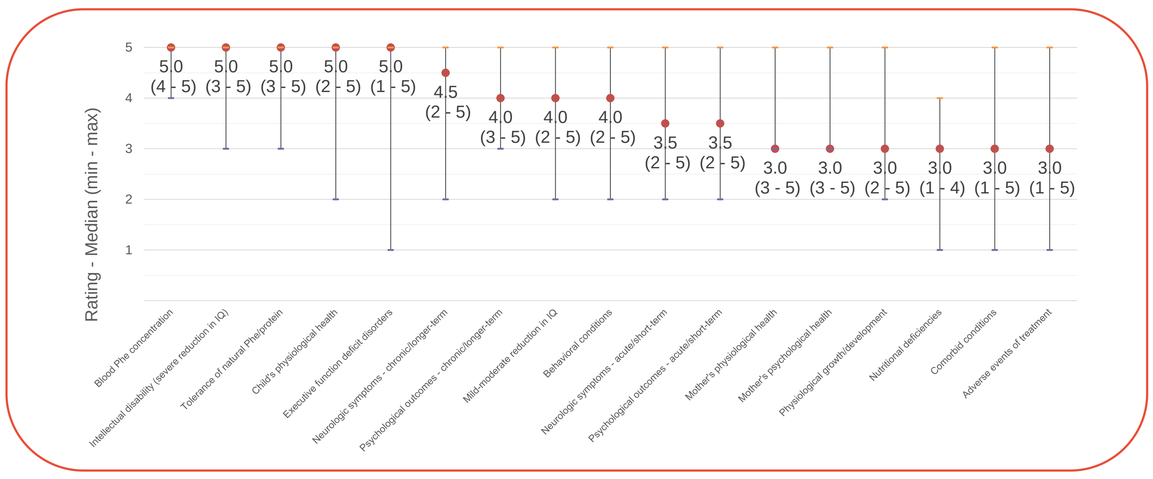
- Consensus is defined as percent agreement ≥ 70%.[10,11]

3. Results:

Preparatory phase

- Clinical experts (N=8) rated the importance of modeling clinical outcomes in CEA on a 1-5 (limited-high) scale (**Figure 2**).
- Five outcomes had a median rating of 5, indicating high importance (**Figure 2**):
  - Blood Phe concentration
  - Intellectual disability (severe reduction in intelligence quotient)
  - Tolerance of natural Phe/protein
  - Child's physiological health (in maternal PKU)
  - Executive function deficit disorders

Figure 2. Median (min-max) rating for importance of modeling clinical outcomes in CEA



- The 17 outcomes queried in the scoping survey were considered comprehensive, with physical disabilities and adults' social engagement/autonomy noted as additional relevant outcomes.
  - An online survey for Round 1 of the Delphi panel, comprising 14 questions, was developed based on the scoping survey results.

Modified Delphi Panel

- Consensus was reached on 9 questions in Round 1, particularly on questions related to the role of uncontrolled Phe levels in clinical consequences of PKU, as well as factors related to unmet need (**Figure 3**).

Figure 3. Delphi panel – Round 1 survey results

Question	Percentage of responses (N=11) (excluding "Don't know") Strongly disagree (1)	Disagree (2)	Neutral (3)	Agree (4)	Strongly agree (5)	Don't know (N)	Consensus (i.e., ≥70% agree or disagree)
1 An individual patient's blood Phe levels are generally expected to be consistent within certain life stages, including (i) childhood to early adolescence (ages 0-11), (ii) adolescence (ages 12-17), and (iii) adulthood (ages ≥18).	0.00%	30.00%	0.00%	40.00%	30.00%	1	✓
2 In real-world management, a realistic (i.e., stable) measurement of a patient's Phe level may be made in less than 6 months.	0.00%	0.00%	0.00%	63.64%	36.36%	-	✓
3 Phe levels of 0-29 µmol/L pose a safety risk for patients.	0.00%	27.27%	0.00%	36.36%	36.36%	-	✓
4 For patients with Phe levels <120 µmol/L, Phe levels higher than 0-29 µmol/L (e.g., 30-60) may pose a safety concern for patients.	9.09%	45.45%	9.09%	36.36%	0.00%	-	
5 Sustained uncontrolled Phe levels in a patient's past are associated with intellectual disability.	0.00%	0.00%	18.18%	27.27%	54.55%	-	✓
6 Sustained uncontrolled Phe levels in a patient's past are associated with outcomes other than intellectual disability.	0.00%	0.00%	0.00%	45.45%	54.55%	-	✓
7 Controlled vs. uncontrolled blood Phe levels are associated with near-term (e.g., within 1-4 weeks) likelihood of ADHD / executive-functioning symptoms.	0.00%	0.00%	18.18%	45.45%	36.36%	-	✓
8 In real-world management, if a patient's Phe levels reached the target range, diet liberalization (addition of dietary Phe) would be conducted only if Phe levels remained in the lower half of the target range.	0.00%	27.27%	27.27%	18.18%	27.27%	-	
9 HRQoL, if considered to include a patient's mental health and psychosocial functioning, would be expected to improve with addition of 2-3 g of natural protein to a patient's diet.	0.00%	27.27%	27.27%	27.27%	18.18%	-	
10 The level of unmet need with the current SoC differs significantly by the 4 sapropterin-experience related subgroups listed (sapropterin-naïve, failure, sub-optimally controlled, well-controlled)	0.00%	0.00%	9.09%	27.27%	63.64%	-	✓
11 The level of unmet need with the current SoC differs significantly by other factors (e.g., age, disease severity, pegvaliase response).	0.00%	9.09%	0.00%	63.64%	27.27%	-	✓
12 Among patients who discontinue sapropterin treatment, negative health outcomes associated with uncontrolled PKU after discontinuation may cause patients to resume sapropterin.	0.00%	30.00%	10.00%	40.00%	20.00%	1	
13 Among patients who discontinue pegvaliase treatment, negative health outcomes associated with uncontrolled PKU after discontinuation may cause patients to resume pegvaliase.	0.00%	20.00%	30.00%	40.00%	10.00%	1	
14 Among patients who reach the target blood Phe range with pharmacotherapy, the pharmacotherapy would be continued indefinitely.	0.00%	18.18%	9.09%	27.27%	45.45%	-	✓

Abbreviations: ADHD, attention deficit hyperactivity disorder; g, gram; HRQoL, health-related quality of life; Phe, phenylalanine; PKU, phenylketonuria; SoC, standard of care; µmol/L, micromole per liter.

4. Discussion & Conclusions:

This ongoing study is developing areas of agreement among a group of international, multidisciplinary medical experts on clinically accurate modeling approaches for CEAs of PKU therapies.

During the preparatory phase, in addition to blood Phe concentration, experts agreed that intellectual disability, tolerance of natural Phe/protein, executive function deficit disorders and the child's physiological health in maternal PKU were highly important clinical outcomes for inclusion in CEA modeling for PKU.

After Round 1 of the Delphi panel, experts have reached consensus on questions highlighting the importance of controlling Phe levels over the disease course in PKU.

A strength of this study was the diversity of experts participating in the panel, with members from a range of medical disciplines which support patients with PKU. As such, the clinical components found to be highly important to modeling PKU are representative of multiple perspectives in PKU care.

Results from this study provide valuable insights into cost-effectiveness modeling in PKU, which address the limitations and critiques that have been highlighted by HTA agencies in previous evaluations of PKU treatments.

Findings from this study may help to inform future CEA in PKU, by establishing expert consensus on PKU outcomes that should be included and clinically-accurate modeling of such outcomes.

5. References:

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