Considerations for Health Economic Modeling in Phenylketonuria (PKU): Insights from a Modified Delphi Panel

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1. BACKGROUND:

Phenylketonuria (PKU) results in elevated blood phenylalanine (Phe) levels, which lead to a wide range of clinical symptoms, including neurocognitive and neurobehavioral impairments.[1]

Burdensome, lifelong dietary management is required to maintain blood Phe levels within recommended treatment guidelines.[2,3] There is progressive poor adherence with age to Phe-restricted diets[4] leading to suboptimal management of blood Phe levels and the potential for neuropsychological symptoms.

Currently, two pharmacological therapies have received regulatory approval for the treatment of 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). A previous review of these HTA evaluations highlighted a number of limitations with the approaches used,[5] including:

- Failure to capture long-term impacts of uncontrolled blood Phe
- Health state definitions not aligning with utility/cost impacts
- A lack of support for diet liberalization modeling
- Implausible or lack of therapy discontinuation modeling
- An absence of modeling of PKU-associated comorbidities, caregiving impacts, and impacts on mothers and/or unborn children in maternal PKU

Given these limitations, consensus on clinically-accurate modeling approaches for CEA would be valuable for assessing novel treatments for PKU.

2. OBJECTIVE

This study aimed to identify areas of consensus among PKU medical experts regarding key clinical components for inclusion in a model.

3. METHODS:

Participants

For the Delphi panel, purposive sampling was used to recruit experts in order to capture potential heterogeneity in clinical perspectives.[6,7]

Eleven participants represented a range of experience (pediatrics, metabolics, genetics; guideline development for PKU; clinical care; clinical study involvement; dietary management) and five countries:

Preparation

Statements for evaluation by the panel were developed with an iterative process encompassing a targeted literature review, expert feedback, a scoping survey.[5,8]

Process

Pilot testing: Conducted with N=4 experts to ensure that the process, instructions, and questions for the survey were clear to the participants.

Round 1: 14-question survey related to clinical outcomes, diet liberalization, unmet need, Phe-level classification, and treatment discontinuation.

- Questions were posed as qualitative statements; participants rated their level of agreement / disagreement using a 5-point Likert scale (plus a "Don't know" option).
- For some questions, additional details were requested (e.g., quantitative parameters) if the participant agreed or disagreed with the statement.

Intermediate review: Participants were provided a summary of anonymized responses and encouraged to share further comments via an online forum.

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

- Consensus was defined as percent agreement or disagreement ≥ 70%.[9,10]

4. RESULTS:

Round 1

N=11 participants (100%) completed the survey.

≥70% agreement or disagreement (i.e. consensus) was reached on 8/14 questions (**Figure, Supplementary table**).

Intermediate review

N=7 (64%) participated in the intermediate review.

The 6 statements not achieving consensus in Round 1, and 1 statement meriting further inquiry, were refined into 10 statements for Round 2 (**Figure, Supplementary table**).

- Statement 1 achieved consensus during the intermediate review; however, participants expressed that the refinements suggested should be considered in Round 2.
- Changes in participant responses on statement 9 and statement 14 were not sufficient to change Round 1 results.

Round 2

N=11 participants (100%) completed the survey.

There was ≥70% agreement or disagreement for 6/10 revised questions (**Figure, Supplementary table**).

Consensus

Consensus was achieved on 8 of the original statements and 6 revised statements. Consensus could not be achieved on 4 statements.

	Round 1 – original statements	Round 2 – revised	
Phe Levels & Associated Outcomes	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).	In clinical practice, most patients will generally (other than due to temporary triggers - e.g., fever) remain controlled or uncontrolled within the following age ranges: 0-4 years, 5-11 years, 12-17 years, 18-30 years, >30 years.	91%
	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.		100%
	3. Phe levels of 0-29 umol/L pose a safety risk for patients.		73%
	4. For patients with Phe levels <120 umol/L, Phe levels higher than 0-29 umol/L (e.g., 30-60) may pose a safety concern for patients.	For patients who are consuming sufficient dietary Phe (i.e., not at risk of nutritional deficiency/growth impairment), Phe levels in the range of 30-120 umol/L may pose a safety concern.	73%
	5. Sustained uncontrolled Phe levels in a patient's past are associated with intellectual disability.		82%
	6. Sustained uncontrolled Phe levels in a patient's past are associated with outcomes other than intellectual disability.	The mechanisms below encompass those (both direct and indirect) that may account for the association of PKU with chronic comorbidities: high-caloric intake from Phe-restricted diet, lack of dietary protein, metabolic abnormalities associated with PKU pathophysiology, metabolic acidosis associated with medical food.	73%
	7. Controlled vs. uncontrolled blood Phe levels are associated with near-term (e.g., within 1-4 weeks) likelihood of ADHD / executive-functioning symptoms.		82%
Diet Liberalization	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.	If upon initiating a new therapy, a pediatric patient's Phe levels were reduced from >360 to consistently 240-299 for three weeks, and the patient expressed desire to consume more dietary Phe, a dietary Phe challenge may be conducted.	91%
		If upon initiating a new therapy, a pediatric patient's Phe levels were reduced from >360 to consistently 300-359 for three weeks, and the patient expressed desire to consume more dietary Phe, a dietary Phe challenge may be conducted.	46%
	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.	Medical-food consumption is reduced with increased dietary Phe (protein) consumption.	55%
Unmet Need	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).		91%
	11. The level of unmet need with the current SoC differs significantly by other factors (e.g., age, disease severity, pegvaliase response).		91%
Treatment Discontinuation	12. Among patients who discontinue sapropterin treatment, negative health outcomes associated with uncontrolled PKU after discontinuation may cause patients to resume sapropterin.	Among patients who discontinue sapropterin treatment due to sub-optimal effectiveness (e.g., Phe levels above target range, or inability to liberalize diet), symptoms of uncontrolled PKU after discontinuation may cause patients to resume sapropterin.	55%
		Among patients who discontinue sapropterin treatment due to side effects (e.g., GI discomfort), symptoms of uncontrolled PKU after discontinuation may cause patients to resume sapropterin.	60%
	13. Among patients who discontinue pegvaliase treatment, negative health outcomes associated with uncontrolled PKU after discontinuation may cause patients to resume pegvaliase.	Among patients who discontinue pegvaliase treatment due to sub-optimal effectiveness (e.g., Phe levels above target range, or inability to liberalize diet), symptoms of uncontrolled PKU after discontinuation may cause patients to resume pegvaliase.	78%
		Among patients who discontinue pegvaliase treatment due to side effects (e.g., GI discomfort), symptoms of uncontrolled PKU after discontinuation may cause patients to resume pegvaliase.	78%
	14. Among patients who reach the target blood Phe range with pharmacotherapy, the pharmacotherapy would be continued indefinitely.		73%

Consensus agreement with statement | Consensus disagreement with statement | No consensus achieved on statement

Abbreviations: ADHD=attention deficit hyperactivity disorder; g=grams; GI=gastrointestinal; HRQoL=health-related quality of life; Phe=phenylalanine; PKU=phenylketonuria; SoC=standard of care

5. DISCUSSION:

This study evaluated consensus perspectives among a group of international, multidisciplinary medical experts on how to model important clinical outcomes of PKU in CEA.

The panel was chosen to reflect heterogeneity in clinical perspectives (e.g. differences in European and United States clinical guidelines).

The panel reached consensus on the majority of statements considered, including statements highlighting the importance of controlling blood Phe levels over the disease course in PKU.

Areas of consensus will provide guidance for economic modeling, (e.g., ascertaining relevant timeframes for different outcomes can help inform the model cycle length).

Consensus was not achieved on statements relating to the potential for changes to medical-food consumption to impact health-related quality of life (statement 9) and long-term sapropterin treatment (i.e., discontinuation and resumption).

These findings indicate heterogeneity in opinion on some aspects of PKU treatment and management; as such, sensitivity analysis in economic modeling may be beneficial to explore uncertainty.

A strength of this study was the diversity in the panel. Members were from a range of medical disciplines which support patients with PKU; most had ≥20 years of experience.

As such, expert insights received on modeling PKU are representative of multiple perspectives in PKU care.

- Limitations included potential selection bias from the purposive sampling method.
- The broad nature of some statements may have posed rating challenges given patient-case heterogeneity encountered in clinical practice (though pilot testing aimed to mitigate this).

6. CONCLUSION

Findings from this study can help inform future CEAs in PKU by establishing expert consensus on outcomes to include, as well as clinically-accurate modeling of such outcomes. These insights address the modeling limitations identified in previous CEAs of PKU treatments.

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