Cost-Utility Analysis (CUA) of Sepiapterin for Treatment of Phenylketonuria (PKU): Development of a *De-novo* Conceptual Model

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Background and objective

- Phenylketonuria (PKU) results from an inborn deficiency in the phenylalanine (Phe) hydroxylase gene, causing reduced processing of Phe, an amino acid contained in dietary protein.[1] A lifelong protein-restricted diet (PRD) is essential to prevent neurotoxic blood Phe levels.[2,3]
- The pharmacological therapies sepiapterin, sapropterin dihydrochloride, and pegvaliase have received approvals in countries that include the US and EU for the treatment of PKU.[4,5,6,7] Sepiapterin is not currently licensed in the United Kingdom.
  - Cost-utility analysis (CUA) for sapropterin dihydrochloride and pegvaliase have used inconsistent approaches, reflecting a lack of consensus on clinically-accurate modeling approaches.[8]
    - Health technology assessment (HTA) agency criticisms of these analyses include the omission of important impacts of PKU, including risk of intellectual disability in childhood, comorbid conditions, and burden of caregiving.[8,9]
    - Additional critiques include health state definitions not aligning with utility and/or cost impacts modeled and diet liberalization modeling being unsupported and likely overstated.[9,10,11]
- As with other rare diseases, there is limited and uncertain evidence in the literature to inform the necessary components of a model for PKU. Research methodologies including surveys and Delphi panels, which solicit insights from clinical experts who have direct experience with PKU disease management, can help address evidence gaps as well as provide face validity for the model structure developed.[12]

This study sought to identify key parameters and structural assumptions for a de-novo model structure for CUA in PKU, informed by insights and consensus from PKU medical experts

Methods

Figure 1. Overall approach for identifying key model parameters and structural assumptions

Targeted review[8]
- Characterized challenges with the approaches of CUAs in PKU from sapropterin and pegvaliase HTAs.

Scoping survey[13]
- Identified which PKU outcomes* to include in a CUA model.
- N=8 clinical-experts (**Table 1**) participated in qualitative discussions and rated importance of each outcome for CUA on a five-point scale.

Modified e-Delphi panel[14]
- Clinical expert participants (11 participants, 5 countries, **Table 1**) rated their agreement on the following topics: clinical outcomes, diet liberalization, unmet need, Phe-level classification and treatment discontinuation.
- Participants reviewed anonymized responses and shared comments.
- Statements that did not previously achieve consensus were reformulated based on feedback.

Online clinical-expert survey[15]
- 30 experts from 15 countries rated their agreement with statements on the plausibility that:

Survey Statement 1	Prevalence of each of 10 comorbidities† is higher in individuals with PKU vs the general population.
Survey Statement 2	Increased natural protein in diet (e.g., consumption of less medical food) may reduce comorbidity risk.
Survey Statement 3	Control of elevated blood Phe levels (i.e., reduction to within the target range) may reduce comorbidity risk.

Development of a conceptual CUA model

Combined evidence from literature with insights and consensus from experts to develop the model structure for the CUA model.

*Outcomes (n=17) were identified from PKU clinical guidelines;[16] †Comorbidities identified through real-world evidence17-19 included: anaemia; asthma; chronic ischaemic heart disease (CIHD); depression; osteoporosis; overweight (body mass index [BMI] ≥25 kg/m^2); renal insufficiency with hypertension; renal insufficiency without hypertension; type 2 diabetes mellites (T2DM); other/unspecified diabetes

Methods continued

- Clinical expertise relevant to PKU included: paediatrics, metabolics, and genetics; guideline development for PKU; clinical care; clinical-study involvement; and dietary management.

Table 1. Clinical-expert participants in the survey and modified e-Delphi panel

	AUS	BRA	CAN	DNK	FRA	DEU	ITA	JPN	NLD	POL	PRT	SVN	TUR	GBR	USA
Scoping survey					n=1	n=1		n=1						n=2	n=3
Modified e-Delphi panel					n=1	n=1		n=1						n=2	n=6
Clinical expert survey	n=2	n=1	n=1	n=1	n=3	n=2	n=1	n=2	n=1	n=1	n=1	n=1	n=4	n=2	n=7

Discussion

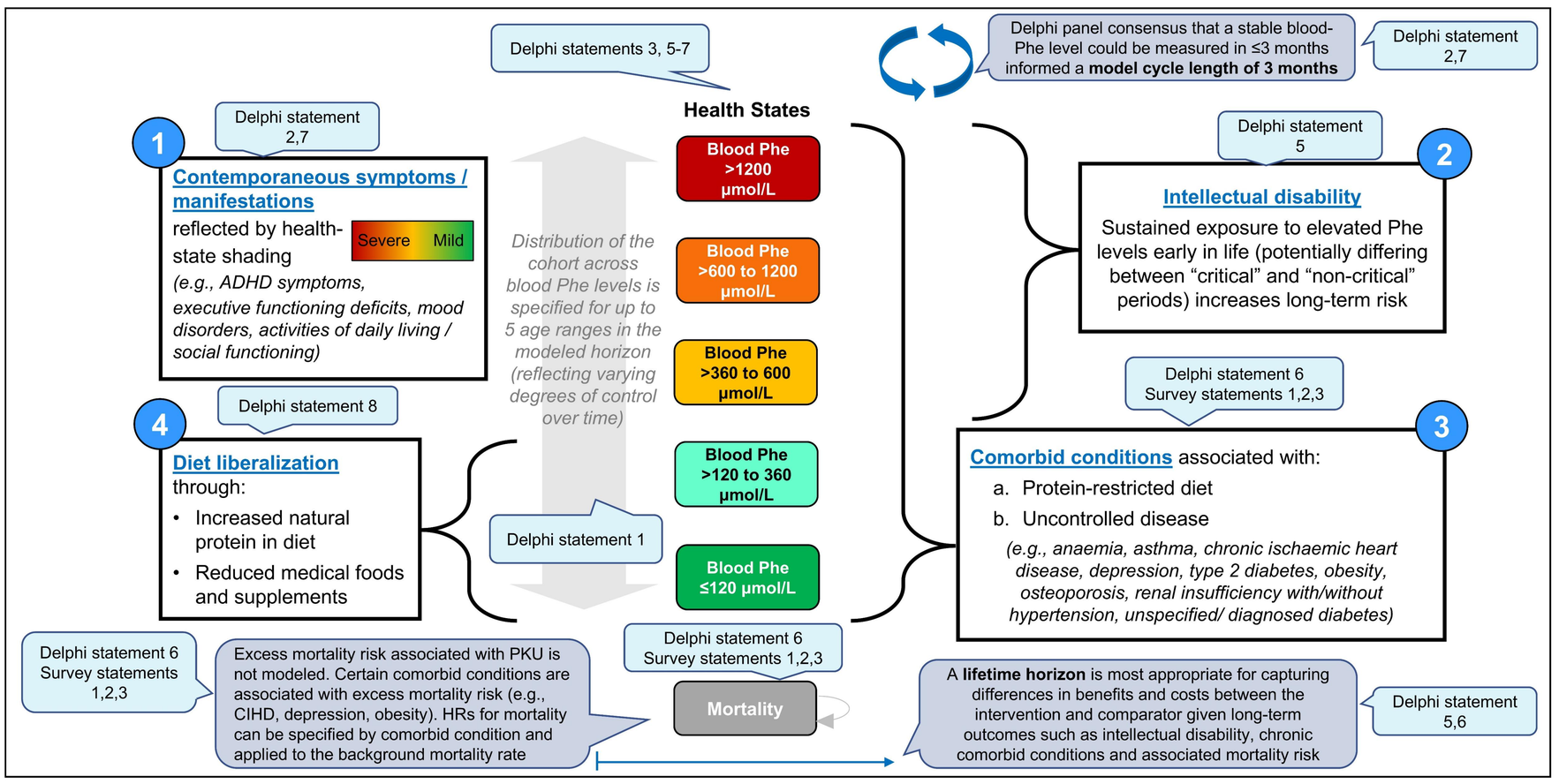
- This study sought expert insight to determine clinically-accurate modeling approaches for CUAs of PKU therapies to develop a CUA model structure for PKU which addresses gaps identified in previous models.
- Insights elicited from clinical experts helped to inform a structure for economic modeling in PKU, which can reflect the heterogeneity in unmet need among individuals with PKU, varying with both blood-Phe levels and diet restrictions, when evaluating relative treatment benefits.
- The heterogeneity of the participants in the survey and panel was notable for several reasons. With members from a range of medical disciplines across 15 countries, expert insights allowed for a broad spectrum of perspectives in PKU care to inform the model design. It also highlighted areas for future research, including how best to characterize the relationship between health-related quality of life (HRQoL) and diet liberalization.

CONCLUSIONS

- In this study, a structured process was conducted to identify challenges and limitations of previous economic modeling structures for PKU, and then to elicit clinical-expert insights and consensus on key parameters and assumptions to ensure the subsequent model had strong face validity.
- Clinical-expert engagement ensured the inclusion of patient-relevant outcomes and clinically-accurate methods of modeling such outcomes in a *de-novo* model. The resulting model structure developed allows for reflecting the heterogeneity in unmet need across patients with PKU, varying with both blood-Phe control and diet restrictions.
- Accordingly, the model structure is flexible for comparing the relative benefits and costs across multiple treatment strategies currently approved for PKU.

Results

Figure 2. Proposed model structure for CUA of PKU treatments



Note: Modified e-Delphi panel statements - *Statement 1* - 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; *Statement 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; *Statement 3* - Phe levels of 0-29 µmol/L pose a safety risk for patients; *Statement 5* - Sustained uncontrolled Phe levels in a patient's past are associated with intellectual disability; *Statement 6* - Sustained uncontrolled Phe levels in a patient's past are associated with outcomes other than intellectual disability; *Statement 7* - Controlled vs. uncontrolled blood Phe levels are associated with near-term (e.g., within 1-4 weeks) likelihood of ADHD / executive-functioning symptoms; *Statement 8* - If upon initiating a new therapy, a paediatric patient's Phe levels were reduced from >360 µmol/L to consistently 240-299 µmol/L for 3 weeks, and the patient expressed desire to consume more dietary Phe, a dietary Phe challenge may be conducted (For a full list of modified e-Delphi panel statements see supplementary figure 1)

- During the modified e-Delphi panel, participants achieved consensus on statements relating to: ages at which individual blood Phe levels are likely to remain controlled or uncontrolled, diet liberalization, comorbidities in PKU, and associations between blood Phe levels and health outcomes.[13]
- In the clinical-expert survey, most participants agreed that increasing natural protein in diet may reduce the risk of a number of comorbidities they agreed were more prevalent in individuals with PKU.[14]
- These findings informed key parameters and assumptions in a *de-novo* cohort state-transition model comprising five health states defined by blood Phe levels, ranging from ≤120 µmol/L to >1200 µmol/L (**Figure 1**).

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ABBREVIATIONS: ADHD, attention deficit hyperactivity disorder; BMI, body mass index; CUA, cost utility analysis; CIHD, chronic ischaemic heart disease; HR: hazard ratio; HRQoL, health related quality of life; HTA, health technology assessment; Phe, phenylalanine; PKU, phenylketonuria; PRD, protein restricted diet; T2DM, type 2 diabetes mellitus.

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