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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 diets⁴ 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.

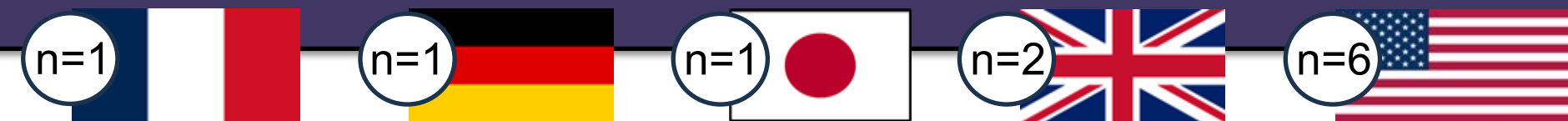
2. OBJECTIVE

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

Pilot testing:

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 $\geq 70\%$.^{9,10}

4. RESULTS:

Round 1

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

$\geq 70\%$ 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.

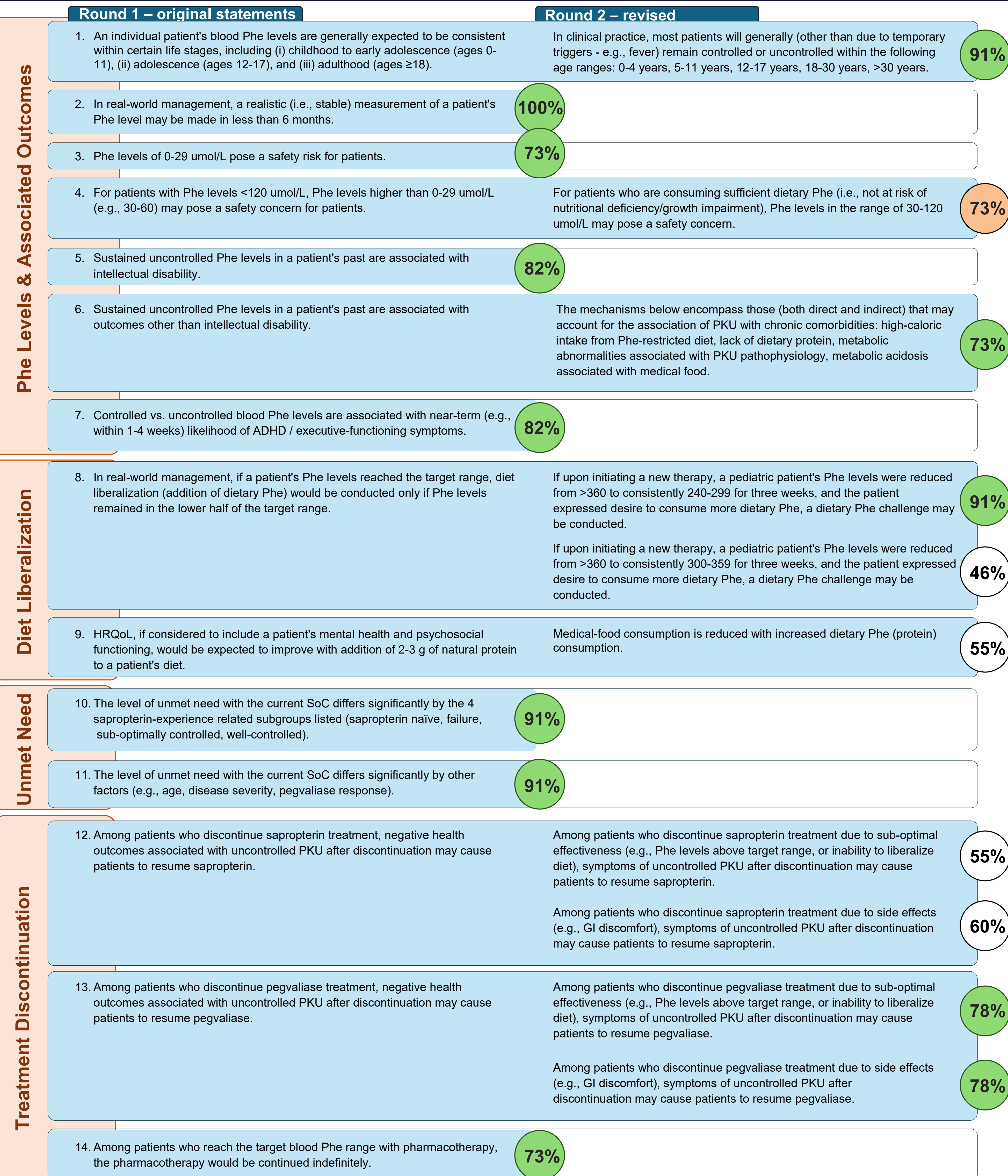
Round 2

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

There was $\geq 70\%$ 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.



Legend: ● 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.

6. References:

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