Core outcome sets for two rare inherited metabolic diseases: Results from a systematic review and multi-stakeholder consensus process

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Background & Objectives

- There is limited evidence regarding the effectiveness of therapies for rare inherited metabolic diseases in children
- Conventional randomized controlled trials (RCTs) are challenging to implement for rare disease treatments:[1]
  - Difficult to attain needed **adequate sample**
  - **Heterogeneity** of benefits across subgroups of patients
  - Often need to rely on **short-term, surrogate endpoints** instead of patient-centred outcomes
- Promising strategies to address these challenges include real-world observational studies; and registry-based RCTs, which embed RCTs within observational studies or registries[2]
- Registry-based RCTs require high-quality standardized collection of outcomes that are meaningful to patients and families, health care providers, and health systems, i.e., a core outcome set (COS)[3]
- No COSs exist for inherited metabolic diseases (IMD)

Study Objectives:

- *Overall study goal:* to **develop a COS for each of two pediatric IMD: phenylketonuria (PKU) and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency**

Phase 1: Systematic Review Methods

Literature Search
- Separate search strategies for PKU, MCAD deficiency, and long-term follow-up of newborn screening (NBS)
- Searched MEDLINE, Embase, and The Cochrane Library
- + grey literature search, citation searching, Core Outcomes Measures in Effectiveness Trials (COMET) database[4]

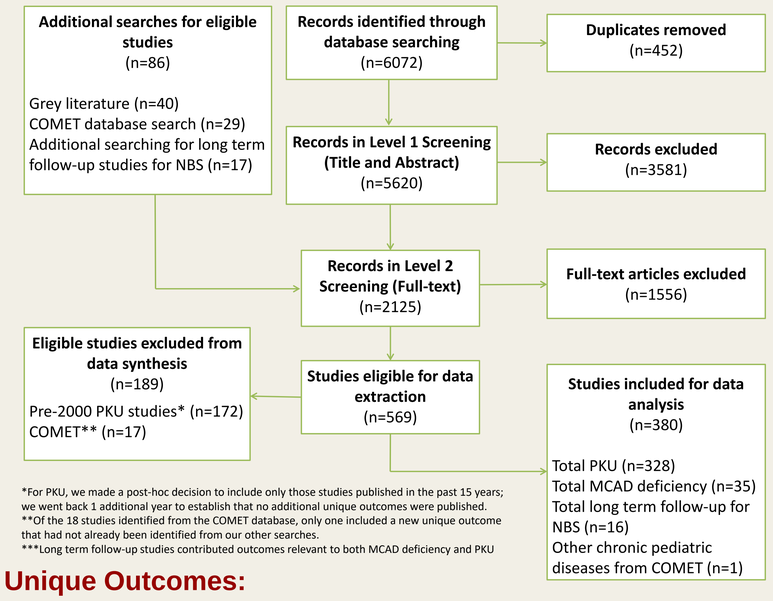
Eligibility Criteria
- *Inclusion:* Primary studies of children (≤18 years old) diagnosed with PKU or MCAD deficiency; long term follow-up for NBS; non-primary studies if recommendations made about outcomes
- *Exclusion:* Case studies and case series with <5 participants

Screening & Selection
- Two independent reviewers
- *Stage 1:* titles & abstracts (exclusion by both reviewers)
- *Stage 2:* full text articles (conflicts at stage 2 resolved by consensus or discussion with third team member)

Data Collection & Analysis
- One reviewer abstracted data; second reviewer verified
- Study outcomes given different names but reflecting the same underlying construct were combined
- Outcomes mapped to a-priori core areas[5,6]

Phase 1: Systematic Review Results

- We identified >5500 potentially relevant articles from database searches and another 86 studies from our additional searches.
- 382 studies were included in the final data synthesis



*For PKU, we made a post-hoc decision to include only those studies published in the past 15 years; we went back 1 additional year to establish that no additional unique outcomes were published.
**Of the 18 studies identified from the COMET database, only one included a new unique outcome that had not already been identified from our other searches.
***Long term follow-up studies contributed outcomes relevant to both MCAD deficiency and PKU

Unique Outcomes:

- From 345 studies relevant to PKU, we identified **97 unique outcomes**
- From 52 studies relevant to MCAD deficiency, we identified **83 unique outcomes**

Phase 2: Internet-Based Delphi Survey

Expert groups (participants)

- Parents of children with PKU (n=18)
- Parents of children with MCAD deficiency (n=19)
- Specialist metabolic physicians/health policy advisors (n=16)

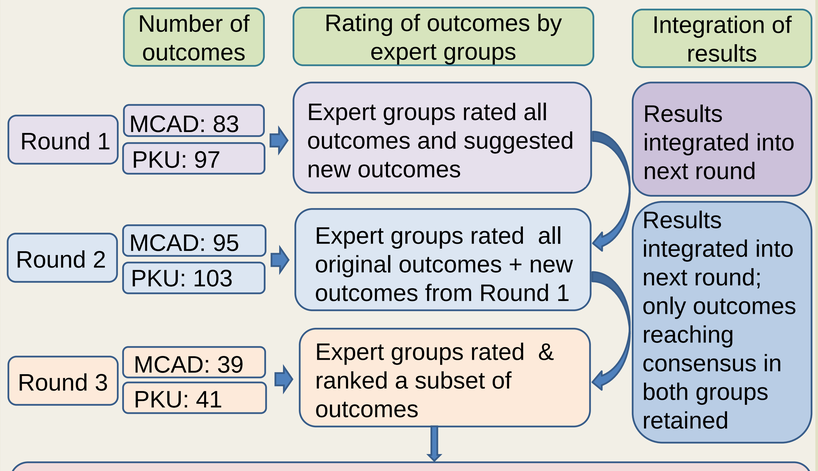
Survey design

- **Round 1:** participants rated the importance of each unique outcome on a 9-point scale

Not important			Important but not critical			Critical		
1	2	3	4	5	6	7	8	9

- **Rounds 2 & 3:** respondents revisited their ratings based on aggregate results
- Consensus: ≥70% of respondents among either expert group scoring outcome as *critical* and <15% scoring it as *not important*

Results overview



- Similar outcomes combined
- Outcomes reaching consensus in at least one group retained
- **20 PKU and 20 MCAD outcomes to discuss at consensus workshop**

Phase 2: Consensus Workshop

Methods:

- A full-day, in-person consensus workshop with 18 attendees:

Patient/family investigators and advisors n=6	Metabolic clinician investigators n=7	Other investigators (researchers and health systems experts) n=5

- The consensus approach involved three steps:
  1) Reviewing findings from round three of the Delphi survey
  2) Discussing each attendee's top 3 most important outcomes using an adapted nominal group technique, plus a brief open discussion
  3) Anonymous voting on 20 outcomes being discussed to determine those to be included in the COSs, using a 3-point scale:

1 – Outcome must be in the COS	2 – Outcome is a strong contender for COS	3 – Outcome can be left out of the COS

- A small group of study investigators met post-workshop to discuss the voting results and to finalize the proposed COSs

The Proposed Core Outcome Sets

Core Area	Outcome
MCAD Deficiency	
Death	Death
Growth and Development	Overall child development
Life Impact	Fasting
	Child quality of life
	Parental experiences with illness care and prevention
Pathophysiological Manifestations	Metabolic decompensation and its associated complications
Resource Use	Access to care
	Emergency department use
PKU	
Growth and Development	Cognition and intelligence/IQ (for children aged 4 years or older)
	Overall child development and functioning
	Executive functioning (for children aged 6 years or older)
Life Impact	Child quality of life including psychosocial and social well-being
	Phenylalanine tolerance
	Adherence to PKU treatment plan
	Child understanding and self-efficacy with management of PKU (as appropriate for age)
Pathophysiological Manifestations	Phenylalanine concentration in the blood or other tissues
Resource Use	Costs of care

Conclusions & Next Steps

- We have reached consensus on proposed COSs for MCAD deficiency and PKU which included 8 and 9 outcomes respectively
- Each of the a-priori defined core areas were represented in the COSs with the exception of "Death" for PKU
- Next steps included determining recommended outcome measurement instruments for each of the proposed core outcomes

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