Establishing core outcomes sets for phenylketonuria (PKU) and medium-chain Acyl-CoA dehydrogenase (MCAD) deficiency in children: Rapid review findings

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Background & Objectives

- Conventional randomized controlled trials (RCTs) are challenging to implement when evaluating new or existing therapies for rare diseases for several reasons,[1] including:
  - Attaining **adequate sample size** to reach planned statistical significance
  - Adequately addressing **heterogeneity** of benefits across subgroups of patients
  - Reliance on **short-term, surrogate endpoints** that have limited importance to patients/caregivers
- Several study designs & analytic methods have been developed to address these challenges
- One such method is the pragmatic registry-based RCT, which supports real-world decision-making by embedding RCTs within observational cohort studies or patient registries[2]
- An important design element in the development of registry-based RCTs and other robust evaluative studies is high-quality standardized collection of data on important outcomes, i.e., a core outcome set (COS)[3]
- There are no COS for studies evaluating care for pediatric inherited metabolic diseases

Study Objectives:

- Overall, this study aims to **develop COSs for phenylketonuria (PKU) and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency** that can be incorporated into evaluative studies
- The objective of the first study phase, presented here, is to **identify a comprehensive list of outcomes reported in past studies of PKU and MCAD deficiency** to inform the second study phase, which includes a consensus process to determine the final COSs
- The study protocol has been published[4]

Rapid Review Design & Methods

Literature search to identify relevant articles

- We developed separate search strategies for PKU, MCAD deficiency, and long-term follow-up (LTFU) initiatives for newborn screening (NBS)
- A combination of controlled vocabulary and keywords were used to search three electronic databases: MEDLINE, Embase, and the Cochrane Library (PKU & MCAD deficiency only)
- We conducted grey literature and citation searches, and we searched other pediatric COSs from the the Core Outcome Measures in Effectiveness Trials (COMET) database[5]

Eligibility criteria

- We included primary studies of children (aged 18 years or younger) diagnosed with PKU or MCAD deficiency; and studies focused on LTFU initiatives for NBS
- We included non-primary studies if recommendations were made regarding outcomes
- To be eligible, studies had to report or recommend at least one outcome
- Case studies and case series with fewer than five participants were excluded

Study screening & selection

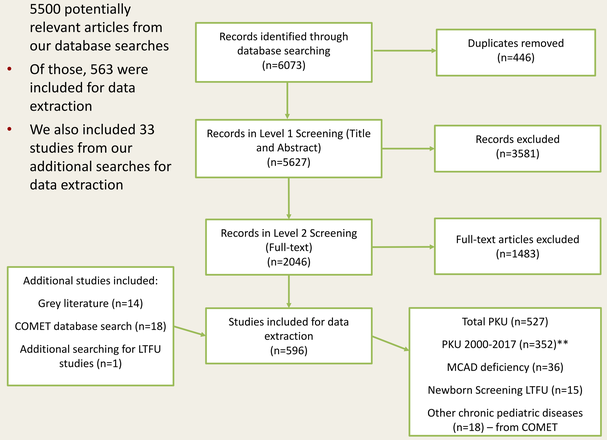
- Two reviewers independently screened retrieved citations for eligibility in two stages: titles & abstracts at stage 1 (using the 'liberal accelerated' approach) and full text articles at stage 2; conflicts at stage 2 were resolved by consensus or discussion with a third team member

Data collection & analysis

- For all included studies, we extracted: publication characteristics, study design, population descriptors, intervention and comparator details (where applicable), and outcomes (general description, information about outcome measurement instruments)
- One reviewer abstracted data from each study and a second reviewer verified the information collected
- We combined outcomes that may have been given different names by study authors but reflected the same underlying construct
- We mapped outcomes to domains within five core areas, guided by previous COMET pediatric research:[6,7] death, life impact, pathophysiological manifestations, growth and development, and resource use

Preliminary Results – PRISMA[8] diagram

- We identified more than 5500 potentially relevant articles from our database searches
- Of those, 563 were included for data extraction
- We also included 33 studies from our additional searches for data extraction



**Note: for PKU, because of the large yield of eligible studies, we made a post-hoc decision to include only those studies published in the past 15 years; we performed a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were published

Preliminary Results – MCAD deficiency outcomes

- In total, 189 outcomes were identified across 38 studies (includes outcomes from 2 NBS LTFU studies)
- From these, we identified 67 unique outcomes for MCAD deficiency
- We organized each of the unique outcomes into five core areas:

Pathophysiological Manifestations

Biomarkers of nutritional and organ-specific health	Acute Disease-Specific Manifestations	Non Disease-Specific Symptoms and Disorders
• Carnitines • Fasting tolerance biomarkers • Nutritional assessment biomarkers • MCAD enzyme activity • Inflammation biomarkers • Liver health biomarkers • Kidney health biomarkers • Muscle health biomarkers • General health biomarkers	• Metabolic decompensation • Encephalopathy • Seizures • Cardiovascular symptoms and disorders • Respiratory symptoms and disorders • Muscle symptoms and disorders • Hypoglycemia • Hyperammonemia • Hyperuricemia • Ketonuria • Metabolic acidosis • Psychogeneic blindness • Chronic sequelae of an acute event	• Clinician-reported health status • Acute infections • Bodily temperature abnormalities • Gastrointestinal symptoms and disorders • Hyperglycemia • Bronchospasm

Growth and Development

Physical Growth and Anthropometry	Cognition and Development
• Height/length • Weight • Body mass index • Failure to thrive • Head circumference	• Cognition and intelligence/IQ • Overall child development • Sensorimotor and motor functioning • Learning difficulties/disabilities • School function and placement

Life Impact

Child Behaviour, Mental Health, and Temperament	Child and Caregiver/Family Life Impact
• Attention-deficit hyperactivity disorder (ADHD) or ADHD-like symptoms • Autism spectrum disorder (ASD) or ASD-like symptoms • Behaviour problems and externalizing mental health or behaviour disorders • Internalizing behaviour • Tic disorder	• Caregiver/family economic impact • Parental experiences with illness care and prevention • Child psychosocial well-being and self-concept • Caregiver/family psychosocial well-being

Disease Management and Feeding Behaviours	
• Age at initial treatment • Infant feeding difficulties • Feeding difficulties • Feeding tube • Meal frequency • Fasting • Fat restriction • Fatty acid supplementation • Long-term use of disease-specific medications or supplements	• Medications or supplements for acute care • Sick day plan • Medication prescription • Non-disease specific treatment/medication/supplement usage • Adherence to prescribed or recommended treatment or management strategy

Death

Death
• Death

Resource Use

Service Use and Costs
• Emergency department usage • Accessibility of emergency hospital treatment • Hospitalization • Outpatient care usage • Costs of care

Preliminary Results – PKU Outcomes

- In total, 479 outcomes were identified across 352 studies
- From these, we identified 79 unique outcomes for PKU
- We organized each of the unique outcomes into five core areas:

Pathophysiological Manifestations

Monitoring of Disease-Specific Biomarkers and Surrogate Outcomes	Monitoring of Non Disease-specific Outcomes and Related Health Issues	
• Frequency of phenylalanine or tyrosine monitoring • Phenylalanine concentration in the blood • Tyrosine concentration in the blood • Phenylalanine to tyrosine ratio • Phenylalanine metabolism and kinetics • Large neutral amino acid (LNAA) concentration in the blood • BH4 malabsorption • Pharmacokinetics of sapropterin	• Bone health • Blood health • Neurological health – Biomarkers and surrogate outcomes • Neurological health – Clinical symptoms and diagnoses • Neurotransmitters • Liver health • Kidney health • Metabolic syndrome/Energy metabolism – Biomarkers and related outcomes • Protein synthesis – Biomarkers	• Vitamins and trace minerals – Biomarkers and related health outcomes • Amino acids other than Phe/Tyr – Biomarkers and surrogate outcomes • Antioxidant status, oxidative stress and inflammation – Biomarkers and surrogate outcomes • Neonatal complications • Dermatological health • Gastrointestinal health • Immune system disorders • Infections • Musculoskeletal health • Respiratory health

Growth and Development

Physical Growth and Anthropometry	Cognition and Development
• Height/length • Weight • Body mass index, overweight, obesity status • Body composition • Head circumference • Growth	• Cognition and intelligence/IQ • General child development • Sensorimotor and motor functioning • Executive functioning • Academic achievement/School performance • Learning disability

Resource Use

Health Services Use
• Health services use and costs

Death

Death
• Death

Life Impact

Child Behaviour, Mental Health, and Temperament	Child Life Impact
• Behaviour problems and externalizing mental health or behaviour disorders • Attention-deficit hyperactivity disorder (ADHD) or ADHD-like symptoms • Internalizing mental health or mood disorders and associated symptoms • Autism spectrum disorder (ASD) or ASD-like symptoms • Atypical behavioural and mental health symptoms other than those specified • Temperament/personality	• Child psychosocial well-being and self-concept • Child social impact and function • Child quality of life • Bodily pain • Sleep problems

Child and Caregiver/Family Life Impact	Caregiver/Family Life Impact
• Strategies used by parents to help children cope with PKU • Perceived control of behaviour and skills	• Caregiver/family economic impact • Caregiver/family psychosocial well-being • Caregiver/family quality of life

Dietary Management and Food Attitudes and Behaviours	
• Age at initial treatment • Infant breast and infant formula feeding • Dietary intake of phenylalanine • Dietary intake of amino acids other than phenylalanine • Dietary intake of medical foods, modified low-protein foods, and protein substitutes • Dietary intake of protein • Dietary intake of energy • Overall dietary intake relative to standards • Dietary intake of fat • Dietary intake of specific fatty acid	• Dietary intake of total cholesterol • Dietary intake of carbohydrates • Dietary intake of fibre • Glycemic index of foods consumed • Dietary intake of vitamins and minerals • Dietary intake of major food groups • Feeding behaviour • Adherence to PKU diet • Phenylalanine tolerance • Liberalization of PKU diet • Child acceptability of PKU diet • Caregiver/family acceptability of PKU diet

Next Steps & Conclusions

- To establish COS from these candidate lists of outcomes for PKU and MCAD deficiency, we will seek input from patients/caregivers, health professionals, and health policy decision-makers using a Delphi survey followed by an in-person team meeting
- To ensure that the final COS incorporate patient and family perspectives, we have partnered with patients/caregivers as study investigators (NP, MS) and via a Family Advisory Forum

Delphi consensus process and final COS development

Round 1: The list of unique outcomes will be sent to stakeholders (patients/caregivers, clinicians, health-system decision-makers) to score the importance of each one.

Round 2: Results from round 1 are summarized and sent back to each participant, together with a reminder of the participant's own score. With this information in mind, participants are asked to score each outcome again.

Further rounds: If consensus is not reached after round 2, the process of providing aggregate results and re-scoring the outcomes can be repeated.

In-person meeting: A face-to-face meeting will be held with the study team (including the Family Advisory Forum) to discuss the results of the Delphi.

Final report: A report will be produced that identifies the final list of outcomes that have been agreed upon as important, i.e., COS

- COS will ultimately support a Canadian registry toward registry-based clinical trials to generate evidence for treatments of these rare diseases

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