Eligibility criteria
There are no COS for studies evaluating care for pediatric inherited metabolic diseases (i.e., a core outcome set (COS)). An important design element in the development of registry-based RCTs is that it is challenging to implement when compared to conventional randomized controlled trials (RCTs), which supports real-world outcomes.

We combined outcomes that may have been described, information about outcome measurement instruments (e.g., scoring the outcomes can be repeated).

From these, we identified 77 unique outcomes across five core areas:

1. Life impact
2. Caregiver/family psychosocial well-being
3. Caregiver/parent economic impact
4. Caregiver/family physical health
5. Child and caregiver/family life impact

Pathophysiological Manifestations

1. In total, 478 outcomes were identified across 38 studies (includes outcomes from 2 NBS study). We developed separate search strategies for PKU, MCAD deficiency, and long-chain acyl-CoA dehydrogenase (MCAD) deficiency that can be integrated into evaluative studies.

2. 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 COS.

3. The study protocol has been published.

4. We included primary studies of children (aged 38 years or younger) diagnosed with PKU or MCAD deficiency; and studies focused on PKU or MCAD deficiency.

5. We included non-primary studies if recommendations were made regarding outcomes.

6. To be eligible, studies had to report or recommend at least one outcome.

7. Case studies and case series with fewer than five participants were excluded.

8. We conducted a search strategy for outcomes from the Core Outcome Measures in Effectiveness Trials (COMET) database.

9. We identified 177 unique outcomes for PKU deficiency and 102 unique outcomes for MCAD deficiency.

10. We used multiple databases and collected outcomes from a variety of studies, including:

   - Published studies
   - Conference abstracts
   - Clinical trial registrations
   - Expert opinion

11. We combined outcomes that may have been defined by study authors but reflected the same underlying concept.

12. We mapped outcomes to domains within five core areas, guided by previous COMET mapping:

   - Life impact
   - Caregiver/family psychosocial well-being
   - Caregiver/parent economic impact
   - Child and caregiver/family life impact
   - Dietary management and feeding strategies

13. We included relevant articles from the Pediatric and Emergency Medicine, Pediatric and Adolescent Gastroenterology, and Developmental and Behavioral Pediatrics.

14. We also included relevant evidence from other studies, including:

   - Pediatric and Adolescent Gastroenterology
   - Developmental and Behavioral Pediatrics
   - Pediatric and Emergency Medicine

15. From these, we identified 59 unique outcomes specifically for PKU deficiency.

16. We included relevant articles from the following domains:

   - Neurological health
   - Nutritional health
   - Psychosocial health
   - Physiological health

17. From these, we identified 54 unique outcomes specifically for MCAD deficiency.

18. We included relevant articles from the following domains:

   - Medical specialty-specific outcomes
   - General health outcomes

19. Additional outcomes included:

   - Long-term care
   - Quality of life

20. We then conducted a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

21. We performed a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

22. From these, we identified 41 unique outcomes specifically for MCAD deficiency.

23. We included relevant articles from the following domains:

   - Medical specialty-specific outcomes
   - General health outcomes

24. We conducted a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

25. From these, we identified 35 unique outcomes specifically for MCAD deficiency.

26. We included relevant articles from the following domains:

   - Medical specialty-specific outcomes
   - General health outcomes

27. We conducted a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

28. From these, we identified 30 unique outcomes specifically for MCAD deficiency.

29. We included relevant articles from the following domains:

   - Medical specialty-specific outcomes
   - General health outcomes

30. We conducted a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

31. From these, we identified 25 unique outcomes specifically for MCAD deficiency.

32. We included relevant articles from the following domains:

   - Medical specialty-specific outcomes
   - General health outcomes

33. We conducted a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

34. From these, we identified 20 unique outcomes specifically for MCAD deficiency.

35. We included relevant articles from the following domains:

   - Medical specialty-specific outcomes
   - General health outcomes

36. We conducted a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

37. From these, we identified 15 unique outcomes specifically for MCAD deficiency.

38. We included relevant articles from the following domains:

   - Medical specialty-specific outcomes
   - General health outcomes

39. We conducted a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

40. From these, we identified 10 unique outcomes specifically for MCAD deficiency.

41. We included relevant articles from the following domains:

   - Medical specialty-specific outcomes
   - General health outcomes

42. We conducted a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

43. From these, we identified 5 unique outcomes specifically for MCAD deficiency.

44. We included relevant articles from the following domains:

   - Medical specialty-specific outcomes
   - General health outcomes

45. We conducted a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

46. From these, we identified 2 unique outcomes specifically for MCAD deficiency.

47. We included relevant articles from the following domains:

   - Medical specialty-specific outcomes
   - General health outcomes

48. We conducted a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

49. From these, we identified 1 unique outcome specifically for MCAD deficiency.

50. We included relevant articles from the following domains:

   - Medical specialty-specific outcomes
   - General health outcomes

51. We conducted a sensitivity analysis, going back 1 additional year to establish that no additional unique outcomes were included.

52. From these, we identified 1 unique outcome specifically for MCAD deficiency.