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ORIGINAL RESEARCH

Development of a core outcome set for pediatric chronic intestinal failure

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Abstract

Background: In research on pediatric chronic intestinal failure, heterogeneity in reported definitions and outcomes exists. This leads to a risk of reporting bias and impossibility of evidence synthesis. Also, reported outcomes should be relevant to both healthcare providers and patients and their parents. Therefore, the aim of this study is to create a core outcome set (COS) to be used in studies on pediatric chronic intestinal failure.

Methods: Candidate outcomes were selected from a recent systematic review. A three-round Delphi study among key stakeholders and a consensus meeting with an expert panel were undertaken to achieve consensus on the COS.

Results: Seventy-two stakeholders (79%) completed all three rounds of the Delphi process. Ninety-eight outcomes were assessed, and five new outcomes were added

Abbreviations: COMET, Core Outcome Measures in Effectiveness Trials; COS, core outcome set; ERNICA, European Reference Network for rare Inherited and Congenital Anomalies; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; GE, gastroenterologist; HCP, healthcare professional; IF, intestinal failure; IFALD, intestinal failure–associated liver disease; OMERACT, Outcome Measures in Rheumatology Initiative; PN, parenteral nutrition.

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after the first round. Ten outcomes were included in the final COS: weaning from parenteral nutrition, growth, mortality, central line–related infection, central line longevity, sepsis not related to central line infection, central line–related thrombosis, intestinal failure–associated liver disease, (serious) adverse events, and health-related quality of life.

Conclusion: This pediatric chronic intestinal failure COS consists of 10 outcomes important for all key stakeholders. Usage of this set in future research should minimize outcome heterogeneity and enhance the value of evidence synthesis. This will lead to better management in this field of rare gastrointestinal conditions.

KEYWORDS

children, core outcome set, Delphi process, intestinal failure, parenteral nutrition

CLINICAL RELEVANCY STATEMENT

This manuscript describes the development of a core outcome set for pediatric chronic intestinal failure. This is a set of outcomes from which at least two should be reported in all studies in this field. This will lead to more outcome homogeneity in future research and increase comparability between studies.

INTRODUCTION

Pediatric chronic intestinal failure (IF) is a rare, heterogeneous disease. Chronic IF can be defined as a critical reduction of functional gut mass below the minimum necessary for adequate digestion and absorption of macronutrients and/or water and electrolytes for adequate growth and development in children. Therefore, intravenous supplementation is required to maintain health and growth.[1,2] Parenteral nutrition (PN) is the primary therapy and is needed to correct or prevent nutrition deficiencies and dehydration when adequate enteral nutrition is not possible.[3] Prevalence of home PN for children with IF varies between 9.6 and 30 per million across studies.[4–6] Complications of pediatric IF and PN are diverse, ranging from IF-associated liver disease (IFALD) and central venous catheter complications to small intestinal bacterial overgrowth.[2,7] Nowadays, in many centers, multidisciplinary teams coordinate the care for these patients, reflecting the complexity of this disease.[8] As a consequence of the formation of these teams, mortality is decreasing, with rates between 6% and 26%.[8–14]

For pediatric IF, research is scarce and the majority of the performed research is of small sample size. A recent systematic review on outcome measures in studies concerning pediatric IF reported 105 different outcome measures among 70 studies.[15] This review concluded that heterogeneity in reported definitions and outcomes exist, posing a potential risk of reporting bias, owing to selective reporting. Furthermore, variability in outcome reporting makes it impossible to synthesize and apply the results of different research studies.[15,16] In addition, reported outcomes should be relevant both to healthcare providers and to patients with IF and their parents. Therefore, the aim of this study was to create a core outcome set (COS) for pediatric chronic IF. A COS is a set of standardized outcomes agreed upon by key stakeholders, including healthcare professionals (HCPs), patients, and their parents. The intention is to report a minimum of two outcomes in each future research study of pediatric chronic IF.

Development of this COS can reduce heterogeneity and outcome reporting bias and represent different key stakeholders' input and opinion. Standardization of reporting of outcomes will enhance comparability between studies, thus making it possible to pool data through meta-analysis. This should ultimately lead to better understanding of the natural course of IF and the development of evidence-based management strategies and guidelines for children with IF.

MATERIAL AND METHODS

The COS was developed in accordance with the Outcome Measures in Rheumatology Initiative (OMERACT) Filter 2.0 and Core Outcome Measures in Effectiveness Trials (COMET) recommendations.[16,17] These are key initiatives for the development of a COS and they aim to achieve consensus on a set of most important outcomes using different methods (e.g. literature systematic review, structured surveys and group discussions) with various stakeholders.

The development of this COS consisted of three stages: inclusion of key stakeholders, a three-round online Delphi process based on data from a recent systematic review, and a consensus meeting. Figure 1 shows an overview of this process.

To ensure practicality, it was prespecified that the draft COS would consist of 10 or fewer outcomes. When >10 outcomes were eligible, inclusion of an outcome was determined based on the following: at least one highest-scored outcome of each of the five OMERACT Filter 2.0 core areas, followed by the next five highest-scored outcomes, regardless of the core area.

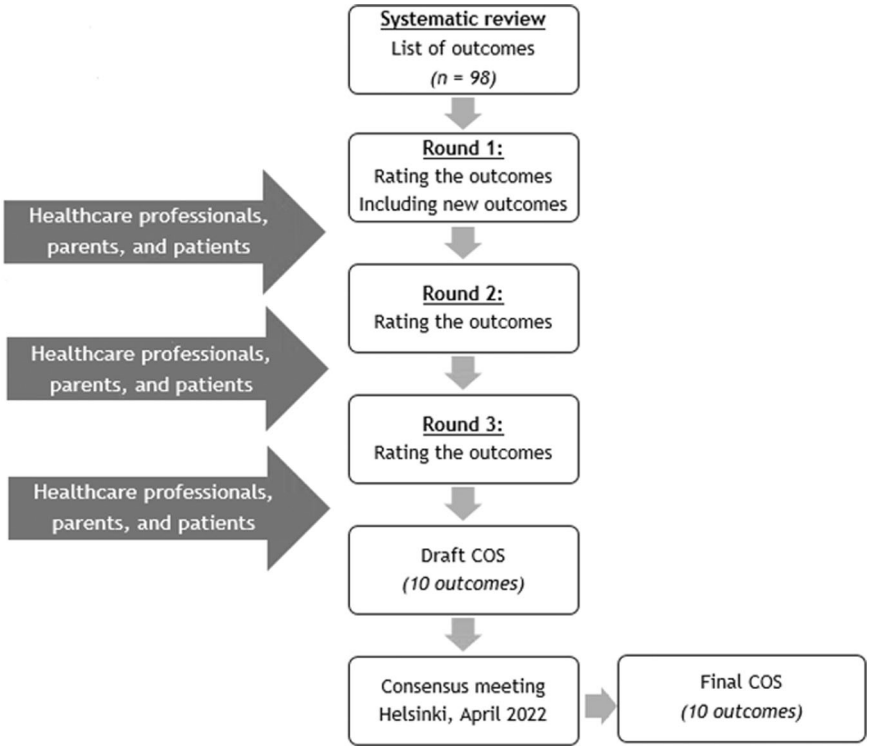

FIGURE 1 Development of a core outcome set through the Delphi process. COS, core outcome set

Highest scored was defined as the greatest percentage of participants scoring the outcome as 7–9.

This study was approved by the research ethical committee of the Amsterdam University Medical Center. Consent to participation was obtained by an electronic consent statement before the questionnaire.

Phase 1: Inclusion of key stakeholders

To ensure that experts were recruited across an adequate breadth of experience of pediatric chronic IF, experts from different categories were recruited by email and included in their respective panel (eg, pediatric gastroenterologist [GE]). It was decided a small number of HCPs specializing in adult IF would also be included because these specialists will care for the pediatric patients after transition into adulthood. For analysis, the stakeholder groups' adult GEs and adult surgeons were combined into the "adult stakeholder group." All potential HCPs were deemed experts if they were members of an IF unit in their hospital. Initially, experts known to the study team were invited. Also, members of the European Reference Network for rare Inherited and Congenital Anomalies (ERNICA) IF Working Group and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Network of Intestinal Failure and Intestinal Transplant in Europe (NITE) were included. Additionally, stakeholders were asked to nominate further experts for participation. HCPs from participating centers from France, Germany, Sweden, United Kingdom, and the Netherlands contacted patients (previously) treated for benign (nonmalignant) chronic IF (12 years or older) and parents/caregivers of these patients. A maximum of one parent per child could be included as a participant.

Participants were deemed to have withdrawn from the process if they did not complete a round of the Delphi process before the deadline.

Phase 2: The Delphi process

The Delphi process consisted of a three-round online, anonymous survey system (DelphiManager). A systematic review was performed to identify candidate outcome measures reported in research studies about pediatric chronic IF.[15] Outcome terms found through this systematic review were assigned to one of the five core areas from the OMERACT Filter 2.0.[17] This framework represents the following five core areas that should be covered by outcomes to ensure full breadth of reporting: life impact, pathophysiological manifestations, resource utilization, adverse events, and mortality. This will lead to a set of both patient-centered and intervention-specific outcomes.

The Delphi process: Round 1

Participants were presented with the list of outcomes identified through the systematic review in random order. Equivalent lay terms for each outcome were developed and piloted by parents without a medical background. Patients and parents were presented outcomes

in their native tongue. Participants were asked to rate the importance of candidate outcomes on a 9-point Likert scale. Scores 1, 2, and 3 were "not that important"; 4, 5, and 6 were "important"; and 7, 8, and 9 were "critically important." Descriptive statistics of the scores for each outcome were calculated per stakeholder group. In addition, participants were asked whether there are any outcomes they consider important but that have not been identified yet. They were able to list as many items as they deemed necessary. Two reviewers independently assessed outcomes reported by participants to determine whether they represented outcomes not already listed in round 1. New outcomes listed by at least one participant were taken forward to round 2 of the Delphi process.

The Delphi process: Round 2

Outcomes were dropped from round 2 if, in round 1, ≥50% of participants in all stakeholder groups scored them 1–3 and <50% of participants scored them 7–9. This allowed participants to focus on outcomes likely to be of greater importance.

Participants completing round 1 were invited to participate in round 2 and were presented with the following: the round 1 score they assigned to each outcome and the descriptive statistics from their panel. Participants were asked to rescore each outcome. The new added outcomes, proposed by the participants in round 1, were presented to and scored by all participants. Descriptive statistics of the scores were again calculated per stakeholder group. Bias from loss of experts between rounds was assessed by determining whether there was any statistical difference in round 1 scores for each outcome measure between experts who have completed both rounds and experts who only completed round 1 using the Mann-Whitney *U* test.

The Delphi process: Round 3

Again, outcomes were dropped from round 3 if, in round 2, ≥50% of participants in all stakeholder groups scored them 1–3 and <50% of participants scored them 7–9.

Participants completing round 2 were invited to participate in round 3 and were presented with the following: the phase 2 score they assigned to each outcome and the descriptive statistics from all panels. Participants were asked to rescore each outcome. Again, descriptive statistics of each outcome were calculated per stakeholder group. Bias from loss of experts between rounds was assessed by determining whether there was any statistical difference in round 1 scores for each outcome measure between experts who have completed all three rounds and experts who only completed round 1 using the Mann-Whitney *U* test. "Consensus in" was defined as ≥70% of participants rating the outcome with a score of 7–9 and <15% rating it as 1–3. "Consensus out" was defined as >70% of participants rating the outcome 1–3 and <15% rating it 7–9. This definition has been proposed by Williamson et al.[18]

Phase 3: Consensus meeting

During an IF Working Group meeting at the ERNICA 6th Annual Meeting 2022 in Helsinki, Finland, a face-to-face consensus meeting was held to finalize the COS with experts in chronic IF. During this meeting, patient representatives were also present. The draft COS, created through the systematic review and the three-round Delphi process, was discussed to agree on the final COS. Consensus was defined as a unanimous decision from the expert panel, reached by discussion.

RESULTS

Participants

A total of 91 participants from eight countries (France, Germany, Sweden, Finland, Italy, United Kingdom, Canada, and the Netherlands) completed the first questionnaire, followed by a participation rate of 86% (*N* = 78) and 79% (*N* = 72) in rounds 2 and 3, respectively. Nineteen participants attended the consensus meeting. The participation rate per stakeholder group is shown in Table 1.

Preliminary COS

The Delphi process: Round 1

A list of 98 outcome measures, identified through the systematic review,[15] was presented to participants. The five highest-scored outcomes in round 1 were weaning from PN (mean score, 8.2), mortality (mean score, 8.1), graft survival (mean score, 7.8), (serious), adverse events (mean score, 7.7), and growth (mean score, 7.6). Five new outcomes, which were not identified through the systematic review, were added to the list by participants: health-related quality of life, neurocognitive development, insulin sensitivity, school attendance, and employment rate.

The Delphi process: Round 2

The five highest-scored outcome measures during round 2 were weaning from PN (mean score, 8.6), mortality (mean score, 8.6), (serious) adverse events (mean score, 8.2), central line–related infection (mean score, 8.1), and growth (mean score, 8.1).

The Delphi process: Round 3

The draft COS was created after round 3. In total, 24 outcome measures were eligible. In Table 2, the draft COS is presented showing the outcomes with the mean scores and the percentage of participants scoring them between 1–3 and 7–9. In Table 3, the mean

TABLE 1 Participation rate in the Delphi process

Participants	Round 1 *N* (% of responding)	Round 2 *N* (% of responding)	Round 3 *N* (% of responding)	Consensus *N* (% of responding)
Total number	*N* = 91	*N* = 78	*N* = 72	*N* = 19
Pediatric GE	24 (26)	21 (27)	18 (25)	6 (31)
Parent	18 (20)	12 (15)	11 (15)	2 (11)
Patient	16 (18)	14 (18)	13 (18)	0
Dietitian	10 (11)	10 (13)	9 (13)	2 (11)
Researcher	6 (7)	6 (8)	6 (8)	1 (5)
Adult care	4 (4)	3 (4)	3 (4)	0
Other	13 (14)	12 (15)	12 (17)	8 (42)

Abbreviation: GE, gastroenterologist.

TABLE 2 Draft core outcome set: Round 3

Outcome	Mean score	1–3 (%)	7–9 (%)
Weaning from PN	8,6	0	100
Growth	8,1	0	95,1
Mortality	8,6	0	92,5
Central line–related infection	8,1	0	92,7
Central line longevity	7,9	0	82,5
Sepsis	7,9	0	92,5
Central line–related thrombosis	7,7	0	92,5
Liver function	7,4	0	90,3
(Serious) adverse events	8,2	0	90,2
HRQL	8,2	0	87,5

Abbreviations: HRQL, health-related quality of life; PN, parenteral nutrition.

TABLE 3 Draft core outcome set scored by panel: Round 3

Outcome	Parents' mean score	Patients' mean score	HCPs' mean score
Weaning from PN	8,6	8,8	8,5
Growth	8,5	8,4	7,8
Mortality	8,3	8,4	8,7
Central line–related infection	8,4	7,6	8,2
Central line longevity	8,2	7,9	7,7
Sepsis	7,2	6,3	8,1
Central line–related thrombosis	7,3	7,1	8,1
Liver function	6,9	6,8	7,6
(Serious) adverse events	7,5	6,9	8,6
HRQL	8,4	7,9	8,0

Abbreviations: HCP, healthcare professional; HRQL, health-related quality of life; PN, parenteral nutrition.

score of all outcome measures included in the draft COS are shown per panel (parents, patients, and HCPs).

Consensus meeting

During the consensus meeting, the draft COS with a list of 10 outcomes was presented, followed by discussion by an expert panel. The expert panel consisted of various stakeholder groups, including six pediatric GEs, six pediatric surgeons, two nutritionists, one nurse specialist IF, one clinical investigator, and two parents. After discussion, the expert panel decided to make two adjustments to the final COS. The outcome measure "sepsis" was unanimously modified to "sepsis not related to central line infection" because "central line–related infection" was already included in the draft COS and both outcomes were seen as different entities. The outcome measure "liver function" was found to be too general and was therefore modified to IFALD. Finally, 10 core outcomes were included in the final COS: weaning from PN, growth, mortality, central line–related infection, central line longevity, sepsis not related to central line infection, central line–related thrombosis, IFALD, (serious) adverse events, and health-related quality of life.

DISCUSSION

Through a systematic review, a three-round Delphi process, and a consensus meeting, a 10-item COS for pediatric chronic IF was developed by patients, parents, and the members of the ERNICA IF Working Group and ESPGHAN NITE. The final COS includes the following outcome measures: weaning from PN, growth, mortality, central line–related infection, central line longevity, sepsis not related to central line infection, central line–related thrombosis, IFALD, (serious) adverse events, and health-related quality of life.

This COS presents the outcomes that are important to measure and report in clinical trials. We suggest reporting a minimum of two described outcomes in every study of pediatric chronic IF. This should lead to more structured outcome reporting in this field without restricting investigators to this set of 10 outcome measures. Other relevant outcomes should be added as needed, and outcome selection is dependent on the type and focus of the clinical study (eg, the study population, design of the study, or the intervention assessed).

In the previously mentioned systematic review[15] on reported outcomes of studies about pediatric IF, these outcomes were reported most frequently as primary and nonprimary outcomes: central line–related infection, mortality, liver enzymes, growth, and PN weaning. It is important to note that the finalized COS is comparable to the results in this review. This implies that our finalized COS can be used in a practical setting, enhancing the applicability in future studies.

As shown in our results, no noticeable difference exists in the average scores in the draft COS between the three stakeholder groups. This top-10 list of outcome measures represents the most relevant outcome set, according to patients, parents, and HCPs. This is in contrast to previous published studies about COSs in pediatric gastrointestinal diseases, in which great heterogeneity between different stakeholder groups was reported.[19–22] In these studies, patients and parents considered outcomes related to quality of life as more important, whereas HCPs rated objective clinical outcomes higher. In our study, however, all stakeholder groups considered comparable outcomes as most important, and no great discrepancies existed. This difference may be explained by the intense and significant medical involvement these parents have in the care for their chronic ill child(ren) and a close, ongoing communication between patients, parents, and their intestinal rehabilitation program. Patients and parents have an important role in the disease management (eg, care of the central venous catheter, administering PN) and prevention of potential complications. This might explain why they perceived objective clinical outcomes as important as HCPs did.

Between 90% and 100% (mean, 91.6%) of all participants found all 10 outcome measures critically important, except for three outcomes. The average score of “liver function” was scored as “important” by patients and parents, whereas HCPs scored it as “critically important.” Despite the role and clinical involvement of parents as mentioned above, HCPs seem to prioritize some clinical outcome measures slightly higher compared with patients and parents. The outcomes “sepsis” and “serious adverse events” were scored as “important” instead of “critically important” by patients. This might be due to unfamiliarity with these terms. To prevent this, equivalent lay terms for each outcome were developed and piloted by parents without a medical background. It might be helpful to pilot these terms by a few pediatric patients in addition to their parents to test their understanding of all outcome terms. Another explanation for the lower score of these outcomes may be that children cannot fully foresee the consequences of these complications because of their age, especially when they have not experienced sepsis themselves.

One of the strengths of this study is the inclusion of patients and parents in addition to HCPs. During both the Delphi process and the consensus meeting, patient representatives were involved. Members of all stakeholder groups had an equal role in the process. Involvement of patients and their parents in the development contributes to the relevancy of this set. Patient representatives are seldom consulted during the design of studies to determine the type of outcomes, yet their involvement is of great importance. This COS is a representation of different stakeholder groups, namely those with expertise and those with personal experience of pediatric chronic IF. This will ensure that outcomes are relevant to patients and parents also and thus enhance the uptake of this outcome set in future studies concerning pediatric chronic IF when more awareness for its implementation is created by investigators. Eventually, these relevant outcomes will contribute to the importance of future research in this field.

Although the method used is a time-consuming process that requires active participation, this study shows a high participation rate of 91 participants in the first round, followed by 78 (86%) and 72 (79%) in the second and third round, respectively. To achieve accuracy, a response rate of at least 70% is needed.[23] Based on previously mentioned COS development studies in gastrointestinal diseases, response rates above 60% could be expected.[19–22] This response rate is a very important strength of our study.

Anonymously collected answers in the Delphi process may lead to bias, as it is not possible to assess differences between respondents and nonrespondents. We tried to decrease the risk of bias from loss of experts between rounds by determining whether there was any statistical difference in scores for each outcome between stakeholder groups who have completed all rounds and experts who only completed the first and/or second round.

However, the anonymity can also be considered as a major strength of the Delphi process, as no direct interaction exists between participants. This will prevent one group from feeling pressure psychologically by another more influential group. Each opinion is given equal importance in the analysis. By contrast, outcomes identified through a systematic review predominantly represent outcomes that researchers found important to measure.[24] Although the absence of qualitative research in the methodology of our study can be seen as a limitation, we tried to incorporate patients' perspective by asking to recommend additional outcomes of importance to them at the end of the first round.[25] The low number of newly added outcomes in the first round suggest that the presented list covered a wide range of outcomes relevant for all stakeholder groups.

The Delphi process has been defined as an iterative process created to combine expert opinion into the most reliable group consensus. It has been criticized as a method that forces consensus and is weakened by not allowing participants to discuss issues.[26] Therefore, the consensus meeting provided participants the opportunity to elaborate on their views. However, participation was limited

to members of ERNICA and two patient representatives. As the results of a Delphi process are highly dependent on the composition of the panel, this might be a limitation of our study.[27]

This is the first COS developed to be used in studies on pediatric chronic IF. It is developed through the Delphi methodology, which makes it possible to represent the pediatric chronic IF community as a whole. We initially focused on what to measure. Subsequently, it is important to determine also "how" to measure these outcomes. Therefore, a literature review will be conducted as next step to identify existing definitions and methods of measuring the outcomes included in the COS.

CONCLUSION

This study presents the first 10-item COS for pediatric chronic IF. This is a standardized collection from which at least two appropriate outcomes should be measured and reported in all studies in this field. Implementation of this COS in future studies will lead to relevant outcomes for all stakeholder groups, reduce reporting bias, and increase the comparability of studies. This will improve the quality of performed studies in this field and provide better recommendations on the management of disease.

AUTHOR CONTRIBUTIONS

Aysenur Demirok contributed to formal analysis, investigation, writing (original draft), and visualization. Sjoerd C. J. Nagelkerke contributed to conceptualization, methodology, formal analysis, investigation, data curation, and writing (review and editing). Marc A. Benninga contributed to investigation, writing (review and editing), and supervision. Jutta Köglmeier, Annika Mutanen, Henrik Arnell, Judith Felcht, Dominique Guimber, Christina Wahlstedt, Yaron Avitzur, and Cécile Lambe contributed to investigation. Merit M. Tabbers contributed to conceptualization, methodology, formal analysis, investigation, writing (review and editing), and supervision.

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CONFLICT OF INTEREST

None declared.

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