

A Core Outcome Set for Pediatric Critical Care

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Objectives: More children are surviving critical illness but are at risk of residual or new health conditions. An evidence-informed and stakeholder-recommended core outcome set is lacking for pedi-

atric critical care outcomes. Our objective was to create a multinational, multistakeholder-recommended pediatric critical care core outcome set for inclusion in clinical and research programs.

Design: A two-round modified Delphi electronic survey was conducted with 333 invited research, clinical, and family/advocate stakeholders. Stakeholders completing the first round were invited to participate in the second. Outcomes scoring greater than 69% “critical” and less than 15% “not important” advanced to round 2 with write-in outcomes considered. The Steering Committee held a virtual consensus conference to determine the final components.

Setting: Multinational survey.

Patients: Stakeholder participants from six continents representing clinicians, researchers, and family/advocates.

Measurements and Main Results: Overall response rates were 75% and 82% for each round. Participants voted on seven Global Domains and 45 Specific Outcomes in round 1, and six Global Domains and 30 Specific Outcomes in round 2. Using overall (three stakeholder groups combined) results, consensus was defined as outcomes scoring greater than 90% “critical” and less than 15% “not important” and were included in the final PICU core outcome set: four Global Domains (Cognitive, Emotional, Physical, and Overall Health) and four Specific Outcomes (Child Health-Related Quality of Life, Pain, Survival, and Communication). Families ($n = 21$) suggested additional critically important outcomes that did not meet consensus, which were included in the PICU core outcome set—extended.

Conclusions: The PICU core outcome set and PICU core outcome set—extended are multistakeholder-recommended resources for clinical and research programs that seek to improve outcomes for children with critical illness and their families. (*Crit Care Med* 2020; XX:00–00)

Key Words: child; critical care; family; outcome assessment; postintensive care syndrome

Approximately 480,000 children and young adults less than 20 years old are admitted to PICUs annually at a cost of \$8 billion in the United States alone (1, 2). Mortality has decreased to 2–4% in high-resource settings (3). However, child and family survivorship and recovery are frequently affected by ongoing and/or new impairments in physical, emotional, cognitive, and/or social health functioning, termed “postintensive care syndrome-pediatrics” (4).

The vast majority of pediatric critical care research studies employ short-term (in-hospital) physiologic or mortality outcomes, with few studies assessing outcomes post hospital discharge (5–9). Researchers report that key monetary and resource barriers to carrying out high-quality trials include assessment of outcomes post hospital discharge (10). Furthermore, heterogeneity in outcome measures and time points selected in studies prohibit systematic review and meta-analysis (11).

The status quo for PICU outcomes is shifting toward inclusion of outcomes prioritized by providers, patients, and

families (12–14) rather than solely by investigators. Core outcome sets (COSs), defined as “a patient outcome, health-related condition, or aspects of health that relevant stakeholders agree are essential to assess in all clinical research studies evaluating outcomes”, have been developed and implemented successfully for other critically ill populations, but not for pediatric critical care (15, 16). Additionally, use of a COS allows for increased ability to compare outcomes across studies and populations and decreases the potential for reporting bias (17).

Our objective was to develop a multistakeholder-informed PICU-COS. The product of this effort is a minimum set of outcome domains that should be incorporated into clinical and research programs to evaluate outcomes of critically ill children and families.

MATERIALS AND METHODS

Study Design

We incorporated recommendations for methodology and quality standards for design and reporting for COS (18–20). This article reports on the Delphi consensus process yielding the final PICU COS. Additional description of the study protocol (21) and preliminary aims were published (6, 22) (L. Olson, unpublished observation, 2020). This project was approved by the University of Utah Institutional Review Board.

Modified, International Delphi Consensus—Process Overview

Delphi Content. Investigators created a list of unique Global Domains and Specific Outcomes from a scoping review, qualitative study, and other relevant sources (13, 14, 16, 23). Domains and Outcomes were paired with lay definitions that were reviewed by the Collaborative Pediatric Critical Care Research Network (CPCCRN)’s Family Network Collaborative, composed of one to two family volunteers from each of the seven centers. The Steering Committee approved the Domains, Outcomes, and lay definitions. The CPCCRN’s Data Coordinating Center prepared the Delphi software.

Stakeholders and Steering Committee Members. The Steering Committee was recruited by the primary investigators. Candidates were invited with consideration for expertise in PICU Outcomes and diversity in background, region, and gender. All were fluent in English.

The Steering Committee invited 333 participants from three stakeholder groups—Research, Clinical, and Family—via an introductory e-mail. After consenting, stakeholders were asked to respond based on their own perspective, except for those who represented an organization. Members of the Steering Committee were included as stakeholders as they represented leaders in pediatric critical care outcomes and families of children with critical illness.

Modified Delphi Consensus Methods. We planned for a minimum of two Delphi rounds to reach consensus. Panel members scored components using the Grading of Recommendations Assessment, Development, and Evaluation Scale,

which consists of a nine-point scale: “not important for inclusion” (scores 1–3), “important but not critical for inclusion” (scores 4–6), “critical for inclusion” (scores 7–9), and “unable to score” (score 10) (24). Global Domains and their related Specific Outcomes were randomized into four different orders and randomly assigned to panel members each round. Stakeholders were given approximately 3 weeks to complete each round. Nonrespondents received a weekly personalized e-mail, telephone call, or text reminder. Stakeholder response rates were calculated as the number of respondents who completed each round as a proportion of those for whom an e-mail invitation was sent. Those who participated in round 1 were invited for round 2.

In round 1, we recorded demographic information and assigned each consented participant a unique identifier. Respondents could propose novel outcomes. A priori criteria for an outcome domain from round 1 to be included in round 2 required greater than 70% of responses rating greater than or equal to 7 and less than 15% of response rating less than 3. The Steering Committee used consensus to confirm the outcomes panel for round 2. The Steering Committee reviewed new outcome suggestions from round 1 to ensure they represented a new contribution for inclusion in round 2.

During round 2 voting, respondents were provided aggregate responses from the first round for all stakeholders and by stakeholder group, their own response from round 1, and new outcomes from round 1. The Steering Committee used consensus to confirm the final COS components taking into account number of domains and importance based on scores by stakeholder group, ultimately as those in round 2 with greater than 90% of responses rating greater than or equal to 7 and less than 15% of response rating less than 3.

Analysis and Reporting. Each outcome’s score was analyzed based on the total number of respondents who answered the question. We report measures of central tendency, score distribution, and score changes by round of PICU COS Global Domains and Specific Outcomes as well as those considered for inclusion.

RESULTS

Steering Committee and Stakeholders

The Steering Committee consisted of 23 members, including at least two representatives from each of the six continents and a heterogeneous group of clinical and research experts as well as a member from the family stakeholder group (**Supplementary Table 1**, Supplemental Digital Content 1, <http://links.lww.com/CCM/F904>). The Steering Committee recommended diverse stakeholder group members ($n = 333$ total): Research ($n = 59$), Clinical ($n = 226$), and Family ($n = 48$) (**Supplementary Table 2**, Supplemental Digital Content 2, <http://links.lww.com/CCM/F905>). **Table 1** describes stakeholder characteristics for those who responded to both rounds. Notably, there were more female respondents for each stakeholder group. Most family respondents were located in

North America (81.0%). All stakeholders reported at least some postsecondary education.

Delphi Round 1

The response rate for round 1 was 251 of 333 (75.0%) overall, and 180 of 226 (80.0%) for clinicians, 38 of 59 (63.3%) for researchers, and 33 of 48 (68.8%) for family stakeholders. The round 1 survey included seven Global Domains and 45 Specific Outcomes (**Fig. 1**). No outcomes met criteria for “not important for inclusion” among any stakeholder group (**Supplementary Table 3**, Supplemental Digital Content 3, <http://links.lww.com/CCM/F906>). There was good general agreement in Global Domain scores among the groups (**Supplementary Table 4**, Supplemental Digital Content 4, <http://links.lww.com/CCM/F907>). Family stakeholder group scores were generally higher than other groups for Specific Outcomes, especially for domains related to family function. Six Global Domains (all except Health Care Utilization) and 22 Specific Outcomes met the a priori cutoff of 70% of responses rating greater than or equal to 7 and less than 15% of response rating less than 3 for inclusion in round 2. Within Global Domains, four of six Specific Outcomes from cognitive function, seven of 10 overall health, four of five physical function, two of five emotional health, three of nine family function, two of six healthcare utilization, and no social function met this threshold.

The Steering Committee elected to include in round 2 an additional four Specific Outcomes that had an overall score from round 1 approaching the inclusion threshold (69–69.9%) and were strongly regarded as “critical” by the Family stakeholder group (Sleep, Parent/ Legal Guardian Quality of Life, Child Participation, Hospital/ICU Readmission).

Participants submitted 61 write-ins from round 1, resulting in five new outcomes voted on during round 2. These included the division of Parent/Legal Guardian Overall Health into four Specific Outcomes (Emotional, Physical, Social, and Overall Function) as well as the addition of a new outcome (New Medical Conditions or Diseases). The remaining write-in responses were either outcome instruments or not new, unique outcomes and were not included. Definitions for some outcomes were modified to clarify criteria (**Supplementary Table 5**, Supplemental Digital Content 5, <http://links.lww.com/CCM/F908>).

Delphi Round 2

The round 2 survey had a response rate of 206 of 251 (82.1%): 150 of 180 (83.3%) for clinicians, 35 of 38 (92.1%) for researchers, and 21 of 33 (63.6%) for family/advocacy stakeholder groups. The round 2 survey included six Global Domains and 30 Specific Outcomes. No outcomes met criteria for “not important for inclusion” among any stakeholder group (**Supplementary Table 6**, Supplemental Digital Content 6, <http://links.lww.com/CCM/F909>). Some participants made relatively minor changes to their scores between rounds (**Fig. 2, A and B**). The Steering Committee approved four Global Domains (Overall, Cognitive, Physical, and Emotional Function) in addition to four Specific Outcomes

TABLE 1. Demographics of Stakeholders Who Responded to Both PICU Core Outcome Set Delphi Rounds

Variables	Stakeholder			Overall (n = 206)
	Clinician (n = 150)	Family (n = 21)	Research (n = 35)	
Age (yr), n (%)				
20–44	67 (44.7)	12 (57.1)	13 (37.1)	92 (44.7)
45–64	72 (48.0)	7 (33.3)	16 (45.7)	95 (46.1)
65+	8 (5.3)	1 (4.8)	4 (11.4)	13 (6.3)
Not reported	3 (2.0)	1 (4.8)	2 (5.7)	6 (2.9)
Gender				
Female	91 (60.7)	15 (71.4)	20 (57.1)	126 (61.2)
Not reported	1 (0.7)	1 (4.8)	1 (2.9)	3 (1.5)
Region, n (%)				
Africa	14 (9.3)	2 (9.5)	4 (11.4)	20 (9.7)
Asia	15 (10.0)	0 (0.0)	3 (8.6)	18 (8.7)
Australia and New Zealand	12 (8.0)	0 (0.0)	4 (11.4)	16 (7.8)
Europe	21 (14.0)	1 (4.8)	6 (17.1)	28 (13.6)
North America	67 (44.7)	17 (81.0)	16 (45.7)	100 (48.5)
South America	17 (11.3)	0 (0.0)	2 (5.7)	19 (9.2)
Not reported	4 (2.7)	1 (4.8)	0 (0.0)	5 (2.4)
Education, n (%)				
Some tertiary (college or vocational) education/training	1 (0.7)	5 (23.8)	0 (0.0)	6 (2.9)
4-yr tertiary (college) degree/ bachelor's degree or vocational license/certificate	9 (6.0)	8 (38.1)	4 (11.4)	21 (10.2)
Some postgraduate or professional schooling	6 (4.0)	2 (9.5)	0 (0.0)	8 (3.9)
Postgraduate or professional degree, including master's, doctorate, medical or law degree	134 (89.3)	6 (28.6)	31 (88.6)	171 (83.0)
Years of experience as clinician, median (interquartile range)	17.0 (9.0–25.0)	Not applicable	19.0 (9.0–30.0)	17.5 (9.0–25.0)

(Child Quality of Life, Survival, Pain, and Communication) that are ultimately included in the final COS (Table 2). Four of seven Family Function Specific Outcomes met a priori criteria for inclusion, but none met the adjusted criteria (Supplementary Table 7, Supplemental Digital Content 7, <http://links.lww.com/CCM/F910>; Supplementary Fig. 1a, Supplemental Digital Content 8, <http://links.lww.com/CCM/F911>; and Supplementary Fig. 1b, Supplemental Digital Content 9, <http://links.lww.com/CCM/F912> [legend: results presented as median (interquartile range) with mean identified by open diamonds and outliers identified by open circles]). Further, hospital and ICU readmission were among the lowest scoring outcomes in round 2. The lowest scoring Specific Outcomes

were some of the newly added family outcomes which had widely disparate scoring among Family, Clinician, and Research stakeholders.

Scoring disparities among stakeholder groups were discussed by the Steering Committee via webinar. Ultimately, to recognize Family Stakeholder priorities, the Steering Committee recommended creation of a PICU COS—Extended tool (Table 2 and Supplementary Fig. 1a, Supplemental Digital Content 8, <http://links.lww.com/CCM/F911>; and Supplementary Fig. 1b, Supplemental Digital Content 9, <http://links.lww.com/CCM/F912> [legend: results presented as median (interquartile range) with mean identified by open diamonds and outliers identified by open circles]). The PICU COS—extended includes 14 Specific

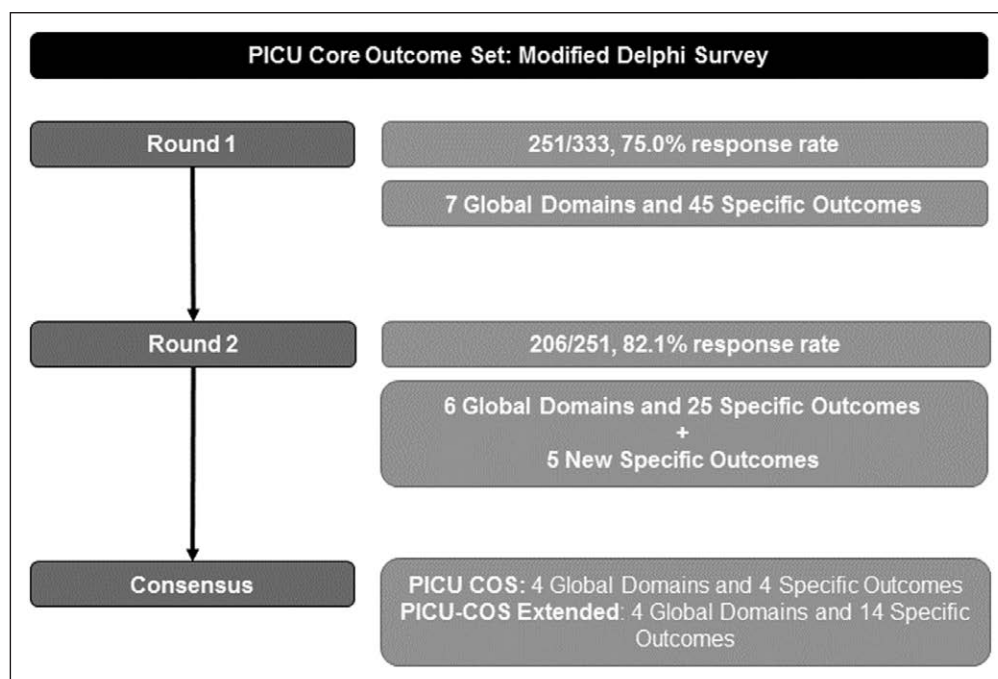


Figure 1. PICU core outcome set (COS): modified Delphi survey flow diagram.

Outcomes that met the “critical for inclusion” threshold by greater than 90% family stakeholders from the Global Domains Overall Health and Family, Emotional, and Physical Function.

DISCUSSION

We developed a multinational, multistakeholder, and evidence informed COS for clinical and research use in pediatric critical illness. Two rounds of a modified Delphi survey led to consensus. A supplemental COS—extended was also created by the Steering Committee to recognize outcomes important to family members that did not meet consensus.

No guidelines exist for the follow-up of pediatric critical care patients as they do for neonates and infants with congenital heart disease (3, 12, 25) or adults surviving critical illness (16). Furthermore, pediatric critical care research programs infrequently include postdischarge outcomes (5, 7, 10). Finally, the status quo for outcome assessment for clinical care and for research has not yet evolved to include input from stakeholders such as patients and families (26, 27).

Development of a multistakeholder-informed COS to guide clinicians and researchers in choosing posthospital discharge outcomes in addition to other outcomes vital to clinical and research aims will increase program value and facilitate evidence robustness (15, 28). We followed international guidelines for the development of COS including a mixed-methods approach to the generation of outcomes and a multinational and multistakeholder Steering Committee and Delphi respondent panel (6, 16, 20, 22).

The final PICU COS features the Global Outcome Domains of Cognitive, Emotional, and Physical Function and Overall Health. In addition, Specific Outcomes under

Cognitive Function (Child Communication) and Overall Health (Child Survival, Health-Related Quality of Life, and Pain) were also included. All three stakeholder groups scored these outcomes as critically important, with some differences in most highly valued outcomes by group, including Global Emotional Function and Communication by Families, and Survival by Researchers and Families. Lasting emotional health effects in children and families affected by pediatric critical illness can be substantial, requiring monitoring and treatment (29). Survival and pain are frequently assessed within the hospital epoch but not post-hospital discharge despite

reports of late pediatric deaths and ongoing pain symptoms reports in adults (9, 30, 31). Health-related quality of life, a subjective outcome incorporating a proxy/patient’s perception of the interplay of multiple outcome domains, was the highest rated Specific Outcome and is one of the more commonly reported postdischarge outcomes in pediatric critical illness (8, 32). Cognitive function postdischarge has been overwhelmingly assessed using measures of intelligence, memory, attention, and/or executive function; reports on child communication function are lacking (33).

Patient and family stakeholders, despite placing generally greater importance on outcomes compared with the other two stakeholder groups, clearly show value preferences for certain outcomes compared with clinicians and researchers. Family functioning is impacted by pediatric critical illness and can also influence the trajectory of recovery and long-term functional outcomes (34, 35). Further, the scope and depth of posthospital discharge problems with sleep and physical function and posttraumatic stress in both children and parents may go unrecognized by many stakeholders outside of the Family group. Hence, we recognized the need for the extended outcome set to promote the outcomes valued by families. Additional goals for inclusion of these additional outcomes are to stimulate and support awareness, education, and research across the inpatient-outpatient spectrum of stakeholders. Post-PICU follow-up clinics are beginning to service this need, but more systematic investment is needed (36, 37).

Implementation of a COS would be facilitated by recommendations for specific instruments for each outcome in a core outcome measurement set (17, 38). Thus, the next task for our Steering Committee is to recommend feasible (e.g.,

low cost, widely available, minimal administration time), reliable, age-appropriate and validated measurement instruments along with recommendations for timing of assessments post-hospital discharge to evaluate outcomes. Some outcomes in the COS may not have validated instruments available that meet these criteria, and there may be overlap in some of the content of outcomes in the COS. These recommendations will require frequent reassessment as new information and outcome measures become available.

Finally, the last aim of the PICU COS program is to strategize for broad dissemination and implementation of the PICU COS. In addition to creation of a Steering Committee and

Delphi stakeholders with diverse membership, we registered this program on the Core Outcome Measures in Effectiveness Trials' Initiative website (<http://www.comet-initiative.org/Studies/Details/1131>). Further, we will publish the PICU COS and PICU COS—extended on the CPCCRN website (<https://www.cpccrn.org/network-projects/>) and Pediatric Acute Lung Injury and Sepsis Investigators POST-PICU Investigator subgroup website (<https://www.palisi.org/subgroups>, in development). We plan to submit abstracts and manuscripts for each program aim and secondary analyses to disseminate academically. We will provide approved fact sheets and infographics to all stakeholders for efficient dissemination

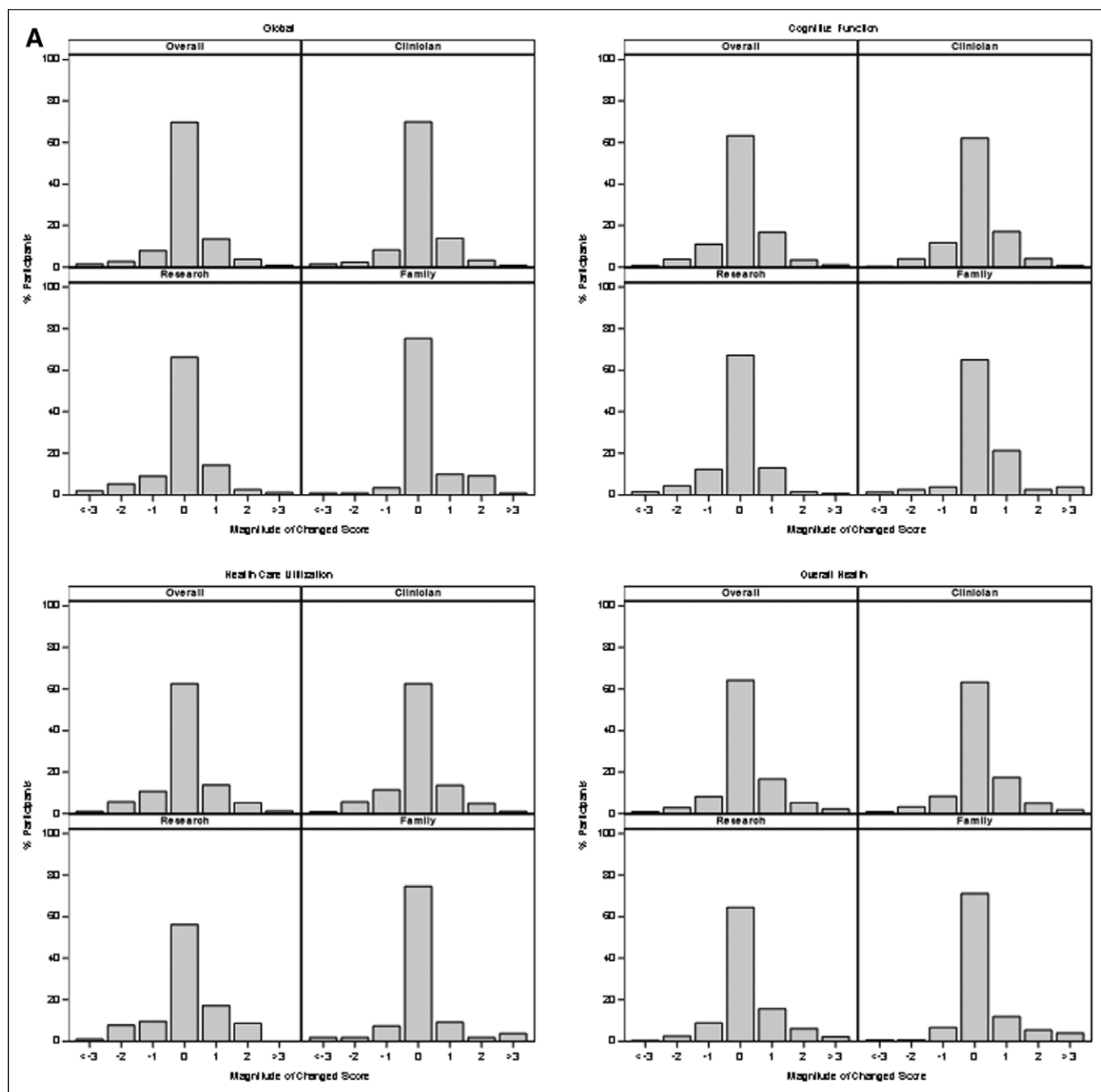


Figure 2. Differences in scores from round 1 to round 2 by PICU core outcome set stakeholder group.

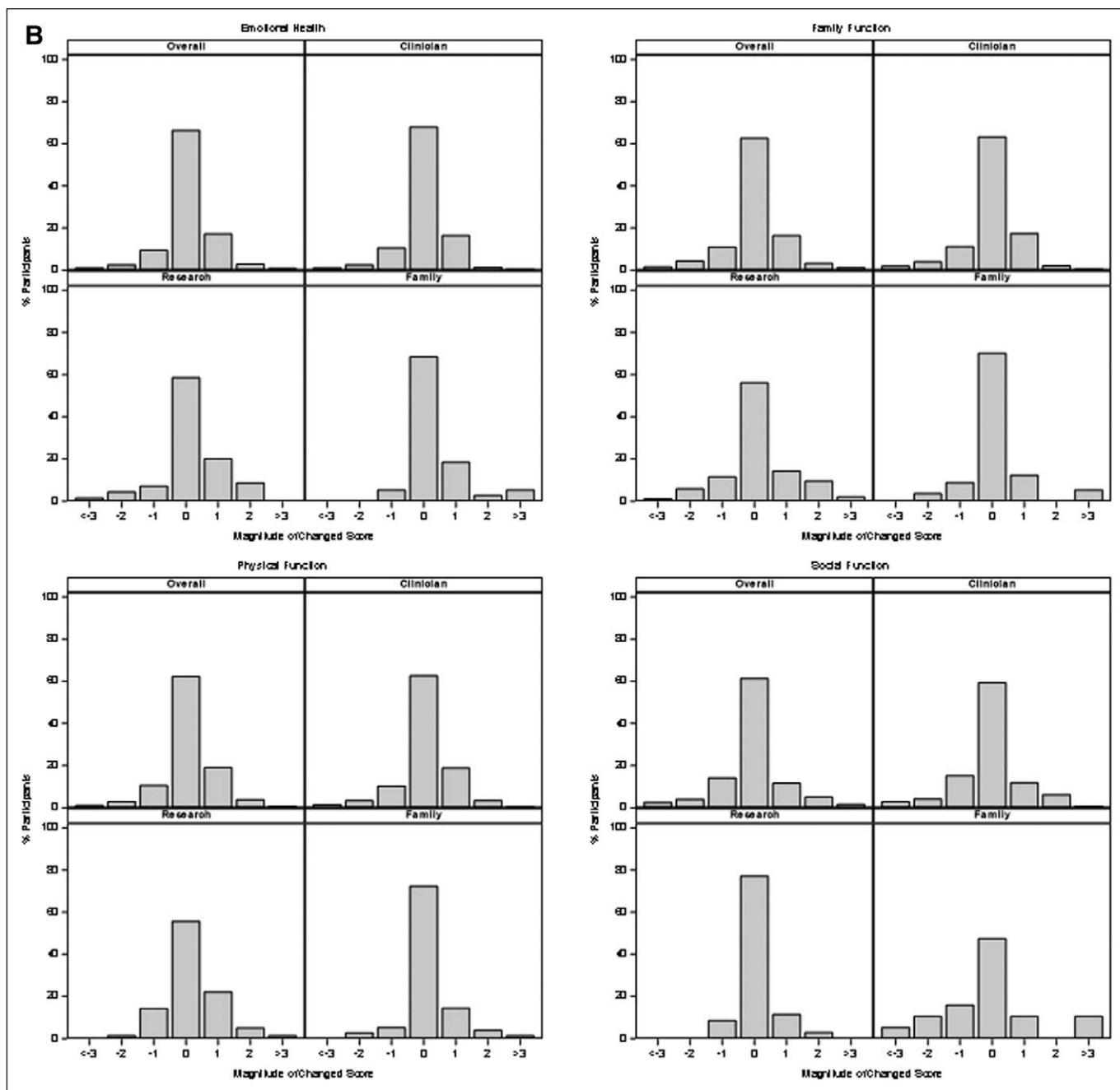


Figure 2. (Continued)

to patient advocates and academic groups. We will develop an efficient process to monitor future use of the PICU COS in research proposals, grants, quality-improvement initiatives, and publications. We will also lead a social media campaign to disseminate the COS after publication.

Although we worked to recruit an equitable number of family stakeholders, this group had the smallest representation in the Delphi. Stakeholders had to be fluent to participate in the Delphi. Thus, we may have missed input from families and other stakeholders with importantly different backgrounds and experiences. Similarly, the number and breadth of geographical distribution of representatives of research funding

agencies, payors, and hospital administrators was relatively small; overall, stakeholders from North America were overrepresented. The PICU COS was created to serve all children with critical illness. However, we recognize that children admitted to PICUs have a diverse range of ages; ethnicities; hospital admission condition, severity, and comorbidities; social determinants of health; family structures; geographical locations; quality of healthcare resources; and access to care; each of which may require an additional personalized approach and evaluation of utility to outcomes selection.

We encourage re-evaluation of the PICU COS content every 5–10 years to improve upon methodology and evolution of

TABLE 2. PICU Core Outcome Set and PICU Core Outcome Set–Extended

PICU COS			
Cognitive Function	Emotional Function	Overall Health	Physical Function
Child communication		Child survival Child health–related quality of life Child pain	
PICU COS–Extended			
Family Function	Overall Health	Emotional Function	Physical Function
Family quality of life	New medical conditions or diseases	Mood and feelings	Organ function
Family relationships	Overall development	Posttraumatic stress disorder: symptoms and growth	Physical mobility
Parent/guardian emotional function	Sleep		Sensory functions
Parent/guardian overall health	Trajectory of recovery		Medical frailty

COS = core outcome set.

best practices for postdischarge outcomes in this rapidly developing field. Finally, we recommend considering the inclusion of patients and families in other aspects of the clinical/research process in addition to outcomes choices.

CONCLUSIONS

The PICU COS and PICU COS–extended are multistakeholder-approved resources for clinical and research programs that seek to more systematically study and improve outcomes for children with critical illness and their families.

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