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Proposed Core Outcomes After Neonatal Sepsis
A Consensus Statement

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Abstract

IMPORTANCE Sepsis is one of the leading causes of neonatal mortality. There is heterogeneity in the outcomes measured and reported in studies of neonatal sepsis. To address this challenge, a core outcome set (COS) for research on neonatal sepsis was needed.

OBJECTIVE The Neonatal Sepsis Core Outcome Set (NESCOS) project aims to develop a COS for research evaluating the effectiveness of neonatal sepsis treatments.

EVIDENCE REVIEW For this consensus statement, the research team obtained ethics approval and used a 4-stage process: (1) a systematic review of qualitative studies, (2) a real-time Delphi (RTD) survey to identify important outcomes for consensus meetings, (3) consensus meetings to finalize the COS, and (4) dissemination of the findings. The study was conducted from May 2, 2022, to October 27, 2023. The steering group and project participants consisted of health care workers, researchers, academics, parents, and parent representatives from low-, middle-, and high-income countries. An RTD survey and consensus meetings were conducted, with measures including a 9-point Likert scale rating (where 1 indicated not at all important and 9 indicated critically important) for outcome importance and a minimum 80% agreement threshold among stakeholders for final COS inclusion. The systematic review identified 19 outcomes, which were combined with outcomes from previous systematic reviews of clinical trials.

FINDINGS The RTD survey included 306 participants, leading to the identification of 55 outcomes for further discussion in consensus meetings. The finalized COS comprises 9 outcomes: all-cause mortality, need for mechanical ventilation, brain injury on imaging, neurologic status at discharge, escalation of antimicrobial therapy, central nervous system infections, multiorgan dysfunction, neurodevelopmental impairment, and quality of life of parents.

CONCLUSIONS AND RELEVANCE This consensus-based COS for research on neonatal sepsis treatments will help standardize the outcomes measured and reported, enhancing the comparability of research findings. Future efforts should focus on establishing standardized and reliable methods for measuring these outcomes.

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Key Points

Question What standardized set of outcomes should be measured and reported in all clinical trials and research studies on neonatal sepsis treatments?

Findings A core outcome set (COS) for neonatal sepsis treatments was created with the involvement of diverse stakeholders. The COS includes 9 key outcomes: all-cause mortality, need for mechanical ventilation, brain injury on imaging, neurologic status at discharge, escalation of antimicrobial therapy, central nervous system infections, multiorgan dysfunction, neurodevelopmental impairment, and quality of life of parents.

Meaning This COS will help to standardize what sepsis outcomes are measured and reported and therefore improve the potential for synthesis across research in this field.

+ Supplemental content

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Introduction

Neonatal sepsis is a leading cause of newborn mortality, affecting approximately 3 million infants annually, with a global mortality rate of 17%.[1-3] Preterm and low-birth-weight neonates are particularly vulnerable to sepsis. The incidence of neonatal sepsis is higher in low- and middle-income countries (LMICs) than in high-income countries (HICs).[3]

Sepsis in neonates can present with nonspecific signs, such as temperature instability, respiratory issues, irritability, or feeding problems, progressing to severe complications, such as multiorgan failure and septic shock.[4] In addition, neonatal sepsis is associated with increased risks of neurodevelopmental impairment within the first year and beyond, including cerebral palsy, cognitive and psychomotor delays, and vision and hearing impairments.[5]

The outcomes measured and reported in neonatal sepsis studies are significantly heterogeneous.[6] This heterogeneity presents substantial challenges in the meta-analysis of studies, thereby complicating the process of drawing definitive conclusions.[2] Furthermore, the complex nature of neonatal sepsis, with its varied presentations across different health care settings and patient populations, adds to this challenge. Neonatal sepsis presents significant heterogeneity in terms of pathogenesis, infective sources, and clinical manifestations. High-income countries often encounter hospital-acquired infections, while community-acquired infections dominate in LMICs.[7] In addition, the predominant pathogens, available diagnostic tools, and treatment resources differ substantially between these settings.[8] Implementing a core outcome set (COS) could mitigate heterogeneity in the sepsis outcomes measured and reported, thereby enhancing evidence synthesis by reducing outcome-reporting bias[9] and ensuring that all trials contribute meaningful and uniform information. A COS identifies and prioritizes outcomes that should be measured and reported for all trials that are related to a particular condition.[10] The importance of these core outcomes lies in their ability to standardize research approaches, facilitate more robust meta-analyses, and enhance the relevance of research findings to various stakeholders. Although core outcomes should be consistently collected, researchers may include other outcomes outside the COS in their studies. This flexibility is essential for capturing a disease's full effect, particularly in sepsis research, where condition-specific outcomes may vary. The use of a COS enables clearer comparison and integration of data across studies, leading to more efficient use of research resources and reduced waste.[11] When implemented effectively, a COS increases the likelihood of measuring and reporting outcomes that are relevant and important for all stakeholders. In COS development, the initial focus is on identifying what to measure, followed by determining how to measure to enhance future adoption.[12] With our project NESCOS (Neonatal Sepsis Core Outcome Set), we aimed to develop a COS for research evaluating the effectiveness of neonatal sepsis treatments.

Methods

Study Overview

This study, conducted from May 2, 2022, to October 27, 2023, received ethics approval from the University of Galway Research Ethics Committee and was registered on the Core Outcome Measures in Effectiveness Trials (COMET) database.[13] The study protocol was detailed previously.[14] Participants were provided with project information, and written consent was obtained through standardized forms. The COS development followed the COS-STAD (Core Outcome Set–Standards for Development) recommendations[15] and is reported according to COS-STAR (Core Outcome Set–Standards for Reporting) guidelines.[16]

Project Design

The COS development comprised 4 stages, as shown in the eFigure in the Supplement. Stage 1 is the qualitative systematic review. This stage aimed to identify key outcomes of neonatal sepsis based on input from parents, health care providers, policymakers, and researchers for inclusion in the Delphi survey. Stage 2 is the Delphi survey. A real-time Delphi (RTD) survey was conducted to select outcomes for further discussion in online consensus meetings. Stage 3 consists of consensus meetings. We held 2 online meetings with key stakeholders to agree on the final COS. Stage 4 is the dissemination and implementation of the final COS.

Stakeholder Involvement

The steering group included neonatologists, pediatricians, infectious disease specialists, obstetricians, microbiologists, midwives, neonatal nurses, researchers, academics, parents of newborns who had neonatal sepsis, and parent representatives from Europe, North America, South America, Australia, and Africa, thus ensuring representation from LMICs and HICs. Stakeholders were invited via professional networks.

In accordance with the COMET Initiative guideline, our public research partners participated in the design and oversight of the COS.[12] We included representatives from organizations such as the Irish Neonatal Health Alliance, Hungary's Melletted a Helyem Egyesület, Brazilian Parents of Preemies' Association (Associacao Brasileira de Pais de Bebes Prematuros), and Preterm Infants Parents Network Uganda. Participants were either native English speakers or were able to participate in English.

Potential Outcome Identification

A potential list of outcomes for inclusion in the COS was identified from a prior systematic review of randomized clinical trials on neonatal sepsis interventions.[6] This review identified 88 unique outcomes across 90 studies.

Qualitative Systematic Review

To ensure relevance to all stakeholders, we conducted a qualitative systematic review, incorporating perspectives from parents, family members, and health care professionals. Studies using ethnography, grounded theory, and mixed methods were analyzed using thematic synthesis. Outcomes were aligned with existing COS frameworks. Full details of the methods are provided elsewhere.[14]

Plain-language explanations were provided for all outcomes included in the Delphi survey. Common outcomes, such as mortality, were adapted from previous COS studies. Where no existing explanations were available, we developed new explanations with guidance from our steering group, especially parents and parent representatives. All plain-language explanations were finalized with the consensus of our Public and Patient Involvement members and other steering group members.

RTD Survey

We used an RTD survey to prioritize outcomes for the consensus meetings, a less time-intensive method than the traditional Delphi process. The RTD survey method enables participants to view real-time responses without multiple rounds.[17] This approach may also reduce the risk of participant attrition.[18]

This method, popular across various fields, has been applied in COS development for neonatal encephalopathy,[19] stillbirth prevention, and bereavement care after stillbirth.[20] A recent randomized clinical trial compared the effectiveness of a traditional Delphi survey approach with an RTD survey method in developing consensus for COS development.[21] Findings suggest that the RTD survey method led to faster completion times and better convergence in outcome ratings.

Our study involved researchers, health care professionals, and parents. Participants from HICs and LMICs were recruited through professional associations, social media, and snowball sampling. The Surveylet platform[22] was used for the RTD survey. Participants rated outcomes on a 9-point Likert scale (where 1 indicated not at all important and 9 indicated critically important).

Outcomes that received a score of 7 to 9 from at least 70% of participants and a score of 1 to 3 from fewer than 15% across all groups were considered for consensus meetings. Those with 50% or fewer participants scoring 7 to 9 within each group were excluded. This consensus criterion is in line with practices used in other COS developments.[23,24]

Consensus Meetings

Two online consensus meetings were held to finalize the COS. Participants from 20 countries across 5 continents, including health care professionals, researchers, and family members, took part. A nonvoting facilitator (D.D.) led the sessions. Participants received a guide before the meetings with a summary of outcomes to be discussed.

The diversity of participants ensured that the variability in neonatal sepsis presentations and resources across different settings was addressed. Outcomes identified through the RTD survey process were discussed, and an anonymous voting system was used. An outcome required at least 80% support from all stakeholder groups to be included in the final COS.

Results

Qualitative Systematic Review

Of 6777 studies initially identified, 6 met our inclusion criteria. Through our analysis, we identified 19 outcomes important to parents of infants who had neonatal sepsis, with the most frequent being parental issues (31.6% [6 of 19]), organ system complications such as those in the gastrointestinal system (26.3% [5 of 19]), and health care worker–related concerns (21.1% [4 of 19]). Other outcomes included general, miscellaneous, survival, and infection. We detail these domains and outcomes in **Table 1**.[25-30]

We mapped the identified outcomes to the domain headings of an existing model[31] for a COS in neonatal research. We integrated our findings with those from the recent systematic review of outcomes in neonatal sepsis clinical trials.[6] The combined list of outcomes was presented in an RTD survey.

Table 1. Domains and Outcomes Identified in the Qualitative Systematic Review

Domain	Studies discussing the domain	Outcome	Studies discussing the outcome
Survival	Rubarth,[25] 2003	Mortality	Rubarth,[25] 2003
Respiratory	Applegate et al,[26] 2020	Tachypnea	Applegate et al,[26] 2020
Gastrointestinal	Murthy et al,[27] 2021; Urbanovská et al,[28] 2020	Necrotising enterocolitis	Murthy et al,[27] 2021
		Interrupted breastfeeding	Murthy et al,[27] 2021; Urbanovská et al,[28] 2020
Neurologic	De et al,[29] 2014	Seizures	De et al,[29] 2014
		Quadriplegia	De et al,[29] 2014
Infection	Applegate et al,[26] 2020	Antimicrobial use	Applegate et al,[26] 2020
Outcomes related to parents	Rubarth,[25] 2003; Murthy et al,[27] 2021; Urbanovská et al,[28] 2020; De et al,[29] 2014; de Zoysa et al,[30] 1998	Support for parents	Murthy et al,[27] 2021; Urbanovská et al,[28] 2020
		Parental bonding with their infant	Murthy et al,[27] 2021; De et al,[29] 2014
		Parental involvement in care	De et al,[29] 2014
		Parental competence in care	Rubarth,[25] 2003; Murthy et al,[27] 2021; De et al,[29] 2014
		Psychological well-being of the parents	Rubarth,[25] 2003; Murthy et al,[27] 2021; De et al,[29] 2014; de Zoysa et al,[30] 1998
		Economic burden on parents	Murthy et al,[27] 2021
Outcomes related to health care workers	Rubarth,[25] 2003; Murthy et al,[27] 2021; De et al,[29] 2014	An effective caring relationship with parents	Rubarth,[25] 2003; Murthy et al,[27] 2021; De et al,[29] 2014
		Communication between parents and health care workers	Rubarth,[25] 2003; Murthy et al,[27] 2021; De et al,[29] 2014
		Job satisfaction of the health care workers	Rubarth,[25] 2003
		Well-being of the health care workers	Rubarth,[25] 2003
General outcomes	Murthy et al,[27] 2021; De et al,[29] 2014; de Zoysa et al,[30] 1998	Normality after discharge	Murthy et al,[27] 2021; De et al,[29] 2014; de Zoysa et al,[30] 1998
Miscellaneous	Murthy et al,[27] 2021; De et al,[29] 2014	Increased body temperature	Murthy et al,[27] 2021; De et al,[29] 2014

RTD Survey

In our RTD survey, 306 participants were enrolled and 228 responded to at least 1 question. Of these, 140 completed the entire survey. We analyzed responses, including incomplete surveys, from all participants to ensure inclusivity and comprehensive data collection.

Approximately 50% of the participants who rated any outcome were neonatologists (108 of 228 [47.4%]), while 22.8% (52 of 228) were researchers, academics, or parent representatives spread across 46 countries, notably Ireland, the US, and Uganda (**Table 2**).

The initial list of outcomes, along with those suggested during the RTD survey, is detailed in eTable 2 in the Supplement. A total of 88 outcomes were identified from the systematic review of trials, and an additional 19 were derived from the qualitative systematic review. After consolidating and eliminating overlapping outcomes, 79 distinct outcomes were retained for inclusion in the RTD survey (eTable 1 in the Supplement). During the survey phase, more than 2 participants suggested the inclusion of the outcomes "infants' quality of life" and "antibiotic resistance." These were added, and participants were invited to reevaluate the survey, which remained open for at least 2 weeks after these additions. At the conclusion of the RTD survey, 55 outcomes met the established criterion for consensus and were presented at the consensus meeting (eTable 2 in the Supplement).

Consensus Meetings

Two online consensus meetings were held in August and October 2023. Each meeting lasted approximately 4 hours. Key stakeholders from diverse fields participated in both meetings, including neonatologists, pediatricians, obstetricians, neonatal nurses, midwives, microbiologists, academic researchers, epidemiologists, and parent group representatives. These participants were from 20 different countries: Barbados, Burkina Faso, Canada, Ethiopia, Gambia, Germany, Hungary, Ireland, Kenya, Malawi, Pakistan, Poland, South Africa, Tanzania, Switzerland, Turkey, Uganda, the UK, the US, and Zambia. Detailed information about the characteristics of participants from both meetings can be found in eTable 3 and eTable 4 in the Supplement.

The initial meeting, comprising 24 participants, centered on deliberating 25 outcomes. Subsequently, the second meeting, attended by 25 stakeholders, addressed an additional 30

Table 2. Characteristics of the Real-Time Delphi Survey Participants

Characteristic	Participants, No. (%) (N = 228)
Country	
Ireland	41 (18.0)
US	31 (13.6)
Uganda	25 (11.0)
Netherlands	17 (7.5)
Switzerland	13 (5.7)
Australia	11 (4.8)
Malawi	10 (4.4)
Other[a]	80 (35.1)
Job	
Neonatologist	108 (47.4)
Pediatrician	21 (9.2)
Researcher	14 (6.1)
Parent representative	13 (5.7)
Neonatal nurse	12 (5.3)
Other[b]	60 (26.3)
Stakeholder groups	
Health care professionals, policymakers	176 (77.2)
Parents, other family members, parent representatives	23 (10.1)
Researchers, academics	29 (12.7)

[a] Includes Andorra, Argentina, Barbados, Belgium, Brazil, Bulgaria, Canada, Denmark, El Salvador, Ethiopia, Finland, France, Gambia, Germany, Ghana, Great Britain, Hungary, India, Italy, Kenya, Lithuania, Mexico, Nepal, Nigeria, Norway, Poland, Romania, Scotland, South Africa, Spain, Sri Lanka, Turkey, Uruguay, Yemen, and Zambia.

[b] Includes academic, general practitioner, midwife, and obstetrician.

outcomes, ultimately culminating in the finalization of the COS. Notably, 15 of the 25 participants in the second meeting had also been present during the first meeting.

Core Outcome Set

The following outcomes are included in the final COS for neonatal sepsis: (1) all-cause mortality, (2) need for mechanical (invasive) ventilation, (3) multiorgan dysfunction, (4) escalation of antimicrobial therapy, (5) brain injury on imaging, (6) neurologic status at discharge, (7) infection of the central nervous system, (8) neurodevelopmental impairment, and (9) parents' quality of life. Details of these outcomes, including plain-language explanations, can be found in **Table 3**. The sequence of outcomes presented does not imply any hierarchical ranking.

Discussion

We developed a COS for studies evaluating neonatal sepsis treatments, aiming to include outcomes relevant to parents, health care professionals, and researchers across diverse settings. The final COS includes 9 outcomes across 7 domains.

Following the COMET Initiative's guidelines,[12] our goal was to standardize outcome reporting to improve consistency and make meta-analyses more reliable. In addition, researchers can include other specific outcomes pertinent to their individual study goals. A COS enhances the feasibility of meta-analyses and helps mitigate research waste.[32] A COS enhances both the feasibility and reliability of meta-analyses, as the current lack of standardized outcomes often prevents data pooling.[33] Moreover, COS adoption facilitates a coherent evidence continuum from trials through systematic reviews to clinical guideline recommendations.[34] Our findings, once widely disseminated, should strengthen the evidence base for neonatal sepsis treatments.

The COMET database plays a vital role in helping researchers avoid unnecessary duplication of effort by providing a centralized repository of COSs. Checking the database in advance is essential, as an existing COS might not fully align with a specific study but could still offer valuable insights if there are areas of overlap. At the time our study commenced in 2022, no COS specifically addressing neonatal sepsis had been developed. To promote transparency and collaboration, we registered our study protocol with the COMET database prior to beginning the project and have continued to update the database with each publication. In 2023, a separate research team registered a protocol titled "Development of a core outcome set for management of neonatal septic shock" in the COMET database.

Table 3. Final Core Outcome Set Outcomes by Domain

Outcome	Outcome domain	Plain language summary
All-cause mortality	Survival	Number of deaths that occur among newborns with neonatal sepsis from any cause
Need for mechanical ventilation	Respiratory	Use of an invasive machine to assist with breathing for newborns who are having difficulty breathing on their own by using a tube that goes to the throat of the infant
Brain injury on imaging	Neurologic	Detection of abnormalities or damage to the newborn's brain using a medical imaging test, such as magnetic resonance imaging or a computed tomography scan; the device may change with the setting
Neurologic status at discharge	Neurologic	Assessment of the infant's reflexes, muscle tone, movement, responsiveness, and any signs of neurologic abnormalities during discharge
Escalation of antimicrobial therapy	Infection	Increasing the intensity or changing the type of antibiotics or antimicrobial drugs used to treat neonatal sepsis when the initial treatment is not effectively controlling the infection or when the infection appears to be worsening
Infections of the central nervous system	Infection	Infections that affect the neonate's brain or spinal cord
Multiorgan dysfunction	Miscellaneous	The impaired function of ≥2 organ systems, as evidenced by clinical and/or laboratory test abnormalities, in an infant with a diagnosis of sepsis, where organ function was normal prior to the onset of sepsis
Neurodevelopmental impairment	Developmental	Neurodevelopmental impairment of the child at 18-24 mo corrected age using a validated tool
Parents' quality of life	Outcomes related to parents	The effect of the neonate's condition and treatment on the quality of life of the family

We included parents and parent representatives from HICs and LMICs in our steering group and subsequent project phases to ensure diverse experiences were represented. Incorporating the parents' or family's perspective throughout the process enhances the study's relevance to patients. Furthermore, it is predicted that collaborating with parents will help facilitate wider dissemination and impact of the COS.[12]

We achieved geographical diversity in our project, with participants from both LMICs and HICs in all stages. Our systematic review included literature from a diverse range of countries, and our RTD survey involved participants from 46 countries. The consensus meetings included attendees from 20 countries across 5 continents. The strong representation from LMICs was of particular importance to our study given the disproportionately high burden of neonatal sepsis in these regions.

Our study focused on consensus about what outcomes to measure in neonatal sepsis trials. The specifics of how and when to measure these outcomes remain critical areas for future research. We suggest that subsequent studies use COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) guidelines[35] to ensure accurate and comprehensive outcome measurement.

Although some outcomes, such as all-cause mortality, are easily quantifiable, others, particularly neurodevelopmental impairment, present greater challenges. Neurodevelopmental metrics are vital for assessing neonatal care effectiveness,[36] encompassing both immediate and prolonged developmental trajectories. The literature often underrepresents the full spectrum of potential neurodevelopmental sequelae by focusing on short-term rather than long-term outcomes, such as motor dysfunctions and specific learning disorders.[37] This could affect the understanding of long-term developmental impacts. We identified several overlapping outcomes with the framework proposed by Webbe et al,[31] including survival and evidence of brain injury on imaging. Although the research by Webbe et al[31] addresses infants primarily in high-income neonatal care settings, ours extends beyond high-income settings to include low-resource environments. Their COS had a different scope, focusing broadly on all neonatal research areas, whereas our COS specifically addresses neonatal sepsis. The inclusion of brain injury on imaging as a core outcome was the subject of extensive discussion during our consensus meetings. It was included with the understanding that, while it may not currently be a feasible measure in underresourced settings, prioritizing this outcome in clinical trials could catalyze enhancements in local health care infrastructure. This, in turn, may help prompt funders to invest in the necessary advancements, thereby facilitating the capacity to assess this critical outcome and, concurrently, ameliorate neonatal health care in those regions.

Furthermore, we identified 7 distinct outcomes not covered by Webbe et al[31] that are needed for mechanical (invasive) ventilation, multiorgan dysfunction, escalation of antimicrobial therapy, neurologic status at discharge, infection of the central nervous system, neurodevelopmental impairment, and parents' quality of life. Our findings indicate that while a general COS can be used as a foundation for developing more customized outcome sets, more specialized COSs for specific conditions within neonatal care are needed.

Neonatal sepsis is a challenging clinical diagnosis to make because of its unspecific symptoms, which makes it difficult to diagnose and treat.[38] Even in HICs, the low positive predictive accuracy of diagnostic testing for newborn sepsis makes it challenging to accurately identify the condition.[39] Underrecognized sickness, delayed household care seeking, and restricted access to qualified health care professionals and high-quality sepsis management services all contribute to elevated mortality rates. Treatment costs often surpass what many families can afford. This especially affects communities where infants in need of medical care cannot access the services, resulting in a high rate of neonatal deaths.[38] Addressing newborn sepsis is a crucial intervention in neonatal care,[40] with the added benefit of contributing to the achievement of Sustainable Development Goals, targeting goal 3.2 by reducing preventable deaths of newborns.[41]

The need for mechanical ventilation is another important outcome, as it indicates the severity of the infection and the potential for respiratory failure.[42] Mechanical ventilation can also result in

adverse effects, including trauma and air leak syndromes that can have an unfavorable effect on long-term results.

Neurologic status at discharge is a critical component in patient outcomes because neonatal sepsis can have major long-term effects on neurodevelopment.[5,36,43-45] There is a higher chance of neurodevelopmental damage, especially in the motor domain, in cases of newborn sepsis.[44,45] Further research to aid rapid early detection of sepsis would improve outcomes and enhance early care.[42,46]

Nevertheless, neurodevelopmental impairment is another crucial outcome in our COS. Neonatal sepsis is associated with an increased risk of neurocognitive impairment across multiple domains, including cognitive development, visual and auditory impairments, and cerebral palsy.[47,48] A systematic review highlighted a significant limitation: the scarcity of longitudinal follow-up data beyond 36 months.[49] Long-term studies are challenging to conduct, requiring tracking children for several years after discharge.[50,51] However, the framework by Marlow[51] for neurodevelopmental outcome assessment in neonatal trials provides valuable guidance. We strongly encourage extended follow-up into school age, when cognitive scores tend to stabilize and motor and sensory outcomes can be more precisely defined.

Neonatal sepsis is characterized by high morbidity and mortality, necessitating the prompt initiation of antimicrobial therapy after culture collection.[52] Escalation of antibiotics is commonly triggered by factors such as clinical deterioration, microbiology results, pathogen identification, and worsening inflammatory biomarkers.[53] In addition to the necessity for antibiotic escalation, the rational use of antimicrobials is a crucial issue in neonatal units, and antimicrobial stewardship interventions should be applied.[54] In low-income settings, limited resources, inadequate microbiological services, and unique pathogens challenge the implementation of outcomes such as escalation of antimicrobial therapy and central nervous system infections.[55] However, including these outcomes in the COS may drive future improvements in health care infrastructure and resource allocation.

Sepsis-associated multiorgan dysfunction may include respiratory, cardiovascular, central nervous system, adrenal, coagulation, immunologic, and kidney dysfunction.[56] In view of the major prognostic relevance of multiorgan dysfunction, it is anticipated that multiorgan dysfunction will be reported as a core outcome in all trials about the treatment of newborn sepsis. The term *multiorgan dysfunction* encompasses potential dysfunctions in the cardiovascular, hematologic, gastrointestinal, and urinary systems, which were not selected as core outcomes by the consensus meeting participants. Therefore, it serves as an umbrella outcome for other possible organ dysfunctions, in addition to the cardiovascular, hematologic, gastrointestinal, and urinary systems, that are not specified as core outcomes but are crucial for the patient's prognosis.[57]

Our COS includes the quality of life of parents as a critical outcome, indicating a conscious attempt to take a holistic approach to neonatal sepsis research. Neonatal sepsis has a dramatic effect on the health of the whole family in addition to the infant with sepsis. Increased stress, a more demanding parenting style, and a bigger family impact were indicated by parents of infants with more medical difficulties.[58] Furthermore, even before the neonatal sepsis diagnosis, rule-out sepsis evaluation was demonstrated to be significantly contributing to parents' financial stress, termination of breastfeeding, iatrogenic consequences, and excessive anxiety.[59] Our COS acknowledges that parents play a crucial role in providing care and support for their newborn and that evaluating the parents' quality of life can help develop compassionate and comprehensive care strategies as well as provide a thorough understanding of the broader impacts of neonatal sepsis.

We integrated qualitative methods in our COS development, capturing diverse stakeholder perspectives, such as those of patients and caregivers, which are often overlooked in clinical trials. Using these methods helps address the complex challenge of ensuring the COS development process is relevant and meaningful to all involved groups.[12] In our study, we combined outcomes from a systematic review of clinical trials[6] with qualitative insights,[60] broadening the scope and relevance of the outcomes.

Although the COS of Webbe et al[31] was adapted by Karumbi et al[61] for low-income settings in Kenya, our COS was developed with stakeholders from diverse income settings to ensure global applicability. If needed, similar adaptation processes could enhance local implementation.

Limitations

Our study faced some limitations, particularly in terms of time constraints that prevented primary qualitative research. Instead, we relied on existing studies, which may have limited the direct input of parents. In addition, our review included only English-language studies, potentially missing other important perspectives.

The scope of our review was ambitious in seeking to capture the views of a broad range of stakeholders; however, we were unable to find qualitative studies that focused on outcomes important to policymakers and researchers related explicitly to treatments for neonatal sepsis. This might lead to an underrepresentation of these groups in our findings. In addition, the lack of policymakers' engagement in our study could have led to their perspectives being underrepresented. Also, the conduct of an RTD survey and consensus meetings exclusively in English will have excluded non–English-speaking participants despite the significant representation of LMICs in these stages.

In recruiting participants for the RTD survey process, we mainly used social media, supplemented by outreach through associations and academic networks. This approach may have overlooked individuals not active on social media or without internet access. This limitation could skew the data, failing to capture the full spectrum of experiences and opinions among our intended audience. Consequently, this aspect of participant selection may affect our findings' generalizability. However, we used an extensive online search to reach more stakeholders to minimize this effect. We deliberately extended the survey period to more than 6 weeks, deviating from our original protocol to ensure broader participation.

Our consensus meetings, while diverse, had an overrepresentation of participants from Ireland and European countries, potentially limiting the global applicability of our findings. However, expert facilitation ensured an equal voice for all participants, helping mitigate regional biases. We also considered challenges specific to low-income countries, including limited diagnostic facilities, infrastructure constraints, and cultural barriers to health care access, in our effort to maintain global relevance of the identified outcomes.

Another limitation of our study is that we did not differentiate outcomes for preterm and full-term neonates. Preterm neonates are at a higher risk of sepsis or infection compared with full-term neonates, and they experience higher mortality rates. In addition, preterm infants with sepsis are more likely to develop impaired neurodevelopment.[62] However, our COS encompasses both groups, as mortality and neurodevelopmental impairment were deemed crucial for both preterm and full-term neonates.

In addition, this COS includes both early-onset sepsis and late-onset sepsis. These 2 types of sepsis differ in cause and pathogens, and their outcomes may vary accordingly.[62] Nevertheless, we considered both early-onset sepsis and late-onset sepsis throughout the development of our COS to ensure broad applicability across neonatal sepsis cases. The outcomes identified in this study offer significant implications for future research. Although our COS provides a strong foundation, the heterogeneity of neonatal sepsis suggests that additional condition-specific outcomes may be necessary. This COS balances universal relevance with adaptability to different contexts. For instance, while brain imaging may not be immediately feasible in all settings, its inclusion in the COS may drive improvements in health care infrastructure and resource allocation over time.

This work focused on determining what to measure, which is a crucial first step in standardizing outcomes research. The COMET Initiative[12] strongly recommends this approach, highlighting the importance of first agreeing on what to measure before determining how to measure it. This approach is gaining traction globally as a fundamental step in improving research quality and comparability.

Conclusions

This research has developed a COS for evaluating neonatal sepsis treatments. Adopting this COS should enhance consistency in sepsis outcome reporting and help reduce bias and variability in this research area. It would also enable more effective data synthesis. Future research endeavors should focus on establishing robust, standardized methods for measuring the sepsis outcomes we have identified within our COS. Future work will focus on developing guidance for implementing this COS across diverse settings. This guidance may include suggestions for context-specific adaptations and alternative measures for settings with limited resources. We also encourage researchers to report on their experiences using this COS, which will inform future refinements and ensure its ongoing relevance and applicability across the spectrum of neonatal sepsis presentations and health care contexts. An important future research priority is establishing a universal consensus definition of neonatal sepsis. A standardized definition would improve the use of the COS, enhance comparability of studies, and support better neonatal health care outcomes.

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SUPPLEMENT.

eTable 1. Plain Language Summaries of the Outcomes
eTable 2. NESCOS Quick View Outcomes
eTable 3. Consensus Meeting 1 Participants
eTable 4. Consensus Meeting 2 Participants
eFigure. Schematic of NESCOS Development