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Review Article

Outcome Reporting in Interventional Necrotizing Enterocolitis Studies: A Systematic Review

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ABSTRACT

Background: Despite an increasing necrotizing enterocolitis (NEC) incidence, treatment strategies have failed to make major advancements towards improved NEC outcomes. Heterogeneity in outcome reporting and a lack of treatment efficacy studies potentially hamper these advancements. We aimed to analyze outcome reporting in recent interventional NEC studies.
Methods: We performed a systematic review identifying interventional studies on NEC between 1st of January 2016 and 1st of June 2023 in MEDLINE, Embase, CENTRAL and Cochrane reviews. Systematic reviews, clinical trials and change-in-practice cohort studies reporting any therapeutic intervention for NEC patients (Bell's stage ≥ IIa) were eligible. We excluded studies on NEC diagnostics or prevention and non-English publications. Outcomes were categorized into five core areas and presented descriptively. The review was registered with PROSPERO (CRD42022302712).
Results: Out of 1.642 screened records, 65 were eligible for full-text review and 15 were finally included for data extraction. Median number of reported outcomes per article was six (range 1–19). We identified 66 unique outcomes, which were mapped to 53 outcome terms. Thirty-four out of the 53 of the outcome terms (64%) were only reported in a single article. Mortality was the most reported outcome (11/15 articles, 73%). Core area 'Adverse outcomes' contained the most outcome terms (n = 19), whereas 'Life impact' contained the least outcome terms (n = 4) and was represented in 3 articles (20%).
Conclusions: Considerable heterogeneity in outcome reporting and a paucity of outcomes concerning 'Life impact' exist in interventional NEC studies. Development of a NEC core outcome set may improve consistency and patient-relevance in outcome reporting.
Study Type: Systematic Review and Meta-Analyses.
Level of Evidence: III.

1. Introduction

Advancements in neonatal care and changes in guidelines for resuscitation of neonates have led to an increasing population of very and extremely preterm neonates, adding to the incidence of necrotizing enterocolitis (NEC) [1]. Despite research efforts over the last decades, infants suffering from NEC still face a mortality rate of 21–35%, with worse outcomes for those needing surgical management [1–4]. Survivors of NEC may suffer from long-term morbidity such as short-bowel syndrome and neurodevelopmental delay in up to 75% of cases [5]. Hence, the need for novel treatments for the improvement of NEC outcomes continues to rise.

Abbreviations: CDS, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CLABSI, Central line-associated blood stream infection; COMET, Core Outcome Measures in Effectiveness Trials; COS, Core outcome set; CRP, C-reactive protein; NEC, Necrotizing enterocolitis; NECCOS, Necrotizing enterocolitis core outcome set; PDA, Patent ductus arteriosus; POD, Postoperative day; PN, Parenteral nutrition; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; RCT, Randomized controlled trial; SR, Systematic review; TPN, Total parenteral nutrition.

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Over the past decade, treatment of NEC has failed to make major advancements affecting outcome [1], possibly due to a lack of treatment efficacy studies in this vulnerable patient population. In addition, the multifactorial nature of NEC leads to a plethora of possible outcomes to report in treatment efficacy studies. Published NEC treatment studies reported heterogenous outcomes, which may not always be relevant to clinicians, scientists or patients and their families. This heterogeneity significantly hampers meta-analyses, as highlighted in a recent systematic review on NEC [4]. Consequently, wide variation in management strategies is maintained and it remains hard to establish evidence-based guidelines and consistently optimize outcomes for infants with NEC.

Outcome reporting in efficacy studies may be improved by establishing a core outcome set (COS) for a certain medical condition [6,7]. A COS entails a recommended set of essential outcome measures to be reported in studies concerning a tested intervention for a medical condition. This COS is established through a standardized consensus process consisting of several survey rounds and a consensus meeting, where the importance of multiple outcomes is scored by all relevant stakeholder groups involved, including family representatives (Delphi method) [8]. A COS allows the input of patients and their family, which is crucial for the societal relevance of future research [9]. Uptake of COS outcomes in treatment efficacy trials is feasible [10], and ensures that a minimum set of standardized outcomes are reported in studies on a certain pathology or treatment. Hence, relevancy of reported outcomes for multiple stakeholders (clinicians, scientists, patients and family) is safeguarded and study results of treatment efficacy studies are likely to be more comparable for systematic reviews (qualitatively) and meta-analyses (quantitatively).

Presently, no such COS for NEC (NECCOS) exists. As a first step towards establishing an international NECCOS, we aimed to identify the outcomes reported in recent literature on NEC. In this systematic review we analyze and summarize outcome reporting in studies investigating any intervention aimed at improving outcome of NEC patients.

2. Methods

This systematic review was conducted in accordance with the PRISMA guidelines for systematic reviews (Supplement 1) [11] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022302712), where the protocol and data collection form template are available.

2.1. Eligibility criteria

Included study types were: systematic reviews (with or without meta-analysis), clinical trials (including randomized and/or controlled trials) and cohort studies including at least ten patients. All studies had to report on the efficacy of any therapeutic intervention aimed at the improvement of NEC outcome. For cohort studies, we considered change-in-practice studies as interventional (i.e., comparing before and after introduction of an intervention or protocol). We defined the study population as infants diagnosed with NEC modified Bell's stage $\geq$ IIa. Studies starting intervention in a NEC population up to two weeks after initial diagnosis were included.

To ensure contemporaneity of the reported outcome measures, we only included articles published in January 2016 or later, which also included trials performed prior to 2016 but published in or after 2016. We excluded studies not published in English, studies on NEC diagnostic techniques or prevention, conference abstracts, registered protocols of trials and studies for which no full-text report was available.

2.2. Search strategy

In consultation with an academic medical information specialist, we composed a search strategy for the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR) (Supplement 2). The last search was conducted on the 1st of June 2023 for all databases. The general search terms are displayed in Table 1. We identified database specific search terms for NEC and included study types (e.g. clinical trial, systematic review) from the respective thesauri and exploded terms where applicable. We generated free text search words for each search subject including commonly used variations and combined search terms and free text using Boolean operators. Searches were limited to a publication date from January 2016 onwards. In MEDLINE and Embase an additional search string excluded animal studies and case reports, for Embase conference abstracts were excluded.

2.3. Study selection

Studies were screened independently by title and abstract by two reviewers (OCvV and DHK) using the systematic review tool Rayyan [12]. Papers considered potentially relevant by either reviewer were included for critical full-text screening against the eligibility criteria. Subsequently, the final set of eligible studies was determined through consensus between the two reviewers. Upon disagreement, the discussion was resolved with a third reviewer (JBFH). The reference lists of included systematic reviews were searched for any relevant studies missed.

2.4. Data extraction & synthesis

Extraction of data was conducted in duplicate and independently by two reviewers (OCvV and DHK). For each included study, we extracted publication year, country, study design, intervention type, population size and all outcomes. We recorded all the reported outcome measures with their respective definition, unit and time point if applicable. Outcomes were also recorded as primary or secondary. An outcome had to be stated as 'primary outcome' in the full-text report or stated in the aim as the single measure of intervention effect to be recorded as primary. Specifically stated baseline characteristics (e.g., birth weight, mode of delivery) were not considered outcome measures and thus not extracted.

Outcomes were mapped to a single 'outcome term' when: 1) they were described as a single outcome item (e.g., 'intraoperative complications' includes 'intraoperative hemorrhage', 'intraoperative death'), or 2) they were similar but with a different definition (e.g., 'Mortality at 30 days' and 'Mortality at discharge' were grouped under 'Mortality'). Described definitions of outcomes were compiled. Each outcome term was categorized in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) taxonomy and the OMERACT Filter 2.0; frameworks safeguarding relevancy of outcomes in different domains for COS [13,14]. These taxonomies both apply the core areas 'Death', 'Physiological or Clinical' (or 'Pathophysiological manifestations'), 'Life Impact', 'Adverse Events' and 'Resource Use'. Each extracted outcome term was assigned to one of these areas and the number of studies and the frequency of reporting an outcome in each core area was determined. All data are presented descriptively in tables and graphs where appropriate. Formal statistical analysis is inappropriate considering the qualitative nature of the extracted data.

Table 1
Search strategy: general search terms and limits per database.

Database	Search terms	Limiting criteria
MEDLINE	necrotizing enterocolitis/necrotising enterocolitis clinical trials/clinical study/controlled study/randomized controlled trial/treatment outcome/outcome/systematic review/meta-analysis	• Publication date 2016 or later • No animal studies or case reports
Embase	necrotizing enterocolitis/necrotising enterocolitis clinical trial/clinical study/controlled study/randomized controlled trial/clinical outcome/outcome assessment/outcomes research/outcome/systematic review/meta-analysis	• Publication date 2016 or later • No animal studies, case reports, conference abstracts
Cochrane Library	necrotizing enterocolitis/necrotising enterocolitis	• Publication date 2016 or later

3. Results

A flow diagram of the study selection process is displayed in Fig. 1. A total of 2.617 titles were retrieved through our search strategy, including 1.279 PubMed, 1.019 Embase, 288 CENTRAL and 31 Cochrane Reviews articles. After deduplication and removal of 91 records published before 2016, 1.642 records were screened and 65 records were full-text reviewed. The reasons for exclusion at screening comprised: preventive study or no infants with NEC in the study population (n = 685); diagnostic study or no intervention (n = 465); wrong publication type (e.g., commentary, narrative review, survey, conference abstract) (n = 397); and non-English publication (n = 36). For 60 full-text reviewed records consensus was reached between the two reviewers, for five records the third reviewer was consulted to agree upon inclusion or exclusion. From the 65 full-text reviewed records, six were excluded because no report was retrievable. Another 44 articles were excluded because no intervention was applied (n = 24), the primary study population was not NEC patients with Bell's stage ≥ IIa (n = 11) or the publication type-criterion was not met (n = 7). One article was excluded because it focused on pharmacology and biochemical effects of a medicine rather than NEC outcome, and one article was excluded due to the lack of NEC-related outcomes in a phase I safety and feasibility study [15,16].

Fifteen articles [17–31] met our eligibility criteria and underwent data extraction (Table 2). Included studies were published between 2017 and 2023, originated from a total of eight countries (United States, Canada, Armenia, Italy, Brazil, China, Denmark, France) and comprised eight systematic reviews [17–20,22,24,28,30], five cohort (change in practice) studies

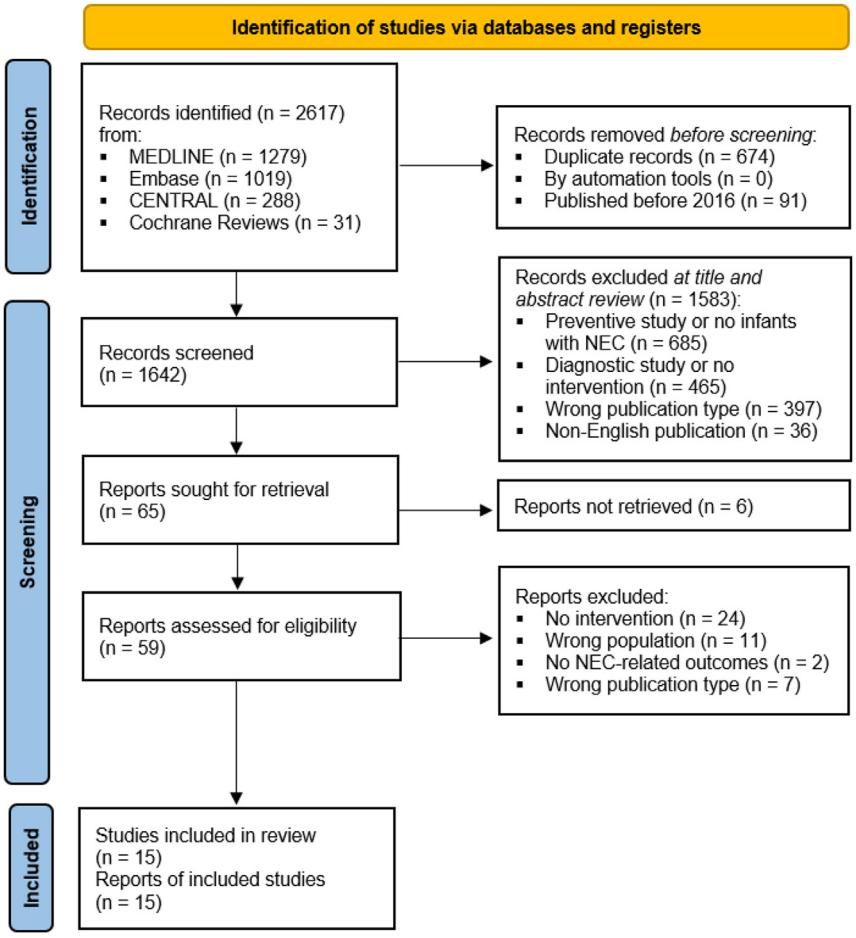


Fig. 1. Article selection displayed in the PRISMA flow diagram.

Table 2
Characteristics of included studies.

First author	Publication year	Country of origin	Study design	Intervention type studied	Stated primary outcome	Number of NEC-related outcomes reported	Sample size
Haricharan [17]	2017	USA	SR	Surgery	Yes	2	616
Hock [18]	2018	Canada	SR	Feeding	Yes	7	91
Pammi [19]	2019	USA	SR	Medication	Yes	9	NA (0)[a]
Van Heesewijk [20]	2020	USA	SR	Surgery	Yes	7	16.288
Quiroz [21]	2020	USA	Cohort	Surgery	Yes	8	108
Patel (2020) [22]	2020	USA	SR	Feeding	Yes	5	229
Harutyunyan [23]	2020	Armenia	Cohort	Medication	Yes	4	200
Donà [24]	2021	Italy	SR	Antibiotics	No	4	3.161
Blakely [25]	2021	USA	RCT	Surgery	Yes	19	308
Gonçalves-Ferri [26]	2021	Brazil	Cohort	Hypothermia	Yes	5	43
Liu [27]	2022	China	RCT	TDP®	Yes	10	103
Gill [28]	2022	Denmark	SR	Antibiotics	Yes	15	375
Patel (2022) [29]	2022	USA	Cohort	Feeding	Yes	6	50
Li [30]	2022	China	SR	Surgery	Yes	1	3280
Montalva [31]	2023	France	Cohort	Surgery	Yes	6	77

NEC, necrotizing enterocolitis; USA, United States of America; SR, systematic review; RCT, randomized controlled trial; TDP®, trade name of medical electromagnetic device [27].
[a] This SR did not identify any studies meeting their eligibility criteria.

[21,23,26,29,31], and two randomized controlled trials [25,27]. The types of interventions studied included surgery (n = 6), feeding practices (n = 3), antibiotic treatment (n = 2), treatment with medication (n = 2), hypothermia (n = 1), and electromagnetic wave therapy (n = 1). Median sample size in the studies was 215 (range 43–16.288) for a total of 24.929 infants. One systematic review did not identify any eligible studies for its search strategy [19], and therefore sample size extraction was not applicable for this included article.

3.1. Reported outcomes

A total of 66 unique outcomes were extracted from 15 articles, which were mapped to 53 outcome terms (Table 3). Specifically, multiple outcomes were included in the terms 'postoperative C-reactive protein trend' (ΔCRP post-op day (POD)-0 and POD-2; CRP on POD-7), 'postoperative surgical complications' (wound infection/dehiscence, stoma prolapse, parastomal hernia, fistula, abdominal culture, intestinal stricture, intra-abdominal abscess), 'intraoperative complications' (intraoperative cardiopulmonary resuscitation, hemorrhage and death) and 'duration of parenteral nutrition' (time to initiation of enteral feeding, time to full enteral feeding). The median number of outcome terms reported per article was six (range 1–19).

The different units and time points for each outcome term, as reported in the articles, are displayed in Supplement 3. Outcomes that were further defined within articles or had varying definitions between articles are shown in Table 4. The most frequently reported outcome term was mortality in 11 (73%) articles, followed by duration of parenteral nutrition in eight (53%) articles and length of hospital stay in seven (47%) studies. Notably, the most reported outcomes (mortality and duration of parenteral nutrition) had the most variable definitions. Of all 53 outcome terms, 34 (64%) were only reported in a single article rather than in multiple articles. Remaining outcome terms were reported in two or more included articles. Mortality was also the outcome term most commonly specified as primary outcome, in eight (57%) articles. One article did not specify a primary outcome [24].

Each of the outcome terms (n = 53) was assigned to one of five core areas. Core area 'Adverse events' contained the most outcome terms (n = 19). The number of outcome terms for the other areas were 17 for 'Physiological or clinical', 11 for 'Resource use', four for 'Life impact' and two for 'Mortality'. The core area 'Adverse events' also had the highest overall frequency of reporting per core area (n = 34 times reported, divided over all papers), followed by 'Resource use' (n = 30) and 'Physiological or clinical' (n = 24) (Fig. 2, Table 3). Core area 'Mortality' was frequently reported overall (n = 12) despite containing only two outcome terms (mortality, survival), whereas 'Life impact' was reported six times over all articles while containing four outcome terms. Each core area was represented in 12 (80%) or more articles, with the exception of 'Life impact' which was only represented in three articles (20%) [18,19,25]. Just two articles (13%) reported at least one outcome in each of the five core areas [19,25].

4. Discussion

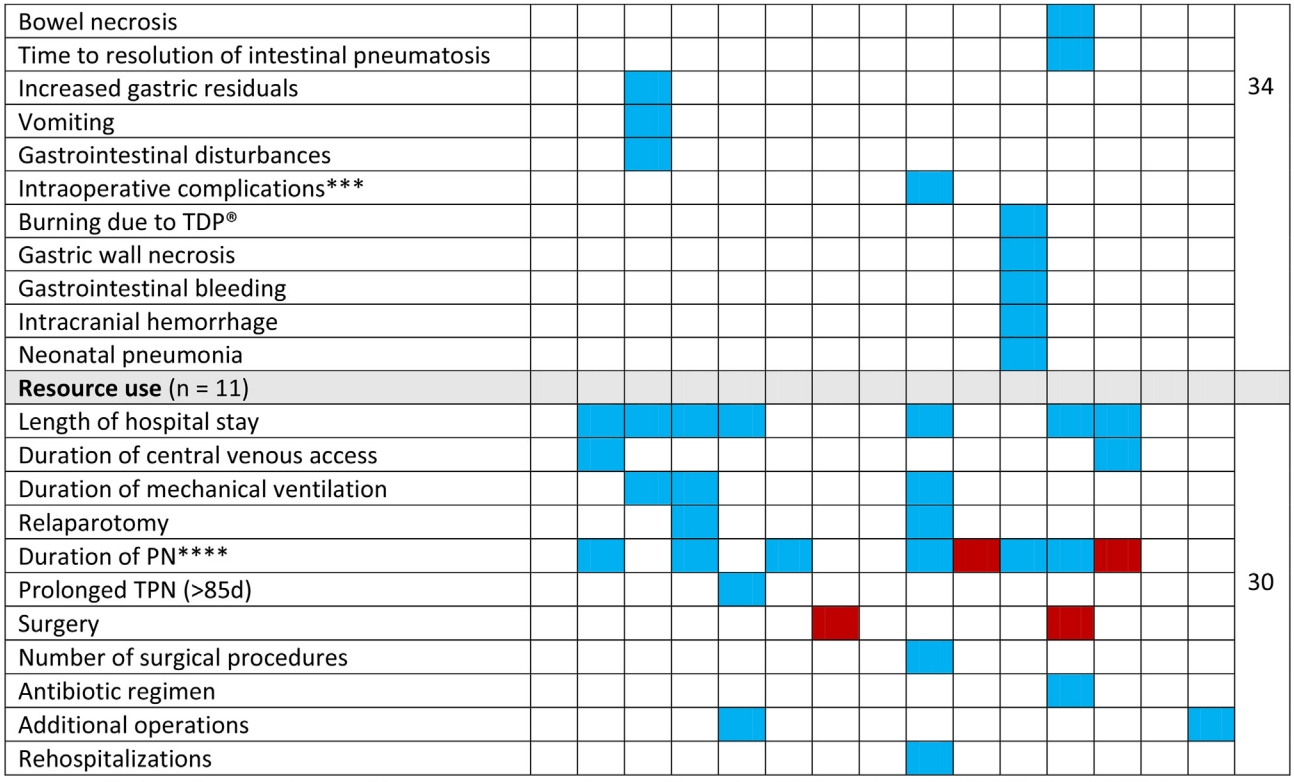
We analyzed outcome reporting in recent interventional studies on NEC. We found 66 unique outcomes in 15 included articles, which were mapped to 53 outcome terms and categorized into five core areas. Additionally, we reported units and time points for outcome terms and the varying outcome definitions encountered in the reviewed articles. We found notable heterogeneity, as 34 out of 53 (64%) outcome terms were only reported in a single article rather than in multiple articles. Among the plethora of outcomes, core area 'Life impact' was underrepresented – a core area that may be considered especially relevant to patients and their families.

Previous analyses on outcome reporting in appendicitis, gastroschisis and Hirschsprung's disease, also found wide heterogeneity in reported outcomes [32–34]. In our study on NEC, heterogeneity might even be greater with 66 unique outcomes found in 15 articles, compared to 62 unique outcomes in 30 articles in a previous study on gastroschisis outcome reporting [34]. This heterogeneity hampers effective data synthesis in systematic reviews and meta-analyses [4], but also hinders interpretation and comparison of current evidence by treating physicians. With NEC, being a rare disease often studied in small numbers of patients, effective and valid data synthesis is crucial to establish evidence-based guidelines. Hence, our findings support the urgency to develop a COS and reduce reporting heterogeneity.

We found that outcomes concerning 'Life impact' were reported in just three studies. Other studies consistently show this core area to be underrepresented in current outcome reporting [32,33]. This may be explained by a lack of patient and parent involvement in

Table 3
Reported outcome terms categorized by core area.

Outcome terms (total n = 53)	Haricharan 2017 [17]	Hock 2018 [18]	Pammi 2019 [19]	Van Heesewijk 2020 [20]	Quiroz 2020 [21]	Patel 2020 [22]	Harutyunyan 2020 [23]	Donà 2021 [24]	Blakely 2021 [25]	Gonçalves-Ferri 2021 [26]	Liu 2022 [27]	Gill 2022 [28]	Patel 2022 [29]	Li 2022 [30]	Montalva 2023 [31]	**Overall frequency per area**
Mortality (n = 2)																
Mortality	■		■	■			■	■	■	■	■	■		■	■	12
Survival					■											
Physiological or clinical (n = 17)																
Sepsis									■		■	■				24
Weight gain and head circumference		■														
Periventricular leukomalacia			■													
Bronchopulmonary dysplasia			■	■												
Peritoneal drain as definitive surgery					■											
Central line-associated blood stream infection		■				■							■			
NEC stage						■	■									
Final bowel length									■							
Severe intraventricular hemorrhage									■							
Extensive bowel resection										■						
Increased volume of milk per day											■					
Velocity of weight gain											■					
Thrombocytopenia												■				
Blood transfusion												■				
Need for nasogastric suction												■				
Need for surgery								■		■						
Postoperative C-reactive protein trend*															■	
Life impact (n = 4)																
Moderate to severe cerebral palsy									■							6
Blindness									■							
Hearing loss									■							
Neurodevelopmental impairment			■	■					■							
Adverse events (n = 19)																
Complications	■				■				■							
NEC recurrence		■				■						■	■			
Post-NEC stricture		■				■		■				■	■		■	
Perioperative hemorrhage					■				■							
Postoperative surgical complications**					■				■							
Intestinal perforation							■	■		■		■				
PN-associated cholestasis									■							
Peritonitis												■				



Red – primary outcome, blue – secondary outcome. *includes ΔCRP post-op day (POD)-0 and POD-2, CRP on POD-7; **includes outcomes: wound infection/dehiscence, stoma prolapse, parastomal hernia, fistula, abdominal culture, intestinal stricture, intra-abdominal abscess; ***includes outcomes: intraoperative cardiopulmonary resuscitation, hemorrhage and death; ****includes outcomes: time to start enteral feeding, time to full enteral feeding. NEC, necrotizing enterocolitis; PN, parenteral nutrition; TDP®, trade name of medical electromagnetic device [27]; TPN, total parenteral nutrition.

design of the included studies. Moreover, clinicians tend to focus on the safety and efficacy of a treatment, which is mostly covered by well-represented core areas such as 'Adverse events' and 'Mortality'. Initiatives such as COMET, but also patient charities and societies, strongly encourage involvement of patients and family in future research [8,9]. Previously established pediatric COS showed that patient and parent involvement in COS development is feasible and allows their input to define (patient-) relevant outcomes in pediatric diseases [35,36]. It is considered a valuable addition by both researchers and patients and their family [37].

The strength of this study is that current limitations in outcome reporting in NEC treatment efficacy studies are exposed. This includes a lack of consistent outcome reporting and a lack of patient and parent involvement, impeding both accurate evidence comparison and patient-relevancy of outcomes. In our systematic review we included multiple publication types such as cohorts, and non-randomized non-controlled clinical trials, ensuring a broad representation of outcome reporting in recent NEC treatment literature. This review forms the basis for development of a COS for NEC; a consensus-based set of important outcomes for consistent future reporting. It also supports involvement of patient and parents, to increase outcomes focusing on life impact.

Despite our focus on interventional studies, certain included systematic reviews contained observational studies besides clinical trials and one did not identify any interventional studies meeting its eligibility criteria. This can be seen as a limitation. However, we considered inclusion appropriate if the systematic review analyzed an intervention aimed at improvement of NEC outcome, since we presume that reported outcomes of this review were formulated based on the studied intervention. The time period of the systematic review from 2016 onwards, chosen in the light of contemporaneity, may be considered another limitation. To ensure no

Table 4
Definitions of outcomes and variations.

Mortality (n = 10)
- All-cause mortality during hospital stay and at 28 days [19]
- All-cause and NEC-related mortality according to results of autopsy and histology [23]
- Death within 30 days after NEC diagnosis or anytime if related to extensive bowel resection [26]
- Death at 18–22 months corrected age [25]

Not explicitly defined (n = 7)

Central line-associated blood stream infection (CLABSI) (n = 3)
- Diagnosed using Centers for Disease Control and Prevention criteria (clinical signs of sepsis, one positive peripheral blood culture, negative urine, tracheal aspirate cultures) [18]
- CLABSI as defined within each study were incorporated within the meta-analysis [22]
- CLABSI was defined as confirmed bloodstream infection with a central line in place on the day or day before the event [29]

Need for surgery (n = 2)
- Signs of intestinal perforation or significant clinical worsening of the patient's general condition despite maximal clinical therapy or positive paracentesis [26]

Not explicitly defined (n = 1)

Neurodevelopmental impairment (n = 3)
- Neurodevelopment delay as assessed by a validated test [19]
- 1) Moderate to severe cerebral palsy with Gross Motor Function Classification System level 2; 2) Bayley-III cognitive composite score <85; 3) severe bilateral visual impairment consistent with vision <20/200; 4) permanent hearing loss despite amplification that prevents communication or understanding the examiner [25]

Not explicitly defined (n = 1)

Postoperative surgical complications (n = 2)
- Wound infection/dehiscence, bleeding, stoma prolapse, parastomal hernia, fistula, positive abdominal culture, other [21]
- Wound dehiscence, intestinal stricture, fistula, intra-abdominal abscess, other [25]

Intestinal perforation (n = 4)
- Diagnosed by abdominal X-ray [23]
- Confirmed by surgical findings [26]

Not explicitly defined (n = 2)

Intraoperative complications (n = 1)
- Intraoperative hemorrhage, cardiopulmonary resuscitation or death [25]

Duration of parenteral nutrition (n = 8)
- Time required to reach full enteral feeding [18,22,25–29] *Further defined as* 140 mL/kg/d [29] or 150 mL/kg/d [18]
- Time to re-initiation of enteral feeds after nil per os for NEC [22,29] *Further defined as trophic feeds up to* 20 mL/kg/d [29]
- Duration of parenteral nutrition [25]
- Duration of total parenteral nutrition [20]

Additional operations (n = 2)
- Rescue laparotomy, delayed closure, creation of ostomy, ostomy closure, bowel stricture resection, PDA ligation [21]
- Early surgical reintervention (within 30 days postoperatively), late surgical reintervention (after 30 days postoperatively) [31]

CLABSI, central line-associated blood stream infection; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus.

important outcomes were missed, a non-systematic screening of interventional NEC studies published before 2016 was conducted. This screening mostly yielded outcomes that can be mapped to our reported outcome terms, with the exception of two clinical scores: the modified SOFA score and an organ failure score (Supplement 4).

Diagnostic and preventive studies were excluded from our review, even though they form a considerable part of scientific publications on NEC. We justified this by our prespecified aim to focus on treatment studies on confirmed NEC as a first step towards a tailored NECCOS. The limited number of treatment efficacy studies

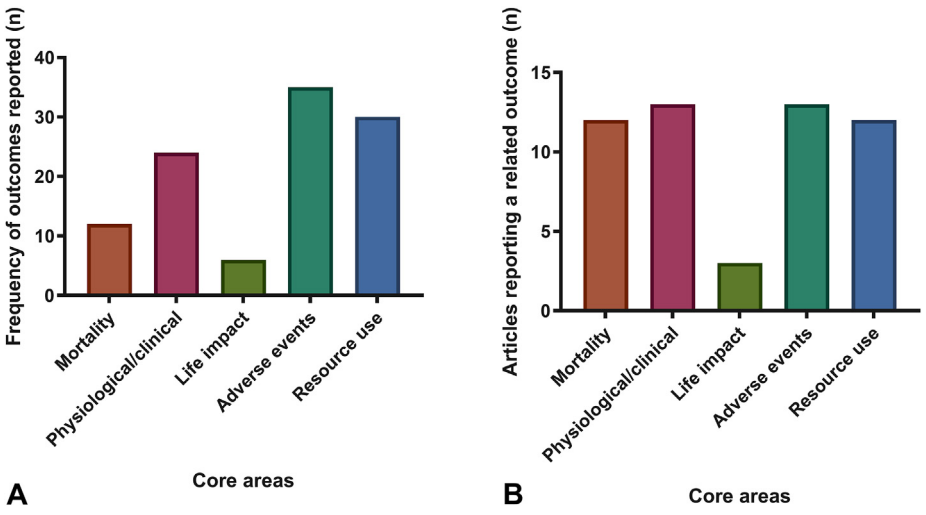


Fig. 2. Representation of core areas in outcome reporting. (A) Frequency of outcomes reported per core area. (B) Number of articles reporting at least one outcome for a core area.

identified by our systematic review highlights the relative paucity of treatment trials for NEC. Yet, studies on novel treatment strategies are crucial to advance outcomes of infants suffering from NEC. A NECCOS focused on outcomes for treatment efficacy studies may stimulate more volume and consistency for this study type.

5. Conclusion

Considerable heterogeneity exists in outcome reporting of interventional NEC studies over the last seven years. In addition, there is a paucity of outcomes in the core area 'Life impact'. Our findings imply hampering of evidence interpretation, meta-analyses for evidence-based guidelines and comparison by clinicians. Future research on treatment efficacy for NEC should report consistent outcomes, and include more outcomes in the 'Life impact' area that may be especially relevant to patients and parents. These findings justify the commitment to developing a COS for NEC.

Previous communication

Not applicable.

Conflicts of interest

All authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2023.06.017.

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