Design and reporting characteristics of clinical trials investigating sedation practices in the paediatric intensive care unit: a scoping review by SCEPTER (Sedation Consortium on Endpoints and Procedures for Treatment, Education and Research)

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ABSTRACT

Objectives: To conduct a scoping review of sedation clinical trials in the paediatric intensive care setting and summarise key methodological elements.

Design: Scoping review.

Data sources: PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature and grey references including ClinicalTrials.gov from database inception to 3 August 2021.

Study selection: All human trials in the English language related to sedation in paediatric critically ill patients were included. After title and abstract screening, full-text review was performed. 29 trials were eligible for final analysis.

Data extraction: A coding manual was developed and pretested. Trial characteristics were double extracted.

Results: The majority of trials were single centre (22/29, 75.9%), parallel group superiority (17/29, 58.6%), double-blinded (18/29, 62.1%) and conducted in an academic setting (29/29, 100.0%). Trial enrolment (>90% planned sample size) was achieved in 65.5% of trials (19/29), and retention (>90% enrolled subjects) in 72.4% of trials (21/29). Protocol violations were reported in nine trials (31.0%). The most commonly studied cohorts were mechanically ventilated patients (28/29, 96.6%) and postsurgical patients (11/29, 37.9%) with inclusion criteria for age ranging from 0–0.5 to 15.0±7.3 years (median ±IQR). The median age of enrolled patients was 1.7 years (IQR: 4.4 years). Patients excluded from trials were those with neurological impairment (21/29, 72.4%), complex disease (20/29, 69.0%) or receipt of neuromuscular blockade (10/29, 34.5%). Trials evaluated drugs/protocols for sedation management (20/29, 69.0%), weaning (3/29, 10.3%), daily interruption (3/29, 10.3%) or protocolisation (3/29, 10.3%). Primary outcome measures were heterogeneous, as were assessment instruments and follow-up durations.

Conclusions: There is substantial heterogeneity in methodological approach in clinical trials evaluating sedation in critically ill paediatric patients. These results provide a basis for the design of future clinical trials to improve the quality of trial data and aid in the development of sedation-related clinical guidelines.

Strengths and limitations of this study

- This is the first scoping review of the literature that has identified all sedation-related clinical trials in the critically ill paediatric population and summarised key methodological elements.
- An extensive, up-to-date search strategy using three databases and grey references was conducted followed by study selection and double data extraction to evaluate inclusion and exclusion criteria, intervention characteristics, measurement instruments and efficacy outcome measures.
- This review was limited by the exclusion of publications in languages other than English, in addition to prospective observational and other interventional studies such as before-and-after studies given the aim of the current study was to assess clinical trial design and reporting.
- Considerations for future trial design and conduct are proposed based on this review’s findings, but these may need to be adapted to be applied to the unique aspects of individual trial objectives.
- Input and consensus from various stakeholders is needed to establish a core set of sedation trial design recommendations and outcome domains in paediatric critical care patients, which may improve the quality and comparability of future trials and aid in the development of sedation-related clinical guidelines.
INTRODUCTION

Sedation of critically ill paediatric patients in the intensive care unit provides anxiolysis and mitigates the stress response, in addition to facilitating the tolerance of respiratory support, invasive procedures and nursing care. An optimal sedation approach can be described as one with ease of initiation and titration, high efficacy and cost-effectiveness, while allowing rapid recovery after discontinuation with minimal adverse effects.

Consensus guidelines, at present, acknowledge the lack of high-quality evidence on which to base practice recommendations for sedation. This lack of evidence has resulted in heterogeneous approaches to management and widespread off-label sedative use across paediatric intensive care units (PICUs). For example, a recent systematic review found that optimal sedation was only achieved in little over half (57.6%) of the time. Of those with suboptimal sedation, assessments found oversedation (31.8%) occurring more frequently than undersedation (10.6%).

Although robust evidence from clinical trials is important in establishing consensus guidelines for optimal sedation in critically ill children, trials remain scarce due to numerous barriers that enhance the complexity of clinical research in this practice area. Tremendous variation in clinical practice exists across medical centres, thereby making the determination of equipoise extremely challenging. In addition, the constraints of clinical care inherent to the high acuity PICU environment lead to challenges in patient recruitment, retention and implementation of intervention in clinical trials.

Existing paediatric critical care trials have been reported to vary widely in their design, conduct and reporting practices. This in turn impedes the ability to meaningfully synthesise results across studies and generate practice recommendations. Recent reviews and recommendations by the Sedation Consortium on Endpoints and Procedures for Treatment, Education and Research are the first to attempt to provide a foundation to guide the design and evaluation of adult and paediatric sedation clinical trials.

In this scoping review, we identified all sedation-related clinical trials in the critically ill paediatric population to assess the current state of key methodological elements. This review focuses on summarising inclusion and exclusion criteria, intervention characteristics, measurement instruments and efficacy outcome measures. The aims of this review are twofold: (1) to identify existing knowledge gaps and challenges related to clinical trial design, particularly those applicable to the paediatric population and (2) to discuss the implications of our findings for future research design. The results of this review have the potential to improve the quality of design and reporting of future sedation-related clinical trials, and promote the interpretability and synthesis of results to aid in the establishment of evidence-based practice guidelines.

METHODS

Study selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension (PRISMA) for Scoping Reviews Checklist was used. This scoping review was not preregistered; it was registered post hoc on Open Science Framework (available at: https://osf.io/mnezu/). PubMed, Embase and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched from database inception through 3 August 2021 for all human clinical trials related to sedation in the PICU setting. Truncated search terms with variations in spelling were used for ‘paediatric critical care,’ ‘sedatives’ and ‘analgesics’ for PubMed with a filter for human clinical trials. These were then translated to the corresponding languages to search Embase and CINAHL (detailed search strategies in online supplemental appendix 1). Clinical trials studying the practice of sedation and/or analgesia, where it was deemed to be a subsidiary component to sedation (eg, continuous opioid infusions administered to intubated, mechanically ventilated patients), were considered to be eligible. Trials published in the English language with full text availability were included. A reference librarian was consulted to review our search strategies, which were optimised through an iterative process of examining the literature and testing the search strategy to ensure maximal capture of pertinent studies.

Sedation-related studies specifically examining assessment scales, pharmacokinetics or pharmacodynamics, or non-pharmacological interventions were not included. We also excluded studies that investigated anaesthetic, sedative or analgesic practices in the operating arena or for intubation and other specific procedures only. Observational studies were omitted, as were trials solely including adults (age greater than 21 years), premature infants or infants in the neonatal ICU. Trials that did not have a control or active intervention (also referred to as the ‘comparator’) arm, in addition to before-and-after studies were also excluded.

Search hits were screened by title and abstract then independently examined through full text review by two authors (JJL or JCP) for inclusion using the Covidence software. A snowballing strategy of inspecting reference lists of key articles was also used to identify relevant studies that may have been missed. An earlier scoping review that identified all published trials in paediatric critical care was examined, and five additional references were added to be screened. ClinicalTrials.gov was also searched; eight unique trials that were not matched to existing publications were identified. These trials are summarised separately, but were not included in the final analysis as there were insufficient data available to extract for the purposes of this scoping review (online supplemental table 1).

Data extraction

A coding manual was developed to extract general trial characteristics, eligibility criteria, intervention...
characteristics and efficacy outcome measures (online supplemental appendix 2). Information on safety and adverse events reporting was not included because these outcomes were beyond the scope of this review. The coding manual was pretested and modified for content and structure in multiple rounds using trials that met inclusion criteria prior to formal extraction. Information was then coded from articles by two authors (JJL or JCP) for final analysis. Discrepancies in coding were discussed among both authors and adjudicated by discussion or a third author (LSS) when necessary.

**Statistical analyses**

All statistical analyses were performed in Microsoft Excel V.15.23. Descriptive statistics were used to summarise trial design and reporting features. Continuous data are reported as median and IQR (IQR=third quartile–first quartile), or range (minimum, maximum). Categorical data are reported as count and percentage (%) where the number of total trials (by subcategory where applicable) was used in the denominator. Some trials had elements which fell into multiple categories, which account for instances in which the count exceeds the total number of trials.

**RESULTS**

In total, there were 1676 unique search hits. After initial title and abstract screening, 165 studies were assessed for full-text eligibility. One hundred and four studies were excluded on the basis of study design (78 observational studies, 20 before-and-after studies, 6 reviews). Other reasons for exclusion included full-text unavailability, non-English language, absent or excluded intervention and comparator (eg, studies solely investigating assessment scales, pharmacokinetics or pharmacodynamics, non-pharmacologic interventions, anaesthetic, sedative or analgesic practices in the operating arena or for intubation and other specific procedures), or wrong patient population (eg, neonates or adults only). Ultimately, 29 trials were included in this scoping review for final analysis. The PRISMA flow diagram is depicted in figure 1.

**Patient and public involvement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.
Trial characteristics

The majority of trials were single centre (22/29, 75.9%), double-blinded (18/29, 62.1%) and a parallel group superiority design (17/29, 58.6%). Eight trials (27.6%) were not blinded in any fashion, and two trials (6.9%) were single-blinded only for outcome assessor. In four trials (13.8%), the design could not be determined, and there was no sample size or power calculation reported.

All trials were conducted in an academic or tertiary care hospital setting, spanning various continents (North America 8/29, 27.6%; South America 1/29, 3.4%; Europe 9/29, 31.0%; Asia 8/29, 27.6%; Africa 2/29, 6.9%; other 1/29, 3.4%). Sponsorship was reported in all but six trials (20.7%). Trials were sponsored by government agencies (7/29, 24.1%), professional organisations/foundations (8/29, 27.6%), institutions or universities (3/29, 10.3%), or industry (3/29, 10.3%).

The vast majority of trials (21/29, 72.4%) were published after 2009 (figure 2). Trial duration lasted at least 1 year in 18 trials (62.1%). In the trials that reported sample size calculation (25/29, 86.2%), the median planned sample size was n=60 with an IQR of 93. 34.5% (10/29) of trials were not able to achieve ≥90% planned enrolment and may, therefore, have been underpowered. 72.4% (21/29) of trials reached ≥90% completion rate. Trial flow details were not consistently available, as 67.9% (n=19) of the 28 trials, which were published after the release of the Consolidated Standards of Reporting Trials (CONSORT) statement, provided a trial flow diagram.

In terms of other specific design characteristics, fewer than one-third of trials reported any use of pretrial staff training (6/29, 20.7%), a run-in period, which was defined as a test period in which the intervention was implemented prior to formal outcome assessment (4/29, 13.8%), or assessment of adherence by staff (9/29, 31.0%). Early termination occurred in three trials (10.3%) and was attributable to an adverse event (1/3, 33.3%), futility (1/3, 33.3%) or slow recruitment (1/3, 33.3%). General trial characteristics are summarised in table 1.

Eligibility criteria

While the inclusion criteria for age was wide (range 0±0.5 to 15.0±7.3 years; not reported 2/29, 6.9%), the ages of enrolled patients for the trials were young (1.7±4.4 years; not reported 2/29, 6.9%). Almost all of the trials (28/29, 96.6%) studied intubated, mechanically ventilated patients. The single trial that did not identify mechanical ventilation as a criterion for inclusion was a weaning trial.27 Of the 28 studies of mechanically ventilated patients, 6 trials (21.4%) examined patients with anticipated early extubation (ie, within 24–48 hours), and 11 studies (39.3%) examined those who needed prolonged intubation (ie, greater than 24–48 hours). In the remaining 11 trials, the duration of mechanical ventilation was not specified. In terms of clinical patient type, post-surgical cardiac (5/29, 17.2%) and post-surgical non-cardiac (6/29, 20.7%) patients were the most commonly studied. A mixed medical and postsurgical population was examined in five trials (17.2%).

Table 2 lists all trial inclusion and exclusion criteria extracted in detail. The most common exclusion criteria that trials reported were: inability to evaluate level of sedation (eg, neurological disease) (21/29, 72.4%), history of drug dependence or withdrawal and previous receipt of sedatives (13/29, 44.8%), receipt of neuromuscular blockers (10/29, 34.5%) or known allergy or adverse reaction to trial drugs (10/29, 34.5%). Severely ill, complex patients (eg, those with haemodynamic instability, major end-organ dysfunction, limited life expectancy, status postemergency or complex surgeries and reoperations, or clinical indications which preclude patient arousal such as open chest, pulmonary hypertension, difficult airway) were also frequently excluded (20/29, 69.0%). Discussion of generalisability occurred in approximately half of the trials (17/29, 58.6%). The effectiveness of randomisation was evaluated in nearly all trials (28/29, 96.6%) with 72.4% (21/29) demonstrating a balanced distribution of characteristics between control and comparator groups.
Intervention characteristics

Trial interventions included comparison of drugs and/or protocols for sedation management (20/29, 69.0%), sedation weaning (3/29, 10.3%), daily interruption of sedation (3/29, 10.3%) and the implementation of a protocolised sedation regimen (3/29, 10.3%). Detailed information on intervention characteristics is presented in table 3.

Providers who administered the intervention were a combination of physicians and nurses in 10 trials (34.5%), physicians, nurses and ancillary staff in 3 trials (10.3%), physicians alone in 8 trials (27.6%), nurses alone in 5 trials (17.2%) and not reported in 3 trials (10.3%). Among the 28 trials examining sedation in intubated, mechanically ventilated patients, 10 trials (35.7%) described ventilator management strategies in their methodology. In all 29 trials included in the review, control and comparator groups received the same types of secondary sedatives in 17 studies (58.6%) and different types of agents in 7 studies (24.1%). Neuromuscular blockade was mostly either not administered (11/29, 37.9%), as prespecified in the trial exclusion criteria, or was not detailed (14/29, 48.3%). Duration of follow-up was extremely heterogeneous, but mostly short term, on the order of days (table 3).

Efficacy assessment and outcome measures

Sedation was assessed using widely variable instruments, including the COMFORT (7/29, 24.1%) or...
## Table 2  Patient eligibility criteria

| Age range for inclusion criteria (years) (median, IQR) | Min 0 (0.5), max 15.0 (7.3) |
|---|---|
| Not reported (n, %) | 2 (6.9) |
| Age of enrolled patients (years) (median, IQR) | 1.7 (4.4) |
| Not reported (n, %) | 2 (6.9) |
| Trial inclusion criteria* (n, %) | |
| Intubated, mechanically ventilated | 28 (96.6) |
| Early extubation (24–48 hours) | 6 (21.4) |
| Prolonged intubation (>24–48 hours) | 11 (39.3) |
| Timeframe of extubation not specified | 11 (39.3) |
| Patient type | |
| Postsurgical cardiac patients only | 5 (17.2) |
| Postsurgical non-cardiac patients only | 6 (20.7) |
| Medical patients only | 2 (6.9) |
| Mixed medical and post-surgical patients, both non-cardiac | 2 (6.9) |
| Mixed medical and postsurgical patients, both cardiac and non-cardiac | 3 (10.3) |
| Trauma patients | 2 (6.9) |
| Trial exclusion criteria* (n, %) | |
| Inability to evaluate level of sedation (eg, neurological disease) | 21 (72.4) |
| Use of neuromuscular blockers | 10 (34.5) |
| Contraindications to arousal (eg, pulmonary hypertension, difficult) | 7 (24.1) |
| Airway, open chest | |
| Limited life expectancy (eg, do not-resuscitate order) | 5 (17.2) |
| Status—postcardiac arrest | 2 (6.9) |
| Consideration for organ procurement | 1 (3.4) |
| Haemodynamic instability (eg, use of vasopressors, inotropes) | 7 (24.1) |
| Respiratory complications | 3 (10.3) |
| Other major end-organ dysfunction | 19 (65.5) |
| Chronic hypertension | 3 (10.3) |
| History of drug dependence or withdrawal, previous receipt of sedatives | 13 (44.8) |
| Pregnancy | 4 (13.8) |
| Enrolment in another conflicting trial or previous enrollment in current trial | 5 (17.2) |
| Known allergy or adverse reaction to trial drug(s) | 10 (34.5) |
| Prematurity | 1 (3.4) |
| Emergency or complex surgeries, reoperation | 5 (17.2) |
| No of trials that discussed generalisability (n, %) | 17 (58.6) |
| Severity of illness evaluated* (n, %) | |
| Yes, by use of score (eg, Paediatric Risk of Mortality, Paediatric Index of Mortality) | 23 (79.3) |

Continued
Comparator (27/29, 93.1%; 27/29, 93.1%, respectively) groups were usually directed by an assigned protocol.

Twenty one (72.4%) trials reported a single primary outcome, which included duration of mechanical ventilation (8/29, 27.6%), cumulative dose of sedative (6/29, 20.7%), time under adequate sedation (4/29, 13.8%) and rescue drug needed (3/29, 10.3%). In four trials (13.8%), there were two or more primary outcome measures. In four trials (13.8%), no primary outcome measure was defined.

**DISCUSSION**

This scoping review found that clinical trials evaluating sedation in critically ill paediatric patients differ considerably in their methodological approaches including general design and eligibility criteria, intervention types,
follow-up, assessments and outcome measures. Varying patient populations (eg, medical vs surgical, cardiac vs non-cardiac, prolonged intubation vs ‘fast track’ or early extubation), polypharmaceutical approaches, and outcomes were investigated, which were further complicated by differences in the implementation of and adherence to protocols for sedation assessment and management. Such heterogeneity makes it difficult to compare results across studies and prevents the use of meta-analysis to synthesise evidence and establish generalisable practice recommendations. A number of gaps and inconsistencies in current trial design and reporting characteristics were identified in this review and warrant further discussion.

**Trial design**

Publications of trials were from various continents with the majority of publications occurring in this past decade. Most trials were small, single centre, and performed in academic children’s hospitals. A substantial number of trials were not blinded in any fashion. While the absence of blinding may introduce a considerable source of bias, this finding should also be considered in the context of clinical constraints built-in to intensive care. Blinding was frequently described to be challenging or not feasible

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**Table 4** Efficacy assessment and outcome measures

| Sedation assessment method* (n, %)          |     |
|-------------------------------------------|-----|
| COMFORT scale                             | 7 (24.1) |
| COMFORT-behaviour scale                   | 6 (20.7) |
| Ramsay/modified ramsay sedation scale     | 7 (24.1) |
| Richmond-agitation sedation scale         | 1 (3.4)  |
| State Behavioural Scale                   | 4 (13.8) |
| Nurse interpretation of sedation score    | 2 (6.9)  |
| Hartwig scale                             | 1 (3.4)  |
| PICU sedation scale                       | 4 (13.8) |
| Modified motor activity assessment scale  | 2 (6.9)  |
| Tracheal suctioning score                 | 4 (13.8) |
| Riker Sedation-Agitation Scale            | 1 (3.4)  |
| Modified Narcotic Withdrawal Scale        | 1 (3.4)  |
| Other                                     | 3 (10.3) |
| Not reported                              | 1 (3.4)  |

**Pain assessment method* (n, %)          |     |
| Faces, legs, activity, cry, consolability (or modified) score | 6 (20.7) |
| Numeric Rating Scale                       | 3 (10.3) |
| Wong-Baker Faces Pain Scale               | 2 (6.9)  |
| Behavioural Pain Score                    | 1 (3.4)  |
| Visual Analogue Score                     | 3 (10.3) |
| Not reported                              | 18 (62.1) |

**Sedation level assessor* (n, %)          |     |
| Physician (second party reporting)        | 4 (13.8) |
| Researcher (second party reporting)       | 6 (20.7) |
| Nurse (second party reporting)            | 18 (62.1) |
| Not reported                              | 5 (17.2) |

**Frequency of sedation level assessment (n, %) |     |
| Every 1 hour or more often                | 7 (24.1) |
| Every 2–4 hours                           | 19 (65.5) |
| Less frequent than every 2–4 hours        | 1 (3.4)  |
| As clinically indicated, not otherwise specified | 2 (6.9) |

**Sedation assessment in control group (n, %) |     |
| Protocolised                               | 25 (86.2) |
| Standard care                              | 4 (13.8)  |

**Sedation management in control group (n, %) |     |
| Protocolised                               | 22 (75.9) |
| Individual physician judgement             | 2 (6.9)   |
| Standard care                              | 5 (17.2)  |

**Sedation assessment in comparator group (n, %) |     |
| Protocolised                               | 27 (93.1) |
| Standard care                              | 2 (6.9)   |

**No of primary outcomes (n, %) |     |
| 1                                        | 21 (72.4) |
| ≥2                                       | 4 (13.8)  |

**Primary outcome measure* (n, %)          |     |
| Cumulative dose of sedative               | 6 (20.7) |
| Time under adequate sedation              | 4 (13.8) |
| Adequate sedation                         | 2 (6.9)  |
| Duration of mechanical ventilation (ie, time to extubation) | 8 (27.6) |
| Length of PICU stay                       | 1 (3.4)  |
| Rescue drug needed                        | 3 (10.3) |
| Not reported                              | 4 (13.8) |
| Other                                     | 6 (20.7) |
| Completion of assigned taper              | 1 (3.4)  |
| Feasibility                               | 1 (3.4)  |
| Ventilatory effects                       | 2 (6.9)  |
| Biochemical markers                       | 1 (3.4)  |
| Withdrawal syndrome                       | 1 (3.4)  |

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*Trials reported multiple sedation and pain assessment methods, assessors and primary outcome measures, which account for total number of trials exceeding n=29.

PICU, paediatric intensive care unit.
to execute depending on the nature of the trial and the
paramount considerations of patient safety and clinical
management.

No clear description of the rationale for sample size
was reported in four trials. While this may have been a
result of reporting omission rather than a deficiency in
design, it is important to note given the fundamental
nature of power calculation in quality trial design. A total
65.5% (19/29) of trials was able to enrol at least 90%
of the planned sample size with a similar proportion of
patients (21/29, 72.4%) who were able to complete the
trial once enrolled. This is a positive finding for recruit-
ment and retention of the trial subjects, since recruit-
ment has historically been described as a major barrier to
conducting paediatric trials. Challenges to recruitment
were multifactorial due to the stress and complexity of the
PICU environment. Consistently cited reasons included
parental and provider reluctance, clinical work burden,
as well as sensitivity in timing of consent. These diffi-
culties may also reflect the greater issue of establishing
consensus on equipoise in intensive care research, owing
to significant variations in clinical practice as a result of
patient-related, provider-related and site-related factors.
Finally, trial completion was challenging, as several trials
noted significant drop-out rates as the clinical course of
enrolled subjects evolved over time. In our analysis, 67.9%
(19/28) of trials provided the CONSORT flow diagram,
which made it difficult to assess trial characteristics.

Eligibility criteria
Based on the inclusion criteria, age spanned a wide range,
but the enrolled patients were young with a median age
of approximately 1.7 years. The vast majority of trials eval-
uated those patients who were mechanically ventilated,
some of whom were expected to be extubated early and
others requiring prolonged intubation. The time frame
was not specified in 11 trials, and the lack of such spec-
cificity may be problematic since patients likely require
different approaches for sedation based on the timing of
extubation. Thus, outcomes may be expected to be
quite variable for patients who had a relatively brief vs
prolonged duration of mechanical ventilation.

Postsurgical patients, either with underlying cardiac
or non-cardiac conditions, were the most commonly
studied. These subpopulations should ideally be studied
separately as unique approaches for sedation, analgesia
and mechanical ventilation are often necessary. Common
criteria for exclusion included the presence of neurolog-
ical disease or other conditions impeding the evaluation
of sedation level and the use of neuromuscular blockers.
Severely ill, complex patients such as those with haemo-
dynamic instability, major end-organ dysfunction, limited
life expectancy or complex medical/surgical histories
were also frequently excluded; these subsets of patients
remain an understudied cohort. Given that paralytics are
frequently administered in actual clinical practice, their
exclusion from clinical trials may be problematic and
limit generalisability. It was frequently noted that while
stringent inclusion and exclusion criteria may improve
homogeneity of the trial population, recruitment and retent-
ion, in turn, become more challenging.

Intervention characteristics
This review found intervention type varied and mostly
compared unique drugs and/or protocols for sedation.
Sedation weaning, interruption and protocolisation were
also areas of interest. Many trials reported the administra-
tion of secondary sedatives in addition to those specific
drugs being evaluated, with approximately a quarter of
trials describing a divergent profile of drugs between the
control and comparator arms. While the administra-
tion of multiple sedatives and analgesics is expected in
the critical care setting where the escalation of care is
commonplace, this serious confounding makes it difficult
to meaningfully interpret the data. Other areas that were
not well described in the majority of trials, such as venti-
lator management strategy and use of neuromuscular
blockade, may be additional confounding factors.

Adherence to protocol is a critical element in trials, but
this was only assessed in 31.0% (9/29) of trials. Similarly,
the use of pretrial training and a run-in period was gener-
ally rare. While these processes would be ideal to ensure
adequate quality, their labour-intensive, time-intensive
and cost-intensive nature may limit their execution in real
practice. Finally, the duration of follow-up was heteroge-
neous in clinical trials, but typically short term, on the
order of days.

Efficacy assessment and outcome measures
Sedation assessment was found to be regularly proto-
colised with frequent assessments performed most often
by bedside nurses. Management of sedation was also directed
by an established protocol in the vast majority of cases,
though protocol adherence was not usually evaluated as
discussed previously. Instruments used to assess sedation
levels varied considerably. The COMFORT or COMFORT-
Behaviour Scales were the most frequently used, though
this varied depending on the age of enrolled subjects and
geography. Although these instruments have been exten-
sively studied and validated for the assessment of sedation
and analgesia in PICU patients, a significant limiting
factor is that they cannot accurately score sedation or
pain when patients are paralysed. The second most
frequently used instrument was the Ramsay/Modified
Ramsay Sedation Scale, but this instrument has only been
validated for adult ICU patients. Additionally, while
these scales can adequately assess sedation, they have not
been designed to evaluate pain.

We found that the scoring of pain, distinct from seda-
tion level, was not reported in the majority of trials. The
discrimination of inadequate sedation versus analgesia
is inherently a difficult clinical problem, though may be
important to consider carefully when evaluating optimal
instrument selection. This issue is particularly chal-
lenging when caring for paediatric patients who are often
unable to verbalise their symptoms or will fully cooperate

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with necessary interventions and bedside care. Indeed, oversedation has been reported to be more of an issue compared with undersedation in the PICU setting. This is likely due to a myriad of issues including difficulties with identifying a patient’s needs, particularly in those aforementioned younger, preverbal patients and a desire to avoid the serious risks of undersedation at all costs such as self-extubation or the removal of lines and devices. Weaning and optimising sedation levels may also naturally be overlooked or suspended when urgent clinical matters requiring immediate attention arise.

The most common primary outcome measures included duration of mechanical ventilation, cumulative dose of sedation, time under adequate sedation and rescue drug needed. While these may be appropriate surrogates to assess clinical efficacy, there are certainly other important outcome dimensions in sedation management that merit consideration for further study. Patient-centred and/or family-centred outcomes is one such example of an outcome domain that is understudied, but may be important to consider, particularly in the paediatric population. The level of patient and/or family satisfaction with the sedation experience can provide a valuable assessment of the effects of analgesia, anxiolysis, amnesia, as well as absence or presence of unfavourable outcomes, all of which may have a significant impact on sedation management (eg, patient and/or family compliance, provider decision making). In addition, while it is recognised that there needs to be a better understanding of the effects of sedation on longer-term outcomes, such as cognition or other brain health-related outcomes, currently, there remains a need for further research.

Outcomes selection should be balanced based on clinical relevance, scientific validity, and feasibility to optimise trial success.

Considerations for future trial design and conduct are proposed in this review (table 5), but these may not be suitable for all sedation trials. An adaptation of these considerations may be more appropriate to be applied to the unique aspects of individual trial objectives and design. The pragmatic trial design may be a useful option to consider as its unique approach allows for broad patient recruitment and the evaluation of interventions in real life, complex practice conditions, which are subject to the influences of various forces present in an open system like the PICU. Pragmatic trials may also be particularly valuable in scenarios where blinding is infeasible, a limitation which was discussed earlier. Cluster design trials with or without stepped-wedge elements, which involve random and sequential crossover of clusters from control to intervention until all clusters are exposed, are another example of a suitable design approach. The Sedation AND Weaning in Children trial provides an exemplary model for how a pragmatic multicentre, stepped-wedge, cluster trial may be successfully carried out in the PICU setting.

| Category                              | Considerations                                                                                                                                 |
|---------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Eligibility                           | ► Report inclusion and exclusion criteria.                                                                                                    |
|                                       | ► Consider how clinical criteria for trial participants (eg, medical vs surgical, cardiac vs non-cardiac) may affect outcome analysis.        |
|                                       | ► If mechanical ventilation is an inclusion criterion, report ventilation strategy and specific parameters in terms of expected duration of ventilation and its plausible effect on outcome analysis. |
| Recruitment and retention             | ► Consider broader inclusion criteria to facilitate recruitment and retention.                                                                  |
|                                       | ► Consider collaboration across multiple sites to ensure adequate statistical power.                                                             |
|                                       | ► Report sample size calculation and rationale.                                                                                               |
|                                       | ► Report CONSORT flow diagram to describe all trial phases (screening, enrolment, randomisation and completion).                              |
|                                       | ► Discuss any challenges with recruitment, retention and adherence and any contributors to either success or failure.                        |
| Intervention, adherence and blinding  | ► Describe intended intervention and trial protocols.                                                                                            |
|                                       | ► Consider monitoring protocol violations and assessing adherence to defined intervention.                                                      |
|                                       | ► Consider the use of pretrial training or a run-in period to promote adherence.                                                               |
|                                       | ► Report the presence or absence of blinding to the intervention and any challenges therein.                                                   |
|                                       | ► Monitor and encourage the use of a consistent set of adjuvant sedatives and paralytics in control and comparator arms.                      |
|                                       | ► Consider the use of a pragmatic or cluster trial design with or without stepped-wedge elements.                                               |
| Efficacy assessment and outcome measures | ► Report the primary outcome measure and whether it was prespecified.                                                                          |
|                                       | ► Indicate how and by whom the outcome measure was assessed.                                                                                   |
|                                       | ► Consider strengths and limitations of assessment instruments during selection process.                                                        |
|                                       | ► Consider extending follow-up duration to include longer term outcomes when possible.                                                         |
|                                       | ► Obtain stakeholder input and consensus to develop a core set of efficacy outcomes.                                                           |

Considerations for future trial design and reporting based on this review’s results are summarised.

CONSORT, Consolidated Standards of Reporting Trials; ICUs, intensive care units.
Strengths and limitations
Strengths of this review include strict adherence to PRISMA guidelines and an exhaustive search strategy to identify all relevant trials up to date, including a snowballing strategy and looking at grey literature. Data extraction of an extensive range of design and reporting elements was executed, and key issues in trial methodology were uncovered.

This review is limited in that we mainly looked at publications of paediatric sedation trials in peer-reviewed literature. Prospective observational and other interventional studies such as before-and-after studies were excluded given the aim of this review was to review trial design and reporting. We acknowledge the significant prevalence and value of other types of studies in informing the paediatric critical care literature addressing sedation practices, and a separate review describing these studies may be worth conducting. We view this review's findings as a starting point for stakeholders' discussions (eg, multidisciplinary experts from academia, industry, FDA, patients and their families) and acknowledge the numerous challenges inherent to the PICU setting, which make the execution of clinical trials exquisitely complex. Lastly, safety and adverse events reporting was not discussed within this review given its present focus on general design and reporting of efficacy outcomes.

CONCLUSIONS
This scoping review examined paediatric sedation clinical trials in the critically ill population and found considerable heterogeneity in design and reporting characteristics. Current gaps and variations in eligibility criteria, intervention characteristics and efficacy outcome measures were summarised, and considerations for trial design and execution were proposed. Findings from this review may provide a basis for the development of a core set of trial design recommendations and outcome domains for sedation trials in paediatric critical care patients, which may improve the quality and comparability of future clinical trials. Input and consensus from various stakeholders is needed to establish evidence-based practice guidelines.

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