

Title: Pediatric perioperative outcomes: protocol for a systematic literature review and identification of a core outcome set for infants, children, and young people requiring anesthesia and surgery

Running head: Pediatric perioperative outcomes

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What is already known about the topic

- Determining how best to measure/define a successful anesthetic in infants, children and young people is an important unmet need.
- Core outcome sets (COS) can improve standardized reporting to inform evidence-based practice, and support evaluation and quality improvement of perioperative care.

What new information this study adds

- Methodology based on the Core Outcome Measures in Effectiveness Trials (COMET) initiative and adult perioperative standardized endpoint projects can identify currently reported pediatric perioperative outcomes.
- Developing an agreed core outcome set for pediatric perioperative care requires consideration of age-specific outcomes and clinical endpoints

SUMMARY

Clinical outcomes are measurable changes in health, function, or quality of life that are important for evaluating the quality of care and comparing the efficacy of interventions. However, clinical outcomes and related measurement tools need to be well-defined, relevant and valid. In adults, Core Outcome Measures in Effectiveness Trials (COMET) methodology has been used to develop core outcome sets for perioperative care. Systematic literature reviews identified Standardized Endpoints (StEP) and valid measurement tools, and consensus across a broader range of relevant stakeholders was achieved via a Delphi process to establish Core Outcome Measures in Perioperative and Anaesthetic Care (COMPAC). Core outcome sets for pediatric perioperative care cannot be directly extrapolated from adult data. The type and weighting of endpoints within particular domains can be influenced by age-dependent differences in the indications for and/or nature of surgery and medical co-morbidities, and the validity and utility of many measurement tools vary significantly with developmental stage and age. Involvement of parents/carers is essential as they frequently act as surrogate responders for preverbal and developmentally delayed children, parental response may influence child outcome, and parental and/or child ranking of outcomes may differ from those of health professionals. Here we describe formation of the international Pediatric Perioperative Outcomes Group, which aims to identify and create validated, broadly applicable, patient-centered outcome measures for infants, children and young people. Methodologies parallel that of the StEP and COMPAC projects, and systematic literature searches have been performed within agreed age-dependent subpopulations to identify reported outcomes and measurement tools. This represents the first steps for developing core outcome sets for pediatric perioperative care.

1 THE NEED FOR CORE OUTCOME SETS FOR PEDIATRIC PERIOPERATIVE CARE

1.1 Rationale for consensus in outcome reporting

Clinical outcomes are measurable changes in health, function or quality of life which, in conjunction with the structures (settings, qualifications of providers, administrative systems for care) and processes (components of care) surrounding care delivery, are important in evaluating the quality of health care in adults^{1,2} and children.^{3,4} However, clinical outcomes and related measurement tools need to be well-defined, relevant and valid to contribute to quality improvement⁵ and to enable comparative trials to assess the clinical efficacy of different interventions.⁶

A number of worldwide initiatives have been established to improve the relevance and consistency of selection of clinical outcomes and their measurement. The Core Outcome Measures in Effectiveness Trials (COMET) initiative^{7,8} supports the development of agreed standardized core outcome sets that can be consistently reported across all trials to: reliably discriminate between beneficial, ineffective or harmful interventions;⁹ allow combination of data in high-quality systematic reviews and meta analyses;¹⁰ compare efficacy of different interventions;⁶ inform evidence-based practice; and drive improvements in care.^{7,8} In addition, standardized and clearly-defined endpoints should be of significance to key stakeholders, relevant to the patient, clinically important, and valid to ensure subsequent impact on health care delivery or policy.¹¹ COMET resources include details of standardized methodology,^{8,12} a database of current and completed projects,⁷ and updated reviews.¹³

A core outcome set (COS) is defined as a minimum set of outcomes to be measured and reported in clinical trials for a specific condition. However, core outcome sets can also be used for research designs other than randomized controlled trials, and for quality improvement projects.¹² Quality improvement initiatives related to surgical and perioperative care, such as the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP)¹⁴ and the Perioperative Quality Improvement Programme in the United Kingdom¹⁵ focus on adult practice, but similar approaches are also relevant for pediatric surgery^{3,16} and perioperative care.^{4,17-19}

1.2 Core outcome sets in adult perioperative care

Determining which outcomes should be used to measure success is a research priority for anesthesia and perioperative care.²⁰ COMET methodology^{8,12} is being utilized to develop core outcome sets for perioperative care in adults (age ≥ 18 years).^{21,22} Systematic reviews have extracted reported outcomes, and expert interpretation and consensus identified Standardized Endpoints (StEP) for Perioperative Medicine, valid measurement tools, and clinically-important times for assessment. In parallel to this 'top-down approach', a 'bottom up' approach to achieve consensus across a broader range of relevant stakeholders that includes patients and carers is achieved via a Delphi process.

Participants rank the importance of proposed endpoints (scale 1-9; 1-3 'not that important or invalid', 4-6 'important but requires revision', 7-9 critical for inclusion'²³). Final recommendations are based on identifying items critical for inclusion, plus rating the face and content validity, reliability and feasibility of the specific endpoints or measurement tools²³ to establish the Core Outcome Measures in Perioperative and Anaesthetic Care (COMPAC).^{21,22} Results have been published across several pre-determined domains²¹ that include: clinical indicators,²⁴ infection and sepsis,²⁵ renal endpoints,²⁶ postoperative cancer outcomes,²⁷ pulmonary complications,²⁸ blood loss and transfusion,²⁹ patient comfort,²³ and patient-centred outcomes.³⁰

1.3 Need for pediatric-specific core outcome sets

Core Outcome Sets for pediatric perioperative care cannot be directly extrapolated from adult data. The type and weighting of endpoints within particular domains can be influenced by age-dependent differences in the type and/or indications for surgery, medical co-morbidities, and the range of complications. In addition to differing from adults, outcomes within pediatric practice may require consideration of specific age-based subpopulations. In adults, ischemic heart disease and myocardial infarction are important cardiovascular outcomes;²¹ whereas congenital heart disease influences mortality,³¹ risk of perioperative cardiac arrest,^{32,33} and potential clinical indicators such as unplanned intensive care admission²⁴ in children. Readmission is a core clinical indicator,²⁴ but reasons for re-hospitalization after discharge also differ between adults and children.³⁴

Perioperative mortality is a key outcome for adult practice. However, odds of death within 48 hours of surgery are much lower in 1-18 year olds than all older age groups, and risk is greatest for neonates and infants under 1 year of age (US National Anesthesia Clinical Outcomes Registry)³⁵ Similarly, data from a tertiary pediatric hospital documents low overall perioperative mortality in children and adolescents, but higher rates in neonates.³¹ Additional levels of physiological instability³⁶ or potential long-term effects on neurodevelopmental outcome³⁷ or pain response³⁸ may also result in core outcome sets for neonates and infants differing from older children.

The validity and utility of many measurement tools vary significantly with developmental stage and age. While important standardized endpoints for patient comfort domains in adults²³ such as pain, postoperative nausea and vomiting, quality of recovery, time to gastrointestinal recovery, time to mobilization and sleep quality, are also important for children, measurement tools are influenced by age and cognitive development (e.g. pain intensity),³⁹ may require further validation across pediatric age groups (e.g. quality of recovery scores), or are not appropriate for all ages (e.g. reporting nausea, mobilization in neonates and infants). Parents/carers frequently act as surrogate responders for preverbal and developmentally delayed children, and play significant roles in reporting outcomes such as pain, analgesic requirements and behavioral change following

discharge.⁴⁰ In addition, as parental response may influence child outcome (eg. parental pain catastrophizing and persistent postsurgical pain⁴¹) parent-reported measures will be relevant for some domains. Engagement of key stakeholders is an important part of the COMET process, and patients' reporting or ranking of different outcomes may differ from those of health professionals.⁴² There is a clear need to include views of children and adolescents where possible, and to involve parents/carers⁴³ and include parent-reported tools in developing core outcome sets for pediatric perioperative care.

1.4 International collaboration in core outcome set (COS) development

Diverse international involvement in core outcome set development helps ensure identification of outcomes that are broadly valid and applicable for use in pediatric populations in different countries around the globe. Consensus requires an international collaboration¹³ as usual practice,⁴⁴ and limited resources⁴⁵ may influence clinical indicators,^{46,47} and the relative importance of different outcomes. Ideally, the validity, reliability and sensitivity to change of measurement tools is confirmed in different populations to ensure accurate translation of instructions for observers (e.g. FLACC score for pain^{48,49}) and child understanding of pictorial representations for self-report (e.g. PONV⁵⁰ or pain⁴⁹). Behavioral outcomes following general anesthesia in children may be influenced by cultural differences, and while the same outcome tools may be used,⁵¹ the weighting of individual items and the consistency of clinically significant cut-off values should be confirmed in different clinical settings and populations (e.g. Pediatric Anesthesia Emergence Delirium Scale in Asian children⁵²).

2 FORMATION OF PEDIATRIC PERIOPERATIVE OUTCOMES GROUP

2.1 Development of the PPOG

The Pediatric Perioperative Outcomes Group (PPOG) is an international collaboration of clinicians and researchers that is pursuing the question "How do we measure/define a successful anesthetic in infants, children and young people?"⁵³ A Steering Committee was formed to decide on foundational work, formalize the PPOG Charter, and appoint a Project Advisory Group that included leaders in pediatric clinical research and quality improvement, as well as representatives from the StEP-COMPAC Group to guide the process of pediatric core outcome set development.

2.2 Registration, group charter, definition of scope and basis for methodology

PPOG methodology aimed to parallel that of the StEP and COMPAC projects for adult perioperative care, and the project was registered with the COMET Initiative (<http://www.comet-initiative.org/studies/details/1096>). Consensus was sought for a phased approach, with an initial focus on systematic reviews of the literature to identify reported outcomes and related

measurement tools. Subsequent phases will include stakeholder consultation to rank candidate outcomes and develop a core outcome set.

The PPOG Charter was approved, and states both the Vision (“To have a set of validated, broadly applicable, patient-centered perioperative core outcome measures in infants, children and young people”) and Aim (“To facilitate the identification and creation of validated, broadly applicable, patient-centered outcome measures for infants, children and young people) of the group. In accordance with established guidelines,^{8,12} the PPOG aims to demonstrate transparency with open and detailed reporting.⁶

The Steering Committee agreed that the scope of the project covers patients under the age of 18 years undergoing anesthesia and surgery, but excluding those having surgery for congenital heart disease. General anesthesia or sedation for non-surgical indications (for instance to facilitate imaging), that may require variable depths of anesthesia/sedation and incorporate a wide range of pharmacological and/or non-pharmacological techniques, was also excluded. The COS would encompass outcomes related to the perioperative care of the patient, i.e. every aspect of patient care before, during and after surgery other than those relating to the technical aspects of surgery and anesthesia itself.²⁰

2.3 Membership

In keeping with COMET recommendations,^{11,12} and as initially planned,⁵³ the PPOG includes international representatives from multiple countries (Table 1). This facilitates searching non-English databases, and will enhance generalizability of results across countries and different health services.

2.4 Identification of pediatric subpopulations and outcome domains

Whereas the StEP-COMPAC is a broad initiative focusing on adults having surgery or major surgery, the PPOG Steering Committee recognized that a single core outcome set would not be broadly applicable to all pediatric perioperative patients. A Delphi process was used to determine the key pediatric subpopulations. In the first step, all members submitted a list of potential candidate subpopulations via a REDCap survey.⁵⁴ The responses were aggregated and ranked in importance in two Delphi survey rounds which were followed by a face-to-face consensus meeting in April 2018. The threshold for consensus was set at 75% agreement.

Through this process, group members agreed that patient age has a significant impact on the type of surgery required, medical co-morbidities, and the validity and utility of different measurement tools. Consensus was reached for the following key age-dependent subpopulations: i) neonates and former preterm infants (up to 60 weeks post conception age); ii) infants less than 1 year (excluding neonates); iii) toddlers and school age children (1-12 years); and iv) adolescents (defined here as 13-17 years).

3 METHODOLOGY FOR PEDIATRIC PERIOPERATIVE OUTCOMES SYSTEMATIC REVIEW

3.1 Bibliographic database search strategy

A systematic search of the EMBASE database identified publications (between 2008 and 2018 inclusive) that reported pediatric perioperative outcomes or outcome measures (Table 2; search strategy). In accordance with the PPOG scope, studies in children undergoing surgery for congenital cardiac disease were excluded with specific search terms. An initial search included all EMBASE-listed journals; while a second search focused on pre-agreed journals identified by the Steering Committee as most likely to publish relevant articles. Results of the two searches were combined. To identify additional papers for either full-text or abstract-only analysis, searches of the Chinese literature database and LILACS (Latin America and Caribbean literature) were performed by group members in the relevant countries using similar search strategies.

3.2 Abstract screening

PPOG members were randomly allocated a number of abstracts to screen on-line, and mark as Included, Excluded or Unsure. Any uncertainties or conflicts regarding abstract inclusion/exclusion were resolved by the Principal Investigator (P.S.). All PPOG members were engaged in a WhatsApp group, overseen by the Principal Investigator, to answer queries or request clarification.

Abstracts were included if they reported outcomes related to aspects of anesthetic and perioperative care, but excluded if outcomes related only to the surgery itself. For example, a trial evaluating postoperative pain following two different types of tonsillectomy patients was included, whereas one reporting anastomotic leakage with two types of bowel surgical technique was excluded. Similarly, anesthesia-specific intra-operative outcomes (such as intraocular pressure during airway manipulation or supraglottic airway leak pressure) were excluded, while trials including outcomes such as anxiety or postoperative vomiting with different anesthesia techniques were included. Trials reporting perioperative relevant outcomes such as length of stay or perioperative complications in addition to anesthesia-specific or surgery-specific outcomes were included. Studies examining sedation in the emergency department, or sedation for other indications or non-surgical procedures, were excluded.

Data related to study type, sample size, study population, age group, perioperative outcome and method of measurement were extracted based on information provided in the abstract only.

3.3 Full text review

With consensus from the Steering Committee, full-text review was limited to pre-agreed anesthesia, pediatric, surgical and general medical journals (Table 3). For each sub-population, full text articles were distributed across the whole PPOG membership for review. Data was entered into a REDCap

database extraction form⁵⁴ with standardized domains: manuscript title; journal; study type (randomized trial, other prospective trial, retrospective or observational study, other); sample size; and study population (e.g. tonsillectomy; orthopedic surgery). Each reported perioperative outcome and related measurement tool was recorded.

3.4 Results of screening and outcomes extraction

Primary screening identified 4161 abstracts that initial reviewers marked as “Included” or “Unsure”. Secondary screening for inclusion and removal of duplicates resulted in 707 abstracts being included for analysis. Abstracts were further distributed into full-text review or abstract only review, and allocated to each age-dependent subpopulation (Figure 1; PRISMA Flow Diagram⁵⁵). Extracted outcome lists were then forwarded to Lead Investigators of each subpopulation for further domain-specific grouping.

3.5 Grouping of perioperative outcomes and thematic domains

It was agreed that key candidate outcome domains would not be determined *a priori* but would instead be defined following the identification of reported outcomes in the systematic reviews, and open to modification following subsequent stakeholder engagement.

Following data extraction, all outcomes and their measures from both full-text and abstract-only arms were combined and organized into a draft set of domains/categories by the lead investigators for each sub-population. Preliminary outcome domains were initially based on COMPAC-StEP groupings (e.g. patient comfort, patient-centered outcomes, clinical indicators, healthcare resource utilization).²¹ Each draft domain set was distributed to all PPOG group members for comment regarding the classification of outcomes and/or the need for reorganization to establish thematic outcome domains. Additional details are reported in the related manuscripts.

4 METHODOLOGY FOR STAKEHOLDER ENGAGEMENT AND SELECTION OF CORE OUTCOME SETS

4.1 Initial stakeholder consultation exercise

Perioperative outcomes that are prioritized by pediatric patients, their families, physicians, and other perioperative healthcare providers remain to be identified and may not be represented in recent published literature. Acknowledging this, the PPOG will employ a bottom-up, co-production approach²¹ to identify additional outcomes that were not among those extracted in the systematic literature reviews. To achieve this, the PPOG investigators will engage patients (when feasible or appropriate), parents, perioperative nurses, surgeons, and anesthesiologists to specify perioperative outcomes that are important to them.

4.2 Identification and recruitment of participants

A purposive sampling approach will be used to recruit a target number of each stakeholder group from each country with representation in PPOG. Stakeholder groups will include surgeons from various pediatric surgical subspecialties (general surgery, otolaryngology, urology, plastic/reconstructive surgery, orthopedic surgery, neurosurgery), patients and parents, anesthesiologists, pre- and post-anesthesia care unit nurses, and surgical ward nurses. The nature of contact and its wording will be tailored to the stakeholder category.

4.3 Data collection and identification of outcomes

A mixed-methods approach will be employed with the above stakeholder groups to explore the question of which outcomes are important for children and families after anesthesia and surgery. This will be accomplished via one-on-one freelist methods (where participants list everything they consider to be relevant),⁵⁶ semi-structured interviews (where researchers use a pre-determined interview schedule as a basis for broader discussion with respondents) , or focus groups (where one or two researchers mediate an open group discussion of several respondents). Stakeholder or site preference, and/or practical or cultural factors will also be considered in selecting the specific methodologies employed. PPOG investigators conducting these stakeholder engagement activities will receive specific training in these techniques by experts at the Mixed Methods Research Laboratory (MMRL) at the University of Pennsylvania. The MMRL will perform interval examinations of collected data for methodologic quality assurance.

4.4 Long list outcome creation/merging, grouping into domains

For each age-based subpopulation, the outcomes identified from the stakeholder consultation exercise will be combined with those identified from the systematic reviews. Subsequently, these long lists will be reviewed, duplicate outcomes removed, and similar outcomes may be grouped together. This process will result in a list of candidate outcomes and outcome domains for the core outcome set for each subpopulation.

4.5 Outcomes ranking by stakeholders with Delphi process and selection of core outcome set outcome domains

The long list of candidate outcomes will be presented to representatives of stakeholder groups in an international multi-round online Delphi survey. Stakeholders will be asked to rate the importance of each of the outcomes presented, using a Likert scale of 1-9 with 1 representing “not important” and 9 representing “very important.” Stakeholders will be engaged in a manner analogous to that used for the initial stakeholder consultation exercise described above, and will include patients, parents, perioperative nurses, surgeons, and anesthesiologists. Delphi survey data will be reviewed by sub population Lead Investigators and the steering committee, with consensus thresholds defined *a priori*.

4.6 Final consensus meeting

Following completion of the Delphi process, a face-to-face consensus meeting of experts will be held to review and finalize the outcome domains in the core outcome set for each subpopulation.

Attendees will be provided with the results of the third Delphi round of outcome ranking, including the scores for each outcome per stakeholder group and status of any consensus. Following discussion moderated by the meeting chair, each outcome that reaches consensus will be identified, and “what to measure” will be included in the finalized COS.

The next phase of the project will address the question “*How do we measure the core outcomes?*” For included items, the face and content validity, reliability and feasibility of the specific endpoints or measurement tools will be considered. Outcomes requiring further development or validation of measurement tools for pediatric populations will be identified. This process will be analogous to the StEP program in adult perioperative care, and will be described and reported in subsequent publications.

5 CONCLUSION

Formation of the international Pediatric Perioperative Outcomes Group, and the use of standardized methodology and systematic literature searches to identify reported outcomes and measurement tools, are the first steps for developing core outcome sets for pediatric perioperative care. Related manuscripts will report results within specific age-related domains. Consultation with key stakeholders, parents/carers and patients will be essential for reaching consensus and ranking key outcomes. In addition, measurement tools for each outcome have been extracted from current literature, and the validity, sensitivity and specificity of tools will be evaluated in subsequent stages to identify age-appropriate standardized endpoints for each outcome.

ETHICAL APPROVAL: Not applicable

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Table 1. PPOG Membership and Committees

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(A) STEERING COMMITTEE			
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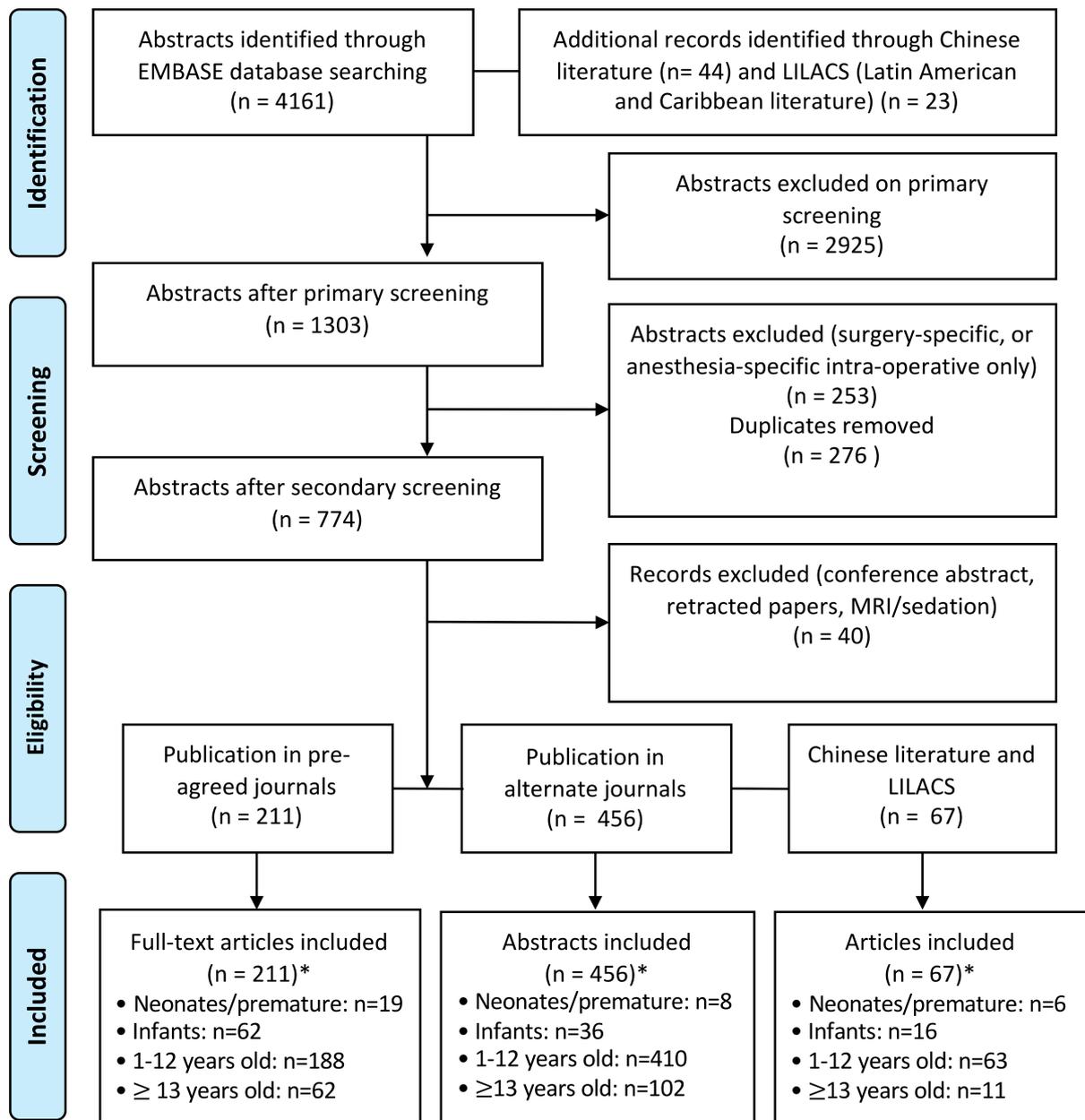
Table 2. EMBASE search strategy

No.	Query 1	Results
#13	#11 AND 'randomized controlled trial'/de AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim)	3,706
#12	#11 AND ('clinical trial'/de OR 'controlled clinical trial'/de OR 'randomized controlled trial'/de) AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim)	7,933
#11	#9 NOT #10	344,000
#10	'heart catheterization'/exp OR 'congenital heart disease'/exp OR 'congenital heart malformation'/exp OR 'history of medicine'/exp OR 'heart disease'/exp	1,832,839
#9	#6 AND #7 AND #8	405,609
#8	'human'/exp	19,561,684
#7	'pediatric*' OR 'paediatric*'	1,514,888
#6	#1 OR #2 OR #3 OR #4 OR #5	7,420,949
#5	'analgesia'/exp OR 'spinal anesthesia'/exp OR 'postoperative analgesia'/exp OR 'analgesic agent'/exp	925,006
#4	('anaesthe*' NEAR/5 'complication*') OR ('anesthe*' NEAR/5 'complication*') OR ('surger*' NEAR/5 'complication*') OR ('surgical*' NEAR/5 'complication*')	461,829
#3	'perioperative period'/exp OR 'perioperative complication'/exp OR 'postoperative period'/exp OR 'postoperative complication'/exp	1,034,794
#2	'surgery'/exp OR 'surgical technique'/exp OR 'surg*'	6,390,798
#1	'an*esth*esia' OR 'an*estheti*' OR 'an*esthesiolog*' OR 'an*esthetic agent'	829,072
No.	Query 2	Results
#21	#20 AND ('clinical trial'/de OR 'controlled clinical trial'/de OR 'randomized controlled trial'/de) AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim)	455
#20	#11 AND #19	8,095
#19	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	117,523
#18	'14968975':is OR 'canadian journal of anesthesia'/jt	5,415
#17	'13652044':is OR 'anaesthesia'/jt	22,835
#16	'14609592':is OR 'paediatric anaesthesia'/jt	5,244
#15	'14716771':is OR 'british journal of anaesthesia'/jt	21,416
#14	'15267598':is OR 'anesthesia and analgesia'/jt	28,550
#13	'13996576':is OR 'acta anaesthesiologica scandinavica'/jt	9,047
#12	'15281175':is OR 'anesthesiology'/jt	25,016
#11	#9 NOT #10	345,769
#10	'heart catheterization'/exp OR 'congenital heart disease'/exp OR 'congenital heart malformation'/exp OR 'history of medicine'/exp OR 'heart disease'/exp	1,840,440
#9	#6 AND #7 AND #8	407,935
#8	'human'/exp	19,644,017
#7	'pediatric*' OR 'paediatric*'	1,521,958
#6	#1 OR #2 OR #3 OR #4 OR #5	7,449,113
#5	'analgesia'/exp OR 'spinal anesthesia'/exp OR 'postoperative analgesia'/exp OR 'analgesic agent'/exp	927,934
#4	('anaesthe*' NEAR/5 'complication*') OR ('anesthe*' NEAR/5 'complication*') OR ('surger*' NEAR/5 'complication*') OR ('surgical*' NEAR/5 'complication*')	463,227
#3	'perioperative period'/exp OR 'peroperative complication'/exp OR 'postoperative complication'/exp OR 'postoperative period'/exp	1,038,980
#2	'surgery'/exp OR 'surgical technique'/exp OR 'surg*'	6,416,067
#1	'an*esth*esia' OR 'an*estheti*' OR 'an*esthesiolog*' OR 'an*esthetic agent'	832,186

Table 3. Journals for full-text review

Anaesthesia and pain	Anaesthesia, Anesthesia & Analgesia, Anesthesiology, British Journal of Anaesthesia, Canadian Journal of Anesthesia, European Journal of Anaesthesiology, Pain, Pediatric Anesthesia, and Regional Anesthesia and Pain Medicine
Surgery	Annals of Surgery, JAMA Surgery, Journal of Pediatric Surgery
Paediatrics	Archives of Disease in Childhood, JAMA Pediatrics, Pediatrics
General Medical	British Medical Journal, JAMA, Lancet, Lancet Respiratory Medicine, New England Journal of Medicine

Fig. 1. PRISMA Flow Diagram



*Some publications included subjects from more than one age-specific subpopulation