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Title: A systematic review of outcomes reported inpediatric perioperative research: A report from the Pediatric Perioperative Outcomes Group

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What is already known about this topic:

- Perioperative outcomes reported up to now in pediatric clinical trials have not been characterized.
- Determining outcomes that have been reported in existing studies is a key step in core outcome set development.

What new information this study adds:

- The Pediatric Perioperative Outcomes Group conducted this systematic review to gather candidate outcomes for future evaluation for inclusion in a core outcome sets for perioperative research in neonates and infants <60 weeks post-conception age, infants, 1-12-year-olds, and adolescents.
- Reported outcomes varied between the different age groups and pain was the most frequently assessed outcome.

Summary:

The Pediatric Perioperative Outcomes Group (PPOG) is an international collaborative of clinical investigators and clinicians within the subspecialty of pediatric anesthesiology and perioperative care which aims to use COMET (Core Outcomes Measures in Effectiveness Trials) methodology to develop core outcome setsfor infants, children and young people that are tailored to the priorities of the pediatric surgical population.Focusing on four age-dependent patient subpopulations determined *a priori* for core outcome set development: i) neonates and former preterm infants (up to 60 weeks postmenstrual age); ii) infants (>60 weeks postmenstrual age - <1 year); iii) toddlers and school age children (>1-<13 years); and iv) adolescents (>13-<18 years), we conducted a systematic review of outcomes reported in perioperative studies that include participants within age-dependent pediatric subpopulations.

Our review of pediatric perioperative controlled trials published from 2008 to 2018 identified 724 articles reporting 3192 outcome measures. The proportion of published trials and the most frequently reported outcomes varied across pre-determined age groups. Outcomes related to patient comfort, particularly pain and analgesic requirement, were the most frequent domain for infants, children and adolescents. Clinical indicators, particularly cardiorespiratory or medication-related adverse events, were the most common outcomes for neonates and infants < 60 weeks and were the second most frequent domain at all other ages. Neonates and infants <60 weeks of age were significantly under-represented in perioperative trials. Patient-centered outcomes, heath care utilization, and bleeding/transfusion related outcomes were less often reported. In most studies, outcomes were measured in the immediate perioperative

period, with the duration often restricted to the post-anesthesia care unit or the first 24 postoperative hours.

The outcomes identified with this systematic review will be combined with patient centered outcomes identified through a subsequent stakeholder engagement study to arrive at a core outcome set for each age-specific group.

1 INTRODUCTION

Around the world, millions of children, including approximately 6 million children in the USA[1] and half a million in the United Kingdom,[2]require anesthesia careannually.However, there are significant global disparities in the delivery and management of childhood surgical and anesthetic conditions.[3] To ensure the delivery of high quality patient-centered care, health care providersshould capture and act on well-defined,meaningful and relevant clinicaloutcome measures to drive further patient-centered improvements.Similarly, assessment using robust and standardized outcome measurement tools is fundamental to the design of high-quality perioperative research. Currently, in pediatric perioperative care, the outcomes used for assessing care in children are not comprehensively characterized, have variable relevance to patients, parents and the multi-disciplinary care team, and are not standardized in any meaningful way. These shortcomings hamper quality improvement effortsandcontribute to ambiguity when assessing the results ofpediatric perioperative trials.Without expert consensus on the most important outcomes, it is unclear to what extent clinical trials are assessing the mostrelevant outcomes forpediatric perioperative care. To address this uncertainty, creation of core outcome sets has been proposed as a means to improve consistency across clinical trials and help facilitate the conduct of high quality systematic reviews.[4] A core outcome set is an agreed standardized collection of outcomes which should be measured and reported, as a minimum, in all trials for a specific clinical area.[5]

Defining themost relevant perioperativeoutcomes that should be measuredis a current research priorityfor adult perioperative care.[6,7]Standardized methodology from the Core Outcomes Measures in Effectiveness Trials (COMET)initiative[5]has been developedto assist in

the creation ofcore outcome setsdesigned to establish a minimum standardized set of outcomes to be measured and reported in perioperative trials.[8]The Pediatric Perioperative Outcomes Group (PPOG) is an international collaborative of investigators and clinicians in pediatric anesthesia and perioperative care[9,10]whose aim is to use COMET methodology[5,8,11] to develop core outcome sets for infants, children and adolescentsthat are tailored to the priorities of the pediatric surgical population.Core outcome set development in pediatric perioperative care parallels the work of COMPAC (Core Outcome Measures in Perioperative and Anaesthetic Care) which is working to define core outcomes for adults undergoing major surgery and StEP (Standardised Endpoints in Perioperative Medicine) which is developing expert consensus-based guidelines for perioperative clinical outcome measurement in adult practice.[6]

Using a Delphi process, PPOG Investigatorsagreed*a priori* on four age-dependent subpopulations for core outcome set development: i. neonates and former preterm infants (up to 60 weeks postmenstrual age); ii. infants (>60 weeks postmenstrual age - <1 year); iii. toddlers and school age children (>1 - <13 years); and iv. adolescents (>13 - <18 years)[10]Pediatric perioperative core outcome set development will follow three stages: i. a systematic review to identify all reported outcomes; ii. a Delphi survey to identify and prioritize outcomes for inclusion in a core outcome set, including additional prospective outcomes identified through engagement of stakeholders[6]; iii. consensus meeting to decide upon on the minimum outcomes for inclusion in the core outcome set.[5]

Here, we present the results of asystematic review of outcomes reported in perioperative studies that include participantswithin age-dependent pediatric subpopulations. Because pediatric perioperative core outcome sets must include a wide range of patients with distinct age-based recovery goals, it is important to understand what outcomes are being used for different age groups. Thus, the aim of this review is to describe the outcomes used in pediatric perioperative clinical trials for each age group and explore the differences that exist between the subpopulations. The outcomes identified with this systematic review will be combined with patient centered outcomes identified through a subsequent stakeholder

engagement study, and evaluated in a multi-round Delphi consensus process to arrive at a core outcome set for each age-specific group.

2 METHODS

The project was registered with the COMET initiative (http://www.comet-initiative.org/studies/details/1096) and a comprehensive description ofour systematic review methodology was prospectively published.[10] An abbreviated overview follows below.

2.1 Literature search and abstract screening

A search of the EMBASE database identified publications (between 2008 and 2018 inclusive) that reported pediatric perioperative outcomes or outcome measures (detailed search terms as previously reported[10]). To identify additional publications, 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. Abstracts returned from the above querieswere systematically screened by PPOG members. Abstracts were included if they reported outcomes related to aspects of anesthetic and perioperative care, but excluded if outcomes related only to the surgeryitself or if they related only to anesthesia-specific intra-operative outcomes (e.g. laryngeal mask airway seal). Studies on sedation in other hospital locations (e.g., emergency department, pediatric sedation service) were excluded from the analysis.

2.2 Outcomes extraction

Extracted data included manuscript title, pediatric age subpopulations included in the study, journal, study design, sample size, surgical population, and each perioperative outcome collected as well as the measurement tool or assessment used (if described). Data were collated using REDCap.[12]Full text reviews were performed for the followingscreen-positive abstracts from specific, pre-identified major anesthesia, pediatric, surgical and general medical journals:*Pediatric Anesthesia, Anaesthesia, Anesthesia & Analgesia, Anesthesiology, British Journal of Anaesthesia, Canadian Journal of Anesthesia, European Journal of Anaesthesiology,*

Pain, Regional Anesthesia and Pain Medicine, Annals of Surgery, JAMA Surgery, Journal of Pediatric Surgery, Archives of Disease in Childhood, JAMA Pediatrics, Pediatrics, British Medical Journal, JAMA, Lancet, Lancet Respiratory Medicine, and *The New England Journal of Medicine*.For all other screen-positive abstracts, outcomes were extracted from the published abstract only.

2.3 Grouping of perioperative outcomes and thematic domains

Following completion of data extraction, the outcomes were merged and sent to the lead investigators for each age-based subpopulation. Lead investigators worked with PPOG co-investigators to group the outcomes into thematic domains, based on groupings outlined byCOMPAC-StEP, which included (among others) patient comfort, clinical indicators, patient-centered outcomes, and healthcare resource utilization.[6]To ensure reliable and consistent reporting, particularly where study subpopulations covered more than one age band, lead investigators collaborated to further refine the groupings.

3 RESULTS

3.1 Distribution of outcomes

After primary and secondary screening, the search queries yielded 724publications, comprising 657articles from EMBASE, 44 articles from the Chinese literature, and 23 articles from the LILACS database (PRISMA Flow Chart, see[10]). A total of 3192 outcomes were extracted and categorized. Citations of publications for outcome extraction for each subpopulation can be found in the Online Supplemental Files. The distribution of articles by subpopulation is presented in Table 1 and the breakdown of the outcomes captured in each domain is presented in Table 2.The number of outcomes extracted for each age group generally mirrored the number of articles examined.

Outcomes measuring postoperative pain and nausea/vomiting predominated in clinical trials in subpopulations older than the neonatal age group. Qualitative, patient-centered, and functional outcomes in the “return to normal function” and “quality of recovery assessment” categories were more frequently reported in the older age groups, while outcomes in the

"cardiovascular/respiratory adverse event" category were more frequently reported in the younger age groups.

3.2 Neonates and Infants <60 weeks Post-Conceptual Age

There were 34 articles that included term and or preterm-born neonates, making up 4.8% of the total articles reviewed (Table 1). Thirteen articles focused exclusively on this patient population while 21 articles included other age groups from infants up to adolescents.In total, 120 outcomes were reported for the neonatal group, with the majority in the clinical indicators domain (Table 2).

Twenty of the studies for this subpopulation investigated primarily an anesthesia or perioperative research question thatinvolved: comparison of anesthetic dose, technique or airway management; pain assessment and management; neurodevelopmental outcome; physiological consequences of intravenous fluids; predictors of failure of spinal anesthesia; and postoperative complications following day-stay surgery.Primary surgical studies compared two surgical techniques or assessed perioperative complications.

Of the120outcomes extracted, the top three outcome domains were clinical indicators (37%), 'other' (28%), andpatient comfort (19%) (Table 2 and Table 3; Figure 1A). Cardiorespiratory events were the most common clinical indicator captured, with respiratory events the most common subdomain. In the 'other' grouphemodynamic and vital sign outcomes were common, and laboratory blood or urine measures dominated this category.Pain and analgesia assessment encompassed a wide range of reported pain measurement tools and a diverse set of endpoints. Apart from one behavioral outcome, the outcomes in the return to normal function category all assessed enteral feeding, either time to first feed or time to full feed (Table 3).

3.3 Infants

There were 112 articles that included infants making up 15% of the total articles reviewed and only 7 articles focused exclusively on this patient population while the other 105 articles included other age groups from neonates up to adolescents (Table 1).In total, 292 outcomes were reported for the infant group,accounting for 9% of all outcomes (Table 2).

The most common outcome domains were patient comfort (47%), clinical indicators (21%), and patient-centered outcomes (12%) (Table 2 and Table 4; Figure 1B). Within the patient comfort domain, pain/analgesia assessment and analgesic requirement made up 57% of the outcomes captured. Cardiorespiratory events were the most common specific outcome within the clinical indicator domain (Table 4).

3.4 1-12-year-olds

There were 683 articles that included children ages 1-12 making up 94% of the total articles reviewed, with 444 articles restricted exclusively to this age range (Table 1). In total, 2181 outcomes were reported for the 1-12 year age group,accounting for 68% of all outcomes (Table 2).

The top three outcome domains were patient comfort (62%), patient-centered outcomes (12%), and clinical indicators (11%) (Table 2 and Table 5; Figure 1C). Within the patient comfort domain, pain/analgesia assessment and analgesic requirement made up 50% of outcomes captured, and pre or postoperative anxiety/agitation made up 31%.Cardiorespiratory events were the most common specific outcome within the clinical indicators domain (Table 5).

3.4 Adolescents (≥13-year-olds)

There were 175 articles that included adolescents (≥13-year-olds) making up 24% of the total articles reviewed and 8 articles focused exclusively on this patient population (Table 1).In total, 599 outcomes were reported for the adolescent group, making up 19% of all outcomes sorted (Table 2).

Of the 599 outcomes extracted, the top three outcome domains were patient comfort (49%), clinical indicators (16%), and patient-centered outcomes (14%) (Table 2 and Table 6; Figure 1D). Within the patient comfort domain, pain/analgesia assessment and analgesic requirement made up 69% of the outcomes captured while postoperative nausea and vomiting made up 18% of outcomes captured. Analgesic medication related adverse events were most common specific outcome within the clinical indicators domain (Table 6).

4 DISCUSSION

The present systematic review of pediatric perioperative controlled trials published over a recent 11-year period identified 724 articles reporting 3192 outcome measures. The proportion of published trials and the most frequently reported outcomesvaried across pre-determined age groups. Outcomes related to patient comfort, particularly pain and analgesic requirement, were the most frequent domain for infants, children and adolescents. Clinical indicators, particularly cardiorespiratory or medication-related adverse events, were the most common outcomes for neonates and infants < 60 weeks and were the second most frequent domain at all other ages. Patient-centered outcomes, heath care utilization, and bleeding/transfusion related outcomes were less often reported. The outcomes identified from this systematic review will be evaluated as candidates for inclusion in age-specific core outcome sets insubsequent phases of the pediatric perioperative outcome project.[9,10]

4.1 Core outcome sets for pediatric care

Core outcome sets are important, as they establish a set of outcomes that should be measured and reported in all clinical trials of specific disease or trial population, and they are being developed with COMET methodology[5] for many pediatric populations. Recent reports include groups based on: surgical procedure (eg. uncomplicated appendicectomy[13]); age group (eg. neonatology[14]); practice setting (eg pediatric intensive care[15]); disease management (eg. acute severe asthma[16]); and specific population-based interventions (eg. neurological impairment and tube feeding[17]). The importance of stakeholder engagement, that includes parents and patients, is widely acknowledged. Initial ranking of outcomes by parents and patients differed from clinicians and researchers in the recent core outcome set for neonatology[14] and when the core outcome set in juvenile idiopathic arthritis was updated to include patients and parents[18]. Similarly, parents and patients will be involved in the subsequent development of the pediatric perioperative core outcome sets, as it remains to be determined how they value commonly measured patient comfort outcomes such as pain, or less frequently measured outcomes such as distress on induction, return to normal function, or outcomes related to clinical indicators. Patient-centered outcomes related to return to normal function, quality of recovery, and parent/patient satisfaction comprised 12-14% of outcomes for older infants, children and adolescents but the relative value of these measures for all

stakeholders, and the most appropriate measurement tools for parents and patients within different age ranges, will require further elucidation in future stages of core outcome set development.

4.2 Outcome domains

In this review, we categorized outcomes into pre-determined domains based on the standardized endpoint (StEP) working groups for adult perioperative care[6]which include: clinical indicators,[19]patient comfort,[20] patient-centered outcomes,[21]infection and sepsis,[22] renal endpoints,[23] postoperative cancer outcomes,[24] blood loss and transfusion,[25] and pulmonary complications,[26]. While pediatric perioperative trials frequently reported outcomes in the patient comfort and clinical indicators domains, some of the additional domain outcomes are less relevant, thus reinforcing the need for specific pediatric perioperative core outcome sets. Individual studies may have insufficient power for evaluating rare complications, but the use of standardized definitions and outcome tools (e.g. perioperative respiratory events[27]) allows data to be combined in subsequent meta-analyses or systematic reviews. In addition, while not all outcomes have been adequately evaluated in controlled trials in children, large audits or prospective quality improvement databases such as the Pediatric National Surgical Quality Improvement Program[28]or the UK basedPaediatric Anesthesia Trainee Research Network[29]can identify clinical indicators of importance to clinicians and families (e.g. mortality risk stratification[30] or unplanned admissions following pediatric day-case surgery[29]).

4.3 Impact of age on frequency of reported outcomes and unmet needs

The type and incidence of outcome assessed, and the dominant outcome domains varied across age groups. This may reflect age-dependent differences in patient factors (e.g. risk and vulnerability to specific adverse outcomes, type of surgery, utility and reliability of measurement tools) or be influenced more generally byclinician and/or researcher priorities, feasibility of recruitment, and funding opportunities. As many studies recruited children across a wide age range there was significant overlap in articles represented across the four subpopulations. While expanding age-based inclusion criteria may increase sample size, the relative importance or drivers for different outcomes may vary with age (eg. higher risk of perioperative cardiac arrest in neonates)[31]. In addition, different measurement tools may be

required for younger and older children, such as the use of observer or self-report assessments of pain intensity[32-34], but variability in sensitivity/specificity and in the metric of different scales can complicate the combined analysis or interpretation of the results. The type of surgery can vary with age and outcomes may be biased towards common procedures (eg. adenotonsillectomy patients in the 1-12 yr old age group). A number of outcomes that could be judged surgery- or site- specific were categorized separately, but for common procedures within certain age groups, these may need to be included in a core outcome set despite lack of generalizability to all types of surgery.

Neonates and infants <60 weeks of age were significantly under-represented in perioperative trials.Specific research challenges in neonates include ethical constraints, technical challenges with some monitoring modalities and sampling, limited sample size, and the increased proportion of emergency surgical presentations.Clinical indicators such as cardiorespiratory events, measures of physiological homeostasis, and medication efficacy were the most frequent outcomes reported in neonates and infants.This likely reflectsclinicians' concerns regarding the increased mortality[35], and vulnerability to adverse cardiorespiratory[31,36,37] and neurological[38]events in neonates and infants.[39]Clinical indicators continued to be a common focus at older ages, with cardiorespiratory events frequently reported throughout infancy and childhood, and analgesic/medication related adverse effects morecommonly assessed in adolescents. Beyond the neonatal period, evaluation of patient comfort outcomes increased and became the dominant domain at all subsequent ages.

Patient comfort domain outcomes at all ages were most frequently related to perioperative pain and analgesic requirement. This focus reflects the significant impact of pain on child and parental distress, ongoing reports of the prevalence of moderate-to-severe pain in up to 30-40% of hospitalized children,[40,41] associations between higher perioperative pain and persistent post-surgical pain,[42] and an increasing emphasis on multimodal or opioid-sparing interventions.[43]A large number of tools were used to measure pain intensity, from observer tools incorporating physiological and/or behavioral parameters in neonates and preverbal children, to pictorial self-report tools for children over 6-8 years, and numerical tools at older ages.It is essential that validated and developmentally appropriate tools are used, and

encompass specific measures for children with cognitive impairment.[32-34]Despite recommendations for core acute pain outcomes to extend beyond measurement of pain intensity and include emotional response, physical recovery, and economic factors,[44] relatively few studies assessed patient and parental anxiety which may influence the experience, report and duration of perioperative pain,[45] psychosocial aspects of pain-related interference with activity, or quality of life.[46]Postoperative nausea and vomiting (PONV)was the most common patient comfort outcome after pain and analgesic requirement in adolescents and in infants.While PONV is associated with significant dissatisfaction in adults,[47,48]and the majority of adults consider avoiding vomiting as important,[49]the relative importance of this outcome has not been specifically assessed in children and adolescents.[50]

Outcomes relating to anxiety or psychological distress either preoperatively or postoperatively were a minor focus of research in children and adolescents. In children (1-12 yr age band), a variety of measurement tools evaluated acute preoperative (anxiety, distress or mask acceptance at induction) and postoperative distress (anxiety, delirium, emergence distress, behavioral change), with some extending to several weeks following discharge. However, despite the current high (reported at between 10 to 30%) and possibly rising prevalence of anxiety, depression and other mental health disorders amongst the adolescent subpopulation globally,[51-57] these factors were rarely assessed in adolescents. Families and patients may feel unprepared for the impact of surgery, and outcomes evaluating the impact of perioperative psychosocial and educational interventions may be an increasing focus.[58,59] It will be important to explore the need for additional focus on the impact of pre-existing and/or perioperative mental health issues on patient well-being and return to normal function with all relevant stakeholders.

In the vast majority of studies, outcomes were measured in the immediate perioperative period, with the duration often restricted to the post-anesthesia care unit or the first 24 postoperative hours. However, more prolonged follow-up in specific age-based populations is required for outcomes related toemergent research priorities,[7]such as potential effects of general anesthesia on the developing brain,[60,61]or factors associated with an increased risk of persistent post-surgical pain.[42,62]While neonatal mortality is declining,[63]the

rate of preterm birth continues to increase,[64] and neonatal comorbidities make significant contributionsto years of life lost and years lived withdisability.[65]Whilethe need for surgery at early gestational ages can be associated with persistent effects on health and cognitive outcome,[66-68]the potential impact of anesthesia drugs and management requires ongoing evaluation.As highlighted in core outcome set for neonatology[14] and pediatric intensive care[15], appropriate use of validated and comparable instruments are needed in studies evaluating long-term outcome.

4.4 Limitations

This systematic review has a number of limitations. A more exhaustive search strategy across a wider time frame may have captured additional outcomes. Outcomes that were deemed "anesthesia-specific" and "surgery-specific" were excluded, butthis process was subjective and may have excluded potentially important or valued outcomes. However, the exclusion criteria were agreed to *a priori* by the PPOG[10], and it is important to note that outcomes of potential importance not captured by this review may be identified by the upcoming stakeholder engagement exercise. Additionally, the review of the literature was initially limited to publications in English. We did expand our search to include the Chinese literature database and LILACS database (Latin America and Caribbean literature). However, it is possible that we have not included clinical trials that were published in other languages including French and German.

5 CONCLUSION AND NEXT STEPS

Developing core outcome sets for pediatric perioperative care requires consideration of age-dependent changes that include, but are not limited to: the relative value placed on different domains such as patient comfort and patient-centered outcomes; physiological, pharmacological and technical factors that influence vulnerability to adverse outcomes; the utility, sensitivity and specificity of measurement tools; the type of surgery required; and cognitive and psychosocial factors that influence patient and/or proxy report.

There is potential for discordance in the value placed on perioperative outcomes by different stakeholder groups. In accordance with COMET methodology,[5] and as previously

reported,[10]the PPOGplans to directly engage stakeholder groups for each age-based subpopulation, to review the published outcomes and elicit additional outcomes of importance for clinical pediatric perioperative research. Stakeholder groups will include patients (where applicable), parents/caregivers, and perioperative physicians and nurses. We intend to conduct this phase of the study at our international collaborators' sites with the expectation that sites will enroll stakeholders consisting of patients and parents (with representation from the different age groups), surgeons, anesthesiologists, and perioperative nurses. This will be followed by a Delphi consensus process, that will include PPOG members as well as patient and parent representatives, to rank the outcomes in terms of their importance for inclusion in core outcome sets for each subpopulation.The core outcome sets will be finalized in a subsequent face-to-face consensus meeting of the PPOG.

Subsequently, PPOG will support the selection of appropriate measurement tools for assessing pediatric perioperative outcomes and these will be included in the finalized core outcome sets. Where no agreed tool exists (in particular for outcomes that are highlighted by the stakeholder engagement process rather than reported in the literature), the aim of PPOG is to support the development and validation of these measurement tools, to facilitate the reliable measurement of perioperative outcomes that really matter for clinicians, researchers, patients and their caregivers.[9]These core outcome sets will be important for guiding future clinical research and quality improvement efforts designed to optimize patients' perioperative outcomes.

Figure 1 : Histograms of frequency of outcomes reported by thematic domain for (A): Neonates and infants <60 weeks post-conception age; (B): Infants, (C): 1-12 year-olds, (D): Adolescents.

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Table 1. Age-based pediatric subpopulation representation in articles for outcomes extraction from EMBASE, Chinese literature, and LILACS database searches

Age group(s)	Number of articles	Percentage
Neonates only	13	1.8
Neonates and infants	13	1.8
Neonates, infants, and 1-12y	4	0.6
Neonates, infants, 1-12y, and adolescents	4	0.6
Infants only	7	1
Infants and 1-12y	68	9.4
Infants, 1-12y, and adolescents	16	2.2
1-12y only	444	61.3
1-12y and adolescents	147	20.3
Adolescents only	8	1.1
Total	724	

Table 2. Distribution of reported outcomes across domain themes in each age-based subpopulation

	Neonates	Infants	1-12 years	>13 years	Total
Patient Comfort (%)	23 (19)	136 (47)	1353 (62)	293 (49)	1805 (57)
Patient-centered outcomes (%)	6 (5)	35 (12)	251 (12)	86 (14)	378 (12)
Bleeding/ transfusion (%)	3 (3)	18 (6)	57 (3)	32 (5)	110 (3)
Healthcare utilization (%)	10 (8)	21 (7)	189 (9)	60 (10)	280 (9)
Clinical indicators (%)	44 (37)	61 (21)	245 (11)	93 (16)	443 (14)
Other (%)	34 (28)	21 (7)	86 (4)	35 (6)	176 (6)
Total	120	292	2181	599	3192

Table 3. Reported perioperative outcomes for the neonate and preterm infant under 60 weeks PCA subpopulation

Outcome domain	Outcome classification	Frequency	Outcomes extracted
Patient Comfort (23 total outcomes)	Pain / analgesia assessment	8	Postoperative pain, pain score (FLACC/NIPS/CRIES/metric not specified/ parent report)
	Analgesic requirement	9	Need for rescue analgesia, analgesic consumption, rescue morphine and total morphine consumption, number of rescue medications, time to first analgesic, switch to alternative technique
	Postoperative nausea / vomiting	4	Postoperative vomiting
	Preoperative behavior / anxiety	0	
	Emergence agitation assessment	0	
	Postoperative sedation / recovery	0	

	assessment		
	Postoperative behavior (post-discharge)	2	Parent report of lethargy/irritability, 5 item behaviour score postoperatively
Patient-centered outcomes (6 total outcomes)	Quality of recovery assessment	0	
	Return to normal function	5	Time to resume full diet/full enteral feed, time to first feed, parent report of general issues (including pain, irritability, feeding, distress, vomiting and lethargy)
	Satisfaction assessment	1	Parental satisfaction (very good, good, fair, and poor)
	Hunger, thirst and fasting duration	0	
Bleeding/ transfusion (3 total outcomes)	Blood loss / bleeding assessment	3	Postoperative bleeding, hemoglobin and hematocrit, hemoglobin before and after transfusion

	Transfusion quantitation	0	
Healthcare utilization (10 total outcomes)	Duration of surgery / anesthesia	3	Total anesthesia time, time to extubation, duration of spinal anesthesia
	PACU length of stay	0	
	ICU length of stay	2	Length of time in ICU, length of time on ventilator
	Hospital length of stay	5	Duration of hospitalisation, postoperative hospital stay, postoperative length of stay, length of stay
	Costs / value outcomes	0	
Clinical indicators (44 total outcomes)	Analgesic / medication-related adverse events	3	Nurse-controlled analgesia (NCA) side-effects – respiratory depression, over-sedation, vomiting and itch, NCA serious adverse effects death or life-threatening event
	Cardiovascular / respiratory adverse event	30	Postoperative respiratory events, atelectasis, apnoea/desaturation, postoperative stridor, need for oxygen, need for bag mask ventilation, parent report of postoperative breathing problems, Cardiopulmonary resuscitation incidence, laryngospasm, bronchospasm, respiratory depression, hypotension,

			moderate hypotension, prolonged hypotension, interventions for hypotension, hemodynamic stability, death
	Other adverse events / adverse event not specified	7	Complications at 30 days after surgery, other complications/morbidity not specified, postoperative dizziness, secondary infection
	Postoperative medical reattendance / readmission	1	Hospital readmission
	Surgical site infection	2	Surgical site or deep wound
	Urinary issues	1	Urinary retention
Other (34 total outcomes)	Hemodynamic / vital signs / laboratory	23	ECG, blood pressure, oxygen saturation, end-tidal CO2, heart rate and mean arterial pressure before and after fluid challenge, urine values, blood glucose, postoperative acid base (serum pH, Base deficit, serum bicarbonate, anion gap), metabolic (free fatty acid, beta-hydroxybutyrate, serum lactate), serum electrolytes (sodium, potassium, calcium), liver function (liver biopsy, AST/ALT, ALP, GGT), endocrine (serum insulin, glucagon, cortisol, glucagon/insulin ratio)
	Development /	6	Cognitive disability, cognitive development, neurodevelopmental outcome age

	disability assessment		2, neuromotor development, disability, sensorimotor disability
	Other	5	Spinal/regional anaesthesia failure rate, rewarming rate, temperature, intraabdominal pressure at time of closure, native liver survival

Table 4. Reported perioperative outcomes for the infant subpopulation

Outcome Domain	**Outcome classification**	**Frequency**	**Outcomes extracted**
Patient Comfort (136 total outcomes)	Pain / analgesia assessment	45	Adequacy of analgesia, pain, nurses opinion of analgesia, pain assessment at recovery, pain at awakening, pain score, pain-free period, postoperative pain, pain-free interval, time to first analgesic administration, time to first analgesic demand, time to first rescue analgesia, total duration of analgesia, analgesic effect, duration of spinal anesthesia, postoperative pain intensity, quality of pain control, success rate of block, parents' opinion of analgesia, comfort score, motor block on awakening
	Analgesic requirement	32	Analgesia, analgesic consumption within 24 hours after surgery, analgesic use/requirement, duration of narcotic use, frequency of rescue analgesia, morphine consumption, need for analgesia, need for opioids postoperatively, number of patients requiring rescue analgesia, postoperative pain, requirement of rescue analgesics in 24-hour period, 24-hour opioid as morphine equivalents, total morphine rescue dose, use of

			analgesic drugs, use of pain medication, requirement for additional postoperative analgesics
	Postoperative nausea / vomiting	26	Emetic episodes, nausea and vomiting, postoperative nausea and vomiting, vomiting, rescue antiemetic requirement
	Preoperative behavior / anxiety	1	Anxiety at separation
	Emergence agitation assessment	17	Agitation, emergence agitation, emergence delirium, delirium
	Postoperative sedation / recovery assessment	8	Duration of sedation in recovery, sedation, postoperative sedation score, recovery from anesthesia, recovery
	Postoperative behavior (post-discharge)	7	Activity, activity level, behavior, behavioral disturbance, behavior type, mental state, parent report of issues including irritability/distress/lethargy
Patient-centered outcomes (35 total	Quality of recovery assessment	1	Quality of recovery

outcomes)			
	Return to normal function	16	Time to full enteral feed, return to full oral intake, oral intake, time to resume feeding, time until liquid and solid oral intake, time to resume full diet, feeding, time to clear liquid intake, time to solid intake, stool passage during first postoperative 24 hours, time to first flatus, time to micturition
	Satisfaction assessment	17	Global satisfaction ratings, satisfaction score, surgeon satisfaction, recovery satisfaction, parental satisfaction, parent/caregiver satisfaction
	Hunger, thirst and fasting duration	1	Duration of preoperative fasting
Bleeding/ transfusion (18 total outcomes)	Blood loss / bleeding assessment	7	Volume of blood loss, blood loss, intraoperative blood loss, postoperative blood loss, primary hemorrhage, grade of surgical field
	Transfusion quantitation	11	Total volume of platelet concentrate transfused, transfusion requirement, total volume of packed red blood cells transfused, need for postoperative blood products, units transfused, blood donor exposures, total volume of fresh frozen plasma transfused, total volume of factor XIII concentrate transfused
Healthcare utilization (21 total	Duration of surgery / anesthesia	4	Total anesthesia time, duration of operation, surgical duration, operative time

outcomes)			
	PACU length of stay	5	Time spent in PACU, time to discharge home, recovery time
	ICU length of stay	2	Intensive care unit length of stay
	Hospital length of stay	5	Length of hospital stay, length of postoperative hospital stay
	Costs / value outcomes	5	Healthcare cost, hospital charge, cost for all transfused blood products and coagulation factors, costs of perioperative laboratory testing, indirect costs to patients/families
Clinical indicators (61 total outcomes)	Analgesic / medication-related adverse events	12	Systemic local anesthetic toxicity, over-sedation, psychotomimetic effects, analgesic side effects, respiratory side effects, pruritis, opioid-related adverse effects, nurse-controlled analgesia side effects, nurse-controlled analgesia serious adverse events, itching
	Cardiovascular / respiratory adverse event	20	Perioperative respiratory adverse events, intraoperative airway obstruction, postoperative airway obstruction, intraoperative cardiorespiratory complications, hypotension, side effects/complications, patient reported postoperative breathing problems, prolonged hypotension, adverse events (incl. bradycardia, hypotension, respiratory depression), intervention for hypotension, laryngospasm, desaturation, apnea, postoperative respiratory adverse events, respiratory depression, oculocardiac reflex incidence
	Other adverse events / adverse	16	Hyponatremia, regional anesthesia failure, hypoglycemia, postoperative acidosis, hyperglycemia, hypernatremia, complications, intraoperative complications, poor oral

	event not specified		feeding, perioperative complications, postoperative complications, postoperative dizziness, recurrent hernia occurrence,
	Postoperative medical reattendance / readmission	6	Discharge status at day 14, number of readmissions, 30-day readmissions, any hospital stay after surgery, Number of parental contacts for medical problems, medical reattendance (seeking unplanned medical attention during follow-up period)
	Surgical site infection	2	Wound infection, surgical site infection incidence
	Urinary issues	5	Urinary retention, uroschesis
Other (21 total outcomes)	Hemodynamic / vital signs / laboratory	13	Postoperative oxygenation, liver function, postoperative coagulation parameters, hemodynamics, heart rate, blood pressure, temperature, SpO_2, plasma anti-diuretic hormone levels, liver function test, urine analysis, blood glucose, postoperative coagulopathy
	Development / disability assessment	3	Cognitive development, neurodevelopmental outcome at age 2 years, neuromotor development
	Other	5	rewarming rate, rate of peripheral venous cannulation success on first attempt, time to peripheral venous cannulation, native liver survival, residual motor blockade

Table 5. Reported perioperative outcomes for 1 to 12 years of age (inclusive) subpopulation

Outcome domain	Outcome classification	Frequency	Outcomes extracted
Patient Comfort (1353 total outcomes)	Pain / analgesia assessment	428	Pain intensity/severity (observer-reported, self-reported, combination of observer and self-report), postoperative pain, pain at awakening, pain in postoperative ward, pain at rest and with swallowing, pain during cough, pain with movement, efficacy of postoperative analgesia, pain at home, nurses' and parents' opinion of analgesia, abdominal pain, discomfort/pain at induction on injection, headache, oropharyngeal pain, otalgia, pain during phlebotomy, pain on mouth opening, painful muscle spasm, postoperative dental pain, postoperative ear pain, postoperative laryngeal pain, postoperative sore throat, phantom limb pain, preference for Smart Phone based pain assessment, shoulder pain, nocturnal awakening,time between regional blockade and first analgesic, duration of block, motor block, motor recovery, motor weakness, onset time of axillary block, postoperative motor function, success rate of block
	Analgesic requirement	248	Amount of fentanyl postoperatively, rescue analgesia, NCA morphine requirements, IV PCA fentanyl consumption, need/requirement for analgesia, duration of narcotic use, analgesia rescue, post-operative rescue fentanyl, rescue analgesics, opioid requirement, time to first analgesic, duration of analgesia, time not requiring morphine, postoperative requirement for morphine, cumulative paracetamol dose, total analgesic amount, total 24 hour analgesia, time to first paracetamol, morphine consumption in PACU, total

			paracetamol demands postoperatively, number of analgesic doses in 48 hours, 48 hourly morphine consumption, frequency of oral pain medication at home, analgesia use over 7 days
	Postoperative nausea / vomiting	195	Nausea, nausea and vomiting, vomiting (incidence/occurrence/severity), emetic episodes, need for rescue antiemetic
	Preoperative behavior / anxiety	237	Pre-operative anxiety, drug acceptance, pre-operative sedation, pre-operative behavior, separation, cannulation / venipuncture anxiety, mask acceptance, behavior at induction
	Emergence agitation assessment	176	emergence agitation, emergence delirium
	Postoperative sedation / recovery assessment	31	post-operative sedation, post-operative drowsiness,
	Postoperative behavior (post-discharge)	38	Post-operative anxiety, post-operative behavior, cognitive and psychological impact
Patient-centered	Quality of recovery	51	Quality of life scores, symptomatic surveys, recovery of fatigue, postoperative activity level, time to leave bed, time to ambulation, return to normal activity,

outcomes (251 total outcomes)	assessment		sleep disruption, sleep pattern post-op, sleep quality, return to school, postoperative recovery at 10 days, functional recovery at 3 months
	Return to normal function	124	recovery time, wake-up, recovery profile, quality of recovery from anesthesia, time to full responsiveness, time to first swallow, oral feeding, oral intake, return to diet, resumption of bowel function, postoperative appetite at home, time to voiding, time with urinary catheter
	Satisfaction Assessment	71	Parent / caregiver satisfaction, clinician / nurse satisfaction, family satisfaction, patient satisfaction
	Hunger, thirst and fasting duration	5	Duration of preoperative fasting, perioperative thirst / hunger, postoperative hunger, dehydration
Bleeding/ transfusion (57 total outcomes)	Blood loss / bleeding assessment	39	Blood loss, coagulopathy, hemoglobin/hematocrit levels, hematoma
	Transfusion quantitation	18	Blood products
Healthcare utilization (189 total	Duration of surgery / anesthesia	78	Pre-operative timings/costs, anesthesia duration, duration of operation, OR efficiency, duration of mechanical ventilation, time to emergence, time to eye opening, time to extubation

outcomes)			
	PACU length of stay	47	Length of stay in PACU, delayed PACU discharge, time taken for readiness for PACU discharge
	Hospital length of stay	46	Hospital stay after surgery, hospital length of stay
	ICU length of stay	4	ICU / PICU length of stay
	Costs / value outcomes	14	Hospital charge/costs, cost-effectiveness, indirect costs to patients/families, costs of transfused blood products, costs of perioperative laboratory testing
Clinical indicators (245 total outcomes)	Analgesic / medication-related adverse events	59	Adverse effects of medication, opioid side-effects, pruritus, NCA serious adverse events, side effects, oversedation, shivering, extrapyramidal symptoms, psychomimetic effects, constipation, gastrointestinal symptoms, regional anesthesia complications, adverse effects of TAP blocks, inadequate anesthesia for procedure
	Cardiovascular / respiratory adverse event	77	Desaturation, respiratory complications / adverse events, laryngospasm, apnea, airway obstruction, excessive secretions, bronchospasm, coughing, respiratory depression, postoperative mechanical ventilation, dysphagia, groaning, pneumonia, hypotension, bradycardia, cardiac arrest, death, oculocardiac reflex, perioperative complications
	Other adverse events / adverse event not	69	Pre-operative adverse events, intraoperative complications, hypothermia, hypo/hypernatremia, hypo/hyperglycemia, postoperative acidosis, complications/adverse events not otherwise specified, postoperative

	specified		complications, conversion to open procedure, incidence of malunion, nasal bleeding, recurrent hernia, postoperative halitosis/odor, trismus, muscle spasm, surgical complications, neurological deficit
	Postoperative medical reattendance / readmission	10	Medical reattendance, readmission to hospital, post-discharge emergency department visits, number of parental contacts
	Surgical site infection	17	Surgical site infection, fever, postoperative infection, time on antibiotics
	Urinary issues	13	Bladder spasms, antispasmodic requirement, requirement for urinary catheter, urinary retention, delayed voiding
Other (86 total outcomes)	Hemodynamic/ vital signs/ laboratory	71	'Stress level', 'stress response', blood glucose, blood pressure, cortisol level, electrolyte balance, fluid requirements, gastric pH, gastric volume, hemodynamics, heart rate, hemodynamic stability, kidney function, liver function, blood pressure, obstructive sleep apnea, oxygen requirement, patient temperature, postoperative coagulation parameters, respiratory rate, tissue healing, urine analysis, weight gain/loss, serum endorphin levels, plasma ADH levels
	Development / disability assessment	2	Intelligence

	Other	13	Peripheral venous cannulation – rate, time to cannulation, number of attempts required; movement at start of surgery, total dose of propofol, ketamine dosage, fentanyl consumption, smooth LMA removal, negative symptoms, parent's need for information, useability / likeability of preoperative preparation programme, acceptability of intervention (chewing gum), mean radiation time

Table 6. Reported perioperative outcomes for the adolescent subpopulation

Outcome Domain	**Outcome classification**	**Frequency**	**Outcomes extracted**
Patient Comfort (293 total outcomes)	Pain / analgesia assessment	131	Immediate postoperative pain, maximum pain, quality of pain relief, pain on injection, pain at rest, abdominal pain, throat pain, pain with cough, pain by postoperative day, muscle spasm, pain intensity with moving, preference for Smart Phone based pain assessment, otalgia, perioperative discomfort, shoulder pain, moderate to severe pain, pain type (incisional, visceral, gas), neuropathic chronic pain symptoms at 3 months, phantom limb pain, groaning
	Analgesic requirement	72	Number of morphine dosages, total morphine dose, milligrams of morphine by kilogram, morphine equivalent daily dosages (MEDD), discontinuation of NCA in favor of alternative approach, time to first narcotic/analgesic, morphine in the first 24 hours,

			morphine in the first 48 hours, proportion of patients using over 200mg/kg of morphine, total analgesic used in recovery room, PCA demand to delivery ratio, percentage of patient with morphine in PACU, ibuprofen in first 24 hours, intraoperative fentanyl, time not requiring morphine
	Postoperative nausea / vomiting	52	Nausea and vomiting incidence, postoperative nausea and vomiting, anti-emetic requirement
	Preoperative behavior / anxiety	15	Patient preoperative anxiety, parental anxiety, state anxiety, behavior at induction, self-report of fear, anxiety at induction
	Emergence agitation assessment	11	Postoperative anxiety, emergence agitation, emergence delirium, severity of emergence delirium
	Postoperative sedation / recovery assessment	4	Degree of sedation, behavior/sedation, postoperative sedation, sedation scores
	Postoperative behavior (post-discharge)	8	Children's postoperative symptoms at home/anxiety scores, mental state, postoperative maladaptive behavior, abnormal behavior, expressions of bad dreams
Patient-centered	Quality of recovery	21	Health related quality of life, quality of patient experience, severity of postoperative disability, ability of patients to participate in physical therapy, quality of life, degree to

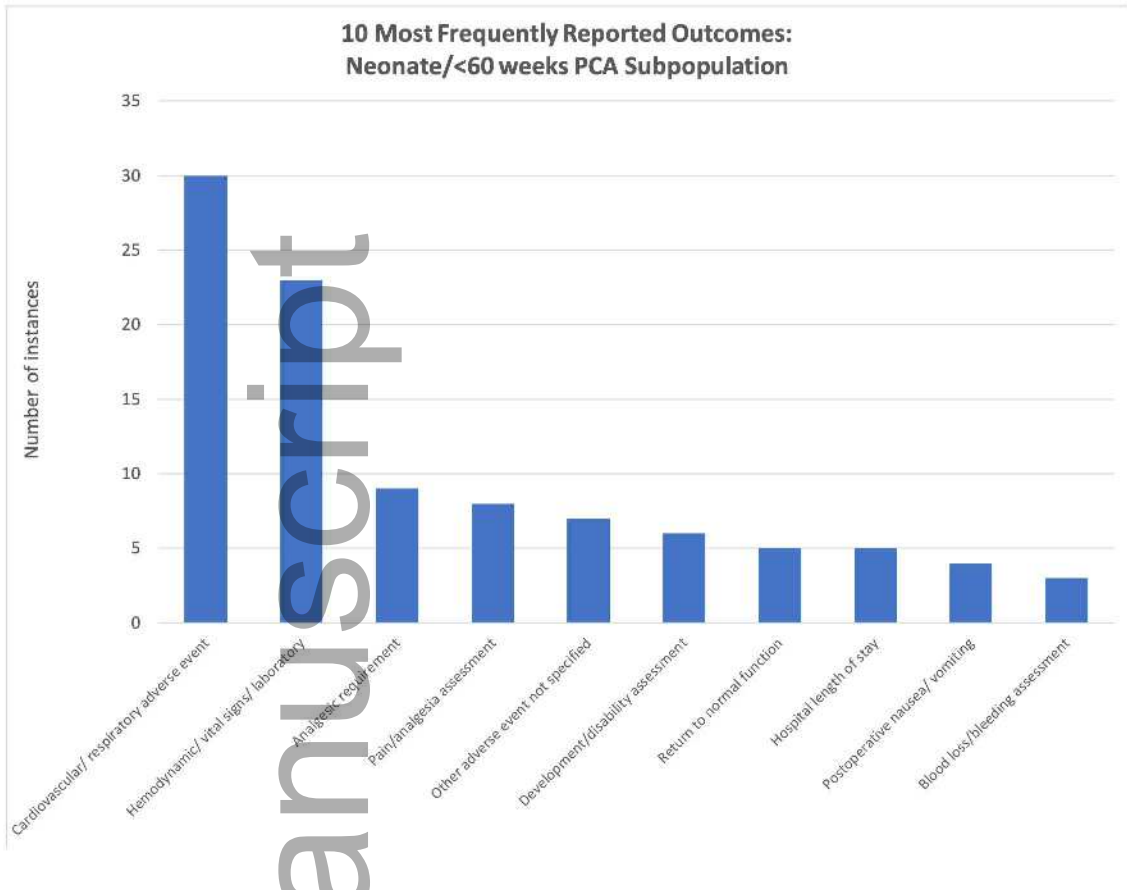
outcomes (86 total outcomes)	assessment		which pain or sedation interfered with the patient's ability to progress in rehabilitation, time to recovery, recovery from fatigue, postoperative recovery at 10 days, functional mobility outcomes, number of times awake at night, sleep quality, postoperative recovery, functional recovery at 3 months, number of sleep hours, days to full activity, days to return to school
	Return to normal function	42	Time to return of normal bowel function, time to first bowel movement, time to first flatus, time to initial diet (clear liquids) postoperatively, oral intake, return to full oral intake, return to normal diet, feed tolerance, time to full diet postoperatively, return of adequate, time to tolerate oral intake, maximum tolerated diet on postoperative days, time to first food, time after surgery that >= 50% of meals were tolerated, time to transition to oral medications, time to return to daily activities, mobility/performance, time to ambulation, return to normal activity, time to leave bed, time to walking, activity level, time to foley removal, time with urinary catheter, time to first micturition, time to first swallow
	Satisfaction assessment	19	Parental satisfaction, satisfaction score, parent satisfaction with pain control, caregiver satisfaction, patient satisfaction, nurse satisfaction, global satisfaction ratings, recovery nurse satisfaction
	Hunger, thirst and fasting duration	4	Per-op thirst /hunger, dehydration, duration of preoperative fasting
Bleeding/	Blood loss /	24	Blood loss, intraoperative blood loss, postoperative bleeding (14 days) stratified by

transfusion (32 total outcomes)	bleeding assessment		severity, postoperative bleeding, total blood loss, bleeding score, postoperative hemorrhage, post tonsillectomy hemorrhage, hematoma, bleeding with readmission or re-operation
	Transfusion quantitation	8	Blood products transfused, total volume of packed cells transfused, allogenic transfusion requirement, blood transfusion rate, amount of transfusion, total volume of platelet concentrate transfused, total volume of fresh frozen plasma transfused, total volume of Factor XIII concentrate transfused
Healthcare utilization (60 total outcomes)	Duration of surgery / anesthesia	17	Duration of operation, operative time, anesthesia time, time to separation from parents, surgery time, time to extubation, time to emergence, duration of surgery/anesthesia, operating room time
	PACU length of stay	10	Recovery time, post procedure discharge time, length of stay in PACU, time to waking in recovery room, delayed PACU discharge
	ICU length of stay	1	Intensive care unit length of stay
	Hospital length of stay	21	Length of hospital stay, days in hospital, time to discharge from the recovery room or hospital, time to discharge, duration of hospitalization, any hospital stay after surgery
	Costs / value outcomes	11	Excess hospital cost, indirect costs to patients/ families, cost-effectiveness, hospital charges, cost, hospital costs
Clinical indicators (93 total	Analgesic / medication-related adverse	35	Opioid-induced pruritis, preoperative sedation, avoidance of any significant opioid side effects, side effect of morphine, over-sedation, analgesic adverse events, itching, opioid-related adverse events, postoperative dizziness, nurse-controlled analgesia side effects,

outcomes)	events		motor block, antipruritic medication, motor recovery, adverse effects of TAP blocks, incidence of postoperative dizziness, nurse-controlled analgesia serious adverse events
	Cardiovascular / respiratory adverse event	19	Postoperative respiratory depression, respiratory depression, perioperative respiratory adverse events, perioperative respiratory adverse events, laryngospasm, bronchospasm, laryngospasm, perioperative respiratory adverse events during the different phases of anesthesia, persistent coughing lasting more than 10 seconds, airway obstruction, coughing, desaturation lasting more than 10 sec, postoperative stridor, cardiac arrest, postoperative mortality
	Other adverse events / adverse event not specified	30	Postoperative hyponatremia, post-anesthesia shivering, hyponatremia, freedom from seizures at 12 months, postoperative acidosis, any occurrence of seizures, fever, hypernatremia, odor, clinically significant postoperative complications, incidence of postoperative fever, incidence of complications, perioperative complications, postoperative complications, adverse events, undesirable effects, side effects, pleural puncture and/or pneumothorax, vascular punctures, surgical complications
	Postoperative medical reattendance / readmission	2	Discharge status at day 14, unplanned medical attention during follow-up period
	Surgical site infection	5	Surgical site infection (superficial or deep), surgical site infection incidence, surgical site infection superficial or deep within 30 days postop
	Urinary issues	2	Uroschesis, incidence of urinary retention

Other (35 total outcomes)	Hemodynamic / vital signs / laboratory	22	Recovery profile, stable hemodynamics, blood glucose, time to spontaneous breathing, heart rate, fluid requirement, incidence of >20% change in systolic blood pressure, blood pressure, SpO2, postoperative oxygenation, cardiovascular stability, mean arterial pressure, plasma ADH levels, oculocardiac reflex, plasma bupivacaine concentration, alloimmunization, acetaminophen concentration, postoperative coagulopathy, gastric pH
	Development / disability assessment	2	Intelligence

A



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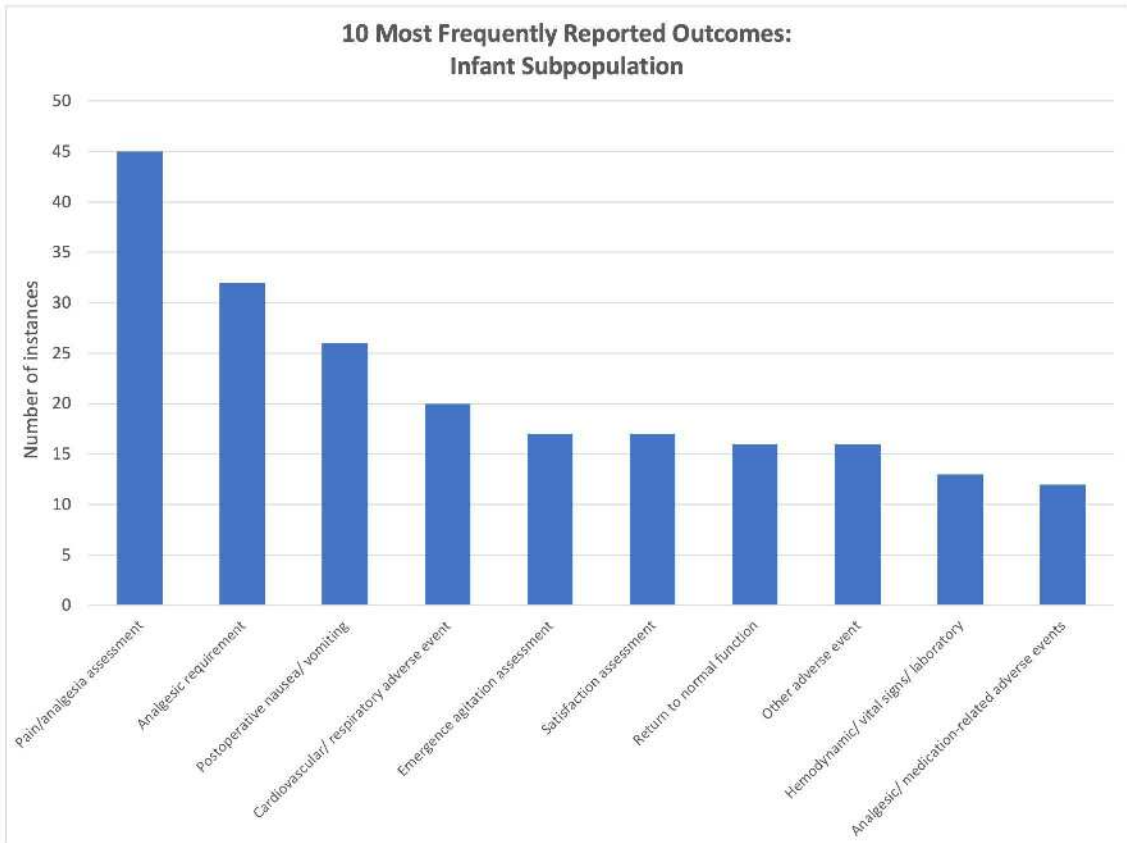

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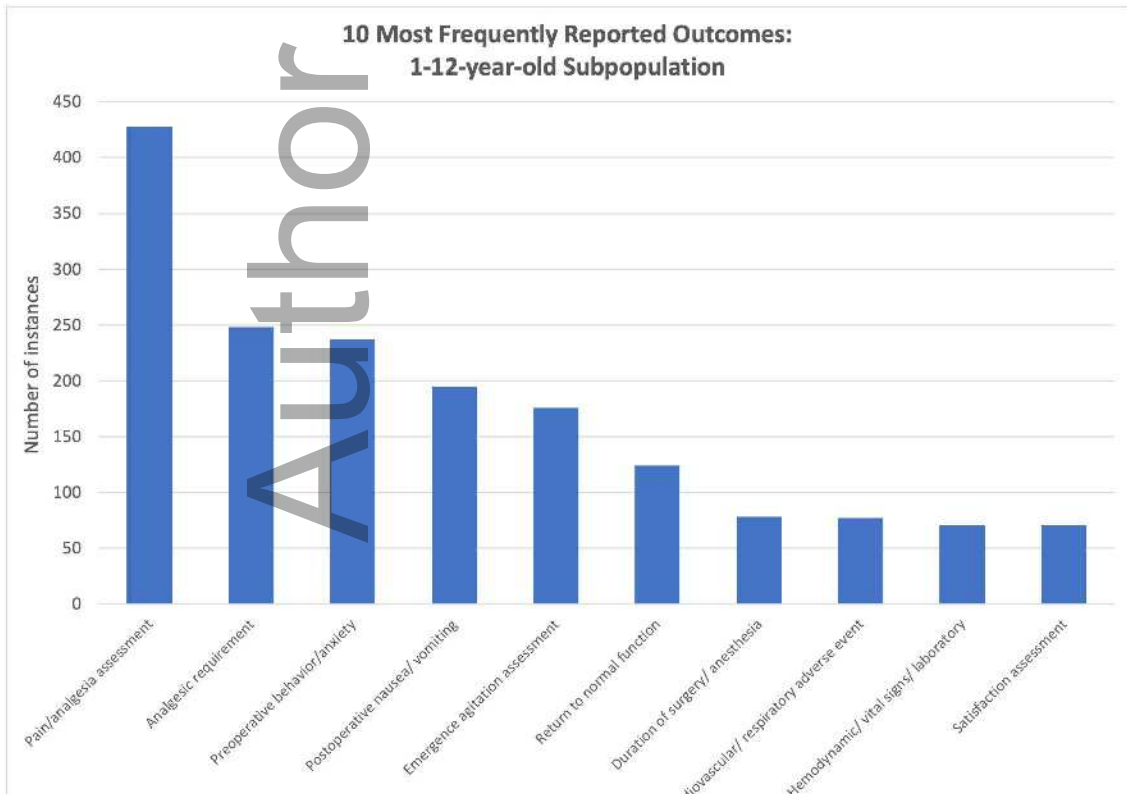

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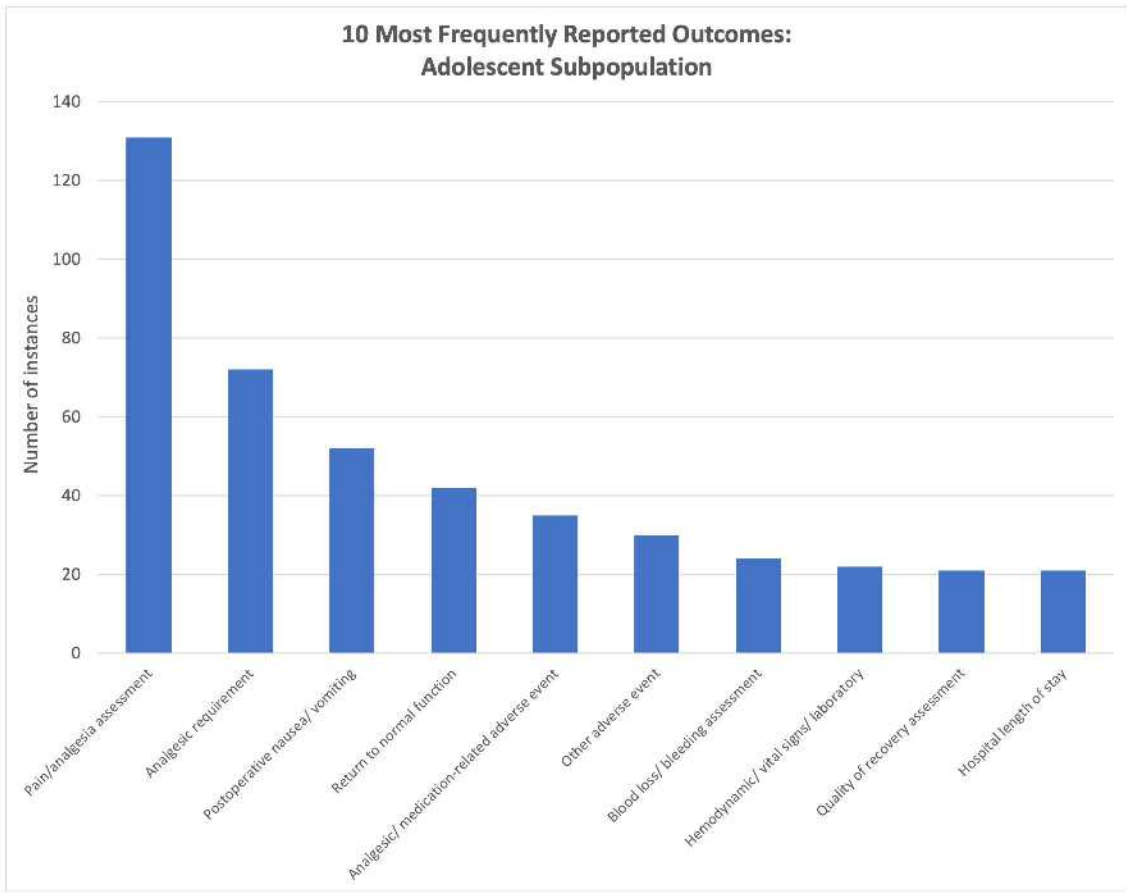

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