Research in young people: ethics and challenges

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I have no disclosures

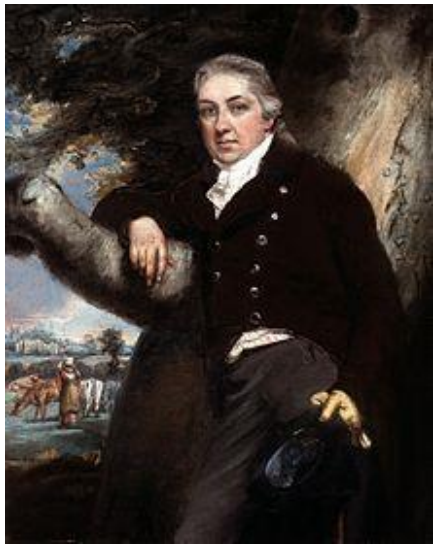
Outline

- History
- The need
- Ethics
- Challenges
- Rare disease and novel therapy

History

- Little research in children prior to 19th century
- Children not valued

First trial in children



- Jenner vaccinated his son with cowpox in 1796
- Then his gardener’s son James Phipps aged 8
- Later repeatedly exposed him to smallpox

19th Century

- Increase interest in children
  - Industrial revolution – healthy children needed to work
  - Romantic period – steadily greater emphasis on the child

- Children in orphanages often used for experiments, or physicians' own children (or their slaves)

- Beginning to understand anatomy, digestion
- Emphasis on vaccination

Early 20th Century

- Continued use of children in orphanages
- Antivivisectionists (animal rights) most vocal group against this

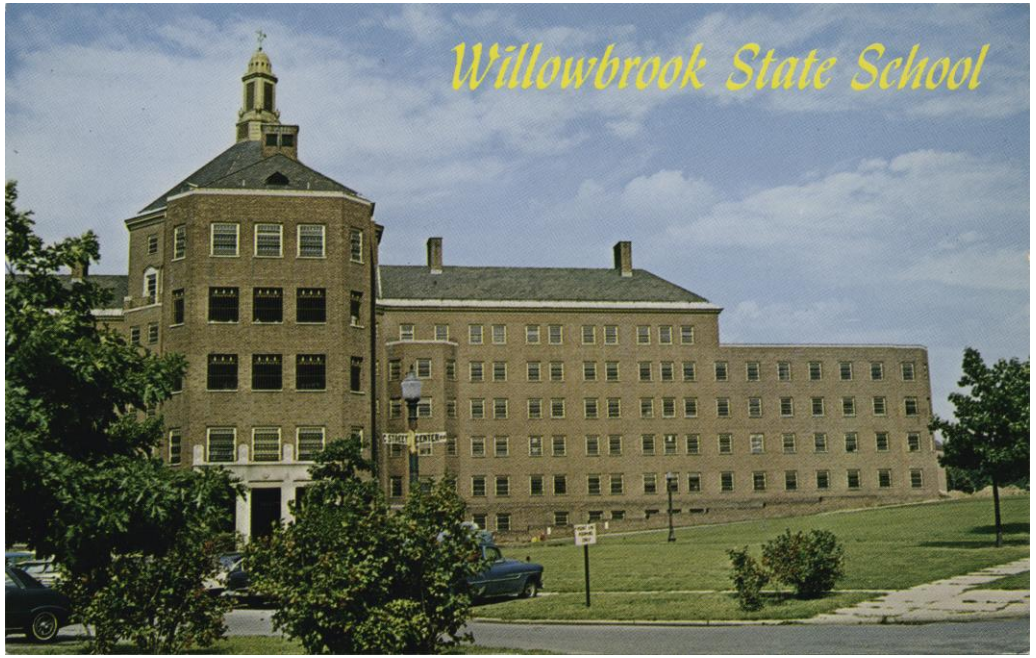
- Diabolical Nazi experiments on children
- Post WW2 – Nuremberg code stated that medical research should be forbidden in those that cannot consent – implying research would be unethical in children

- This tended to be ignored

Willowbrook State School experiments

- Large home for mentally disabled in New York
- 1960s
- Deliberately infected children with hepatitis

- Raised awareness about research in children



Late 20th century

- Emphasis on protecting children – greater scrutiny of protocols, minimization of risk
- Pharma and researchers tended to avoid clinical trials in children
- Financial disincentive
  - Smaller market for Pharma,
  - More obstacles to do paediatric trials

Bias persists today

- Paediatric trials 15-20% of registered trials
- Even fewer trials in those with the greatest disease burden
  - Neonates
  - Diseases impacting Low & Middle Income Countries

- Most medicines used in children are still unlicensed or off label
- No RCT data in more than half of interventions in children

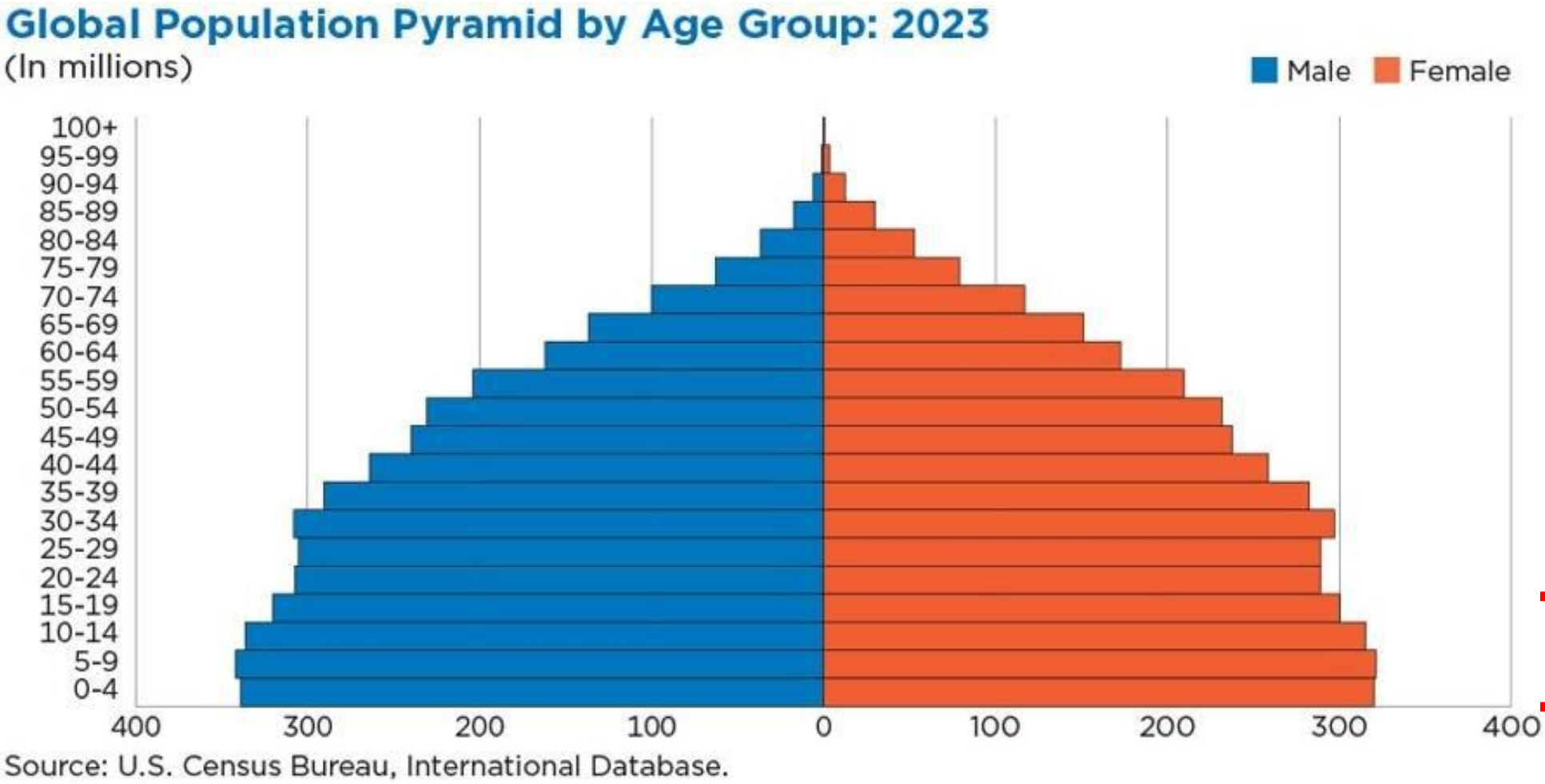
Bias persists today

- Vast majority of trial protocols exclude children
- Sometimes biologically valid to do so
- Sometimes ethically appropriate
- Mostly just done automatically

- *Maybe* things will change as sexism and agism challenges the selection of populations for trials

The need

The need



2.5 Billion Children and young people

How many children have anaesthesia

- Australia ~ 200,000
- UK ~ half a million
- USA ~ 6 million
- Rest of the world - ?

Why the need for paediatric research

- Different diseases, comorbidities
- Physiology different
- Pharmacology different
  - Pharmacokinetics
  - Pharmacodynamics
  - Toxicity
- Psychosocial framework and environment different

- <10% of drugs can easily extrapolate adult data to children

Examples of paediatric toxicity

- Tetracycline – severe enamel dysplasia
- Chloramphenicol – grey baby syndrome

Another need for paediatric research

- Many “adult” diseases have their origin in children
  - Mental health
  - Cardiovascular disease
  - Obesity

Ethics

Ethics

- Children are classified as vulnerable:
    - Unable to fully understand and thus provide sufficient consent
    - Risk of coercion by parents, peers or researchers
    - Conflicting values between parents and children
- Being vulnerable needs extra protection

Consent

- *Infants:* unable to take part in the discussion & can't consent
- *Young children with limited capacity to understand:* limited discussion but can't consent
- *Young people with developing maturity:* capacity to understand but still vulnerable – consent required but not sufficient
- *Mature young people:* not vulnerable - consent required and sufficient

- Consent tailored to maturity and not set at particular ages
- Assent *versus* Consent

Dissent

- A child’s refusal must be respected – within the context of their maturity
- If not sufficiently mature, then dissent may be over-ruled by parents if participation is in the child’s best interests

Other ethical requirements

- Research must be relevant to children
- Only if it cannot be done in adults
- As well as being vulnerable and limited understanding, children have limited, or no capacity to be altruistic – reduces the acceptability of risk and hence risk must be minimal

- Levels of “acceptable risks” not well defined
- Acceptable risk requires consideration of risk *versus* real or potential benefit *versus* value to others

“…researchers must establish that there is no reason to believe that participation is contrary to that child’s or young person’s best interests.”

“particular tension between not placing children at risk in studies of new interventions and the need for knowledge about how such interventions are best used for children”

Trial phase

- Phase I clinical trials are done to test a new biomedical intervention for the first time in a small group of people (e.g. 20-80) to evaluate safety (e.g. to determine a safe dosage range and identify side effects).
- Phase II clinical trials are done to study an intervention in a larger group of people (several hundred) to determine efficacy (that is, whether it works as intended) and to further evaluate its safety.
- Phase III studies are done to study the efficacy of an intervention in large groups of trial participants (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions (or to non-interventional standard care). Phase III studies are also used to monitor adverse effects and to collect information that will allow the intervention to be used safely
- Phase IV studies are done after an intervention has been marketed. These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use over longer periods of time. They may also be used to investigate the potential use of the intervention in a different condition, or in combination with other therapies.

What phase trials are done in children?

- Safety data, efficacy and kinetics usually established in adults first
- Typically phase three in children

- Except if the condition only occurs in children or can only be delivered in children
  - E.g. surfactant, gene therapies
- Or, if toxicity and safety likely different in children
- If the disease has a different natural history in children
- If there are no other therapies

Challenges

Challenges – diversity

- Children are a very heterogenous population

- Wide range of ages
  - Developing physiology
  - Developing psychosocially

- Wide range of diseases and conditions

Challenges – numbers

- Diversity means smaller numbers
- Also, many rare diseases in children

- Ways to generate numbers
  - Adaptive designs
  - Collaboration
  - Extensive networks

Challenges – participation

- Both clinicians and parents may be reluctant to participate – concerned about risk and safety
- Enrolment
  - Extra time required to discuss participation
  - Include the child in the discussion
  - Approached early and in an appropriate setting

- Parents often do see it as a positive experience – access to treatment, helping other children, better care, etc
- Children may also see it as a positive experience

Challenges – participant information sheets

- Age appropriate
- Context appropriate

- Use of videos, pictures etc

Challenges – waiver of consent

- Minimal risk
- Significant value
- Impractical to get consent

- The parents are often there…

Challenges – child appropriate environment

- Staff trained in paediatric care
- Facilities designed to accommodate children
- Processes for reducing anxiety for procedures
- Paediatric resuscitation available etc

Challenges – the right questions

- Trials and research can’t answer every question
- Need to carefully choose which one is important
- Extensive stakeholder engagement before and during design
- Consumer input
- Consider research prioritisation processes

Which problems?

Pediatric Anesthesia

EDITORIAL

In search of the big question

What are the big unanswered questions in pediatric anesthesia? Where should we focus our research and what discoveries would readers find interesting in our journal? To answer this, a group of academic pediatric anesthetists were asked to state their five big questions. They were asked what are the questions we need answered to improve pediatric anesthesia care. What answers would help us reduce the problems that are common and/or have a significant burden or morbidity? Board members of this journal, scientific committee members of the Association of Paediatric Anaesthetists of Great Britain and Ireland and scientific committee members of the Society for Pediatric Anesthesia in New Zealand and Australia, and scientific committee and past presidents of the Society of Pediatric Anesthesia were asked to contribute.

There were 23 respondents: 13 from the USA, three each from the UK and Australia, and one each from New Zealand, Switzerland, Belgium, and Austria. Most listed many more than five questions. A striking aspect of the responses was the very broad range of questions raised. The 10 most commonly cited questions are listed below, and to avoid any personal bias, I have mentioned all their questions in the following editorial.

Perhaps not surprisingly, the single commonest question was related to neurotoxicity of anesthetics to the developing brain. Is the neurotoxicity clinically relevant, which children are most at risk at what age and which agents are more neurotoxic? More than half responders ranked this high in their list of questions.

There were also general questions in pharmacology. What are the effects of age on pharmacokinetics, pharmacodynamics, safety, and side effects? Furthermore, what are the target effects we are actually looking for in small children and how do we measure them? Neonates were highlighted as the age group with the greatest knowledge gap in pharmacology. Several respondents also mentioned the importance of determining the role for the emerging field of pharmacogenomics.

After neurotoxicity, the most frequently cited questions surrounded the role of regional nerve blockade in children. Does neuraxial anesthesia improve outcome compared with general anesthesia, and, more importantly, nearly a third of respondents asked whether regional blockade under general anesthesia really improves outcome. Other questions related to regional anesthesia were as follows: Is there significant muscular damage with local anesthesia infiltration and does regional anesthesia really mask compartment syndrome?

There were several questions related to equipment, monitoring, and new technologies. How can we measure depth of anesthesia in small children and will this reduce awareness? What role does NIRS have in pediatric anesthesia? How can we measure cardiac output with noninvasive techniques and what is the most reliable and relevant way to measure temperature? How can we use closed loop anesthesia in children, especially related to exhaled or intermittent blood monitoring of propofol for TIVA? Indeed what is the role of TIVA in children and neonates? How do we monitor cerebral perfusion, especially in neonates and what is the optimal blood pressure? Similarly to the problem of setting the appropriate target effect in pharmacology, when considering developing or applying new technologies in children, often the question was how can we validate the technology when we are unsure what end point we should aim for? Another question was how do we best use the flood of information available through improved information technology? Conversely is the increasing focus on information and new technology distracting us from acquiring and using basic clinical skills?

Questions related to anesthesia complications included the following: How do we reduce the risk of laryngospasm, is oxygen therapy toxic, and what anesthetic technique best reduces inflammatory responses? Predicting outcome and evaluating risk were also recognized as important questions. Can we develop a pediatric risk score that is better than the ASA status and what risks should be discussed with consent? Also how can we use population-based data to better understand risk and mechanisms underlying complications?

The postoperative period was an area rich in questions. How do we reduce the incidence of postoperative pain, nausea, vomiting, sore throat, and delirium? How can we reduce nausea when we can't effectively measure nausea in small children? Is long-term postoperative behavior change a real phenomenon in children and is it related to neurotoxicity?

Many questions related to fluid management. What fluid should we give and how much? At what hematocrit should we transfuse and if we don't use blood should we use colloid or crystalloid for volume replacement? How do we reduce transfusion error and what are the long-term effects of transfusion in children?

There were a few questions that related to specific diseases or procedures, for example, what is the optimal management of children with obesity, obstructive

Pediatric Anesthesia

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References

1 Liao GQ, Wang H, Zhu GY *et al.* Management of acquired bronchobiliary fistula: a systematic literature review of 68 cases published in 30 years. *World J Gastroenterol* 2011; **17**: 3842–3849.
2 Eryigit H, Ortas S, Urek S *et al.* Management of acquired bronchobiliary fistula: 3 case reports and a literature review. *J Cardiothorac Surg* 2007; **2**: 52.
3 Tocchi A, Mazzoni G, Miccini M *et al.* Treatment of hydatid bronchobiliary fistula: 30 years of experience. *Liver Int* 2007; **27**: 209–214.
4 Mitra S, Bhatia N, Dey N *et al.* Bronchobiliary fistula: an anesthetic challenge!. *J Clin. Anesth. Age* 2009; **21**: 360–362.
5 Campos JH. Effects of oxygenation during selective lobar versus total lung collapse with or without continuous positive airway pressure. *Anesth Analg* 1997; **85**: 583–586.

Still in search of the big question

Sir—In 2012, an editorial in this journal presented a list of what various academic pediatric anesthesia researchers thought were the big unanswered questions in our specialty (1). The aim was to identify where we should direct our research effort. Asking a handful of researchers resulted in a cacophony of broad-ranging topics. Of course, what the researchers think is important may not reflect what the specialty thinks is important. Therefore, I took the top questions proposed by the researchers and asked the audience at the 2102 annual scientific meeting of the Society of Pediatric Anesthetists of New Zealand and Australia to rate the questions in terms of what they thought was important. They were asked to rate the questions as: (i) Very important, number one priority, will change what I do, (ii) Important, will probably change what I do, (iii) Interesting but unlikely to change what I do, (iv) Already known, satisfactory level of knowledge, not worth doing the research, and (v) Don't care, waste of money doing the research. The meeting had over 200 attendees from a range of pediatric anesthesia practices. *Poll Everywhere*™ software was used.

The results are presented in the Table 1. The most pressing issue was clearly seen to be the optimization of postdischarge pain. While the academics had overwhelmingly indicated that neurotoxicity was the most pressing issue, the broader group listed this second, well-behind postdischarge pain and not much ahead of IV fluid. Given the vast gaps in our knowledge, it was somewhat surprising to see pharmacology and age ranked at the bottom.

The next and most important step in identifying the important research question is to determine what families and the health dollar providers see as important and to consider our knowledge gaps from their perspective.

Table 1 Conference audience ratings of the big questions

	Number polled	Very important, %	Important, %	Interesting, %	Already known, %	Don't care, %
How to optimize postdischarge pain management in children?	98	59	29	5	2	5
What is the clinical relevance of neurotoxicity of general anesthetics in children?	71	44	37	14	0	6
What is the optimal IV fluid for children?	99	40	36	12	7	4
What are the long term consequences of opioid use and how can we reduce the side effects of opioids in children?	88	33	39	23	3	2
How do we eliminate emergence agitation?	97	29	35	23	8	5
Does regional blockade improve outcome in children?	90	26	39	24	9	2
What is the best anesthetic management for children with pulmonary hypertension?	95	21	35	24	17	3
What is the optimal sedation and analgesic regime for children in pediatric intensive care unit?	96	20	38	26	0	17
How do the pharmacokinetics and pharmacodynamics of anesthetic and analgesic drugs change with age?	93	14	24	39	12	12

- Those that *we* worry about

Davidson, 2012 & 2013

- What is the clinical relevance of neurotoxicity of general anesthetics?
- Does regional blockade improve outcome in children?
- What is the best anesthetic management for children with pulmonary hypertension?
- How do we eliminate emergence agitation?
- What is the optimal intravenous fluid?
- How do pharmacokinetics and pharmacodynamics change with age?
- What is the optimal sedation and analgesia in pediatric intensive care?
- How do we optimize postdischarge pain management?
- How can we use pharmacogenetic information in children?
- What are the long-term consequences of opioid use in children and how can we reduce the side effects of opioids?

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RESEARCH REPORT

Pediatric Anesthesia WILEY

Consumer research priorities for pediatric anesthesia and perioperative medicine

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Section Editor: Joseph Cravero

Abstract

Background: Consumer-driven research is increasingly being prioritized.

Aim: Our aim was to partner with consumers to identify the top 10 research priorities for pediatric anesthesia and perioperative medicine. The ACORN (Anesthesia Consumer Research Network) was formed to collaborate with children and families across Australia.

Methods: A prospective online survey was developed to generate research ideas from consumers. The survey was developed in Qualtrics, a survey research platform. Consumers were invited to participate through poster advertising, social media posts, via consumer networks at participating hospitals and in addition 35 national consumer/patient representative organizations were approached. We also conducted a similar idea generating survey for clinicians through email invitation and via Twitter. A second round of surveys was conducted to prioritize the long list of research questions and a shortlist of priorities developed. A single consensus meeting was held, and a final consensus list of top 10 priorities emerged.

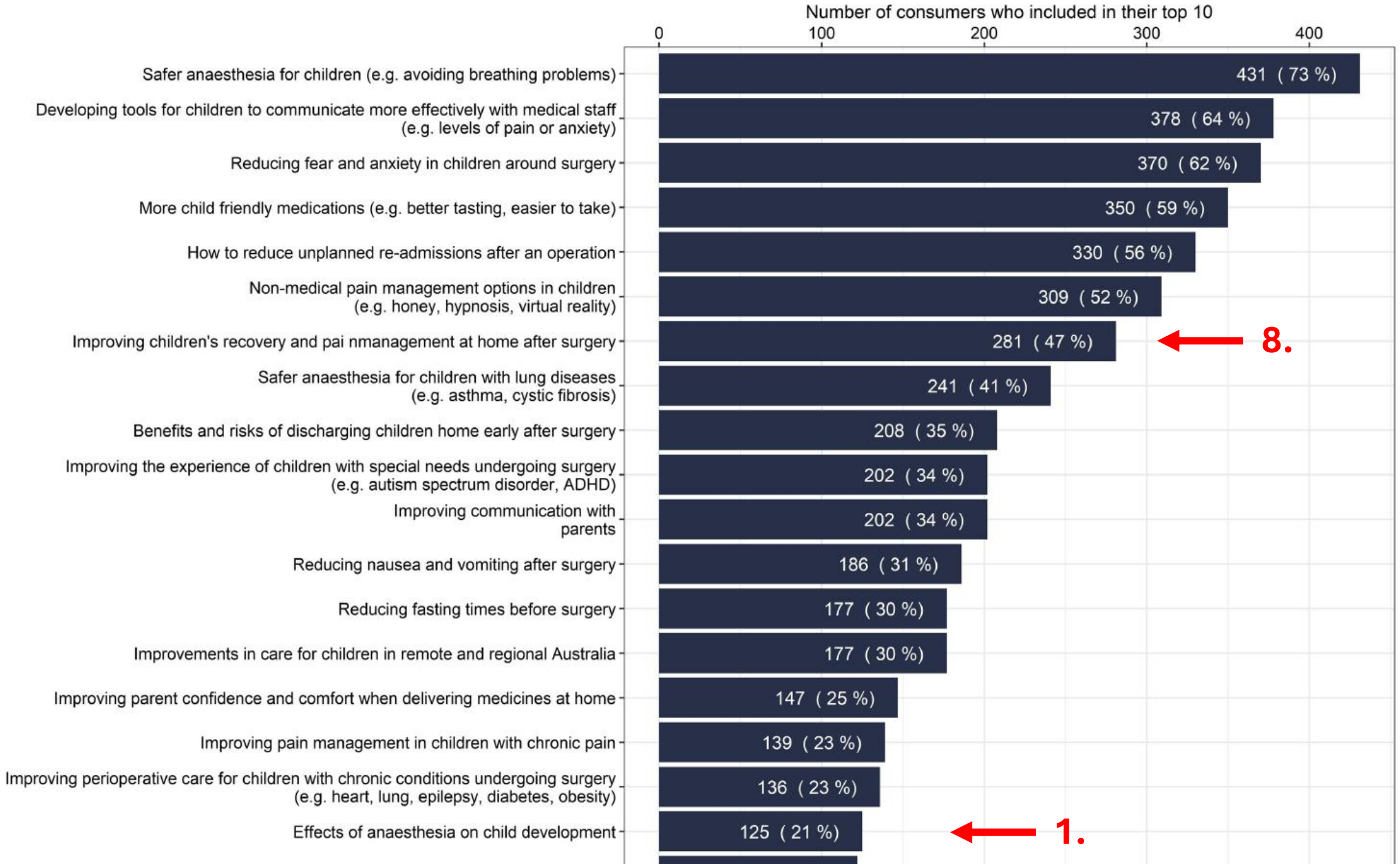
Results: A total of 281 research ideas were submitted between 356 consumers in the idea generating survey and from four consumer/patient representative groups. Seventy-five clinicians responded to the clinician idea generation survey. This was consolidated into 20 research ideas/themes for the second survey for each group. 566 responses were received to the consumer prioritization top 10 survey and 525 responses to the clinician survey. The consensus meeting produced the final 10 consumer research priorities.

Conclusion: This study has given Australian consumers the opportunity to shape the anesthesia and perioperative medicine research agenda for pediatric patients both nationally and internationally.

KEYWORDS
anesthesia, consumers, pediatric, perioperative medicine, Priority setting

- Those that our patients and families worry about

Sommerfield et al. 2023


Number of consumers who included in their top 10
0
100
200
300
400
Safer anaesthesia for children (e.g. avoiding breathing problems)
431 (73 %)
Developing tools for children to communicate more effectively with medical staff (e.g. levels of pain or anxiety)
378 (64 %)
Reducing fear and anxiety in children around surgery
370 (62 %)
More child friendly medications (e.g. better tasting, easier to take)
350 (59 %)
How to reduce unplanned re-admissions after an operation
330 (56 %)
Non-medical pain management options in children (e.g. honey, hypnosis, virtual reality)
309 (52 %)
Improving children's recovery and pai nmanagement at home after surgery
281 (47 %)
8.
Safer anaesthesia for children with lung diseases (e.g. asthma, cystic fibrosis)
241 (41 %)
Benefits and risks of discharging children home early after surgery
208 (35 %)
Improving the experience of children with special needs undergoing surgery (e.g. autism spectrum disorder, ADHD)
202 (34 %)
Improving communication with parents
202 (34 %)
Reducing nausea and vomiting after surgery
186 (31 %)
Reducing fasting times before surgery
177 (30 %)
Improvements in care for children in remote and regional Australia
177 (30 %)
Improving parent confidence and comfort when delivering medicines at home
147 (25 %)
Improving pain management in children with chronic pain
139 (23 %)
Improving perioperative care for children with chronic conditions undergoing surgery (e.g. heart, lung, epilepsy, diabetes, obesity)
136 (23 %)
Effects of anaesthesia on child development
125 (21 %)
1.

Child consumer input

- Increasingly important for all stages of research
- Australia somewhat slow to take up
- Must be done well to be effective
- Engage children and parents

Study design

- Experimenting on children demands the highest quality research

- Right question
- Involve a statistician
- Right design to answer the question accurately and efficiently
- Right outcomes
- Sufficient numbers

Challenges – dose

- Can you simply extrapolate from adults?
- Dose finding studies required?
- Dosing needs to be appropriate for range of ages/weights
- Appropriate formulation for children

- Similar issues for non-drug interventions

Challenges – pharmacokinetics

- Blood sampling harder in children
- Limited sensitive micro-analytical techniques

- Opportunistic sampling may be the best

Pilot studies

- Often essential in paediatrics due to the particular challenges

- How easy is it to recruit?
- Will families be accepting of randomisation?
- Is the intervention feasible and accepted?
- Is it feasible to collect the outcome measures?
- Do you need data on the variability in outcome measures?
- How many data are likely missing?

Challenges – outcomes

- Many outcomes simply extrapolated from adults
- Must be appropriate for children
- Must be appropriate for the age range(s)
- Validated in all age ranges? Normative data for all ages?
- Clear processes for generating outcomes
- Patient & family centred
- Patient reported outcomes may be more difficult
- Rare “significant” outcomes – how reliable are the surrogate outcomes?
- Long term outcomes often desirable

Pediatric Perioperative Outcomes Group

- COPAC: Core Outcome Measures for Peri-operative and Anaesthetic Care
  - Stakeholders: patients, families, clinicians, nurses
  - Which domains to include in the core outcome sets
- StEP: Standardising Endpoints in Perioperative medicine
  - Delphi process to choose best outcomes within the domains

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EDITORIAL

WILEY Pediatric Anesthesia

Pediatric perioperative outcomes group: Defining core outcomes for pediatric anesthesia and perioperative medicine

In 2015, the joint National Institute of Academic Anaesthesia/James Lind Alliance Research Priority Setting Partnership published a top 10 list of research priorities for anesthesia and perioperative care in the UK.[1] These priorities were developed through a systematic process that engaged physicians, patients, and the public with the intent of identifying research questions broadly relevant to pertinent stakeholders. A subsequent editorial in this journal highlighted 4 priorities applicable to the care of children.[2]

One of the questions relevant to both adults and children was "What outcomes should we use to measure the 'success' of anesthesia and perioperative care?" However, this research priority generates many more questions: What outcomes matter most to our patients and their families? What outcomes are most important to clinicians? What are the fundamental outcomes for clinical researchers? Are these outcomes aligned? Do we and can we routinely measure these outcomes, either in clinical practice or in clinical trials?

Core outcome sets have been developed to address these questions across a wide range of medical disciplines. Consensus-based standardized outcomes are defined with the aim of reducing variability in the use and reporting of outcomes in clinical trials. In 2010, The Core Outcome Measures in Effectiveness Trials (COMET) initiative was launched with the goal of fostering core outcome set development throughout medicine, and now provides a resource for core outcome set developers (http://www.comet-initiative.org).[3] The COMET initiative promotes the use of evidence-based review together with clinician, researcher, and patient participation in the development process. Through conscientious engagement of these parties, the COMET methodology ensures that clinically meaningful patient-centered outcomes are identified.

Core outcome sets are intended to be a minimum set of outcomes for inclusion in all trials in a given population. As such, the intent is not to narrow the scope of trials to a few preselected outcomes, but rather to ensure that certain fundamental outcomes with standard definitions are included in all trials conducted in that population. It is therefore expected that researchers will include other outcomes relevant to their specific studies.[3] Importantly, core outcome sets are intended not only for use in clinical research but also for incorporation into data systems used in clinical practice to support clinical audits and quality improvement activities.

So why do we need core outcome sets? Our ability to compare and synthesize results of clinical trials and investigations is often limited by variability in the outcomes utilized and reported. Even when the same "outcome" is used, variability in how that outcome is defined can make comparison of different trial results difficult. The use of standardized outcomes would greatly enhance the value of individual study results by enabling them to be seamlessly integrated into meta-analyses. The ability to combine results of multiple trials also helps address an ethical obligation of clinical research by enhancing the benefits and generalizability of data derived from human subject participation in research and minimizing unnecessary duplication.

Using COMET methodology, a core outcome set for adult perioperative medicine is being developed by a group of perioperative medicine clinicians and researchers. This initiative is described in greater detail elsewhere,[4,5] but in essence there are 2 parallel projects. COMPAC (Core Outcome Measures for Perioperative and Anesthetic Care) is a collaborative effort that seeks input from patients, care givers, nurses, and physicians to determine what outcome domains should be included in a perioperative core outcome set. The parallel StEP (Standardizing Endpoints in Perioperative medicine) project is an expert-based Delphi consensus-driven effort to define how the specific outcomes within these domains should be measured.[5]

Both COMPAC and StEP focus on perioperative care of adults having major surgery, and as such many of the outcomes are more specifically relevant to adult and elderly patients (eg, major adverse cardiac events, stroke, postoperative cognitive decline). While there are some commonalities and overlap of outcomes relevant in both adults and children, it is apparent to anyone who takes care of children that many of the concerns of adult patients are less relevant or do not apply to pediatric populations. For example, for patient comfort outcomes, there are similar clinically relevant endpoints (postoperative nausea and vomiting, pain measurement, quality of recovery) but the measurement scales of adults cannot be applied in children. Age-specific scales and measures are needed for these items. In contrast, cardiovascular adverse events (eg, myocardial injury, arrhythmias, venous thromboembolism), postoperative respiratory complications, and acute kidney injury are much less common in children, whereas others such as acute airway incidents are more specific for children.

Recognizing this, an international group of investigators has formed the Pediatric Perioperative Outcomes Group, and taken up the task of pursuing the question "How do we measure/define a successful anesthetic *in infants, children, and young people*?" Through a process similar to that of our adult counterparts, work has begun to develop a core outcome set applicable to pediatric perioperative care. Currently, investigators from Australia, China, Europe, India, New Zealand, South Africa, the United Kingdom, and the United States are involved, but additional opportunities for clinicians and

Pediatric Perioperative Outcomes Group members are in Appendix 1.

- 4 age groups
  - Neonates < 60 weeks PMA
  - Infants <1 year
  - Toddlers and school age children 1-13 years
  - Adolescents 13-18 years
- 724 research papers 2008-2018
- 3192 outcomes – sorted into domains

- Great variability
- Many poorly validated

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SPECIAL INTEREST ARTICLE

Pediatric Anesthesia WILEY

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

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The right outcome

- Sometimes need years of work
  - Find the outcomes that matter
  - Develop the tools to measure those outcomes

Outcome problems – pain

- Post op pain
  - Dozens of different measures
  - Pain on function or at rest
  - What time points to measure it
  - Maximal or average pain

Outcome problems – behaviour

- Vernon Post Hospitalisation Behaviour Questionnaire
  - 27 measures of behaviour
  - Developed 1966
  - Never properly validated
  - Not logical (activity, use of pacifier etc)
  - No consensus on how to interpret the data
    - Absolute or relative behaviour
    - Continuous or dichotomous outcome
    - No way to accommodate *improvements* in behaviour

Outcome problems – anxiety on induction

- Modified Yale Preoperative Anxiety Scale
  - Activity
  - Emotional Expressivity
  - Vocalisations
  - State of Apparent Arousal
  - Use of parent
- Designed to assess premedication and preparation strategies
- What if there is no parent?
- Not applicable to distraction techniques

Outcome problems – emergence delirium

- Mostly measuring agitation
- Even in the best scale (PAED) there is significant overlap between pain and delirium

Outcome problems – Blood Pressure

- What is a “normal” intraoperative blood pressure in a child?
- What is an unacceptable blood pressure?
- What about infants and neonates

Outcome problems – anaesthetic in a neonate

- What is the best anaesthetic in a neonate?
  - How do we measure consciousness?
  - How do we measure amnesia?
  - What other outcomes are we worried about?

Challenges – funding

- Paediatric research is more difficult and hence expensive
- No extra funding for paediatric research

- Priorities often on adult health

Challenges – expertise

- Lack of skills
- Lack of mentorship

- Importance of international collaboration and networks

Incentives to increase paediatric research

Encouraging paediatric trials

- United Nations 1989 “Convention on the Rights of the Child”

- Right to have research evidence for commonly used treatments in children
- Reasonable to include children in the developmental pipeline for drugs likely to be used in children

Encouraging trials – legislation for Pharma

- USA 1997 Legislation
- EU 2007 Legislation
- Pharma obliged to evaluate safety and efficacy in all appropriate ages
- Have paediatric data in the product label
- Paediatric appropriate formulations
- Submit a “Pediatric Development Plan” & “Paediatric Investigation Plan”

- Penalised if no consideration of paediatric trials
- 6 month patent extension if they conduct paediatric trials

Encouraging trials – legislation for Pharma

- Moderate increase in activity
- Mostly in endocrinology, oncology, infectious diseases and cardiovascular disease
- Drugs where there is a huge adult market rather then addressing paediatric burden of disease
- Off patent drugs still understudied

USA 2011

- National Institute of Child Health and Human Development Pediatric Trial Network

- Specific funding for trials in off patent drugs

EU 2011

- Invested in creating a pan European paediatric trial network
- Education & training
- Streamlining processes

UK 2005

- National Institute for Health Research Medicines for Children Research Network
- Government funded

Rare disease and novel therapies

Rare diseases

- Definition: <5 in 10,000
- Majority in childhood
- One in twenty children have a rare disease
- Many don’t live to 5th birthday

- Novel therapies are often the *only* therapy
- Life changing therapy

Novel therapies

- Gene Therapies
- Cellular therapies
- CAR T
- mRNA technologies
- Antisense oligonucleotides
- Bacteriophage

Novel therapies research challenges

- Understanding the regulatory framework
- Institutional and hospital processes in place
- Education staff and the public
- Expertise in ethic committees
- Facilities for safe preparation and delivery
- Fair processes to select the children
- Plan for transition to standard care – who will pay

- Must be a strategic priority for the country/hospital/institution

Paediatric research in low resource settings

- Expertise
- Time
- Money
- Access to the literature

Low resource settings

- Focus on *your* problems
- Consider Health Services Research – how to provide the best outcomes with what you have

- Build collaborations in your region
- Build relationships with established groups of researchers

Summary

- There is a great need for paediatric research including paediatric anaesthesia
- Numerous challenges
- Major challenge is having the right outcome measures
- Focus on the important problems for *your* patients
- Collaborate

Thank you

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